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Quantifying the mediating effects of smoking and occupational exposures in the relation between education and lung cancer – the ICARE study

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Key-words

Lung cancer, incidence, France, men, smoking, occupational exposure

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Abstract

Background

Smoking only partly explains the higher lung cancer incidence observed among socially deprived people. Occupational exposures may account for part of these inequalities, but this issue has been little investigated. We investigated the extent to which smoking and occupational exposures to asbestos, silica and diesel motor exhaust mediated the association between education and lung cancer incidence in men.

Methods

We analyzed data from a large French population-based case-control study (1,976 lung cancers, 2,648 controls). Detailed information on lifelong tobacco consumption and occupational exposures to various carcinogens was collected. We conducted inverse probability-weighted marginal structural models.

Results

A strong association was observed between education and lung cancer. The indirect effect through smoking varied by educational level, with the strongest indirect effect observed for those with the lowest education (OR=1.34 (1.14-1.57)). The indirect effect through occupational exposures was substantial among men with primary (OR=1.22 (1.15-1.30) for asbestos and silica) or vocational secondary education (OR=1.18 (1.12-1.25)). The contribution of smoking to educational differences in lung cancer incidence ranged from 22% (10-34) for men with primary education to 31% (-3-84) for men with a high school degree. The contribution of occupational exposures to asbestos and silica ranged from 15% (10-20) for men with a high school degree to 20% (13-28) for men with vocational secondary education.

Conclusion

Our results highlight the urgent need for public health policies that aim at decreasing exposure to carcinogens at work, in addition to tobacco control policies, if we want to reduce socioeconomic inequalities in the cancer field.

Introduction

Large inequalities are consistently reported for male lung cancer incidence, with higher incidence rates among men with low socioeconomic position (SEP). Several studies have investigated the underlying mechanisms, the majority focusing on smoking. Most studies [1-5], although not all [6], found that smoking only partly accounted for these inequalities, including an analysis based on never smokers [7]. The possible role of other risk factors has almost never been investigated. However, there is some evidence that occupational exposures to carcinogens partly accounted for the higher lung cancer incidence rates among men with a low SEP. Occupational exposures were nevertheless assessed in a crude way through the number of jobs with possible exposure to carcinogens whatever the level of exposure in the job [8].

Studies investigating the role of risk factors as mediators in the association between SEP and lung cancer have based their conclusions on the comparison of statistical models with and without adjustment for the potential mediator, and on the estimation of the direct effect of SEP on lung cancer incidence once adjusting for the potential mediators. These are possibly biased methods for assessing mediation [9, 10]. In addition, even in the absence of confounding, it is generally not possible to assess the magnitude of the indirect effect between SEP and lung cancer that is mediated by the risk factors investigated.

Recent developments in mediation analyses allow formally separating the direct and indirect effects between an exposure and an outcome while accounting for multiple mediators [11, 12]. These methods will improve our understanding of socioeconomic inequalities in lung cancer in two different ways. First, they will provide a precise estimation of the mediated effects through other risk factors in addition to smoking. Second, they will allow for different mediated effects for each socioeconomic category when using a measure of SEP with more than two categories. The aim of this analysis was to apply these newly developed methods to study the extent to which smoking and occupational exposures to asbestos, silica and diesel motor exhaust mediated the association between education and lung cancer incidence.

Methods

Study population

The ICARE study is a multi-center population-based case-control study conducted in France from 2001 through 2007 in 10 French *"départements"* (administrative areas) covered by a cancer register.

The cases were all patients newly diagnosed with a primary, histologically confirmed malignant tumour of lung or head and neck cancers during the study period and who were aged 75 or less at diagnosis. The control group was selected from the general population of the same geographical areas (*département*) by random digit dialing, with frequency matching to all cases by sex and age. Additional stratification was used to achieve a distribution by socioeconomic status among the controls comparable to that of the general population. The study design has been described in details previously [13].

The present analysis was restricted to male lung cancer cases (International Classification of Diseases, 10th Revision codes C33-34) and male controls. Indeed, studying inequalities in lung cancer risk would require a specific approach among women due to the contrasted and even reverse associations between education and smoking in different age groups among women. Among the 3865 male lung cancers identified as eligible from the cancer register files, 403 (10%) could not be reached, 653 (17%) were deceased and 197 (5%) were too sick to be interviewed. Among the 2,612 who were contacted, 2,276 agreed to participate to the study (87%). Of the 3,618 eligible male controls, 212 (6%) could not be reached. Among the 3,406 who were contacted, 2,780 (82%) agreed to participate to the study.

Subjects were interviewed face-to-face by trained interviewers, using a standardized questionnaire collecting detailed information about socio-demographic characteristics, lifetime tobacco consumption (type, period of consumption, frequency of consumption and quantities consumed for each period) and lifetime occupational history (covering all jobs held for at least 1 month).

Among the 2,276 lung cancers and 2,780 controls who participated to the study, some participants could not answer the whole questionnaire due to health problems. They filled in a restricted questionnaire instead that did not include information on education. We therefore conducted the analyses among subjects who answered the whole questionnaire (2,074 cases and 2,720 controls).

Measure of smoking and occupational exposures

Lifelong cigarette smoking was captured by the cumulative smoking index (CSI), which takes into account total duration of smoking, time since cessation and average number of cigarettes smoked per day [14]. A never smoker was considered having smoked less than 100 cigarettes in his lifetime. The CSI of never smokers is null. The properties of the CSI have been assessed and evaluated. In our data, the CSI varied linearly with lung cancer risk [15].

For each job, occupation and industrial activity were coded blind to the case-control status using respectively the International Standard Classification of Occupations 1968 (ISCO) and the French Nomenclature of Activities (NAF). Occupational exposure to asbestos and crystalline silica was then assessed using job-exposure matrices (JEM) specifically developed for France [16]. For each

combination of an ISCO and a NAF code, the JEM assigned three indices of exposure: a probability of exposure, an intensity of exposure and a frequency of exposure. The indices were provided for different calendar periods between 1947 and 2007 to account for possible variations in exposure over time. For each subject, we derived from its entire occupational history a cumulative level of exposure to asbestos and crystalline silica obtained as the sum over all jobs of the product of the exposure intensity, probability, frequency and duration (using midpoints of each class).

Assessment of exposure to diesel motor exhaust (DME) (ever/never) was collected for each job and based on self-report. This information was missing for about 13% of all jobs, spread among 25% of men. We combined the ISCO code with the NAF code for each job. Missing values for exposure to DME were replaced by the modal category observed in the same ISCO-NAF combination among subjects with complete data. DME exposure was assessed from the questionnaire on a case-by-case basis when the modal category included less than 60% of the subjects. The association between lung cancer and ever exposure to DME was similar when using this variable and when restricting the analysis to complete case data [17].

Analysis

We investigated the role of three mediators in the association between education and lung cancer using the mediation methods recently proposed by Lange [12, 11]. The syntax is provided elsewhere [11, 12]. We adapted the method to account for the case-control design of our study following the strategy proposed by VanderWeele and Vansteelandt.[18] The mediation methods allow quantifying the natural direct and indirect effects of an exposure (here education) on an outcome (here lung cancer) while accounting for multiple mediators (here smoking and occupational exposures). Natural direct effect is defined as the change in lung cancer risk that would be observed if education could change (from high to lower) but leaving the mediators unchanged with the value observed among high educated. Natural indirect effect is defined as the change in lung cancer when education is kept fixed (high education) but the mediator is changed to the value it would take if education was changed (from high to lower). The natural indirect or mediated effect can be interpreted as the effect of education mediated through a specific factor.

The method is based on marginal structural models relying on several assumptions: 1/ there is no unmeasured confounding for the exposure-outcome, exposure-mediator and mediator-outcome relationship; 2/ there is no variable affected by the exposure that confounds any of the mediator-outcome relationship; 3/ the mediators have no causal effect on each other. Education was included using the following categorization (primary, lower secondary or vocational upper secondary, high school, tertiary). Three successive models were performed. Age (<=50, 51-57, 58-65 and >65) and residence area (ten *départements*) and the number of jobs held (<3, 3, 4-5 and ≥6) were introduced

in all models as confounding categorical variables. In model 1, we adjusted for smoking using the CSI as a continuous variable. In model 2, we additionally adjusted for combined exposure to asbestos and silica as a categorical variable. Almost all men exposed to silica are also exposed to asbestos. Therefore, introducing asbestos and silica as two different mediators does not provide stable estimates because the two variables are not independent conditionally to education and the confounding factors. We first categorized exposure to asbestos and silica into none, low and high exposure. The cut-off was defined as the median of the cumulative index of exposure among exposed controls. The combined exposure to asbestos and silica variable was then created as follows: never exposed to asbestos nor silica, low exposure (no exposure to one carcinogen and low or high exposure to the other carcinogen; low exposure to both carcinogens) and high exposure (exposed to both carcinogens with high exposure to at least one). In model 3, we additionally adjusted for exposure to DME as a binary variable (ever/never).

Men with missing education were excluded from the analyses but coded as primary educated in sensitivity analyses (n=84). These sensitivity analyses lead to similar results and are not presented. Data with other missing values were excluded (n=86). A total of 98 cases and 72 controls were excluded from the analyses (4%).

Sensitivity analyses were also conducted to assess the potential residual confounding by misclassification of smoking and occupational exposures. We randomly increased smoking consumption for 15% of ever smokers by selecting a higher smoking consumption value in the dataset. We increased occupational exposures to the immediately higher category among 5% randomly selected men (see supplementary material).

All models performed include the calculation of stabilized weights to assess the direct and indirect effects. For more stable results we attributed to the 1% highest and 1% lowest weights the value of the 99^{th} and the first percentile. Confidence intervals (CI) were calculated using a bootstrap resampling method with 5000 replications. Analyses were conducted using SAS 9.4 and R version 3.1.2.

Results

Table 1 here

The analysis was based on 1976 lung cancer cases and 2648 controls. The characteristics of the controls by educational level are presented in Table 1. Smoking consumption as well as occupational exposure to asbestos, silica and DME increased as education decreased. Smoking consumption increased regularly with decreasing education; occupational exposures, though, seemed to be highly concentrated among men with vocational secondary education or lower education. The total effect of educational level and the effect of each mediator on lung cancer are presented in Table 2. A gradient between education and lung cancer risk was reported. When compared with men with university degree, risk ranged from 1.62 (95% CI 1.28-2.04) among men with high school degree to 3.85 (3.18-4.66) among primary educated. All mediators were associated with lung cancer risk. The association with DME was nevertheless modest as expected.

Tables 2 and 3 here

Natural direct and indirect effects conditional on confounders are presented in Table 3. In the model including all mediators, the effect mediated through smoking (or indirect effect of education through smoking) varied by educational level with the strongest indirect effect observed for those with primary education when compared with tertiary educated (OR=1.35 (1.15-1.58)). It can be interpreted as follows: a higher smoking consumption among men with primary education account for a 35% higher lung cancer risk in this group when compared with men with tertiary education. The indirect effect through exposure to asbestos and silica was lower but substantial among men with primary education (OR=1.23 (1.15-1.31)) or with vocational secondary education (OR=1.19 (1.12-1.25)). A small effect mediated through DME was observed (OR=1.03 (1.00-1.07) among men with primary education). When all mediators were accounted for, the direct effect of education on lung cancer remained substantial among men with up to vocational secondary education when compared with tertiary education. Among men with a high school degree, the direct effect of education became non-significant although still elevated when exposure to asbestos and silica was introduced in the model.

The proportion of the total effect of educational level mediated by the mediators on the log odds scale is presented in table 3. When all mediators are accounted for simultaneously, smoking accounted for a smaller part of the effect risk for primary educated men (22% (10-34)) than for the two other educational groups (28% (13-46) for men with vocational secondary education and 31% (-3-84) for men with a high school degree). The contribution of occupational exposures to asbestos and silica to the excess lung cancer risk was largest for men with vocational secondary education (20% (13-28)) and smallest for men with a high school degree (12% (4-27)).

Discussion

Using recently developed methods, our analysis provides new insights into mediation and the pathways between education and lung cancer. We estimated the effect mediated through smoking and occupational exposures in three educational groups, instead of only contrasting low to high education. Our findings suggest that the mediation mechanisms differ by education level. The indirect effect through smoking was stronger among the lowest educated men due to longer and heavier consumption in this group [19, 20], but still substantial for men with high school degree. The indirect effect through occupational exposures was large and similar among men with primary or vocational secondary education but was modest among men with a high school degree when compared with tertiary educated. Mostly manual jobs lead to occupational exposures to carcinogens and in France these jobs are concentrated among men with primary or vocational secondary education.

In our data, smoking accounted for a substantial part of educational differences in lung cancer although smaller than what is reported in the literature [1-5]. Educational differences in smoking among the French male population were small among men born before 1955 [19, 21] and smaller than those observed in many other countries [22], which is likely to explain this finding. Finally, the contribution of smoking to educational differences in lung cancer varied by educational level and was the largest for men with a high school degree. This counterintuitive result is the consequence of a small indirect effect through smoking when compared to the total effect of education on lung cancer incidence especially among the lowest educated. Educational differences in smoking have dramatically increased among younger male cohorts in France [23, 21]; therefore the indirect effect through smoking and the contribution of smoking to educational differences in lung cancer incidence are likely to increase in the coming years.

The available literature, although based on very few studies suffering from limited information about occupational exposures [24, 25], suggested a role of occupational exposures in social inequalities in lung cancer incidence. Our study is the first to provide a detailed quantification of the contribution of occupational exposures to educational differences in lung cancer incidence and confirms the substantial contribution of occupational exposures to these inequalities. In our data, among men with less than a high school degree, this contribution was similar to that of smoking.

Several hypotheses could explain the remaining inequalities among the lowest educated. First, we cannot rule out residual confounding by smoking. This would occur in all educational groups but may

be larger among the lowest educated due to longer and heavier consumptions [19, 20]. Second, although we already showed a substantial contribution of occupational exposures to educational differences in lung cancer incidence, we may have underestimated this contribution as we did not account for some lung cancer carcinogens (e.g. chromium VI or nickel) because of no data availability. We nevertheless adjusted for the three carcinogens with the highest number of attributable lung cancer cases [26]. Finally, other risk factors such as poor diet [27] or physical inactivity [28], more prevalent among the lowest educated [29, 30], may also account for part of the remaining direct effect between education and lung cancer. In addition, air pollution is associated with an increased lung cancer risk [31, 32]. However, the association between lower SEP and air pollution, although observed in some settings [33], is not clear in France where it differs by geographical context.[34]

The ICARE study is a large case-control study on lung cancer and occupational risk factors. The participation rate was over 80% in cases and controls. Recall bias is a well-known weakness of case-control studies. Therefore we paid special attention to data collection. Detailed information was collected by trained interviewers during face-to-face interviews, with a standardized questionnaire, and in a similar manner among cases and controls.

We collected detailed information on lifetime tobacco consumption, with information on the different types and quantity consumed for the different consumption periods. However, we did not account for differences in the type of tobacco smoked (brown or blond, use of filter) in our measure of lifelong smoking. Although around 26% of men (age standardized figure) reported being never smokers in France in 2005 [20], a proportion close to our figures (28%), we cannot rule out an underestimation of tobacco consumption, which may differ by education [35], and therefore possibly bias our estimates for smoking.

Occupational exposures were assessed thanks to the lifetime job history. Self-reported occupational history is usually considered as reliable [36]. Occupations were coded blind to the case-control status. Occupational exposure to asbestos and silica was assessed through specific JEMs developed for France. A JEM generates only non-differential misclassification which could result in an underestimation of the association between the carcinogens and lung cancer and an underestimation of the indirect effect through occupational exposures. Previous studies have validated these JEMs [37, 38]. Lifetime prevalence of asbestos and silica exposure among our controls was close to that estimated in France [16]. Therefore, we believe that our data for occupational exposure to asbestos and silica are of good quality. Regarding exposure to DME, we

cannot exclude a recall bias. However, 26.2% of our controls reported at least one job with DME exposure, a proportion close to that found in an Italian study [39].

Sensitivity analyses suggested that possible misclassification of smoking and occupational exposures did not account for our findings. Although the indirect effects were smaller in the sensitivity analyses than in our main analyses, the main conclusions did not change. For instance, the indirect effect among primary educated men for smoking decreased from 1.35 (1.15-1.58) to 1.27 (1.09-1.47). In addition, the indirect effects for occupational exposures were not affected by smoking misclassification (see supplementary material).

The methods that we used rely on several assumptions. We checked these assumptions by testing exposure-mediator interaction on outcome and independence between mediators conditional on exposure and confounders. In addition the stability of our estimates for the indirect effects of each mediator when successively introduced in the models suggests that the three mediators investigated represent distinct non-intertwined causal pathways and that our models are valid. The methods that we used do not always lead to stable estimates when using continuous mediator. Nevertheless, considering the CSI as a categorical or a continuous variable led to almost identical results. We therefore kept the CSI as a continuous variable in order not to reduce the statistical power by categorization and to minimise the number of variables in our models. Finally, a lack of statistical power cannot be ruled out for men with a high school degree and may account for the results in this group, namely the non significant direct effect after accounting for smoking and the proportion explained by the direct and the indirect effects lower than 100% when accounting for occupational exposure.

In conclusion, our study provides additional evidence that smoking does not account for all social inequalities in lung cancer risk. Our analyses stress the importance of occupational exposures in the genesis of social inequalities in lung cancer. This risk factor is often overlooked in social epidemiology where most studies concentrate on behavioural risk factors. Noteworthy, among men with up to vocational secondary education, the indirect effect through occupational exposures to asbestos, silica and DME was only slightly smaller than the indirect effect through smoking. Therefore tackling only smoking will leave large inequalities among a significant part of the French male population. Our results highlight the need for policy efforts to reduce both tobacco consumption and occupational exposures among men. There is now a substantial body of literature evaluating the effect of tobacco control policies on reducing social inequalities in smoking [40-42]. Most strategies, including those implemented in France during the last decade, focused on modifying individual behaviors. However,

the observed trends in smoking rates by SEP in France [19] as elsewhere [43] showed that such strategies largely failed to reduce inequalities in smoking. Policies should be implemented in a more comprehensive framework and address the social conditions and determinants where behaviors are rooted [44]. Given the dramatic increase in educational differences in smoking in France among younger generations, such policies are urgently needed to limit the burden of smoking in socioeconomic inequalities in health in the future. If progress have been achieved towards the reduction of workers exposure to carcinogens, continued efforts are needed. Active policies aiming at decreasing occupational exposures at workplace through legislation and the use of protection devices for workers would be efficient to reduce inequalities and would save a substantial number of lung cancer cases in particular among low educated men.

Table 1: Characteristics of controls according to educational level. Icare 2002-2007 men.

	No diploma or primary	Vocational secondary	High school	Tertiary	*P value*
Cumulative lifetime cigarette consumption (CSI)					
Never smoker	151 (28.4)	291 (27.2)	85 (27.8)	246 (33.3)	0.04
Mean (SD) among ever smoker	1.45 (0.71)	1.29 (0.69)	1.22 (0.72)	1.09 (0.72)	<0.001
Combined exposure to asbestos and silica[a]					<0.001
Never exposed	144 (27.1)	301 (28.1)	160 (52.3)	473 (64.0)	
Low	246 (46.2)	503 (47.0)	116 (37.9)	230 (31.1)	
High	142 (26.7)	267 (24.9)	30 (9.8)	36 (4.9)	
Diesel motor exhaust (DME) exposure					<0.001
Never	361 (67.9)	733 (68.4)	228 (74.5)	633 (85.7)	
Ever	171 (32.1)	338 (31.6)	78 (25.5)	106 (14.3)	

Data are presented as n (%) or mean (standard deviation, SD)

[a] low exposure = no exposure to asbestos or silica and low or high exposure to silica or asbestos; or low exposure to asbestos and silica

high exposure = exposed to asbestos and silica with high exposure to asbestos and/or silica

Cumulative level of asbestos (fibers/mL.year): Low : <0.27 / High : ≥0.27

Cumulative level of silica (mg/m3.year) : Low : <0.14 / High : ≥0.14

Table 2: Total effect of educational level and effects of each mediator on lung cancer risk. Icare 2002-2007 men

	Cases (n=1976)	**Controls (n=2648)**	***OR*[†] *(95% CI)***	***P value***
Highest educational level				<0.001
No diploma or primary education	678 (34.3)	532 (20.1)	3.85 (3.18-4.66)	
Vocational secondary education	851 (43.1)	1071 (40.4)	2.32 (1.95-2.75)	
High school	181 (9.2)	306 (11.6)	1.62 (1.28-2.04)	
Tertiary	266 (13.5)	739 (27.9)	Ref.	
Cumulative lifetime cigarette consumption (CSI)			6.67 (5.98-7.44)	<0.001
Never smoker	52 (2.6)	773 (29.2)		
Mean (SD) among ever smoker	1.65 (0.59)	0.92 (0.64)		
Combined exposure to asbestos and silica[a]				<0.001
Never exposed	544 (27.5)	1078 (40.7)	Ref.	
Low	828 (41.9)	1095 (41.4)	1.60 (1.39-1.84)	
High	604 (30.6)	475 (17.9)	2.88 (2.44-3.41)	
Diesel motor exhaust (DME) exposure				<0.001
Never	1378 (69.7)	1955 (73.8)	Ref.	
Ever	598 (30.3)	693 (26.2)	1.34 (1.17-1.53)	

Data are presented as n (%) or mean (standard deviation, SD)

[†]Adjusted for age and department and number of jobs

[a] low exposure = no exposure to asbestos or silica and low or high exposure to silica or asbestos; or low exposure to asbestos and silica

high exposure = exposed to asbestos and silica with high exposure to asbestos and/or silica

Cumulative level of asbestos (fibers/mL.year): Low : <0.27 / High : ≥0.27

Cumulative level of silica (mg/m3.year) : Low : <0.14 / High : ≥0.14

Table 3: Direct and mediated effects (OR and 95% confidence intervals) of educational level on lung cancer for each mediator derived from the marginal structural models including multiple mediators. Icare 2002-2007 men.

	Primary -> Tertiary	Proportion (%)[a]	Vocational secondary -> Tertiary	Proportion (%)[a]	High school -> Tertiary	Proportion (%)[a]
Smoking as mediator						
Direct effect	2.85 (2.22-3.72)	78 (64-90)	1.84 (1.49-2.30)	72 (54-88)	1.41 (1.05-1.90)	71 (16-108)
Indirect effect through CSI	1.35 (1.15-1.58)	22 (10-35)	1.28 (1.12-1.46)	29 (13-47)	1.17 (0.98-1.40)	32 (-3-87)
Smoking and combined exposure to asbestos and silica as mediators						
Direct effect	2.23 (1.73-2.94)	59 (44-74)	1.51 (1.21-1.90)	49 (25-68)	1.24 (0.91-1.70)	45 (-31-87)
Indirect effect through CSI	1.34 (1.14-1.57)	22 (10-34)	1.27 (1.12-1.45)	29 (13-46)	1.16 (0.98-1.38)	31 (-3-84)
Indirect effect through asbestos and silica	1.23 (1.15-1.31)	15 (10-20)	1.19 (1.12-1.25)	20 (13-29)	1.06 (1.03-1.11)	13 (5-29)
Smoking, combined exposure to asbestos and silica and exposure to DME as mediators						
Direct effect	2.09 (1.60-2.78)	54 (38-70)	1.41 (1.11-1.79)	40 (14-61)	1.17 (0.86-1.62)	34 (-52-78)
Indirect effect through CSI	1.34 (1.14-1.57)	22 (10-34)	1.27 (1.12-1.44)	28 (13-46)	1.16 (0.98-1.38)	31 (-3-84)
Indirect effect through asbestos and silica	1.22 (1.15-1.30)	15 (10-20)	1.18 (1.12-1.25)	20 (13-28)	1.06 (1.02-1.10)	12 (4-27)
Indirect effect through DME	1.03 (1.00-1.07)	2 (0-5)	1.02 (1.00-1.05)	3 (0-6)	1.02 (1.00-1.04)	3 (0-11)

CSI: Comprehensive smoking index; DME: diesel motor exhaust

[a] Proportion = $\ln(OR_{indirect})/\ln(OR_{total})$, with OR_{total} as shown in table 2

Corresponds to the proportion of the total effect of education on lung cancer risk mediated by the mediator (when compared with tertiary educated) (on the log odds scale)

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