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OCCUPATIONAL EXPOSURES CONTRIBUTE TO EDUCATIONAL INEQUALITIES IN LUNG CANCER INCIDENCE AMONG MEN. EVIDENCE FROM THE EPIC PROSPECTIVE COHORT STUDY.

Short title: Occupation and educational inequalities in lung cancer

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Keywords: Lung cancer incidence, education, men, occupational exposure

Novelty and impact of the findings

Our study revealed that the impact of occupational exposures on educational inequalities in lung cancer incidence exists while of modest magnitude. Occupational exposures explained about 14% of remaining inequalities, when smoking and diet are already adjusted for.

Public and occupational health policies that aim at decreasing occupational exposure to carcinogens would help to reduce socioeconomic inequalities in the cancer field.

ABSTRACT

The aim of this study is to investigate to what extent occupational exposures may explain socioeconomic inequalities in lung cancer incidence after adjusting for smoking and dietary factors. Analyses were based on a subsample of the European Prospective Investigation into Cancer and Nutrition (EPIC study), a prospective cohort. Analyses included 703 incident lung cancer cases among men in Denmark, the UK, Germany, Italy, Spain and Greece. Socioeconomic position was measured using the highest level of education. Estimates of relative indices of inequality (RII) were computed with Cox regression models. We first adjusted for smoking (with detailed information on duration and quantity) and dietary factors (fruits and vegetables consumption) and then for occupational exposures. Exposure to three carcinogens (asbestos, heavy metals and polycyclic aromatic hydrocarbons) was analyzed. Occupational exposures explained 14% of the socioeconomic inequalities remaining after adjustment for smoking and fruits and vegetables consumption. Inequalities remained nevertheless statistically significant. The RII decreased from 1.87 (95% CI: 1.36-2.56) to 1.75 (1.27-2.41). The decrease was more pronounced when adjusting for asbestos than for heavy metals or PAH. Analyses by birth cohort suggested an effect of occupational exposures among older men, while due to small number of endpoints no conclusion could be drawn about the role of occupational exposures in educational inequalities among younger men. Our study revealed that the impact of occupational exposures on socioeconomic inequalities in cancer incidence, rarely studied until now, exists while of modest magnitude.

INTRODUCTION

Socioeconomic inequalities are observed in lung cancer incidence. Using various socioeconomic indicators such as education, occupational class, income or deprivation index, studies generally reported a higher risk among subjects with a lower socioeconomic position¹⁻⁴. To explain these inequalities, a common hypothesis is that a higher exposure to risk factors explains the higher incidence of lung cancer in low socioeconomic groups. In other words, the risk factors are seen as intermediate variables or mediators between education and the onset of lung cancer^{5,6}. Smoking is the major risk factor for lung cancer, with a population attributable fraction around 85%⁷. Consequently, this risk factor should be considered first when investigating the mechanisms leading to socioeconomic inequalities in lung cancer incidence. However, studies found that smoking only partly explained these inequalities⁸⁻¹⁰. This suggests that other mediators may account for part of residual inequalities. Occupational exposures may be one of those. Indeed, exposure to several substances including asbestos, arsenic compounds, heavy metals, polycyclic aromatic hydrocarbons (PAH), silica, radon or welding fumes have been associated with lung cancer incidence¹¹. In addition, these exposures are more prevalent among subjects with lower socioeconomic position. To our knowledge, only one study tried to estimate the contribution of occupational exposures to socioeconomic inequalities in lung cancer incidence and showed that occupational exposures did not explain any additional socioeconomic inequalities – when already adjusted for smoking¹². This study was, however, based on a highly selected cohort. In addition to this fragmentary evidence, one tentative estimate suggested that around 50% of socioeconomic inequalities in lung cancer mortality could be attributable to occupational exposures, but this estimate did not adjust for tobacco consumption¹³. The role of occupational exposures in socioeconomic inequalities in lung cancer incidence remains thus largely unknown.

We already investigated the role of smoking in educational inequalities in lung cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC study) and found that tobacco consumption partly explained these inequalities. Adjustment for smoking decreased educational differences in lung cancer incidence by 50 to 65%¹⁴. Fruits and vegetables consumption hardly explained any additional inequalities. In the EPIC study, occupational exposures to several carcinogens

were available for a subsample. In this paper, we aim to investigate the role of occupational exposures in explaining the remaining educational differences in lung cancer incidence after adjustment for smoking and dietary factors among men in Europe using the EPIC cohort.

METHODS

The EPIC cohort is a multi center prospective cohort conducted in 23 centers in 10 European countries. The EPIC cohort has been extensively described elsewhere ^{15, 16}. More than 500,000 men and women were recruited during the 1990s. In this analysis, the end of the follow-up period occurred between December 2002 and December 2006. The mean follow-up was 8.4 years. At recruitment, all subjects filled in a questionnaire providing detailed information on many risk factors including smoking history and dietary factors. In 15 of the 23 centers (Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), Greece, Denmark (Copenhagen, Aarhus), Germany (Heidelberg and Postdam), Italy (Turin, Varese, Florence, Ragusa) and the UK (Cambridge)), the questionnaire included several questions on the occupational history of the participants, focusing on 52 selected occupations (or industries) that have been previously linked to developing cancer. In an earlier analysis on occupational exposures and lung cancer incidence in the EPIC cohort ¹⁷, the authors developed exposure ‘scores’ for each of the following carcinogenic exposures: asbestos, heavy metals, PAH, environmental tobacco smoke (ETS), and silica. For each exposure, a group of experts selected all occupations (from the list of 52) exposing to this carcinogen. The exhaustive list can be found elsewhere ¹⁷. The exposure ‘score’ was computed as the sum of the reported jobs (or employments) included in the list selected for each carcinogenic exposure. This score was then coded categorically in 4 classes: never exposed (reference category), exposed in 1 job, 2 jobs, 3 jobs and more regardless of length of employment. This crude score was developed because no information was available in the EPIC cohort regarding the duration or the level of the occupational exposure. However, previous analyses have shown a consistent association between this score and lung cancer incidence in the EPIC cohort ¹⁷.

The outcome variable was first primary lung cancer (ICD 10: C33-C34). We measured socioeconomic position using the highest level of education attained categorized into only primary education or less,

vocational secondary education, other secondary education, university or vocational post-secondary education. Subjects with prevalent cancer at baseline (except non-melanoma skin cancer) or with length of follow-up equal to zero (4%) were excluded from the analysis. We also excluded subjects with a ratio of energy intake to energy expenditure in the top and bottom 1%, subjects with missing information on smoking status, diet or education and subjects with missing information on date of diagnosis for an incident cancer prior to the incident lung cancer because we could not define their censor date (n=16,139). The date of diagnosis was available for all primary lung cancer cases. We restricted the analyses to men because of the low number of cases occurring among women exposed to any carcinogen (5 in Germany, 11 in the UK, 40 in Denmark, 4 in Spain and 1 in Greece, and no information on occupational exposures among women in Italy) (n=131,505). The analysis was finally based on 88,265 men and included 703 incident lung cancer cases.

Analyses were conducted with Cox regression models. Analyses were stratified on center and age at baseline (in 1 year age categories). We computed hazard ratios (HR). To overcome problems due to differences in educational distributions between different countries or generations, we computed relative indices of inequality (RII) to quantify socioeconomic inequalities¹⁸. The calculation of the RII is based on a relative measure of education. This is a ranked variable that equals, for each educational group, to the mean proportion of the population with a *higher* level of education and is computed as follows. If the highest educational group comprises 20% of the population, this ranked variable is assigned a value of $0.20/2=0.10$. If the next highest educational group comprises 30% of the population, it is assigned a value of $0.20+0.30/2=0.35$, etc. We computed this ranked variable by center and age categories. We then regressed the cancer incidence on this ranked variable using a Cox regression model. The RII corresponds to the estimate obtained for this ranked variable and quantifies the linear effect of the relative level of education on lung cancer risk. Thus, the RII expresses inequality within the whole socioeconomic continuum and can be interpreted as the ratio of lung cancer incidence between the lowest educated (0th percentile) and the highest educated (100th percentile). As the measure of the socioeconomic position takes into account the size and relative position of each

educational group, it is well adapted to compare populations with different educational distributions and thus fits well with the design of this study.

We considered several models, all stratified on age at baseline and center: 1) a crude model including education only, 2) a reference model adjusted for smoking and dietary factors, 3) a full model adjusted for smoking, dietary factors and occupational exposures.

The reference model was developed in a previous analysis¹⁴ and included smoking status (never, current and former smoker), three continuous variables related to tobacco consumption (age at start, current quantity smoked (number of cigarettes/day), duration of smoking) and several combinations of these variables (a quadratic term for current quantity smoked, two interaction terms between duration and quantity and between age at start and duration), as well as a dummy variable for missing values for the current quantity smoked (for duration of smoking and age at start, missing values were rare and replaced by the median). We also introduced total fruits and vegetables consumption as a continuous variable and the interaction between smoking status and this dietary variable.

The full model included, in addition to the smoking and dietary variables, the score developed for exposure to asbestos, to PAH and to heavy metals. We first introduced each score separately and then the three scores simultaneously. We did not analyze exposure to ETS or silica because of the too small number of cases occurring among exposed men (ETS: 36; silica: 27).

We conducted analyses by birth cohort as some occupational exposures may have been more prevalent in the past. This allowed indirectly accounting for time-varying aspects of occupational exposures. As there was no a priori hypothesis to define the birth cohort, we used the median of years of birth, 1941, as cut-off point and conducted analyses among men born before or after 1941.

We tested the decrease in RII when adjusting for occupational exposures. We used a method developed in a paper from Lunn and McNeil to analyze competing risks in survival analysis using readily available standard programs for fitting Cox's^{19,20}. We adapted this method for our purpose, which was the comparison of the RII estimates from a model with and without adjustment for occupational

exposures. We used the Cochran's Q test to examine the heterogeneity between birth cohorts in educational inequalities (measured with RII). The test statistic is computed by summing the squared difference between each birth cohort specific-RII and the overall RII, weighted by the inverse of the estimated variance of each country specific-RII.

RESULTS

The proportion of men ever employed in a job involving exposure to one of these three carcinogens, asbestos, PAH or heavy metal, was higher among men with primary education or less or with vocational secondary education (Table 1). This proportion showed a marked non linear gradient with education, with an important gap between the two upper and the two lower categories of education. Having jobs involving exposure to PAH was less frequent than having jobs involving exposure to asbestos or heavy metals, especially among men with university or vocational post-secondary education. This pattern was found among all men and in both birth cohorts. We found a clear association between number of jobs involving exposure to asbestos and lung cancer incidence. This association was weaker and statistically nonsignificant for exposure to heavy metals and absent for exposure to PAH (Table 2).

Table 3 presents the relative indices of inequality for education in the different models. Adjustment for number of jobs involving occupational exposure to each carcinogen separately reduced the magnitude of inequality – already adjusted for smoking and fruits and vegetables consumption – in male lung cancer incidence. The decrease was larger and statistically significant for asbestos ($p=0.01$). When the three carcinogens were introduced simultaneously into the model, the RII decreased from 1.87 to 1.75. We observed a significant decrease ($p=0.05$) in the excess risk by 14%, from 87% to 75%. The residual RII remained significant when adjusting for number of jobs involving occupational exposure to asbestos, PAH or heavy metals.

The interaction with birth cohort was significant in all models (test for heterogeneity: $p=0.03$ in crude model, $p=0.01$ in reference model, and $p=0.02$ in model further adjusted for all occupational

exposures). Among men born before 1941, we observed large inequalities that were reduced when adjusting for smoking and dietary factors and further reduced when additionally adjusting for number of jobs involving occupational exposures. The decrease in inequalities when adjusting for all occupational exposures was statistically significant, but the RII remained statistically significant (RII=2.14; 95% CI 1.47-3.12). Estimates were smaller among men born after 1941. The risk estimates were close to 1 and confidence intervals were wide and no longer statistically significant once smoking and dietary factors were adjusted for.

In addition to RII, we also computed HR by education (Table 4). Among all men, occupational exposures, as measured by the number of jobs involving such exposures, explained part of the higher lung cancer incidence found among men with vocational secondary education and especially among men with primary education or less. The same applies to men born before or in 1941. Even after adjustment for occupational exposures, lung cancer risks remained statistically significantly elevated for men with vocational secondary education or primary education or less when compared with men with university or vocational post-secondary education. A different pattern of inequalities was observed among younger men. The highest lung cancer risk was found among men with other secondary education. This excess risk was not reduced when occupational exposures were introduced in the model. The risk estimate was however based on small numbers and did not reach statistical significance. As the RII quantifies the linear relationship between the outcome and the independent variable, it is thus not well adapted to measure inequalities in this case. However, the HRs are consistent with the RII and show a larger effect of occupational exposures in educational inequalities in lung cancer incidence among older men.

DISCUSSION

We investigated the role of occupational exposures in educational inequalities in male lung cancer incidence and found that they explained about 14% of inequalities that remained when smoking and diet were already adjusted for.

Occupational exposures were quantified as the number of jobs held involving exposure to specific carcinogens. This information, although imprecise, was however the best available information in the EPIC cohort. Moreover a consistent association has been found in the cohort between this score and lung cancer risk ¹⁷. Some limitations related to the assessment of occupational exposures should nevertheless be addressed. The classification for occupational exposures was based on job titles. Error and misclassification in measurement may have occurred especially because of insufficient information. At least three limitations can be cited: the method used was based on an a priori list of hazardous occupations which is not exhaustive; the classification of jobs according to common exposures may be somewhat inaccurate; no information on duration, level or intensity of exposure was available. Because we selected all potentially hazardous occupations, we may have considered as exposed many subjects who are in reality not exposed to any carcinogen. Conversely, part of the subjects classified as non exposed are probably to some extent truly exposed. This misclassification is unlikely to differ by vital status but may differ by education. In particular it could be that we missed the exposure more among high educated people, because the hazardous occupations are more widespread among low educated men. It is unfortunately not possible to say to what extent this misclassification biased our estimates of educational inequalities ²¹. In addition, the level of misclassification may differ by carcinogen. It is for instance certainly easier to detect and select occupations exposing to asbestos than to PAH. There is also a low background exposure to PAH in many occupations, which is not observed for the other carcinogens.

Imprecision in measurement of occupational exposures and confounding due to smoking should also be considered. Previous analyses based on the whole EPIC cohort suggested that residual confounding by smoking could not totally account for the residual educational inequalities observed in lung cancer incidence when adjusting for smoking and dietary factors ¹⁴ and that other factors were likely to be involved. Information about exposure to several carcinogens such as welding fumes was not available in our study and our estimates may be conservative. However, adjusting for exposure to ETS and silica did not change the risk estimates (results not shown).

The association found in this study between occupational exposures and lung cancer incidence reflects the situation in job employment several years ago. Occupational exposures at work may have decreased in Europe during the last decades and characteristics of occupational exposure (substance, intensity, duration) may therefore differ by birth cohort. For instance, many countries have now prohibited exposure to asbestos²². This was done during the 1980s in some countries like the Nordic countries or Germany but later in France or Spain. We conducted analyses by birth cohort to investigate possible cohort differences in occupational exposures. Our findings are not totally conclusive. They nevertheless suggest a clear effect of occupational exposures in educational inequalities in lung cancer incidence among older men, which may be due to a high exposure to occupational carcinogens in the past. We considered smoking, fruits and vegetables consumption and occupational exposures as mediators between education and the onset of lung cancer⁵. Educational inequalities in lung cancer incidence nevertheless remained large and statistically significant among older men after adjusting for these factors. In addition to residual confounding by smoking, diet and occupational exposures, other factors may also explain an additional part of inequalities. The literature does not support any effect of psychosocial factors²⁵. Conversely, environmental exposures to pollution or ETS at home²⁶ as well as other risk factors such as physical activity²⁷ may play a role in socioeconomic inequalities.

Among younger men, as the analyses are based on small numbers, we cannot totally rule out that chance fluctuations have caused some of the observed observations. Therefore, we cannot draw firm conclusions based on our results. Moreover, the lag time between exposure to carcinogen and the onset of lung cancer should be taken into account. The mean age at diagnosis among men born after 1941 was 55. Because of the potentially long lag times between exposure to carcinogen and cancer incidence, this generation may not be old enough to see any clear effect of exposure to carcinogens on lung cancer incidence, and consequently on educational inequalities in lung cancer incidence. Finally, it should be noted that these results relate to relative inequalities. Because the baseline hazards strongly differ between age groups, the conclusions regarding absolute inequalities may be partly different.

We used education as a marker of the socioeconomic position^{23, 24}. Education is an individual measure of socioeconomic position and allows classification of all individuals, including those who do not work and are retired. Higher education may be associated with health through different pathways: subjects with higher education may be more receptive to prevention messages, and may have a higher ability to change their health behaviour and to better utilize the health care system²⁴. As in all studies including data from different countries, we cannot rule out possible inconsistencies between centres in the educational classification. However, we dedicated special effort to minimize these problems and used a common classification in all centres for education.

Our study revealed that the impact of occupational exposures on educational inequalities in lung cancer incidence, rarely studied until now, exists but is of modest magnitude. Public and occupational health policies that aim at decreasing exposure to carcinogens at work would probably help to reduce socioeconomic inequalities in the cancer field. However, tobacco control is and remains the key element of any strategy aiming at reducing socioeconomic inequalities in cancer incidence in general and in lung cancer incidence in particular.

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Table 1: Number of lung cancer cases and prevalence of different occupational exposures by education.

Men. EPIC cohort

	All	Primary education or less	Vocational secondary education	Other secondary education	University or vocational post- secondary education
All men					
Number of subjects	88,265	35,286	21,064	9,800	22,115
Cases of lung cancer	703	401	163	49	90
% men exposed to (N_{E+}^1)					
Asbestos	19.7 (187)	26.1 (124)	21.6 (38)	10.1 (7)	12.0 (18)
Heavy metals	23.6 (203)	29.2 (135)	28.3 (41)	17.0 (6)	13.2 (21)
PAH	16.3 (146)	23.6 (105)	17.5 (20)	9.8 (6)	6.6 (15)
Men born before or in 1941					
Number of subjects	43,573	20,916	9,791	3,582	9,284
Cases of lung cancer	551	339	125	26	61
% men exposed to (N_{E+}^1)					
Asbestos	20.1 (144)	24.8 (97)	20.3 (29)	10.6 (5)	13.2 (13)
Heavy metals	23.3 (162)	27.2 (117)	25.7 (26)	13.7 (2)	15.7 (17)
PAH	16.0 (117)	21.6 (89)	15.2 (15)	8.2 (2)	7.0 (11)
Men born after 1941					
Number of subjects	44,692	14,370	11,273	6,218	12,831
Cases of lung cancer	152	62	38	23	29
% men exposed to (N_{E+}^1)					
Asbestos	19.3 (43)	28.0 (27)	22.8 (9)	9.8 (2)	11.2 (5)
Heavy metals	23.9 (41)	32.1 (18)	30.5 (15)	18.9 (4)	11.5 (4)
PAH	16.7 (29)	26.4 (16)	19.5 (5)	10.8 (4)	6.3 (4)

1: Number of lung cancer cases among exposed men

Table 2: Hazard ratios associated with occupational exposure to different carcinogens. Men. EPIC cohort

Occupational exposure (nb jobs held with this specific exposure)	HR	95% CI
Exposure to asbestos*		
3+	1.65	1.11-2.46
2	1.34	0.95-1.89
1	1.16	0.95-1.42
Never	1	
Exposure to heavy metals*		
3+	1.21	0.94-1.54
2	1.24	0.96-1.62
1	1.03	0.77-1.38
Never	1	
Exposure to PAH*		
3+	1.02	0.68-1.53
2	1.06	0.80-1.39
1	1.14	0.87-1.49
Never	1	

All models are stratified on centre and age at baseline.

*The model includes each occupational exposure separately and smoking status (never smoker (reference category), current smoker, former smoker), age at starting (continuous, for ever smoker), duration of smoking (continuous, for ever smoker), current quantity (continuous, among current smokers), a quadratic term for current quantity, two interaction terms (quantity*duration and age at starting*duration), a dummy variable for missing variables for current quantity, fruits and vegetables consumption (continuous variable, per 100g) and an interaction term between smoking status and fruits and vegetables consumption, and education.

Table 3: Relative indices of inequality (RII) for education and their corresponding 95% confidence intervals (95% CI) for lung cancer among all men and by birth cohort. EPIC cohort.

	N ¹	RII	95% CI	p for decrease in RII ⁴
All men (N=703)				
Crude model		3.01	2.21-4.09	
Reference model ²		1.87	1.36-2.56	
+ exposure to asbestos ³	187	1.76	1.28-2.41	0.01
+ exposure to heavy metals ³	203	1.83	1.33-2.50	0.13
+ exposure to PAH ³	146	1.84	1.34-2.53	0.55
+ exposure to asbestos, heavy metals, and PAH ³	359	1.75	1.27-2.41	0.05
Men born before or in 1941 (N=551)				
Crude model		3.58	2.50-5.13	
Reference model ²		2.33	1.61-3.36	
+ exposure to asbestos ³	144	2.22	1.53-3.21	0.05
+ exposure to heavy metals ³	162	2.25	1.56-3.25	0.08
+ exposure to PAH ³	117	2.25	1.55-3.26	0.34
+ exposure to asbestos, heavy metals, and PAH ³	287	2.14	1.47-3.12	0.03
Men born after 1941 (N=152)				
Crude model		1.68	0.91-3.13	
Reference model ²		0.94	0.50-1.77	
+ exposure to asbestos ³	43	0.81	0.42-1.54	0.04
+ exposure to heavy metals ³	41	0.93	0.49-1.76	0.72
+ exposure to PAH ³	29	0.97	0.51-1.85	0.61
+ exposure to asbestos, heavy metals, and PAH ³	72	0.88	0.46-1.69	0.46

All models are stratified on centre and age at baseline (in 1 year age categories).

1: Number of cases exposed to the carcinogen

2: The reference model includes smoking status (never smoker (reference category), current smoker, former smoker), age at starting (continuous, for ever smoker), duration of smoking (continuous, for ever smoker), current quantity (continuous, among current smokers), a quadratic term for current quantity, two interaction terms (quantity*duration and age at starting*duration), a dummy variable for missing variables for current quantity, fruits and vegetables consumption (continuous variable, per 100g) and an interaction term between smoking status and fruits and vegetables consumption.

3: Occupational exposures are coded into four categories: never exposed, exposed during in one job, exposed in two jobs, exposed in three jobs or more.

4: p-value for test for decrease in RII after adjustment for occupational exposures when compared with RII from the reference model

Table 4: Hazard ratios (HR) for education and their corresponding 95% confidence intervals for lung cancer among all men and by birth cohort. EPIC cohort.

	University or vocational post- secondary education	Other secondary education	Vocational secondary education	Primary education or less
All men				
Crude model	1	1.44 (1.01-2.06)	1.79 (1.38-2.33)	2.31 (1.81-2.95)
Reference model	1	1.18 (0.83-1.70)	1.39 (1.07-1.81)	1.60 (1.25-2.05)
Reference model + all occupational exposures	1	1.19 (0.83-1.70)	1.36 (1.04-1.77)	1.53 (1.20-1.97)
Men born before or in 1941				
Crude model	1	1.10 (0.69-1.76)	1.88 (1.38-2.57)	2.47 (1.85-3.29)
Reference model	1	0.95 (0.59-1.51)	1.51 (1.10-2.06)	1.78 (1.33-2.37)
Reference model + all occupational exposures	1	0.96 (0.60-1.53)	1.46 (1.06-2.00)	1.69 (1.26-2.26)
Men born after 1941				
Crude model	1	2.20 (1.24-3.90)	1.57 (0.96-2.57)	1.76 (1.09-2.84)
Reference model	1	1.60 (0.90-2.85)	1.13 (0.69-1.85)	1.13 (0.70-1.82)
Reference model + all occupational exposures	1	1.59 (0.89-2.83)	1.11 (0.67-1.84)	1.07 (0.65-1.76)