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ORIGINAL ARTICLE

Age at occupational exposure to combustion products and lung cancer risk among men in Stockholm, Sweden

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Abstract
Purpose Occupational exposure to combustion products rich in polycyclic aromatic hydrocarbons and particles is associated with an increased risk of lung cancer. This study aimed to evaluate whether the risk depended on the age at which the individuals were exposed.
Methods Data from 1042 lung cancer cases and 2364 frequency-matched population controls selected from all men aged 40–75 years residing in Stockholm County, Sweden, at any time between 1985 and 1990, included detailed questionnaire information on occupational, residential, and smoking history. Occupational exposures were assessed by an occupational hygienist, and exposure to air pollution from road traffic was estimated based on dispersion models.
Results We found that individuals exposed to combustion products in their twenties were at higher risk than those never exposed (adjusted OR = 1.46; 95 % CI 1.02, 2.10). The association was still evident after adjusting for a number of potential confounders, including lifetime cumulative exposure and latency. No clear association was found in those exposed at older ages.
Conclusions Exposure to combustion products at a young age was associated with elevated risk of lung cancer. Exposure-reduction programs should be aware of the susceptibility of the younger employees.

Keywords Cancer risk · Combustion products · Polycyclic aromatic hydrocarbons · Age at exposure

Abbreviations

CI	Confidence interval
n	Count
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
μg	Micrograms

Introduction

High and long-term occupational exposure to combustion products rich in polycyclic aromatic hydrocarbons (PAH) and particles is associated with a substantially increased lung cancer risk (International Agency for Research on Cancer 2012; Boffetta et al. 1997). Around 980,000 workers in the European Union were estimated to be exposed to PAH (Kauppinen et al. 2000). Despite the large numbers of exposed workers, to what extent age at exposure determines risk is yet largely unknown. Starting smoking at a young age is known to be associated with a higher risk of lung cancer, after adjusting for total tobacco dose (Hegmann et al. 1993; Papadopoulos et al. 2011). Starting smoking early also leads to increased formation of DNA adducts more likely than starting later in life (Wiencke et al. 1999). However, an early start is often associated with a longer duration, and it is generally difficult to disentangle the effect of these two determinants.

The aim of the present work was to investigate the influence of age at exposure in a large dataset from a

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population-based case–control study of lung cancer with access to lifetime occupational and smoking histories in addition to other determinants of lung cancer risk. Such information is important as it can inform decision-making processes in better tailoring preventive programs and policies for exposed workers. Previous findings from the same study group have shown a consistent association between occupational exposure to combustion products and lung cancer risk, while adjusting for smoking habits, environmental air pollution, and residential radon (Gustavsson et al. 2000).

Materials and methods

Study base

The methods utilized for data collection and exposure assessment were described in detail earlier (Gustavsson et al. 2000; Nyberg et al. 2000; Bellander et al. 2001) and are briefly summarized here. The study population comprised all men aged 40–75 years who were residents of Stockholm County, Sweden, at any time between 1985 and 1990. All cases of lung cancer diagnosed from January 1, 1985, to December 31, 1990, were identified from the regional cancer register of Stockholm County. Controls were randomly selected from a national official register of the Swedish population among male Stockholm residents and frequency-matched to the cases with regard to age in 5-year groups and year of inclusion in the study (1985–1990). Two control groups were included. The first group, "population controls," was selected with no restrictions among men who were alive at the end of each inclusion year. The second group of controls, "mortality-matched controls," was frequency-matched to the cases with regard to vital status as of December 31, 1990. The deceased controls were selected among people who had not died from causes related to tobacco smoking. The following diagnoses were excluded from the referents: cancers of the upper gastrointestinal organs, liver and biliary passages, pancreas, respiratory organs, and urinary bladder, as well as ischemic heart disease, aortic aneurysm, bronchitis and emphysema, peptic ulcer, cirrhosis of the liver, or external causes.

A postal questionnaire was sent to the study subjects, or to the next of kin for deceased subjects. The questionnaires were supplemented by telephone interview if answers were incomplete. The response rate was high for both cases (87 %; $n = 1042$) and controls (85 %; $n = 2364$). The questionnaire gathered information on lifetime occupational history, residential history since 1950, and lifetime smoking history. The occupational history included company name and location, occupation title, and work tasks for each work period of at least 1 year during the subject's lifetime. The intensity and probability of exposure to combustion products were assessed case by case for every work period by an occupational hygienist blinded to the case/control status of the individuals. The assessments were based on published and unpublished reports of exposure levels specific for occupational work task, time period if available, and on personal contacts and experience (Gustavsson et al. 2000). Time period-specific annual arithmetic average exposure levels of benzo(α)pyrene (BaP) were classified on a four-level quantitative scale. Benzo(α)pyrene (BaP) was used as an indicator of exposure to combustion products from organic material such as wood, coke, oil, and coal, not including motor exhaust. Examples of high-exposed occupations were chimney sweeps, firefighters, foundry workers, and flame cutters. Cumulative exposure, expressed as μg-years of BaP, was calculated as the product of the intensity, the probability, and the duration of the exposure, within each decade of life (21–30, 31–40, 41–50, and 51–60 years) and cumulatively over the lifetime in the person's occupational history. For example, a worker that was not exposed in a specific decade would be assigned zero cumulative exposure in that decade.

Smoking habits were coded into indicator variables for former smoking (≥2 years since quitting) and current smoking of 1–10, 11–20, and >20 cigarettes/day or the corresponding amount of tobacco. In addition, we considered time since smoking cessation and intensity of smoking within classes of intensity among current smokers.

Radon exposure for each residence was estimated from geographic data on ground radon and data on building material and house types. Historic environmental levels of nitrogen dioxide at each residence were estimated based on emission databases and dispersion models and used as an indicator of non-occupational exposure to air pollutants from road traffic (Bellander et al. 2001).

The study was approved by the Ethics Committee of the Karolinska Institutet.

Statistical analysis

We explored the effects of cumulative exposure over lifetime and cumulative exposure within age decades 21–30, 31–40, 41–50, and 51–60 years. We utilized two main statistical approaches: (1) logistic regression and (2) quantile regression.

With the first approach, we estimated odds ratios of lung cancer for exposed versus non-exposed individuals, while with the second approach, we estimated differences at the 90th, 95th, and 98th percentiles of exposure to combustion products between cases and controls. We estimated crude and adjusted odds ratios and percentile differences. The adjustment was made for known potential confounders that are listed in the footnotes of the tables. We included the

Table 1 Prevalence of risk factors in cases and controls

	Controls $n = 2364$	Cases $n = 1042$	P value[a]
Radon exposure above median (%)	50.25	49.42	0.655
Environmental air pollution >90th percentile (%)	9.35	11.52	0.052
Smoking habits, average consumption			0.001
Never smokers (%)	29.82	3.45	
Ex-smokers (%)	35.70	26.20	
1–10 cigarettes/day (%)	13.24	13.72	
11–20 cigarettes/day (%)	15.36	33.40	
21+ cigarettes/day (%)	5.88	23.22	

[a] Chi-square test

Table 2 Proportion of exposed, mean, 95th percentile, and standard deviation of exposure to combustion products (μg-years of BaP) over lifetime and by age decades at exposure

	Controls				Cases			
	Exposed (%)	Mean	95th percentile	Standard deviation	Exposed (%)	Mean	95th percentile	Standard deviation
Lifetime exposure	16	3.73	14.81	17.70	21	6.51	46.75	24.79
Exposure in age decades								
Age 21–30 year	12	0.99	2.55	5.34	16	1.52	11.87	6.34
Age 31–40 year	12	0.98	2.55	5.09	16	1.76	11.90	7.43
Age 41–50 year	11	0.87	2.55	4.94	14	1.57	5.38	7.32
Age 51–60 year	8	0.61	1.50	4.14	12	1.06	2.55	5.90

matching variables, age, year of inclusion and their interaction, as covariates in all regression models by means of indicator variables. For comparison, we also applied conditional logistic regression for the first statistical approach and design-based bootstrap for the second (Jung 1996; Lipsitz et al. 1997). The results were congruent between the different types of analyses.

We also considered latency time, defined as elapsed time from first exposure to study entry. Among the 604 exposed individuals, 14 (2.3 %) had the first exposure less than 20 years before study entry and 4 (0.7 %) in less than 15 years. We repeated the analyses after excluding these individuals, and the results remained nearly unchanged. We also stratified the analysis based on latency above and below 30 years. The results did not differ substantially between latency strata. We also performed a sensitivity analysis by excluding one of the two referent groups in turn. The results were consistent with those obtained from the pooled referent group and are not shown. All analyses were performed with Stata version 13 (StataCorp, College Station, TX).

Results

Table 1 provides information on exposure to tobacco smoking, ambient air pollution, and radon in cases and controls. As expected, smoking habits differed markedly between cases and controls, and a similar tendency was also observed for air pollution. The Pearson's correlation coefficients between cumulative exposures to combustion products in different age decades varied between 0.35 and 0.86. The observed correlation was larger for consecutive decades and decreased as the time distance increased (results not shown in tables).

Table 2 shows the distribution of exposure to combustion products in cases and controls. The proportion of exposed individuals and the 95th percentile of exposure were higher in cases than in controls. For example, the 95th percentile of lifetime cumulative exposure to combustion products was nearly 32 μg of benzo(α)pyrene/m^3 larger (or more than three times larger) in cases than in controls. Differences between cases and controls were observed in all decades of life but were more conspicuous in younger age groups.

Table 3 reports the odds ratios of lung cancer for exposed versus non-exposed individuals in different age decades. Exposure at younger age seemed to be associated with lung cancer risk. The adjusted estimate for the odds ratio for exposure to combustion products in the twenties was 1.46 (95 % CI 1.02, 2.10). It appears that individuals who were exposed later on in life but not in their twenties did not show a significant increased risk. Table 4 shows the 95th percentile adjusted difference between cases and controls in cumulative lifetime exposure and by age decade. Exposure to combustion products was significantly

Table 3 Estimates and 95 % confidence intervals of the odds ratio for the risk of lung cancer for individuals exposed versus unexposed to combustion products, by age decades at exposure

	OR[a]	95 % CI		OR[b]	95 % CI	
Exposed at age 21–30 (yes vs. no)	1.36	0.99	1.87	1.46	1.02	2.10
Exposed at age 31–40 (yes vs. no)	0.82	0.50	1.35	0.83	0.48	1.43
Exposed at age 41–50 (yes vs. no)	1.22	0.70	2.12	1.00	0.54	1.84
Exposed at age 51–60 (yes vs. no)	1.16	0.73	1.82	1.14	0.69	1.89

[a] Adjusted for matching variables (age group and year of inclusion)

[b] Adjusted for matching variables (age group and year of inclusion), lifetime cumulative exposure to combustion products, exposure to radon, environmental air pollution, smoking habits, daily average tobacco consumption, time of smoking cessation

OR odds ratio, *CI* confidence interval

Table 4 Estimated 95th percentile difference of exposure to combustion products between cases and controls over lifetime and within each age decade at exposure

	95th percentile difference[a]	95 % CI		*P* value
Lifetime exposure	25.78	23.65	27.90	<0.001
Age group				
21–30	8.88	8.57	9.19	<0.001
31–40	7.73	7.32	8.15	<0.001
41–50	2.19	1.93	2.45	<0.001
51–60	0.68	0.56	0.80	<0.001

CI confidence interval

[a] Adjusted for matching variables (age group and year of inclusion), exposure to radon, environmental air pollution, smoking habits, daily average tobacco consumption, time of smoking cessation

larger in cases than in controls at all age decades. The estimated 95th percentile difference in lifetime exposure was 25.78 μg (95 % CI 23.65, 27.90). Differences were larger at younger age decades of exposure and nearly vanished for exposure after age 50. The differences at the 90th and the 98th percentiles showed a comparable trend over the age decades, with smaller differences at the 90th percentile and larger at the 98th (results are not shown in tables).

Discussion

The results from both logistic regression and quantile regression analyses consistently indicated a stronger effect of exposure to combustion products during the age period 20–29 years than during later decades in life. The analysis was adjusted for total lifetime cumulative dose of combustion products in addition to tobacco smoking, residential air pollution, and radon exposure. A separate analysis found no influence of latency on the results.

While the present study had the advantage of a large dataset with more than 1000 cases of lung cancer, the number of study subjects occupationally exposed to combustion product was limited.

Exposure misclassification is frequent in community-based studies relying on self-assessed occupational histories (Lewné et al. 2006, 2007, 2011; Blair et al. 2007). Biomonitoring represents a promising tool for capturing exposure to combustion products rich in PAH, through PAH metabolites as markers of internal dose and carcinogen-DNA adducts as measure of effective dose (Wolff et al. 1989; Talaska et al. 2014). However, it is unlikely that there should be strong differential misclassification between cases and controls with respect to decades in life. The exposure assessment was blinded to case–control status, and an extra group of mortality-matched controls was included to specifically evaluate the potential differential in the occupational and residential history between cases, whose history was mainly reported by next of kin, and controls, whose history was mainly self-reported. Nevertheless, the effect of recall bias on the results may not be entirely ruled out.

Our findings support the hypothesis that occupational exposure to combustion products, involving exposure to both PAH and particles, is associated with a higher risk of lung cancer if exposure occurs during the decade 20–29 years of life rather than later. This is in line with what has been found for tobacco smoking. A case–control study of 282 lung cancer cases and 3282 controls from Utah, USA, found a higher lung cancer risk among men starting smoking before age 19 than among those starting later, and a higher risk for women starting before age 25 than later (Hegmann et al. 1993). A population-based case–control study from France including 648 female lung cancer cases and 775 controls showed that women who started smoking before the age of 25 had a greater risk of lung cancer than women who started after the age of 25 (Papadopoulos et al. 2011). Our study was based on men only and gives no information on this topic among women.

A greater susceptibility for carcinogenesis following exposure at younger ages is also supported by studies of DNA adducts. Exposure to BaP leads to the formation of

BaP–DNA adducts, which may contribute to mutagenesis and subsequent carcinogenesis. Exposure to BaP led to a two- to eightfold increase in levels of BaP–DNA adducts in young animals when compared with older animals (Boerrigter et al. 1995). Increase in DNA adducts has also been observed in lung cancer patients that started smoking at a younger age compared with those that started later in life (Wiencke et al. 1999). The highest levels were found in smokers that started before the age of 15 years.

The present study has important strengths if compared to many other studies on occupational lung cancer, including a detailed occupational and residential history which permits controlling for relevant risk factors for lung cancer such as smoking and ambient air pollution exposure, the inclusion of only incident cases of lung cancer, and a high response rate.

The methodology for assessment of residential exposure to air pollution has been used in many other studies, which have shown excess risks for lung cancer, myocardial infarction and asthma related to traffic-generated pollution (Nyberg et al. 2000; Rosenlund et al. 2006; Nordling et al. 2008). It is of interest that the lung cancer risks associated with exposure to air pollution from road traffic were seen primarily after a 20-year latency period.

Conclusions

Occupational exposure to combustion products rich in PAH and particles was associated with an increased lung cancer risk. Exposure in the age decade 20–29 years had a larger detrimental effect than that in any other decades later in life and suggests that reductions of exposure may be particularly important for younger people. The findings are congruous with those documented by previous studies on tobacco smoking on lung cancer.

Conflict of interest The authors declare that they have no conflict of interest.

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