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Can we quantify "Avoidable Lung cancer" by socioeconomic position (SEP)? The example of occupation as a hidden determinant of social inequalities in health

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List of Acronyms

AF(s): Attributable Fraction(s)
CEI: Cumulative Exposure Index
CSI: Comprehensive Smoking Index
CSP: Catégories Socio-Professionnelles
DME: Diesel Motor Exhaust
IARC: International Agency for Research on Cancer
ICARE: Investigation of occupational and environmental CAuses of REspiratory cancers
INSEE: National Institute for Statistics and Economic Studies
INSERM: French National Institute of Health and Medical Research
ISCO: International Standard Classification of Occupations
JEM(s): Job Exposure Matrix (Matrices)
NAF: French Nomenclature of Activities (Nomenclature d'activités Françaises)
OR: Odds Ratio
PAF(s): Population Attributable Fraction(s)
SEP: Socio-economic position
TBQ: task-based questionnaire
TCS: Time Since Cessation

Abstract:

Background

Many studies attempted to measure health inequalities based on the Socioeconomic position (SEP), where they seemed to be concentrated within lower SEP groups. Many indicators have been also used try to quantify the SEP based on education, occupation or income. However, occupation-based indicators tend to be less use, while they may better capture work-related inequalities. Previous studies observed an association between lung cancer and lower SEP, which could not be fully explained by behavioural factors such as smoking. Occupational exposures could contribute to these inequalities as many carcinogens are still present in workplaces till nowadays, even after the ban of asbestos in more and more countries.

Aim

Apply the attributable risk approach to compare the burden of work-related lung cancer between different socio-economic groups taking three occupational exposures (e.g. asbestos, silica and Diesel Motor Exhaust (DME)) as well as smoking into account.

Methods

Secondary analysis of the population-based case-control study ICARE study was conducted. The study included 2926 lung cancer cases and 3555 frequency-matched controls covering 13% of the French population. We applied different modelling strategies to compare 3 sources of variation in the attributable fractions estimates (exposure metrics, interaction with SEP and SEP indicator) using standard STATA packages (Aflogit).

Results

The analysis was based on men-only due to the limited number of exposures among women. The population Attributable Fraction (PAF) for the whole study sample for the combined indicator of asbestos, silica and DME was 32.7% 95%CI (24.6-39.9), while the total PAFs for the exposed Blue-collar workers compared to non-exposed groups regardless of their SEP was 26.9% 95%CI (21.9- 31.7).

Conclusion

The population health impact of these occupational exposures concentrates within lower SEP groups (Blue-collar workers and lower educated groups). Our results point to the necessity to combine SEP indicators and proximal risk factors into the PAF approach in order to capture work-related cancer inequalities.

Keywords

Health inequalities, Attributable fraction, Occupational exposures, Lung cancer, Socioeconomic Position.

Résumé

Contexte

De nombreuses études ont tenté de mesurer les inégalités de santé sur la base de la position socio-économique (PSE), où elles semblaient se concentrer dans les groupes de PSE inférieurs. Plusieurs indicateurs ont été utilisés pour quantifier le PSE en fonction de l’éducation, de la profession ou du revenu. Les indicateurs basés sur les professions sont relativement moins utilisés, or ils sont susceptibles de mieux rendre compte des inégalités liées aux conditions de travail. Des études antérieures ont mis en évidence une association entre le cancer du poumon et la PSE, qui ne peut pas être entièrement expliquée par les facteurs comportementaux tels que le tabagisme. Les expositions professionnelles pourraient contribuer à ces inégalités, car même après l'interdiction de l'amiante dans un nombre croissant de pays, de nombreux agents cancérogènes sont encore présents sur les lieux de travail.

Objectif:
Nous avons appliqué la méthode du risque attribuable pour comparer le fardeau du cancer du poumon lié au travail entre différents groupes socioéconomiques prenant en compte trois cancérogènes professionnels (amiante, silice crystalline et gaz d'échappement diesel), ainsi que le tabagisme.

Matériel et méthodes:
Nous avons réalisé une analyse secondaire de l'étude cas-témoins ICARE conduite en population générale. L’étude comprenait 2926 cas de cancer du poumon et 3555 témoins (appariement de fréquence). Nous avons appliqué différentes stratéfies de modélisation afin de comparer les sources de variations des fractions attribuables (type d’indicateur d’exposition, interaction avec la PSE et type d’indicateur de PSE) à l'aide de modules routines sous STATA (Aflogit).

Résultats:
Les analyses ont été conduites chez les hommes seuls étant donné le faible nombre d’expositions retrouvées chez les femmes. La fraction attribuable en population (FAP) pour l’indicateur combiné d’exposition à l’amiante, à la silice et et au diesel était de 32,7% IC95% (24,6-39,9), alors que le total des FAP pour les ouvriers exposés comparés à l’ensemble des groupes non exposés était de 26,9% 95%IC (21,9-31,7).

Conclusion:
L’impact sanitaire des expositions professionnelles se concentre dans les groupes de PSE inférieurs (cols bleus et faibles niveaux d’instruction). Nos résultats sulinent la nécessité de combiner indicateurs de PSE et facteurs de risques proximaux dans l’approche par FAP afin de saisir les inégalités sociales de cancer liées au travail.

Mots clés:
Inégalités sociales de santé, fraction attribuable, expositions professionnelles, cancer du poumon, position socioéconomique.

Introduction

The “inverse care law” was first introduced in 1971 by Julian Tudor (Tudor Hart, 1971) who stated that: “The availability of good medical care tends to vary inversely with the need for the population served”. Later in 2008, Nancy Krieger introduced “The inverse hazard law” where she stated:” The accumulation of health hazards tends to vary inversely with the power and resources of the populations affected”(Krieger et al., 2008), in which she argued how social factors can affect health inequalities. These laws drew more attention to the relationship between health and what we now use to call the ”social determinants”, as health inequalities are related to health coverage, insurance, living and working conditions(CSDH, 2008)

Studying these social determinants quantitatively implies to measure the socioeconomic position (SEP) of individuals. SEP has many indicators as education, household amenities, occupational class, and income (Galobardes et al., 2006a, 2006b). Some studies chose education, favouring the stability of this indicator, because it does not change much over time, and it is not affected by the personal health status in adult life, contrary to occupation. However, one of the problems raised when using the educational level is the change of educational systems through time and across different countries, which can be confusing when different birth cohorts are included (Galobardes et al., 2006a, 2006b).

Income is the best indicator of material living standard (d’Errico et al., 2017). Yet it can include a wide range of heterogeneity in the same social class and is usually more difficult to inform accurately. Also, household amenities can be an indicator of living conditions and easily collected, however, they lack consistency and cannot be applied to large geographical areas (Galobardes et al., 2006a, 2006b).

Finally, occupation-based indicators may be favoured to capture health inequalities among different population subgroups, as work in itself acts as a base for the social class (Eyles et al., 2018). However, the social class will always confound the relationship between occupation and health status, as workers from high social classes will land in better jobs with less exposure to work-related hazards and will have access to better health care and living conditions (Galobardes et al., 2006a, 2006b).

As different studies tried to quantify health inequalities, different results were found according to the SEP indicator used, the outcome under observation, and the use of absolute or relative measures of risk (d'Errico et al., 2017) (Galobardes et al., 2006a, 2006b) (Clougherty et al., 2010a). While many UK studies favour occupational class, educational data are better recorded in the US so that many studies used this indicator(Smith et al., 1998).

Here are but a few examples of the differences that may be observed while using different SEP indicators and study designs. In Europe, a reduction in mortality among the less educated was recorded in many countries after 1990, which may be related to the decrease of the cardiovascular diseases mortality; still, there was an increase in inequalities related to premature mortality between most and less educated groups. This points to the need for more investigation for the causes of health inequalities among low educated especially those related to smoking and alcohol, the authors pointed (Mackenbach et al., 2015).

On the other hand, the ongoing LIFEPATH project which included 11 adult cohorts from different European countries over the last 30 years (d'Errico et al., 2017) showed an 81% higher mortality risk in the lowest as compared to the highest occupational class among men.

Now moving to more specific occupations, a UK study used census data and death records to rank more than 60 occupational groups according to mortality. Mortality rates were three times higher for men in elementary construction work who had the highest rates of all groups compared to health professionals who had the lowest rates, while women in the garment trade and factories showed also three times higher mortality rates than women in teaching and business professionals (Katikireddi et al., 2017).

The Euro-GBD-SE consortium used the occupational class in their comparative study to assess health inequalities among middle-aged men of 14 European countries (Toch-Marquardt et al., 2014a). An increase in health inequalities was observed between the lower class and other occupational classes. This study introduced important results within the French population. Indeed, comparing rates between lowest and highest occupational class, France was among the countries with the largest inequalities for all-cause mortality, and cancer was an important contributor, with a population attributable fraction of 29% of lower occupational class, which means that 29% of cancer deaths could have been avoided if all occupational classes had the same all cancer-related mortality rate as the upper-non manual workers.

Few studies have attempted to quantify the respective contribution of known risk factors to these observed occupational class differences, especially beyond the behavioural risk factors. People from low SEP do tend to have more unhealthy behaviour like smoking and alcohol drinking (Pampel et al., 2010). Yet, in a pooled analysis of twelve case-control studies conducted between 1986-2010 in Canada and Europe (SYNERGY study), it was observed a significant association between lower SEP and lung cancer, with a social gradient that remained significant even after adjustment for smoking. As already mentioned earlier, one possible explanation is that those people also tend to have different employment and working conditions (Hovanec et al., 2018).

Lately, the International Agency for Research on Cancer (IARC) released a report quantifying the number and proportion of cancer attributable to 13 different groups of risk factors at the population level. While according to this study, smoking accounted for 54142 and 12008 (28% and 12%) cancer cases in males and females respectively (Cao et al., 2018), around 7905 new cases were attributed to occupational exposures (7336 among men and 569 among women) (Marant Micallef et al., 2019a). This constitutes around 2.3% of the whole new cancer cases in France (3.9% for men, 0.4% for women).

Lung cancer was the most common type of cancer attributed to occupational exposures in France with 5621 cases in men (89% of all work-related cases) and 294 cases in women (80% of work-related cases) (Marant Micallef et al., 2019a), as most carcinogens can be inhaled through work, even if the workers are often unaware. Men were more exposed to carcinogenic occupational exposures than women (Marant Micallef et al., 2019a), which probably explain the disproportion between men and women, although some authors have suggested gender bias against women could also contribute (Betansedi et al., 2018). Some of the main agents leading to lung cancer in France are still present in the working environment, such as chromium VI compounds, silica dust, and diesel exhausts (Marant Micallef et al., 2018). Moreover, they tend to concentrate among less qualified and lower SEP groups (Havet et al., 2017).

In the last decades, attributable fractions (AF) have been increasingly used by public health organizations trying to measure the potential impact of different interventions related to modifiable risk factors in terms of the avoidable burden of disease at the population level (Steenland and Armstrong, 2006). This gave the AF tool the power to influence stakeholders and decision makers. To our knowledge, AF has rarely been used to quantify the impact of different risk factors depending on SEP, with the recent exception of smoking and cancer (Menvielle et al., 2018).

While attempting to quantify the burden of avoidable lung cancer, it yet seems important first to take into account not only behavioural but also work-related factors; and then to complement the usual population-wide approaches with a focus on specific sub-groups defined by SEP, as the modifiable exposures (behavioural, work-related and others) are not evenly distributed.

1. Study aim and main objectives

1.1. Aim

Apply the attributable risk approach to compare the burden of work-related lung cancer between different socio-economic groups taking three occupational exposures (e.g. asbestos, silica and Diesel Motor Exhaust (DME)) as well as smoking into account.

1.2. Objectives

1. Quantify the burden of lung cancer related to occupational exposures (asbestos, silica, and DME) within different Socio-economic groups.
2. Quantify the burden related to occupational exposures (asbestos, silica, and DME) in lower and intermediate socio-economic groups compared to Higher socioeconomic groups.
3. Identify sources of variation in the estimates, notably due to the SEP indicator.

2. Methods

3.1 Study Design

We conducted a secondary analysis of the ICARE study (Investigation of occupational and environmental CAuses of REspiratory cancers) (Luce et al., 2011). ICARE is a multicenter population-based case-control study. The study was conducted between 2001 and 2007, in 10 French administrative departments out of the 11 departments with a general cancer registry(table.1). The study covered different geographical areas around France with a population of 7.5 million people (about 13% of the French population).

Lung cancer cases aged from 18 to 75 years were considered eligible for the study. The cases were recruited from the newly diagnosed and histologically confirmed lung cancer cases at the time of the study (code C33 and C34 according to the International Classification of Diseases for Oncology, 3rd edition). The study randomly recruited controls with no previous history of lung cancer from the population in the same residential departments by using incidence density sampling and frequency matching to the cases by age (4 age groups: 40<, 40-54, 55-64, 55-64, and 65-74 years), administrative department and gender.

Further stratification based on socioeconomic status was done to obtain a comparable distribution between controls and the general population in the same departments (Guida et al., 2011). Recruitment of controls was based on multiple waves every 2 months each, thus, to achieve the approximately 1:1 control to case ratio, based on the number of newly diagnosed cases in the registries during this time period. The ICARE study included 2926 lung cancers cases, 3555 controls and 2415 head and neck cancer cases, the later were not included in our analysis.

3.2. Data Collection

Face-to-face interviews were conducted by the ICARE team using standardized questionnaires to collect information on lifetime occupational history (including all jobs held at least 1-month), occupational exposures to known or suspected carcinogens (self-reported),
education, active and passive smoking, alcohol drinking, family history of cancers and complementary socio-demographic data.

All occupations were coded according to the International Standard Classification of Occupations (ISCO) of the International Labour Organization, 1968 revision, and branches of industry according to the French Nomenclature of Activities (Nomenclature d'activités Françaises: NAF) of the National Institute for Statistics and Economic Studies (INSEE), 1999 edition. A full description of the ICARE study design and methods can be found in (Guida et al., 2011; Luce et al., 2011).

3.3. Ethical approval

The ICARE study was approved by the institutional review board of the French National Institute of Health and Medical Research (IRB-Inserm, no. 01-036). Confidentiality was guaranteed, and participants signed informed consent as recommended by the French Data Protection Authority, which also approved the study (CNIL no. 90120).

3.4. Exposures Assessment

Asbestos and Silica

The ICARE team assessed exposure to asbestos and silica dust based on French Job Exposure Matrix (JEMs)(Févotte et al., 2011). Different metrics of exposure were available in the database: the dichotomous/binary (Ever/never) indicator was created by the ICARE study group based on the probability of being exposed, where everyone with a non-null probability was considered as ever exposed. As this is a sensitive definition of exposure, for this analysis we developed another indicator based on a definition that would lie on specificity, e.g. a probability higher than 30% for asbestos and 25% for Silica. We also used an ordinal variable based on quartiles of the Cumulative Exposure Index (CEI) provided by the ICARE study. The CEI is designed to calculate the amount of exposure through the whole work history considering the total durations of different jobs, the frequency, the probability and intensity of exposure based on specific tasks, also the frequency and intensity of the exposure based on the work atmosphere. The CEI for asbestos was calculated by the number of fibers per milliliter per year, while for silica CEI is calculated in milligram per m^3 per year. The quartiles were based on the group of exposed controls for men and women separately, so we can observe the different effects based on dose-response.

Diesel motor exhausts

DME exposure was assessed based on a question in the general questionnaire (self-report) in the ICARE study based on Yes/No/I don't know.

Combined index for different exposures

Our three main exposure of interest (Asbestos, Silica, and DME) are known to co-occur sometimes in the same work environment or appear at different times within the work history. For this analysis a combined exposure index based on binary sensitive exposure variables (Never/Ever) to be consistent with the DME binary indicator was developed. Four categories were created: never exposed to any of the three lung carcinogens, exposed to exactly one, two and three carcinogens.

Smoking

The Comprehensive Smoking Index (CSI) combines the duration of smoking, time since cessation (TSC) and intensity of smoking based on the number of cigarettes per day, CSI is calculated as null for non- smoker; a person who smoked less than 100 cigarettes during lifetime (Leffondré et al., 2006).

3.5. Occupation-based socioeconomic position

The socioeconomic position at the time of the interview included 8 main categories based on the French CSP ("catégories socio-professionnelles") classification scheme (Managers, self-employed, farmers, intermediate occupations, clerks/sales/service workers, blue collar workers, retired and unemployed). We substituted the retired and unemployed with their last job held as used in the original stratification of the ICARE study and used this combined indicator as our main variable of stratification in the analysis. In order to identify sources of variation in the estimates, we used different occupation-based indicators for SEP in addition to this modified one. The other indicators were respectively based on the 1st job held and the longest held job throughout the entire work history (combining all the jobs in the same category).

3.6. Education

Education was classified into five categories: Primary or Elementary, Middle school, high school, and University and unknown), we excluded the unknown category in our analysis.

3.7. Statistical analysis

Adjustment on potential confounders

Statistical analysis was performed using Stata 15.0 release (Copyright 1985-2017 StataCorp LLC). Comparison of cases and controls through binary analysis used Wilcoxon rank-sum test for continuous variables and Chi-squared test for categorical variables.

Multiple unconditional logistic regression models were conducted separately for men and women. The first set of models (referred to as the core models) were adjusted for age in quintiles, departments and CSI as a continuous variable, as previous analysis on ICARE study proved the linearity between lung cancer risk and CSI (Guida et al., 2011; Matrat et al., 2015; Tarnaud et al., 2012). The second set of models (referred to as further adjusted models) added mutual adjustment on the three occupational carcinogens. When the binary indicator for a single carcinogen was the main exposure of interest, other occupational exposures were also defined in binary terms, whereas the models were adjusted on the quartile-based indicators when the main exposure of interest was defined in quartiles (except for DME which was binary).

3.8. Sources of variation in the estimates

In order to identify sources of variation in the estimates, different strategies were used in the analysis. The first step tested different occupational exposure metrics to assess the total occupation-based burden for men and women separately. The second step aimed at estimating attributable fractions by SEP. Three different strategies were compared:

(1) stratification based on the current socioeconomic position to assess the burden of occupational exposure within the same group based on the original stratification by the ICARE study; (2) interaction between occupational exposure and SEP with the non-

exposed managers/professionals as the reference group; (3) disaggregation of occupational exposure impact by SEP through the choice of the non-exposed (irrespective of SEP) as the reference group. The third and last step looked at the influence of the SEP indicator by comparing the results based on the last, first and longest held occupation, as well as education level.

The results of tests were considered significant based on an alpha-risk level set *a priori* to 0.05, and all confidence intervals are also reported for alpha=0.05 (e.g. CI are 95% CI).

3.9. Attributable fraction estimation

For the calculation of AFs and their 95% CI from logistic models, we used the "aflogit" procedure in STATA (Brady, 1998) , which is based on the method by Greenland and Drecher (Greenland and Drescher, 1993), for the case-control studies using frequency matched method like the one used in ICARE. We calculated AFs only based on the statistically significant associations (OR>1 with P-Value less than 0.05), and for those models using quartiles, the overall AF was estimated as a sum across the significant quartile(s)(Miettinen, 1974; Wacholder et al., 1994). We also tried the punafcc to compare both methods, but no significant difference was observed(Newson, 2013).

4.Results:

4.1. Description of the study sample

This analysis includes 2926 lung cancer cases (650 women, 2276 men) and 3555 controls (775 women, 2780 men). Men hence formed 5056 e.g. 78.0% of the study sample, while the number of women was 1425 (22.0%). Table 1 illustrates selected Sociodemographic characteristics of the study population. The proportion of managers and professionals among men in the control group was higher than in cases ($p<10^{-3}$), also for university and high school, the proportion of controls among men was higher compared to cases ($p<10^{-3}$). While in women the proportion of managers/professionals, intermediate occupations and clerical/sales/ service jobs was higher in the control group than in cases ($p<10^{-3}$), the proportions of middle/higher educated women were higher in controls as compared to cases(p=0.001).

Table 1 Selected characteristics of the study population

	Men					Women			
	Controls		Cases			Controls		Cases	
Age (years)	**Mean**	**95% CI**	**Mean**	**95% CI**		**Mean**	**95% CI**	**Mean**	**95% CI**
Continuous	58.0	57.7-58.4	60.3	59.9-60.7		60.4	59.6-61.1	57.48	56.7-58.3
P-Value	*$<10^{-3}$*					*$<10^{-3}$*			
Quintiles	**N**	**%**	**N**	**%**	**Quintiles**	**N**	**%**	**N**	**%**
<48.3	565	20.3	226	9.9	<49.3	155	20.0	141	21.7
48.3<56.4	555	20.0	542	23.8	49.3<59.1	157	20.3	227	34.9
56.4<61.3	557	20.0	427	18.8	59.1<66.7	154	19.9	139	21.4
61.3<67.6	553	19.9	507	22.3	66.7<70.7	156	20.1	58	8.9
67.6≤	550	19.8	574	25.2	70.7≤	153	19.7	85	13.1
P-Value	*$<10^{-3}$*					*$<10^{-3}$*			
	N	**%**	**N**	**%**		**N**	**%**	**N**	**%**
Departments									
Calvados	358	12.9	272	12.0		104	13.4	82	12.6
Doubs+ Territoire de Belfort	112	4.0	106	4.70		31	4.0	43	6.6
Hérault	360	13.0	252	11.1		90	11.6	82	12.6
Isère	407	14.6	371	16.3		94	12.1	105	16.2
Loire Atlantique	311	11.2	273	12.0		93	12.0	77	11.9
Manche	247	8.9	262	11.5		65	8.4	58	8.9
Bas-Rhin	360	13.0	302	13.3		109	14.1	96	14.8
Haut-Rhin	360	13.0	302	13.3		29	3.7	17	2.6
Somme	387	14.0	269	11.8		112	14.5	52	8.0
Vendée	149	5.4	113	5.0		48	6.2	38	5.9
P-Value		*0.004*					*0.005*		
Socioeconomic position (Current)									
Managers & professionals	612	22.0	258	11.3		89	11.5	60	9.2
Self-employed	208	7.5	172	7.6		38	4.9	34	5.2
Farmers	176	6.3	67	2.9		29	3.7	8	1.2
Intermediate occupations	598	21.5	361	15.9		123	15.9	84	12.9
Clerks/Sales & service workers	288	10.4	235	10.3		372	48.0	309	47.8
Blue-collar workers	896	32.2	1156	50.8		108	13.9	122	18.8
Missing	2	0.1	27	1.2		16	2.0	33	5.1
P-value	*$<10^{-3}$*					*$<10^{-3}$*			
Socioeconomic position (Longest)									
Managers & professionals	544	19.5	238	10.4		74	9.6	50	7.7
Self-employed	152	5.5	139	6.1		25	3.2	28	4.3
Farmers	168	6.0	69	3.0		29	3.7	8	1.2

Continue Table 1 Selected characteristics of the study population

	Men				Women			
	Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%
Intermediate occupations	564	20.3	314	13.8	131	16.9	73	11.2
Clerks/Sales & service workers	297	10.7	218	9.6	375	48.4	321	49.4
Blue-collar workers	1053	37.9	1267	55.67	125	16.1	135	20.8
Missing	2	0.1	31	1.4	16	2.1	35	5.4
P-value	*$<10^{-3}$*				*$<10^{-3}$*			
Socioeconomic position (First)								
Managers & professionals	276	9.9	112	4.9	44	5.7	39	6.0
Self-employed	39	1.4	40	1.8	11	1.4	15	2.3
Farmers	47	1.7	46	2.0	10	1.3	2	0.3
Intermediate occupations	355	12.8	173	7.6	119	15.3	59	9.1
Clerks/Sales & service workers	389	14.0	272	11.9	361	46.6	327	50.3
Blue-collar workers	1672	60.1	1606	70.6	214	27.6	175	26.9
Missing	2	0.1	27	1.2	16	2.1	33	5.1
P-value	*$<10^{-3}$*				*$<10^{-3}$*			
Education:								
Primary /Elementary	521	18.7	675	22.66	242	31.2	204	31.4
Middle	1081	38.9	869	38.2	270	34.8	208	32.0
High school	310	11.2	185	8.1	90	11.6	72	11.1
University	752	27.1	273	12.0	149	19.2	110	16.9
Missing	116	4.2	274	12.0	24	3.1	56	8.6
P-value	*$<10^{-3}$*				*0.001*			

Table 2 shows the distribution of exposures among men and women, cases and controls separately. Using the sensitive indicator (Never/Ever) for Asbestos, we can observe higher proportion of exposures among men cases compared to men controls with 70.2% exposed among cases compared to 58.1 % among controls, ($p<10^{-3}$), while in women we can observe lesser exposure for both cases and controls (19.8 %, 19.9%,p=0.2), and both are quite similar. Using the specific binary indicator changed the results for both men and women, as expected, the proportions of exposed decreased in all groups, but for men the exposed among cases remained higher than in controls (47.0% and 34.4%, $p<10^{-3}$), while in women the proportion of exposure among cases became higher than in controls (8.0% for cases compared to 4.1% in controls, p=0.001). The quartiles distribution showed higher proportions in the 3rd and

4th quartiles compared to the 1st and 2nd quartiles for both men and women cases as compared to controls ($p<10^{-3}$).

For silica, the proportion of exposed controls was 23.2% and for cases 35.0% among men using the sensitive binary indicator ($p<10^{-3}$), and respectively 0.5% and 1.4% among women (p=0.06).As expected, the proportion of exposed decreased though slightly with the specific binary indicator, and the differences between cases and controls remained significant ($p<10^{-3}$ for men and p=0.02 for women). While the difference among men remained significant when using quartiles ($p<10^{-3}$), it was not significant among women (p=0.02) (with very few observations though).

Exposure to DME differed between cases and controls among men (p=0.02) and women (p=0.02) while again exposure was lesser in the later.

Using the combined exposure indicator, there was a significant difference in distribution between cases and controls for both men and women. The higher concentration in both cases and controls within men were for the one- carcinogen category (30.9%, 31.8% respectively), and two- carcinogens categories (34.1% and 25.0% respectively), but it was less in the three- carcinogens category (11.4%, 8.4% respectively). In women there were very few numbers of multi-exposed participants and small difference could be found (p=0.01). While the non-exposed proportion among men was 22.1% for cases and 34.3% for controls ($p<10^{-3}$), the proportion of non-exposed among women was 67.1% and 71.1% for cases and controls respectively (p=0.01).

Finally, we could observe a difference in the means for CSI between cases and controls and between men and women. CSI mean for men control equal 0.65 (CI 0.63-0.68), vs. 1.62 CI 1.59-1.64) for cases ($p<10^{-3}$), and for women it was 0.29 (CI 0.26-0.33) for controls and 1.1 (CI 1.03-1.16) for cases ($p<10^{-3}$).

Table 2 Distribution of exposures among cases and controls, men and women

	Men					**Women**				
	Controls		**Cases**		***P***	**Controls**		**Cases**		***P***
Smoking	Mean	95% CI	Mean	95% CI		Mean	95% CI	Mean	95% CI	
CSI	0.6	0.63- 0.68	1.6	1.59-1.64	*$<10^{-3}$*	0.29	0.26-0.33	1.1	1.03-1.16	*$<10^{-3}$*
	N	%	N	%		N	%	N	%	
Asbestos										
Never, CEI =0	1165	41.9	665	29.2	*$<10^{-3}$*	621	80.1	518	79.7	*0.2*
Ever (se)	1615	58.1	1597	70.2		154	19.9	129	19.8	
Missing	0	0.0	14	0.6		0	0.0	3	0.5	

Continue table 2 Distribution of exposures among cases and controls, men and women

	Men					Women				
	Control		Cases		*P*	Control		Cases		*P*
	N	%	N	%		N	%	N	%	
Never (sp) *P ≤ 30 %*	1823	65.6	1192	52.4	*<10^{-3}*	743	95.9	595	91.5	*0.001*
Ever (sp) P>30 %	957	34.4	1070	47.0		32	4.1	52	8.0	
Missing	0	0.0	14	0.6		0	0.0	3	0.5	
Quartiles					*<10^{-3}*					*<10^{-3}*
Never	1165	41.9	665	29.2		621	80.1	518	79.7	
Q1	404	14.5	303	13.3		41	5.3	16	2.5	
Q2	404	14.5	310	13.6		36	4.7	14	2.2	
Q3	404	14.5	420	18.5		39	5.0	51	7.8	
Q4	403	14.5	556	24.4		38	4.9	47	7.2	
Missing	0	0.0	22	1		0	0.0	4	0.6	
Silica										
Never, CEI=0	2121	76.3	1448	63.6	*<10^{-3}*	760	98.1	624	96.0	*0.06*
Ever (se)	645	23.2	795	35.0		4	0.5	9	1.4	
Missing	14	0.5	33	1.4		11	1.4	17	2.6	
Never *P* ≤ 25 %	2187	78.7	1506	66.2	*<10^{-3}*	762	98.3	624	96.0	*0.02*
Ever *P* >25 %	579	20.8	737	32.4		2	0.3	8	1.2	
Missing	14	0.5	33	1.4		11	1.4	18	2.8	
Quartiles										
Never	2121	76.3	1448	63.6	*<10^{-3}*	760	98.1	624	96.0	*0.14*
Q1	163	5.9	110	4.8		1	0.1	1	0.2	
Q2	162	5.8	170	7.5		1	0.1	4	0.6	
Q3	159	5.7	243	10.7		1	0.1	4	0.6	
Q4	161	5.8	266	11.7		1	0.1	0	0.0	
Missing	14	0.5	39	1.7		11	1.4	17	2.6	
DME					*0.02*					*0.02*
Never	2059	74.1	1620	71.2		704	90.8	569	87.5	
Ever	721	25.9	654	28.7		56	7.2	53	8.2	
Missing	0	0.0	2	0.1		15	1.9	28	4.3	
Combined Indicator of occupational exposures										
Never exposed	954	34.3	502	22.1	*<10^{-3}*	551	71.1	436	67.1	*0.01*
One carcinogen	884	31.8	703	30.9		184	23.7	151	23.2	
Two carcinogens	695	25.0	776	34.1		14	1.8	18	2.8	
Three carcinogens	233	8.4	260	11.4		0	0	0	0	
Missing	14	0.5	35	1.5		26	3.4	45	6.9	

CSI: Comprehensive Smoking Index

CEI: Cumulative Exposure Index

Q1: 1st quartile, Q2: 2nd quartile, Q3: 3rd quartile, and Q4: quartile

4.2. Variations in PAFs estimates

4.2.1. First step: variations due to exposure metrics

As mentioned previously, our first step of analysis was to calculate the burden of lung cancer related to exposure to selected occupational exposures for the whole study population by sex. We were able to calculate PAFs among men subjects (Table 3), but we could not include any results related to women population as all the results were insignificant (e.g. p-value > 0.05 for all the ORs, see Table 1 Annex).

Table 3 Simple and further adjusted estimations of PAFs for Men based on different exposure metrics

	Core model[1]				Mutual Adjustment[2]			
	OR	***P***	**PAF %**	**95% CI**	***OR***	***P***	**PAF %**	**CI**
Asbestos								
Ever/Never (se)	1.6	$<10^{-3}$	27.7	20.4-34.3	1.5	10^{-3}	23.1	14.4-31.0
Ever/Never (sp)	1.5	$<10^{-3}$	15.2	10.0-20.2	1.3	10^{-3}	11.7	5.4-17.5
Quartiles								
Q1	1.4	0.002	3.9	1.1-6.6	1.4	0.006	3.7	0.0-6.5
Q2	1.5	0.001	4.4	1.6-7.0	1.4	0.003	4.0	1.2-6.7
Q3	1.7	$p<10^{-3}$	7.4	4.7-10.9	1.5	10^{-3}	6.5	3.2-9.7
Q4	1.9	$p<10^{-3}$	11.9	8.6-15.1	1.6	10^{-3}	9.8	5.6-13.7
Total	-	-	27.6	20.4-34.2	-	-	23.9	4.2-31.7
Silica								
Ever/Never (Se)	1.6	$p<10^{-3}$	12.6	8.3 -16.7	1.3	0.002	8.3	3.2-13.2
Ever/Never (Sp)	1.6	$p<10^{-3}$	11.7	7.6 – 15.6	1.4	10^{-3}	8.8	4.0-13.3
Quartiles								
Q1	1.0	0.04	n.a.	n.a.	0.8	0.2	n.a.	n.a.
Q2	1.3	$<10^{-3}$	1.9	-0.4-4.2	1.1	0.6	n.a.	n.a.
Q3	1.8	$<10^{-3}$	4.9	2.6-7.2	1.5	0.008	3.4	0.7- 6.1
Q4	1.9	$<10^{-3}$	5.7	3.3-8.1	1.6	0.002	4.2	1.4-6.9
Total	-	-	12.6	8.9- 16.2	-	-	7.7	3.7-11.4
DME								
Ever/Never (self-report)	1.2	$<10^{-3}$	4.9	0.6 – 9.0	1.1	0.3	n.a.	n.a.
Combined indicator of occupational exposures								
One carcinogen	1.5	$<10^{-3}$	10.5	6.1-14.8	-	-	-	-
Two carcinogens	1.9	$<10^{-3}$	16.2	11.9-20.2	-	-	-	-
Three carcinogens	2.1	$<10^{-3}$	6.0	3.7-8.3	-	-	-	-
Total	-	-	32.7	24.6-39.9	-	-	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

The PAF for asbestos using the binary sensitive indicator was 27.7% CI (20.4-34.3), while after mutual adjustment (for silica and DME) it decreased to 23.1% CI (14.4-31.0). The estimated PAF for the binary specific indicator was 15.2% CI (10.0-20.2), and after mutual adjustment it was reduced to 11.7% CI (5.4-17.5). PAFs for the Asbestos CEI quartiles was 27.6% CI (20.4-34.2) and after mutual adjustment, it was reduced to 23.93% CI (4.2- 31.7), which is in accordance with the results based on the binary sensitive indicator. The PAF for the binary sensitive silica indicator was 12.6% CI (8.3-16.7) and after mutual adjustment it decreased to 8.3% CI (3.2-13.2). Contrary to asbestos it did not change much when using the specific indicator. The total PAFs for silica CEI 2nd, 3rd & 4th quartiles were 12.6% CI (8.9- 16.2) and after mutual adjustment, it was 7.7 % CI (3.7-11.4).

The PAFs for DME was 4.9% CI (0.6-9.1), but after mutual adjustment the results were insignificant (Table 1 Annex).

The combined occupational exposures indicator showed PAFs equal to 10.5% CI (6.1-14.8) for one carcinogen, 16.2% CI (11.9-20.2) for two and for the three carcinogens combined 6.0% CI (3.7-8.3), with a total across the three categories summing up to 32.7% CI (24.6-39.9).

4.2.2. Second step: variations due to the choice of comparison group

Strategy 1: Stratification on current occupation

Table 4 reports the attributable fractions obtained after stratifying the models on the current occupation-based SEP indicator (e.g. current CSP) in order to estimates AF within different socio-economic groups.

Among the self-employed, the AF for asbestos was 15.1% CI (5.4-23.8) based on the 4th CEI quartile alone and did not change much after mutual adjustment 14.4% CI (2.9-24.4). For silica it was 7.60% CI (-0.04-14.7) based on the 4th CEI quartile alone, but after mutual adjustment we could not calculate the AF as the odds ratio were insignificant. No other exposure variable showed a significant association with the risk of lung cancer.

Within the intermediate occupations group, the AF for the sensitive Asbestos binary indicator was 30.5% CI (14.6-43.2) and after mutual adjustment the AF was 28.6% CI (10.4-43.2). The total AFs for asbestos CEI quartiles among this group reached 29.8% CI (13.7-43.0) and after mutual adjustment 15.7% CI (6.9-23.7). For Silica the AF using the sensitive indicator was 11.5% CI (1.4-20.7), while after mutual adjustment the results were insignificant, in contradiction with the binary specific indicator which resulted in 12.4% CI (2.7-21.1) and after adjustment 11.2% CI (0.5-20.7). Results for DME did not reach significance. The AF for only one carcinogen category within the combined indicator for occupational exposures was 13.2% CI (3.3- 22.), for two carcinogens 13.8% CI (4.4-22.3), and for the three carcinogens combined 6.8% CI (1.4-11.9) and the total AFs for the three categories amounted to 33.7% CI (16.2-47.6).

Table 4 Simple and further adjusted estimations of AFs for Men based on stratification on the current occupation

	Self-employed				**Intermediate**				**Blue collar workers**			
	Core model[1]		**Adjusted[2]**		**Core model[1]**		**Adjusted[2]**		**Core model[1]**		**Adjusted[2]**	
	AF	**95% CI**	**AF**	**95% CI**	**AF**	**95% CI**	**AF**	**95% CI**	**AF**	**95% CI**	**AF**	**95% CI**
Asbestos												
Ever/Never (se)	n.a.		n.a.	n.a.	30.5	14.6-43.2	28.6	10.4-43.2	n.a.	n.a.	n.a.	n.a.
Ever/Never (Sp)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Quartiles												
Q1	n.a.	n.a.	n.a.	n.a.	7.13	1.2-12.7	6.9	0.9-12.7	n.a.	n.a.	n.a.	n.a.
Q2	n.a.	n.a.	n.a.	n.a.	9	2.6-15.0	8.8	2.1-15.0	n.a.	n.a.	n.a.	n.a.
Q3	n.a.	n.a.	n.a.	n.a.	8.2	1.3-14.6	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q4	15.1	5.4-23.8	14.4	3.0-24.4	5.5	-3.0-13.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Totals	15.1	5.4-23.8	14.4	3-24.4	29.8	13.7-43.0	15.7	6.9-23.7	n.a.	n.a.	n.a.	n.a.
Silica												
Ever/Never (se)	n.a.	n.a.	n.a.	n.a.	11.5	1.4-20.7	n.a.	n.a.	10.7	1.5-19.1	n.a.	n.a.
Ever/Never (sp)	n.a.	n.a.	n.a.	n.a.	12.4	2.7-21.1	11.2	0.5-20.7	n.a.	n.a.	n.a.	n.a.
Q1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a..	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.1	1-8.9	4.4	0.02-8.6
Q4	7.6	-0.04-14.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total	7.6	-0.04-14.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.05	0.9-8.9	4.4	0.03-8.6
DME												
Ever/Never (self-report)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Combined Indicator of occupational exposures												
One carcinogen	n.a.	n.a.	-	-	13.2	3.3-22.0	-.	-	n.a.	n.a.	-	-
Two carcinogens	n.a.	n.a.	-	-	13.8	4.4-22.3	-	-	n.a.	n.a.	-	-
Three carcinogens	n.a.	n.a.	-	-	6.8	1.4-11.9	-	-	n.a.	n.a.	-	-
Total	n.a.	n.a.	-	-	33.7	16.2-47.6	-	-	n.a.	n.a.	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Among blue-collar workers, the results were generally insignificant except for silica sensitive binary indicator (AF 10.7% CI (1.5-19.1)), the 3rd CEI quartile of Silica (AF 5.1% CI (1-8.9)), even after adjustment for Asbestos e.g. 4.4% CI (0.03-8.6).

The results among managers/professionals, farmers, and clerical/sales/service workers were not shown, as there was no significant OR for any of the occupational exposure indicators.

<u>Strategy 2: Comparison of different CSP groups with managers/professionals</u>

Table 5 reports the second strategy where the interaction between occupational exposure and SEP is studied through the choice of the non-exposed managers/professionals as the reference group.

We only calculated PAFs for clerical/sales/service workers and blue-collar workers, as the results were insignificant for self-employed, intermediate occupations and farmers, for all the models (see Annex).

Comparing exposed blue-collar workers with the reference group, the PAF for asbestos sensitive binary indicator was 29.6% CI (23.9-34.9), after mutual adjustment it was 28.1% CI (21.7-34.0). While using the specific binary indicator PAF was 21.9% CI (17.8-25.9) and after mutual adjustment 20.6% CI (15.9-25.1). The total PAF for asbestos CEI quartiles was 29.6% CI (23.9-34.9), and after mutual adjustment 27.5% CI (20.9-33.6). For silica using the sensitive binary indicator PAF was 16.5% CI (13.2-19.8), and after mutual adjustment decreased to 14.7% CI (11.2-18.0), while the PAF 15.4% CI (12.2-18.4) by using the specific binary indicator and after mutual adjustment 14.7% CI (11.2-18.0). The sum of PAFs for silica CEI quartiles was 15.1% CI (12.1-18.0), and after mutual adjustment 12.5 % CI (8.6-16.3). For DME the PAF was 11.7% CI (8.8-14.5), and after mutual adjustment 10.0% CI (6.6-13.3). The combined indicator for occupational exposures showed a total PAF of 28.6% CI (22.9-33.9).

For clerical/sales/service workers the results were less significant for many exposure indicators. However, the PAF for asbestos sensitive binary indicator was 2.7% CI (0.8-45), and after mutual adjustment 2.6% CI (0.7-4.4). The PAF for asbestos binary specific indicator was 1.0% CI (-07-2.7), and after mutual adjustment the result was insignificant. The PAF for asbestos CEI quartiles were 2.3% CI (0.5-4.1), and after mutual adjustment 1.2% CI (-0.4-2.9). For, Silica, the PAF for the sensitive binary indicator was insignificant, while the specific indicator was 0.9% CI (-0.8-2.5), and after mutual adjustment 0.8% CI (-0.82.5). The only significant silica CEI quartile was the 3rd one, with PAF 0.7% CI (-0.9-2.2), and after mutual adjustment 0.6% CI (-0.9-2.2).

The PAF for DME was 1.5% CI (-0.2-3.2) and mutual adjustment did not change much (1.4% CI (-0.3-3.1)). The total PAF for the sum of the three categories of the combined indicator of occupational exposures was 3.1% CI (1.1-5.1).

Table 5: Simple and further adjusted estimations of PAFs for Men based on the comparison of exposed CSP groups with non-exposed managers/professional (longest held occupation)

	Clerical/ Sales / service workers				Blue-Collar workers			
	Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]	
	PAF	95% CI	PAF	95% CI	PAF	95% C I	PAF	95% CI
Asbestos								
Ever/Never (se)	2.7	0.8-4.5	2.6	0.7-4.4	29.6	23.9-34.9	28.1	21.7-34.0
Ever /Never (Sp)	1.0	-0.7-2.7	n.a.	n.a.	21.9	17.8-25.9	20.6	15.9-25.1
Never Exposed								
Q1	1.0	-0.6-2.7	n.a.	n.a.	4.0	2.1-5.9	3.8	1.8-5.7
Q2	0.6	-0.9-2.1	0.6	-1.0-2.1	4.19	1.9-6.4	3.8	1.5-6.1
Q3	0.8	-0.8-2.3	0.7	-0.9-2.3	8.5	6.0-10.9	7.9	5.3-10.6
Q4	-	-	-	-	13.0	10.1-15.7	11.9	8.6-15.2
Totals	2.3	0.5-4.1	1.2	-0.4-2.9	29.6	23.9-34.9	27.5	20.9-33.6
Silica								
Ever/Never (se)	n.a.	n.a.	n.a.	n.a.	16.5	13.2-19.8	14.8	10.9-18.6
Ever/Never (sp)	0.9	-0.8-2.5	0.8	-0.8-2.5	15.4	12.2-18.4	14.6	11.1-18.0
Quartiles								
Q1	n.a.	n.a.	n.a.	n.a.	1.4	-0.4-3.1	n.a.	n.a.
Q2	n.a.	n.a.	n.a.	n.a.	3.1	1.2-5.0	2.3	0.2-4.5
Q3	0.7	-0.9-2.2	0.6	-0.9-2.2	5.3	3.3-7.2	4.5	2.4-6.6
Q4					6.7	4.6-8.8	5.2	3.3-8.1
Total	0.7	-0.9-2.2	0.6	-0.9-2.2	15.1	12.1-18.0	12.5	8.5-16.3
DME								
Ever/Never (self-report)	1.5	-0.2-3.2	1.4	-0.3-3.1	11.7	8.8-14.5	10.0	6.6-13.3
Combined indicator of occupational exposures								
One carcinogen	1.3	-0.5-3.1			8.7	6.6-12.6	-	-
Two carcinogens	1.3	-0.24-2.9			14.4	11.2-17.5	-	-
Three carcinogens	0.5	-1.0-2.1			5.5	3.4-7.5	-	-
Total	3.1	1.1-5.1			28.6	22.9-33.9	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Strategy 3: Comparison of each exposed occupational group with all non-exposed

Table 6 reports the output of the third strategy where the disaggregation of occupational exposure impact by SEP is studied through the choice of the non-exposed (irrespective of SEP) as the reference group, also based on the longest held occupation (sum of total duration spent in different CSP through the entire work history). PAFs for our selected occupational exposures were higher for blue-collar workers than other CSP groups. The PAF for asbestos sensitive binary indicator was

24.1% CI (19.2-28.6), and after mutual adjustment the PAF was 21.7% CI (16.1-27.1). While the PAF for the specific binary indicator was 14.8% CI (2.1-10.7), and after mutual adjustment it was 12.2% CI (7.3-16.8), the sum of PAFs for asbestos CEI quartiles was 24.2% CI (19.4-28.7), and after mutual adjustment 21.1% CI (15.2-26.6). For silica sensitive binary indicator, the PAF was 12.2% CI (8.8-15.5), and after mutual adjustment it was 10.2% CI (6.4-13.9). While by using the specific binary indicator, the PAF was 10.8% CI (7.5-14.0), and after mutual adjustment 8.8 % CI (5.0-12.5). The sum of PAFs for silica CEI quartiles was 11.6% CI (8.5-14.6), and after mutual adjustment 7.5% CI (4.2-10.6). For DME, the PAF was 6.3% CI (3.1-9.4), and after mutual adjustment 3.9% CI (0.3-7.4). The sum of PAFs for the three categories of the combined indicator for occupational exposures was 26.9% CI (21.9- 31.7).

All the results for the intermediate CSP group were insignificant, while the self-employed, and clerical/sales/service workers showed some significant results for different occupational exposures indicators.

For self-employed the PAF for asbestos sensitive binary indicator was 1.2% CI (-0.7-3.0), while after mutual adjustment the result was insignificant. The results for both the core and adjusted models for the specific binary indicator were also insignificant. The 4th quartile for asbestos CEI had PAF equal 0.9% CI (0.6-2.5), and it did not change after mutual adjustment. Both silica sensitive and specific binary indicators were insignificant, while the 4th quartile for CEI showed PAF of 0.5% CI (-1.1-2.0). The PAF for the 2nd category in the combined indicator of occupational exposures was 0.9% CI (-0.8-2.6).

For clerical/sales/service workers group, the PAF was 2.1% CI (0.1-3.9) for asbestos sensitive binary indicator, while after adjustment it was 1.9% CI (-0.1-39). The PAF for the 2nd quartile of asbestos CEI was 0.5% CI (-1.1-2.0), and it did no change after adjustment. The 3rd quartile for silica CEI has PAF of 0.6% CI (0.9-2.1), and after adjustment, the result was insignificant. The total of the 2nd and 3rd categories in the combined indicator of occupational exposures was 1.5% CI (-0.2-3.2).

4.2.3. Third step: variations due to SEP indicator

Finally, we studied the variation of estimates based on different SEP indicators, particularly occupation-based (longest held occupation) in comparison with education-based groups. Table 7 reports the results after adopting the 3rd strategy of estimation by SEP, e.g. where each exposed SEP group was compared to all non-exposed (irrespective of SEP) to allow disaggregation of the overall PAF between different SEP groups.

Table 6: Contribution of each CSP group to the overall burden of lung cancer related to occupational exposures (Simple and further adjusted estimations of PAFs for Men based on the comparison of exposed CSP groups with all non-exposed, irrespective of CSP (longest held occupation)

	Self-employed				Clerical \Sales \ Service workers				Blue collar workers				Total attributed fractions			
	Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]	
	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI	PAFs	95% CI
Asbestos																
Ever/Never (se)	1.2	-0.7-3.0	n.a.	n.a.	2.1	0.1-3.9	1.9	-0.1-3.9	24.1	19.2-28.6	21.7	16.1-27.1	27.3	21.8-32.4	23.6	17.5-29.3
Ever/Never (Sp)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	14.8	10.7-18.7	12.2	7.3-16.8	14.8	2.1-10.7	12.2	7.3-16.8
Never Exposed																
Q1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3.3	1.3-5.2	3.0	0.9-5.0	n.a.	n.a.	n.a.	n.a.
Q2	n.a.	n.a.	n.a.	n.a.	0.5	-1.1-2.0	0.5	-1.1-2.0	3.0	0.7-5.2	2.5	0.1-4.8	n.a.	n.a.	n.a.	n.a.
Q3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	7.0	4.5-9.4	6.1	3.4-8.8	n.a.	n.a.	n.a.	n.a.
Q4	0.9	0.6-2.5	0.9	0.8-2.4	n.a.	n.a.	n.a.	n.a.	11.0	8.2-13.7	9.5	6.1-12.7	n.a.	n.a.	n.a.	n.a.
Totals	0.9	0.6-2.5	0.9	0.8-2.4	n.a.	n.a.	n.a.	n.a.	24.2	19.4-28.7	21.1	15.2-26.6	25.6	2.4-30.3	22.4	16.4-28.0
Silica																
Ever/Never (se)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	12.2	8.8-15.5	10.2	6.4-13.9	12.2	8.8-15.5	10.2	6.4-13.9
Ever/Never (sp)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	10.8	7.5-14.0	8.8	5.0-12.5	10.8	7.5-14.0	8.8	5.0-12.5
Quartiles																
Q1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2.0	-0.05-4.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q3	n.a.	n.a.	n.a.	n.a.	0.6	-0.9-2.1	n.a.	n.a.	4.2	2.2-6.2	3.3	1.0-5.5	n.a.	n.a.	n.a.	n.a.
Q4	0.5	-1.1-2.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.4	3.1-7.5	4.2	1.6-6.6	n.a.	n.a.	n.a.	n.a
Total	0.5	-1.1-20	n.a.	n.a.	0.6	-0.9-2.1	n.a.	n.a.	11.6	8.5-14.6	7.5	4.2-10.6	12.7	9.5-15.8	7.5	4.2-10.6
DME																
Ever/Never	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	6.3	3.1-9.4	3.9	0.3-7.4	6.3	3.1-9.4	3.9	0.3-7.4
Combined indicator of occupational exposures																
One carcinogen	n.a.	n.a.	-	-	n.a.	n.a.	-	-	7.8	7.9-10.6	-	-	n.a.	n.a.	-	-
Two carcinogens	0.9	-0.8-2.6	-	-	1.0	-0.7-2.7	-	-	13.9	10.8-16.9	-	-	n.a.	n.a.	-	-
Three carcinogens	n.a.	n.a.	-	-	0.5	-1.1-2.0	-	-	5.3	3.2-7.4	-	-	n.a.	n.a.	-	-
Total	0.9	-0.8-2.6	-	-	1.5	-0.2-3.2	-	-	26.9	21.9-31.7	-	-	29.4	23.9-34.4	-	-

n.a.: not applicable, p-value<0.05, 1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

The results by education were only significant for the primary/elementary groups and middle school groups, not in high school and university.

For the primary/elementary group the PAF for asbestos sensitive binary indicator was 14.9% CI (11.6-18.2), and after mutual adjustment 13.7% CI (9.9-17.3). Using asbestos specific binary indicator, PAF was 8.7% CI (5.9-11.5), and after adjustment 7.6% CI (4.4-10.6). The total PAFs calculated for asbestos CEI quartiles were 14.9% CI (11.6-18.2), and after adjustment 13.5% CI (9.6-17.1). For Silica exposure the PAF for the sensitive binary indicator was 6.9% CI (4.2-9.5), and after adjustment 5.4% CI (2.4-8.4). By using silica specific binary indicator, the estimate PAF was 6.3% CI (3.6-8.8), and after adjustment 5.3% CI (2.4-8.1). The sum of estimated PAFs among the three significant quartiles for silica CEI was 6.5% CI (3.9-9.0), and after adjustment 4.9% CI (1.9-7.9). For DME, the estimated PAF was 3.5% CI (0.8-6.1), and after adjustment 2.6% CI (-0.3-5.4). For the combined indicator of occupational exposures, the sum of estimated PAFs was 16.4% CI (13.4-20.3).

For the middle education group, the estimated PAF for asbestos sensitive binary indicator was 13.1% CI (8.6-17.5), and after adjustment 11.1% CI (5.8-16.0). Using the specific binary indicator, the estimated PAF was 7.3% CI (3.3-11.1), and after adjustment 4.9% CI (0.4-9.4). The sum of estimated PAFs for the significant quartiles for asbestos CEI was 11.9% CI (7.9-15.9), and after adjustment 10.2% CI (5.3-14.7).

For silica, the estimated PAF for the sensitive binary indicator was 5.4% CI (2.2-8.4), and for the specific binary indicator 4.7% CI (1.6-7.7), the results for both exposures indicators became insignificant after mutual adjustment. Using the quartile indicator for silica CEI, the sum of the PAFs for the 3rd and 4th quartiles was 4.6% CI (2.2-7.0), and after mutual adjustment, only the 4thquartile was still significant with estimated PAF 1.8% CI (-0.4-3.9).

For the DME self-reported indicator, the estimated PAF was 3.5% CI (0.4-6.5), and after adjustment the results became insignificant. Using the combined indicator for occupational exposures. The sum of the estimated PAFs for the three categories together was 15.3% CI (10.5-19.8).

The 2nd and 3rd strategy did not allow to report any estimation of the burden of occupational exposures for women SEP groups (both occupation- and education-based), as only few random results were observed (data not shown).

Table 7 Contribution of each education group to the overall burden of lung cancer related to occupational exposures (Simple and further adjusted estimations of PAFs for Men based on the comparison of exposed education groups with all non-exposed, irrespective of education)

	Primary/Elementary education				Middle education				Total attributed fraction			
	Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]		Core model[1]		Adjusted[2]	
	PAF	95% CI	PAF	95% CI	PAF	95% CI	PAF	95% CI	PAF	95% CI	PAF	95% CI
Asbestos												
Ever/Never (se)	14.9	11.6-18.2	13.7	9.9-17.3	13.1	8.6-17.5	11.1	5.8-16.0	28.1	21.9-33.7	24.7	17.4-31.4
Ever/Never (sp)	8.7	5.9-11.5	7.6	4.4-10.6	7.3	3.3-11.1	4.9	0.4-9.4	16	11.1-20.7	12.6	6.6-18.1
Quartiles												
Q1	2.8	0.8-4.9	2.7	0.6-4.8	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q2	2.7	0.7-4.5	2.5	0.5-4.4	2.3	0.02-4.5	2.0	-0.3-4.3	n.a.	n.a.	n.a.	n.a.
Q3	4.2	2.0-6.3	3.7	1.4-5.9	3.6	1.2-5.9	3.2	0.6-5.7	n.a.	n.a.	n.a.	n.a.
Q4	5.3	3.1-7.4	4.6	2.2-6.9	6.1	3.3-8.9	4.9	1.8-8.1	n.a.	n.a.	n.a.	n.a.
Total	14.9	11.6-18.2	13.5	9.6-17.1	11.9	7.9-15.9	10.2	5.3-14.7	26.9	21.2-32.3	23.6	16.6-30.1
Silica												
Ever/Never (Se)	6.9	4.2-9.5	5.4	2.4-8.4	5.4	2.2-8.4	n.a.	n.a.	12.2	8.2-16.1	5.4	2.4-8.4
Ever/Never (Sp)	6.3	3.6-8.8	5.3	2.4-8.1	4.7	1.6-7.7	n.a.	n.a.	11.0	7.1-14.7		
Quartiles												
Q1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q2	1.7	-0.2-3.4	1.4	-0.5-3.2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q3	2.3	0.3-4.2	1.7	-0.4-3.8	2.2	0.1-4.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Q4	2.6	0.5-4.7	1.8	-0.5-4.1	2.4	0.4-4.4	1.8	-0.4-3.9	n.a.	n.a.	n.a.	n.a.
Total	6.5	3.9-9.0	4.9	1.9-7.9	4.6	2.2-7.0	1.8	-0.4-3.9	11.1	7.9-14.3	6.7	3.2-10.1
DME												
Ever/Never (self-report)	3.5	0.8-6.1	2.6	-0.3-5.4	3.5	0.4-6.5	n.a.	n.a.	6.9	3.1-10.8	2.6	-0.3-5.41
Combined Indicator of occupational exposure												
One carcinogen	6.3	3.8-8.6	-	-	4.7	1.8-7.4	-	-	n.a.	n.a.	-	-
Two carcinogens	8.1	5.7-10.4	-	-	7.1	3.9-10.1	-	-	n.a.	n.a.	-	-
Three carcinogens	2.6	0.6-4.5	-	-	3.6	1.6-5.6	-	-	n.a.	n.a.	-	-
Total	16.9	13.4-20.3			15.3	10.5-19.8			32.2	25.6-38.3		

n.a.: not applicable, p-value<0.05, 1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

The graphs below show the summary of the main results

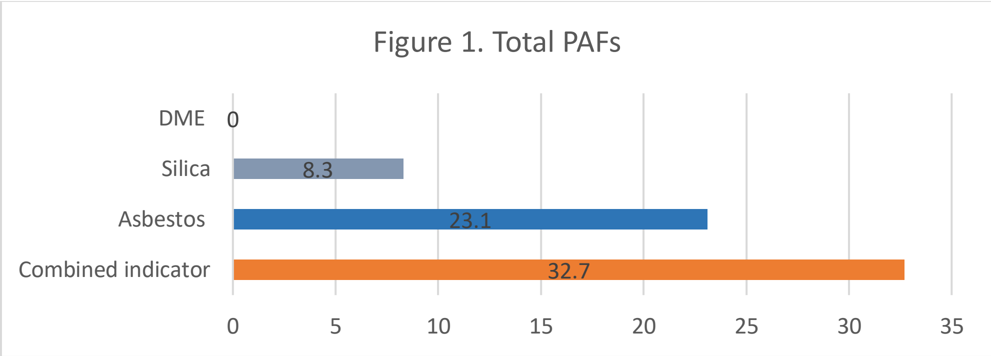

Figure 1: Overall burden of lung cancer related to the 3 occupational exposures for the whole men sample. Sensitive binary indicators of exposure and mutual adjustment (results taken from Table 3)

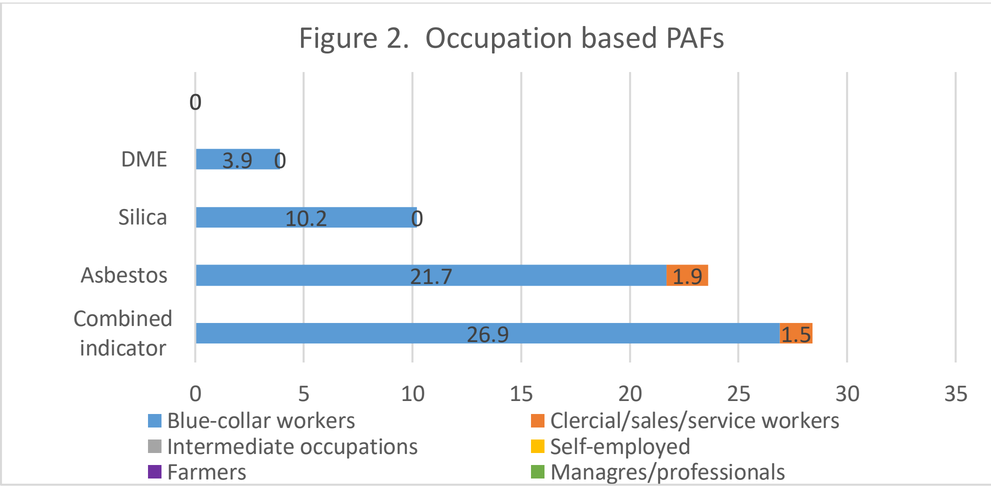

Figure 2: Contribution of each occupation-based SEP group to the overall burden of lung cancer related to the 3 occupational exposures. SEP groups based on the longest occupation held, sensitive binary indicators of exposure and mutual adjustment (results taken from Table 6)

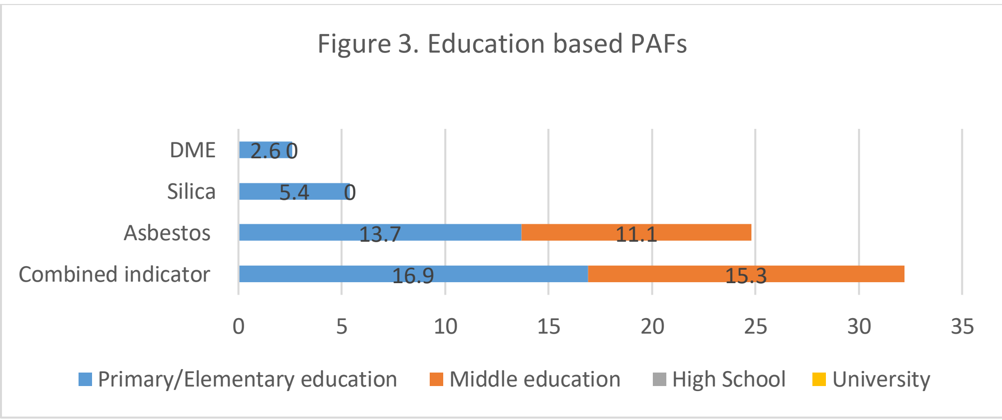

Figure 3: Contribution of each education-based SEP group to the overall burden of lung cancer related to the 3 occupational exposures. Sensitive binary indicators of exposure and mutual adjustment (results taken from Table 7)

None of the results significantly changed when using PUNAF procedure (Newson, 2013) as an alternative for aflogit (data not shown).

5.Discussion:

5.1. Summary of main findings

Our main aim was to apply the attributable risk approach to compare the burden of work-related lung cancer between different socio-economic groups. We re-analysed a population-based case-control study and chose three known carcinogens found in the workplace (asbestos, silica and DME) which are specifically relevant to men (Marant Micallef et al., 2018).

We investigated different sources of variations in the estimates.

First, using different exposure metrics yielded different results. While binary sensitive indicators and quartiles based on CEI usually showed consistent results, the specific indicators (P>30% for asbestos, and P>25%) resulted, as expected, in lower PAF estimations for asbestos, which dropped from 27.7% CI (20.4-34.3) to 15.2% CI (10.0-20.2).

For Silica using the specific indicator conversely did not change much the overall PAF (e.g. 12.6% CI (8.3-16) compared to 11.7% CI (7.6-15.6)).

The PAF for DME was usually much lower (around 4.9%) and could not be derived after mutual adjustment as ORs were insignificant.

Finally, the total PAF for the three categories of the combined indicator of occupational exposures was 32.7% CI (24.6-39.9) and still 31.4% after mutual adjustment, suggesting that one third of lung cancer cases could have been avoided in men if those three exposures had been eliminated from workplaces.

The second source of variation studied was the choice of the socio-economic comparison group and what it brings to estimate the burden of work-related lung cancer according to SEP.

Our first strategy used stratification on the current occupation. Most of the results for the different CSP groups were insignificant, except for intermediate occupations that showed many significant results.

The 2nd strategy in this step was based on comparing different exposed CSP groups to the group of non-exposed managers/professional defined by longest held CSP. The highest PAFs were found for exposed blue-collar workers compared to non-exposed managers/professionals, reaching 28.6% CI (22.9-33.9) for the combined indicator of occupational exposures. Other CSP groups either contributed marginally or not at all. Results were also consistent while using the third strategy comparing each exposed CSP group to non-exposed subjects regardless their CSP. The PAF across combined carcinogens summed up to 26.9% CI (21.9-31.7) for blue collar workers. This means that occupational exposures and their population health impact actually concentrate among BCW, a long-known reality that to our knowledge had never been quantified through a PAF approach. This conclusion was not changed much when using another indicator based on education, where PAFs concentrated among the primary/elementary education and middle education groups.

5.2. Comparison of findings with those reported in the literature

In our 1st step of the overall estimation, PAFs for asbestos, silica and DME were higher than in the latest published study by Iarc (as PAFs for asbestos and silica among men were 9.3% and 1.5% respectively)(Marant Micallef et al., 2019a)However they used a different approach (e.g. the Levin formula) and sources of data(Marant Micallef et al., 2018). Our estimates were conversely comparable with others based on case-control studies, although our results were a bit lower than those published by (Wild et al., 2012), (e.g. PAFs for asbestos, silica and DME were 31%,17% and 14% respectively). However, their analysis was based on one geographical area (North Lorraine, France), which has a high industrial footprint. And our estimations were higher than those published by (De Matteis et al., 2012), which were based on a case-control study conducted in Italy covering around 80% of the population (PAFs for asbestos and silica were 18.1% and 7.0% respectively, with non-significant results for DME). As expected, using the specific binary indicator gave different results than the sensitive binary one, however the sensitive indicator was more consistent with the quartiles-based indicator, which can be a better estimation for dose-response effect. Therefore, we kept the sensitive indicators in building the combined indicator. DME had the lowest estimated PAF, and after mutual adjustment the results were insignificant. Finally, all the estimates for asbestos were higher than those for silica and DME, which is consistent with previous studies pointing asbestos as the main occupational exposure contributing to lung cancer, followed by silica.

Our results for the second step may not be directly compared to other studies due to the combination between occupational exposures and SEP, a combination that to our knowledge had never been explored in that way. However it may come as a complement to previous studies which tried to assess the burden of occupational exposures in general (Marant Micallef et al., 2019b, 2018), and the burden related to health inequalities separately (Toch-Marquardt et al., 2014b) in an attempt to combine these too approaches together.

The 1st strategy (e.g. stratification) comparing cases and controls within the same SEP group might not be the best tool to estimate the burden of occupational exposures by SEP as it can bias the results towards null, or yield insignificant result due to the already well described problem of over-exposed control groups,(table 6,Annex) (Wynder and Stellman, 1992). Occupational exposures indeed concentrate among blue-collar workers. Also using the current or last job may not be the most accurate occupation-based SEP indicator, due to the heterogeneity within these groups. The significant results found in the current intermediate occupations group based on stratification may well be due to such heterogeneity. Indeed, among the 959 subjects in this group, 488 of them had their first occupation as blue-collar workers. This may mean they have been exposed early in their career, before moving to another occupational group. Moreover, it has been shown that subjects having the same CEI for asbestos may experience different risks based on the timing of exposure: someone who had a higher intensity of exposure in earlier years in working life may be exposed to higher risk of lung cancer than those who had lower intensity (or no exposure) in these early years, in other words higher intensity but later in life (Lévêque et al., 2018).

In order to overcome this problem of heterogeneity and over-exposed controls, it would hence be interesting to try an alternative approach of stratification based on basic (Levin-like) formula that combine prevalence of exposures (based on national surveys) and RR taken from meta-analysis (Poole, 2015). This approach was yet beyond the scope of the present study.

The 2nd and 3rd strategies further attempted to integrate SEP in the calculations. They differ slightly based on the comparison (reference) group which in one case is the lower-risk group (non-exposed managers/professionals) and in the other is the whole non-exposed group (irrespective of SEP). For these comparisons we chose the occupation of the longest duration among the sum of all durations of occupations throughout the whole work history, which can be more consistent with the CEI for occupational exposures and can give a more informative result for the dominant SEP in the person's history. In both approaches, the population impact concentrates among the blue-collar workers group, which clearly shows that the burden of work-related lung cancer usually assessed at the general population level lies within this group.

Using education as an alternative SEP indicator consistently indicated the concentration of the excess risk related to occupational exposures among the lower education groups as primary/elementary and middle education groups. However, we assume that the occupation-based strategy is more accurate, due to the change of education system over time, and due to the fact that most of blue-collar workers lie within these two groups. Also, education won't allow us to estimate the burden of work-related cancer related to certain occupations, which is essential in more detailed analysis for certain occupations and exposures especially those related to women.

5.3. Strengths

This is the first study to our knowledge attempting to assess how PAFs for occupational exposures distribute between different socio-economic groups.

Calculating PAFs based on case-control studies became more frequent in the past two decades. It allows to have more accurate estimates than the classic Levin-formula (and derived formulas) based approaches.(Coughlin et al., 1994). Using the unconditional logistic regression for calculating PAFs actually allowed us to adjust for potential confounders (in particular smoking) and for other occupational exposures as well, with an exposure definition consistent between prevalence of exposure and relative risk measure (here ORs).

Moreover, the French ICARE case-control study is one of the largest population based-case control studies on lung cancer that assessed several occupational exposures, and already proved its validity (Guida et al., 2011; Luce et al., 2011) .The detailed questionnaires for the occupational history, smoking, and socio-demographic information, allowed us to have accurate estimates for the prevalence of different exposures between different groups, and not to use different estimates from different sources which might not be consistent with each other even after harmonization.

The lifelong occupational exposure assessment with adjustment on a precise indicator of smoking history (CSI), allowed us to investigate the variation in estimation based on the different occupational exposure indicators (binary, sensitive, specific, quartiles, combined exposures) while adjusting accurately on smoking. Also having CEI indicators, which was categorized later into quartiles, allowed us to observe some dose-response effect.

Our analysis was not restricted only to education or occupation but included both which allowed us to observe the difference between choosing different SEP indicators.

5.4. Limitations

We conducted our analysis for only three known lung cancer carcinogens (asbestos, silica and DME), which can affect the risk estimates for lung cancer related to occupational exposures in general. However previous studies have shown that asbestos is the leading occupational exposure contributing to lung cancer, and silica dust is also an important contributor. Our estimate of DME was quite rough and based on self-report, which may explain the inconsistency of some results after mutual adjustment.

Those exposures, while not covering all the main carcinogens encountered by men in the workplace other the last decades in high income countries, are obviously not the most relevant for women. This gender bias in the choice (and availability) of relevant exposures did not allow us to show any results related to women. As women can be affected by different occupational exposures in other settings (Atramont et al., 2016), e.g. chlorinated solvents (Barul et al., 2017), It would be very valuable to perform a distinct study where main exposures, exposures assessment methods and their metrics have been chosen gender sensitive. We also obviously lacked power when working on subgroups based on SEP, and typically in women where in some exposure categories the number of subjects was less than 5, or equal to 0 in many occasions.

Interactions between occupational exposures and smoking were not taken into account as it would have made the interpretation in terms of AF too complex. However previous studies suggested an interaction lying between additive and multiplicative for asbestos (Gustavsson et al., 2002) and possibly multiplicative for silica (De Matteis et al., 2012) although this is still debated (El Zoghbi et al., 2017) that could modify the results among sub-groups of SEP which are co-exposed.

Finally, the use of JEMs and of self-report to assess lifetime occupational exposures may have led to potential non-differential misclassification and a probable bias towards the null. Some papers suggested that lifelong task-based questionnaire (TBQ)(Bourgkard et al., 2013), and case-by-case expert assessment (Ge et al., 2018), shall be considered as better assessment methods.

6. Implications for public health research

As stated previously, to our knowledge, this is the 1st study to compare the burden of work-related lung cancer between different socio-economic groups.

As most studies aimed to quantify the PAF related to occupational exposures among the whole population, or quantify the health disparities related to socio-economic position, we believe that our simple method integrating both measurements could allow to better estimate the real health burden of these exposures, among the populations where they are mostly concentrated.

This study may also draw more attention for the need to assess the variation of estimation by using different SEP indicators, for instance when discussing compensation issues. For instance, based on the previous study by Lévêque (Lévêque et al., 2018), it becomes clear that a detailed job history should be considered in the assessment of occupational exposure effect, taking into account the time of exposure, which can be neglected when using ever/never indicator related to occupation or last job held.

Our results also highlight the need for assessment methods more specific to different SEP groups, especially among women and lower SEP groups (Bertin et al., 2018; Counil and Henry, 2019), and that more attention should be given to the social determinants of health especially those occupation-based that are often overlooked when addressing health inequalities (Clougherty et al., 2010b).

7.References

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8.Annex:

Table 1 Simple and further adjusted estimations of ORs for Men& Women based on different exposure metrics

	Men						Women					
	Core model[1]			Adjusted[2]			Core model[1]			Adjusted[2]		
	OR	*P*	95% CI	OR	*P*	95% CI	OR	*P*	95% CI	OR	*P*	95% CI
Asbestos												
Ever/Never (se)	1.6	$<10^{-3}$	1.4-1.9	1.5	$<10^{-3}$	1.3-1.7	0.9	0.7	0.7-1.3	1.0	0.8	0.7-1.3
Ever/Never (sp)	1.5	$<10^{-3}$	1.3-1.7	1.3	0.001	1.1-1.5	1.5	0.2	0.9-2.5	1.5	0.1	0.9-2.6
Quartiles												
Q1	1.4	0.002	1.1-1.8	1.4	0.008	1.1-1.7	0.6	0.1	0.3-1.1	0.6	0.1	0.3-1.2
Q2	1.5	0.001	1.2-1.8	1.4	0.003	1.1-1.8	0.7	0.4	0.4-1.5	0.8	0.5	0.4-1.6
Q3	1.7	$<10^{-3}$	1.3-2.0	1.5	$<10^{-3}$	1.2-1.9	1.2	0.6	0.7-1.9	1.2	0.5	0.7-2.0
Q4	1.9	$<10^{-3}$	1.6-2.4	1.6	$<10^{-3}$	1.3-2.1	1.2	0.6	0.7-2.0	1.2	0.5	0.7-2.0
Silica												
Ever/Never (Se)	1.5	$<10^{-3}$	1.3-1.8	1.3	0.002	1.1-1.5	1.5	0.6	0.4-6.0	1.6	0.5	0.4-6.3
Ever/Never (Sp)	1.6	$<10^{-3}$	1.3-1.8	1.4	0.001	1.1-1.6	1.6	0.6	0.3-8.7	1.5	0.6	0.3-8.7
Quartiles												
Q1	1.0	0.9	0.7-1.3	0.8	0.2	0.6-1.1	0.6	0.1	0.3-1.1	0.6	0.1	0.3-1.9
Q2	1.3	0.04	1.0-1.8	1.1	0.6	0.8-1.5	0.7	0.4	0.4-1.5	0.8	0.5	0.4-1.6
Q3	1.8	$<10^{-3}$	1.4-2.4	1.5	0.008	1.1-1.9	1.2	0.6	0.7-2.0	1.2	0.5	0.7-2.0
Q4	1.9	$<10^{-3}$	1.5-2.5	1.5	0.003	1.2-2.0	1.2	0.6	0.7-2.0	1.2	0.5	0.7-2.0
DME												
Ever/Never (self-report)	1.2	0.02	1.0-1.4	1.1	0.3	0.9-1.3	1.1	0.8	0.7-1.7	1.0	0.9	0.7-1.6
Combined indicator of occupational exposures												
One carcinogen	1.5	$<10^{-3}$	1.3-1.8	-	-	-	1.1	0.7	0.8-1.4	-	-	-
Two carcinogens	1.9	$<10^{-3}$	1.6-2.3	-	-	-	0.8	0.6	0.3-1.8	-	-	-
Three carcinogens	2.1	$<10^{-3}$	1.6-2.7	-	-	-	-	-	-	-	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Table 2 Simple and further adjusted estimations of ORs for Men based on stratification on the current occupation

	Self-employed						Intermediate occupations						Blue collar workers					
	Core model[1]			Adjusted[2]			Core model[1]			Adjusted[2]			Core model[1]			Adjusted[2]		
	OR	*P*	95% CI	OR	*P*	95% CI	OR	*P*	95 % CI	OR	*P*	95% CI	OR	*P*	95% CI	OR	*P*	95% CI
Asbestos																		
Ever/Never (se)	1.5	0.1	0.9-2.7	1.5	0.2	0.8-2.8	1.8	0.001	1.3-2.6	1.7	0.004	1.2-2.5	1.2	0.2	0.9-1.6	1.1	0.5	0.8-1.5
Ever/Never (sp)	1.6	0.1	1.0-2.8	1.5	0.2	0.8-2.8	1.3	0.1	0.9-1.8	1.1	0.7	0.7-1.6	1.1	0.2	0.9-1.5	1.1	0.3	0.9-1.5
Quartiles																		
Q1	1.2	0.7	0.5-3.0	1.1	0.8	0.4-2.9	2.1	0.006	1.2-3.5	2.1	0.01	1.2-3.5	1.3	0.3	0.8-1.9	1.2	0.4	0.8-1.8
Q2	1.8	0.2	0.8-4.2	1.8	0.2	0.7-4.4	2.1	0.003	1.3-3.5	2.1	0.005	1.2-3.4	1.0	0.9	0.7-1.5	1.0	0.9	0.7-1.4
Q3	0.6	0.4	0.3-1.6	0.6	0.3	0.2-1.6	1.9	0.1	1.2-3.1	1.6	0.07	1.0-2.7	1.2	0.4	0.8-1.6	1.1	0.6	0.8-1.6
Q4	2.9	0.004	1.4-5.8	2.6	0.03	1.1-6.3	1.4	0.2	0.9-2.2	1.0	1.0	0.6-1.8	1.4	0.1	1.0-1.9	1.2	0.2	0.8-1.8
Silica																		
Ever/Never (Se)	1.5	0.2	0.8-2.7	1.2	0.5	0.6-2.4	1.5	0.02	1.1-2.2	1.2	0.4	0.8-1.8	1.3	0.03	1.0-1.6	1.3	0.05	1.0-1.6
Ever/Never (Sp)	1.6	0.1	0.9-3.0	1.3	0.4	0.7-2.5	1.6	0.01	1.1-2.3	1.5	0.04	1.0-2.3	1.2	0.1	1.0-1.5	1.2	0.2	0.9-1.5
Quartiles																		
Q1	0.7	0.5	0.2-2.0	0.5	0.3	0.2-1.6	1.7	0.1	0.8-3.5	1.5	0.3	0.7-3.3	0.9	0.8	0.6-1.5	0.9	0.7	0.6-1.4
Q2	1.3	9.7	0.4-4.3	1.0	1.0	0.3-3.7	1.3	0.4	0.7-2.3	1.2	0.5	0.7-2.3	1.2	0.4	0.8-1.7	1.1	0.6	0.7-1.7
Q3	1.5	0.5	0.5-4.2	0.9	0.9	0.3-3.0	1.6	0.1	0.9-2.8	1.6	0.2	0.8-3.0	1.6	0.02	1.1-2.2	1.5	0.05	1.0-2.1
Q4	2.9	0.02	1.1-7.2	1.7	0.4	0.6-4.8	1.6	0.2	0.8-3.6	1.8	0.2	0.8-4.1	1.3	0.08	1.0-1.8	1.3	0.2	0.9-1.8
DME																		
Ever/Never (self-report)	0.9	0.8	0.5-1.7	0.8	0.5	0.4-1.5	1.3	0.2	0.9-1.9	1.1	0.7	0.7-1.7	1.0	1.0	0.8-1.3	1.0	0.9	0.8-1.2
One carcinogen	1.4	0.3	0.7-2.7				1.7	0.01	1.1-2.6				1.1	0.6	0.8-1.6			
Two carcinogens	1.6	0.1	0.9-3.1				1.9	0.006	1.2-2.9				1.3	0.1	0.9-2.0			
Three carcinogens	1.4	0.5	0.5-4.2				2.5	0.003	1.4-4.6				1.3	0.2	0.9-2.1			

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Table 3 Simple and further adjusted estimations of ORs for Men based on the comparison of exposed CSP groups with non-exposed managers/professional (longest held occupation)

	Clerical/Sales/Service workers						Blue collar workers					
	Core model[1]			Adjusted[2]			Core model[1]			Adjusted[2]		
	OR	***P***	**95% CI**	**OR**	***P*`**	**95% CI**	**OR**	***P***	**95% CI**	**OR**	***P***	**95% CI**
Asbestos												
Ever/Never (se)	2.2	$<10^{-3}$	1.5-3.4	2.1	$<10^{-3}$	1.4-3.2	2.6	$<10^{-3}$	2.0-3.3	2.4	$<10^{-3}$	1.8-3.1
Ever/Never (Sp)	1.9	$<10^{-3}$	1.1-3.2	1.7	$<10^{-3}$	1.0-2.9	2.6	$<10^{-3}$	2.0-3.3	2.3	$<10^{-3}$	1.8-3.0
Never-Exposed managers	Ref			Ref			Ref			Ref		
Quartiles												
Q1	2.2	0.02	1.2-3.8	2.1	0.02	1.1-3.8	2.7	$<10^{-3}$	1.8-3.9	2.4	$<10^{-3}$	1.6-3.6
Q2	3.1	0.01	1.4-7.1	3.2	0.01	1.4-7.1	2.0	$<10^{-3}$	1.4-2.8	1.8	$<10^{-3}$	1.3-2.6
Q3	2.4	0.2	1.2-4.8	2.1	0.05	1.0-4.3	2.6	$<10^{-3}$	1.9-3.5	2.3	$<10^{-3}$	1.7-3.2
Q4	1.5	0.4	0.6-3.5	1.2	0.7	0.5-2.9	2.9	$<10^{-3}$	2.1-3.9	2.4	$<10^{-3}$	1.8-3.4
Silica												
Ever/Never (se)	2.0	0.02	1.1-3.6	1.7	0.1	1.0-3.2	2.6	$<10^{-3}$	2.0-3.4	2.3	$<10^{-3}$	1.7-3.0
Ever/Never (sp)	2.0	0.02	1.1-3.7	1.9	0.04	1.0-3.5	2.7	$<10^{-3}$	2.1-3.4	2.5	$<10^{-3}$	1.9-3.2
Quartiles												
Q1	1.4	0.5	0.5-4.2	1.2	0.8	0.4-3.5	1.8	0.01	1.2-2.8	1.4	0.2	0.9-2.2
Q2	1.7	0.4	0.6-4.9	1.3	0.6	0.4-3.8	2.2	$<10^{-3}$	1.5-3.2	1.7	0.01	1.1-2.6
Q3	4.0	0.01	1.5-11.0	3.1	0.03	1.1-8.5	3.1	$<10^{-3}$	2.2-4.5	2.4	$<10^{-3}$	1.6-3.5
Q4	0.8	0.7	0.2-3.3	0.6	0.5	0.1-2.5	3.0	$<10^{-3}$	2.1-4.2	2.3	$<10^{-3}$	1.6-3.3
DME												
Ever/ Never (self-report)	2.3	0.001	1.4-3.7	2.1	0.004	1.3-3.4	2.5	$<10^{-3}$	1.9-3.3	2.1	$<10^{-3}$	1.6-2.8
Combined indicator of occupational exposures												
One carcinogen	1.8	0.02	1.1-2.9	-	-	-	2.3	$<10^{-3}$	1.7-3.1	-	-	-
Two carcinogens	2.4	0.004	1.3-4.4	-	-	-	2.9	$<10^{-3}$	2.1-3.9	-	-	-
Three carcinogens	3.3	0.01	1.4-8.1	-	-	-	2.9	$<10^{-3}$	2.0-4.1	-	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Table 4: Contribution of each CSP group to the overall burden of lung cancer related to occupational exposures (Simple and further adjusted estimations of ORs for Men based on the comparison of exposed CSP groups with all non-exposed, irrespective of CSP (longest held occupation)

	Self -employed						**Clerical \Sales \ Service workers**						**Blue collar workers**					
	Core model[1]			**Adjusted[2]**			**Core model[1]**			**Adjusted[2]**			**Core model[1]**			**Adjusted[2]**		
	OR	***P***	**95%CI**	**OR**	***P***	**95%CI**	**OR**	***P***	**95%CI**	**OR**	***P***	**95%CI**	**OR**	**P**	**95%CI**	**OR**	**P**	**95%CI**
Asbestos																		
Ever/Never (se)	1.5	0.1	1.0-2.2	1.4	0.1	0.9-2.1	1.2	0.003	1.2-2.5	1.6	0.009	1.1-2.4	2.0	$<10^{-3}$	1.2-2.5	1.8	$<10^{-3}$	2.2
Ever/Never (Sp)	1.3	0.2	0.8-2.2	1.2	0.4	0.7-2.0	1.2	0.3	0.8-2.0	1.1	0.7	0.7-1.8	1.7	$<10^{-3}$	1.5-2.0	1.5	$<10^{-3}$	1.3-1.8
Never Exposed																		
Q1	1.2	0.8	0.6-3.9	1.1	0.9	0.4-2.8	1.6	0.1	0.9-2.9	1.6	0.1	0.9-2.9	2.1	$<10^{-3}$	1.5-2.9	1.9	$<10^{-3}$	1.3-2.6
Q2	2.0	0.1	0.9-4.7	2.0	0.1	0.8-4.7	2.4	0.03	1.1-5.4	2.5	0.02	1.1-5.4	1.5	0.002	1.2-2.0	1.4	0.01	1.1-1.9
Q3	0.4	0.05	0.2-1.0	0.4	0.03	0.1-0.9	1.8	0.1	0.9-3.6	1.6	0.17	0.8-3.2	2.0	$<10^{-3}$	1.6-2.6	1.8	$<10^{-3}$	1.4-2.3
Q4	2.7	0.00 3	1.4-5.1	2.2	0.02	1.2-4.3	1.2	0.7	0.5-2.7	0.9	0.9	0.4-2.2	2.2	$<10^{-3}$	1.8-2.8	1.9	$<10^{-3}$	1.5-2.4
Silica																		
Ever/Never (se)	1.7	0.09	0.9-3.1	1.4	0.2	0.8-2.7	1.4	0.2	0.8-2.5	1.2	0.5	0.7-2.1	1.8	$<10^{-3}$	1.5-2.2	1.6	$<10^{-3}$	1.3-1.9
Ever/Never(sp)	1.8	0.06	1.1-3.4	1.6	0.1	0.9-3.1	1.4	0.3	0.8-2.4	1.2	0.5	0.7-2.2	1.8	$<10^{-3}$	1.5-2.1	1.6	$<10^{-3}$	1.3-1.9
Quartiles																		
Q1	1.7	0.4	0.4-6.9	1.6	0.5	0.4-6.5	1.0	1.0	0.3-3.0	0.9	0.8	0.3-2.5	1.3	0.2	0.9-1.9	1.0	0.9	0.7-1.5
Q2	0.5	0.3	0.1-2.3	0.4	0.2	0.1-1.9	1.2	0.8	0.4-3.4	0.9	0.9	0.3-2.8	1.6	0.01	1.1-2.2	1.2	0.2	0.9-1.8
Q3	1.5	0.5	0.4-5.8	1.2	0.8	0.3-4.4	2.9	0.04	1.0-7.7	2.2	0.1	0.8-6.1	2.2	$<10^{-3}$	1.6-3.0	1.7	0.001	1.2-2.4
Q4	2.6	0.03	1.1-6.4	2.0	0.1	0.8-5.0	0.5	0.4	0.1-2.3	0.4	0.2	0.1-1.8	2.1	$<10^{-3}$	1.6-2.8	1.7	0.001	1.2-2.3
DME																		
Ever/Never	0.8	0.5	0.4-1.5	0.7	0.4	0.4-1.4	1.3	0.2	0.8-2.1	1.3	0.2	0.8-2.1	1.5	$<10^{-3}$	1.2-1.8	1.3	0.03	1.0-1.5
Combined indicator of occupational carcinogens																		
One carcinogen	1.3	0.4	0.7-2.3	-	-	-	1.4	0.1	0.9-2.2	-	-	-	1.8	$<10^{-3}$	1.5-2.3	-	-	-
Two carcinogens	1.7	0.04	1.0-2.9	-	-	-	1.9	0.02	1.1-3.4	-	-	-	2.3	$<10^{-3}$	1.9-2.9	-	-	-
Three carcinogens	1.5	0.6	0.3-7.3	-	-	-	2.7	0.03	1.1-6.3	-	-	-	2.3	$<10^{-3}$	1.7-2.1	-	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Table 5 Contribution of each education group to the overall burden of lung cancer related to occupational exposures (Simple and further adjusted estimations of ORs for Men based on the comparison of exposed education groups with all non-exposed, irrespective of education)

	Primary/Elementary education						Middle education					
	Core model[1]			Adjusted[2]			Core model[1]			Adjusted[2]		
	OR	***P***	**95%CI**	**OR**	***P***	**95%CI**	**OR**	***P***	**95%CI**	**OR**	***P***	**95%CI**
Asbestos												
Ever/Never (se)	2.3	$<10^{-3}$	1.8-2.8	2.1	$<10^{-3}$	1.6-2.6	1.6	$<10^{-3}$	1.4-1.9	1.5	$<10^{-3}$	1.2-1.8
Ever/Never (Sp)	2.1	$<10^{-3}$	1.6-2.6	1.8	$<10^{-3}$	1.4-2.3	1.4	$<10^{-3}$	1.2-1.7	1.3	0.03	1.0-1.5
Never Exposed	Ref.			Ref.			Ref.			Ref.		
Q1	2.0	$<10^{-3}$	1.4-2.8	1.9	0.001	1.3-2.7	1.4	0.1	1.0-1.9	1.3	0.2	0.9-1.9
Q2	2.4	$<10^{-3}$	1.6-3.5	2.2	$<10^{-3}$	1.5-3.3	1.5	0.008	1.1-2.0	1.4	0.02	1.0-1.9
Q3	2.2	$<10^{-3}$	1.6-3.1	1.9	$<10^{-3}$	1.4-2.7	1.7	$<10^{-3}$	1.3-2.2	1.5	0.005	1.1-2.0
Q4	2.6	$<10^{-3}$	1.8-3.6	2.1	$<10^{-3}$	1.5-3.1	1.8	$<10^{-3}$	1.4-2.3	1.5	0.002	1.1-2.0
Silica												
Ever/Never (se)	2.0	$<10^{-3}$	1.5-2.6	1.6	$<10^{-3}$	1.3-2.1	1.5	$<10^{-3}$	1.2-1.8	1.2	0.1	1.0-1.5
Ever/Never (sp)	1.9	$<10^{-3}$	1.5-2.5	1.7	$<10^{-3}$	1.3-2.2	1.4	0.001	-1.1-1.8	1.2	0.1	1.0-1.5
Quartiles												
Q1	1.5	0.30	7-3.1	1.2	0.6	0.6-2.6	1.2	0.4	0.8-1.9	1.0	0.9	0.6-1.5
Q2	2.4	0.002	1.4-4.1	1.9	0.02	1.1-3.3	1.0	1.0	0.7-1.5	0.8	0.3	0.5-1.2
Q3	2.1	0.001	1.3-3.3	1.7	0.03	1.0-2.6	1.7	0.004	1.2-2.5	1.4	0.1	9.9-2.0
Q4	1.9	0.002	1.3-2.8	1.5	0.05	1.0-2.3	2.0	0.001	1.3-2.9	1.5	0.03	1.0-2.3
DME												
Ever/Never (Self- reported)	1.5	0.003	1.1-2.0	1.3	0.04	1.0-1.7	1.3	0.01	1.0-1.6	1.1	0.2	0.9-1.4
Combined Indicator of occupational carcinogens												
One carcinogen	2.2	0.1	1.02.0	-	-	-	1.5	$<10^{-3}$	1.2-2.0	-	-	-
Two carcinogens	2.7	$<10^{-3}$	1.7-2.9	-	-	-	1.7	$<10^{-3}$	1.4-2.2	-	-	-
Three carcinogens	2.2	$<10^{-3}$	1.5-3.4	-	-	-	2.3	$<10^{-3}$	1.6-3.2	-	-	-

n.a.: not applicable, p-value<0.05

1 adjusted for age quintiles, CSI, and departments

2 same as core model, and further adjustment for the other occupational exposures

Table 6 Distribution of exposures among cases and controls within men group, according to bases on the current occupation, longest and first occupation held.

	Current occupation				Longest held occupation				First Held occupation			
	Controls		Cases		Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%	N	%	N	%
Asbestos												
Never, CEI =0	162	18.1	166	14.4	180	17.1	176	13.9	341	20.4	242	15.1
Ever (se)	734	81.9	990	85.6	873	82.9	1091	86.1	1331	79.6	1364	84.9%
Missing	0	0	0	0	0	0	0	0	0	0	0	0
P-Value	*0.02*				*0.03*				*$<10^{-3}$*			
Never (sp) ***P ≤ 30 %***	403	45.0	435	37.6	451	42.8	465	36.7	820	49.0	641	39.9
Ever (sp) **P>30 %**	493	55.0	721	62.4	602	57.2	802	63.3	852	51.0	965	60.1
Missing	0	0.0	0	0	0.0	0		0.0	0	0.00	0	0.00
P-value	*0.001*				*0.003*				*$<10^{-3}$*			
Quartiles												
Never	162	18.1	166	14.4	180	17.1	176	13.9	341	20.4	242	15.1
Q1	109	12.2	138	11.9	120	11.4	145	11.4	274	16.4	216	13.4
Q2	181	20.2	176	15.2	225	21.4	190	15.0	333	19.9	258	16.1
Q3	211	23.5	270	23.4	247	23.4	310	24.5	359	21.5	376	23.4
Q4	233	26.0	402	34.8	281	26.7	446	35.2	365	21.8	511	31.8
Missing	0	0.0	4	0.3	0	0.0	0	0.0	0	0.0	3	0.2
P-value	*$<10^{-3}$*					*$<10^{-3}$*			*$<10^{-3}$*			
Silica												
Never, CEI=0	551	61.5	602	52.1	647	61.4	665	52.5	1126	67.3	903	56.2
Ever (se)	342	38.2	545	47.1	402	38.2	593	46.8	541	32.4	693	43.2
Missing	3	0.3	9	0.8	4	0.4	9	0.7	5	0.3	10	0.6
P-value	*$<10^{-3}$*				*$<10^{-3}$*				*$<10^{-3}$*			
Never ***P*** **≤ 25 %**	576	64.3	643	55.6	673	63.9	710	56.0	1166	69.7	953	59.3
Ever ***P*** **>25 %**	317	35.4	504	43.6	376	35.7	548	43.3	501	30.0	643	40.0
Missing	3	0.3	9	0.8	4	0.4	9	0.7	5	0.3	10	0.6
P-value		*$<10^{-3}$*			*$<10^{-3}$*				*$<10^{-3}$*			
Quartiles												
Never	551	61.5	602	52.1	647	61.4	665	52.5	1126	67.3	903	56.2
Q1	69	7.7	62	5.4	81	7.7	67	5.3	112	6.7	85	5.3
Q2	83	9.3	112	9.7	103	9.8	126	9.9	139	8.3	143	8.9
Q3	77	8.6	160	13.8	94	8.9	173	13.6	140	8.4	214	13.3
Q4	113	12.6	207	17.9	124	11.8	225	17.8	150	9.0	248	15.5
Missing	3	0.3	13	1.1	4	0.4	11	0.9	5	0.3	13	0.8
p-value	*$<10^{-3}$*				*$<10^{-3}$*					*$<10^{-3}$*		
DME (Self-reported)												
Never	586	65.4	766	66.3	684	65.0	833	65.8	1124	67.2	1090	67.9
Ever	310	34.6	390	33.7	369	35.0	434	34.2	548	32.8	516	23.1
P-value		0.7			0.7					0.7		
Combined Indicator of occupational exposures												
Never exposed	115	12.8	111	9.6	128	12.1	115	9.1	253	15.1	168	10.5
One carcinogen	307	34.3	345	29.8	359	34.1	384	30.3	615	36.8	524	32.6
Two carcinogens	336	37.5	502	43.4	404	38.4	552	43.6	597	35.7	673	41.9
Three carcinogens	135	15.1	189	16.4	158	15.0	207	16.3	202	12.1	231	14.4
Missing	3	0.3	9	0.8	4	0.4	9	0.7	5	0.3	10	0.6
P-value	*0.006*				0.01				*$<10^{-3}$*			