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Second hand smoke, age of exposure and lung cancer risk☆

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Summary
Background: Exposure to second hand smoke (SHS) has been identified as a risk factor for lung cancer for three decades. It is also known that the lung continues to grow from birth to adulthood, when lung growth stops. We hypothesize that after adjusting for active cigarette smoking, if SHS exposure took place during the period of growth, i.e. in the earlier part of life (0—25 years of age) the risk of lung cancer is greater compared to an exposure occurring after age 25.
Method: Second hand smoke exposure was self-reported for three different activities (leisure, work and at home) for this study population of 1669 cases and 1263 controls. We created variables that captured location of exposure and timing of first exposure with respect to a study participant's age (0—25, >25 years of age). Multiple logistic regressions were used to study the association between SHS exposure and lung cancer, adjusting for age, gender and active smoking variables.
Result: For study participants that were exposed to SHS at both activities (work and leisure) and compared to one or no activity, the adjusted odds ratio (AOR) for lung cancer was 1.30 (1.08—1.57) when exposure occurred between birth and age 25 and 0.66 (0.21—1.57) if exposure occurred after age 25 years. Respective results for non-smokers were 1.29 (0.82—2.02) and 0.87 (0.22—3.38), and current and ex-smokers combined 1.28 (1.04—1.58) and 0.66 (0.15—2.85).

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Conclusion: All individuals exposed to SHS have a higher risk of lung cancer. Furthermore, this study suggests that subjects first exposed before age 25 have a higher lung cancer risk compared to those for whom first exposure occurred after age 25 years.

1. Introduction

Lung cancer is the leading cause of cancer death for both men and women in the United States. Past studies have demonstrated the association between active cigarette smoking (mainstream smoke, MSS) or second hand smoke (SHS) exposure and the risk of adult non-small cell lung cancer (NSCLC). However, less is known about the effect of the age of exposure, particularly to SHS, on the risk of NSCLC [1—3]. Most studies [4—18] have focused on paternal and maternal smoking during pregnancy and the effect on childhood illnesses and cancers in general or more recently the risk of lung cancer for non-smoking women exposed to tobacco smoke during childhood [19—28]. Very few studies [19,22,29,30] have focused on the effect of the period of exposure relevant for lung cancer development while also assessing the significance of lifetime exposure by location.

The lung continues to grow from birth to adulthood [31] and most lung growth is over by age 18 [32—34], but lung volume continues to expand to 25, suggesting additional growth may occur [35—39]. Exposure of target organs to carcinogens during periods of rapid cell division or childhood is known to increase the risk of cancer and elevated exposure to carcinogens has been associated with higher levels of both DNA-adducts and somatic aberrations in cancer cells and may lead to genetic abnormalities that result in the development into cancer [40,41].

SHS consists of emissions from cigarettes, pipes and cigars, as well as exhaled materials from MSS, which contains several chemicals including over 50 known carcinogens [40,42,43]. The concentrations of benzol(*a*)pyrene, toluene, dimethylnitrosamines in SHS is much higher than in MSS, and the smaller particles in SHS are more likely to be deposited in the lung. SHS may induce DNA-adducts, sister chromosome exchange [44], oxidative DNA damage [45,46], and increased number of *p53* mutations in lung cancer [47,48], suggesting a similar etiologic mechanism for cases exposed to SHS and to MSS.

SHS exposure may occur at home (including childhood exposure from parents/other family members and exposure from spouse/family members in adulthood), at work (occupational exposure), and at leisure (exposure at public places other than work). Due to public health education and as a result of legislation in several developed countries, exposure to second hand smoke is declining at work and public places but direct marketing to younger populations by tobacco companies has contributed to continued high exposure among youths [49—52]. The intensity or frequency of exposure in work places has been noted to be generally higher than that of at home or leisure places [53], and results from a previous study has suggested that SHS exposure at work places may have a stronger effect on NSCLC risk than exposure at home or at leisure places [54].

We hypothesize that after adjusting for active cigarette smoking, if the SHS exposure took place during the critical period of growth, i.e. in the earlier part of life (0—25 years of age) the risk of lung cancer is greater compared to an exposure occurring after age 25.

2. Materials and methods

2.1. Study population

This study was reviewed and approved by the Institutional Review Boards of the Massachusetts General Hospital and the Harvard School of Public Health. The study population of 1669 cases and 1263 controls is derived from a large case—control study evaluating the molecular epidemiology of lung cancer, which began in 1992 at the Massachusetts General Hospital (MGH). Eligible cases included any person over the age of 18 years, with a diagnosis of primary lung cancer. An MGH lung pathologist confirmed all cases. The controls were the friends or spouses of cancer patients or the friends or spouses of other surgery patients in the same hospital. Potential controls that carried a previous diagnosis of any cancer (other than non-melanoma skin cancer) were excluded from participation. Controls were recruited among friends and non-blood-related family members of the cases (usually spouses) (41%). If friends of lung cancer patients were not available, controls were recruited from friends and family of patients either receiving thoracic surgery, chemotherapy or radiation treatment for a condition other than lung cancer (59%).

2.2. Data collection

Interviewer-administered questionnaires (a modified version of the detailed American Thoracic Society health questionnaire) collected information on demographics, occupational exposures, and detailed smoking histories from each subject. Some participants chose to complete the questionnaire at home, and return it by mail in a self-addressed stamped envelope. Participants were contacted by telephone when there was missing data. Age, gender, race, weight, education, medical history, smoking history, family history of cancer, work history, exposure to various substances, participation in many activities, and food preparation and consumption data were collected. Smoking status was defined as non-smoker (smoked less than one cigarette per day for less than a year), ex-smoker (quit smoking at least 1 month prior to diagnosis) and current smoker (at time of diagnosis). Pack—years were calculated to estimate the cumulative exposure to smoking by multiplying the number of packs smoked per day by the number of years smoked. Second hand smoke exposure was self-reported for three different activities (leisure, work and at home) and determined from information obtained in the health questionnaire. Exposure for each location was categorized as an indicator variable equal to 1 if the participant reported

exposure to SHS and equal to 0 otherwise. We created a similar indicator variable that captured timing of first exposure with respect to a study participant's age (0—25, >25 years of age).

Population characteristics were tabulated, and significant differences in the distribution of the principal covariates were tested using the Chi-square, Fisher exact, and Student's *t*-tests, were appropriate. Multiple logistic regressions was used to assess the association between second hand smoke and lung cancer risk, adjusting for age, gender, indicator variables for smoking status (non-smoker, ex-smoker and current smoker) and a continuous variable for cumulative smoking exposure (pack—years).

2.3. Statistical analysis

Demographic and clinical information were compared across smoking and SHS locations for both cases and controls. Multiple logistic regression was used to assess the association between SHS and lung cancer risk, adjusting for age (continuous variable), gender, indicator variables for smoking status (non-smoker, ex-smoker and current smoker), a continuous variable for cumulative smoking exposure (pack—years) and an indicator variable for alcohol intake (yes and no). Where indicated, the odds ratio (OR) and 95% confidence intervals (CI) for the risk of lung cancer was calculated from these models. All statistical testing was done at the two-sided 0.05 level, and SAS software Version 9.1 (SAS Institute, Cary, NC) was used.

3. Results

3.1. Patient characteristics

There were a total of 1669 cases and 1263 controls. The distribution of demographic and clinical characteristics by smoking status is summarized in Table 1. Overall median age (standard deviation) was 62 years [12], males were 49%; 604 (21%) non-smokers, 1464 (50%) ex-smokers, 864 (29%) current smokers; median pack—years (standard deviation) for ex- and current smokers 39 [37]. Patients with early stage (stages I and II) numbered 803 (50%), with adenocarcinoma 698 (42%), squamous 339 (21%) and others 615 (37%).

Table 2 shows the distribution of SHS exposure by location and age at exposure. No exposure to SHS at work or leisure 212 (7%), one activity 727 (25%), or both 1993 (68%). Persons with exposure to SHS between birth and age 25 numbered 403 (14%), and after age 25, 2529 (86%). Exposure at home was excluded from further analysis since there was little variability by outcome status (most subjects reported exposure from birth).

Adjusted odds ratios of SHS at work and leisure are shown in Table 3. For study participants who were exposed to SHS at both activities and compared to one or no activity, the adjusted odds ratio (AOR) for lung cancer was 1.30 (1.08—1.57) when exposure occurred between birth and age 25 and 0.66 (0.21—1.57) if exposure occurred after age 25 years. Respective results for non-smokers were: 1.29 (0.82—2.02) and 0.87 (0.22—3.38), and for current and ex-smokers combined: 1.28 (1.04—1.58) and 0.66 (0.15—2.85).

4. Discussion

Previous studies of biochemical markers of exposure and toxicological studies, confirm that there is a causal association between the risk of NSCLC and exposure to SHS (2). Similar conclusions have been reached by past summary scientific reports [43,55]. We suggest further that subjects first exposed before age 25 have a higher lung cancer risk compared to those for whom first exposure occurred after age 25 years. Consistent results are seen in our study for different smoking categories, i.e. current, past and non-smokers. Our results go to further support the hypothesis that SHS has a similar harmful effect as for cases exposed to MSS.

Growing evidence [19,22,29,30] suggests that exposure to SHS in childhood increases the risk of lung cancer in adulthood. With the decline of adult smoking in public and work places in the United States and Europe but still very prevalent in other regions around the world, SHS exposure and associated risks are still a major source of uncontrolled exposure in younger individuals, especially in children without the ability to negotiate a smoke-free environment at home, work or leisure. Most lung cancers occur in smokers but still a significant proportion (approximately 10%) develops in lifetime non-smokers [56] and approximately 3000 lung cancer deaths occur each year among adult non-smokers in the United States as a result of exposure to SHS [57]. No risk-free level of exposure to SHS exists [43] and exposure to SHS has also been linked with slowed lung growth in children [58]. In a study that investigated the effects of SHS exposure in childhood and the subsequent risk of lung cancer among female primary lung cancer cases and their hospital-based controls (matched on age, residential area and lifetime smoking status), Wang and colleagues [30] showed that passive smoking from household exposure to tobacco smoke significantly increased the risk of lung cancer for both smoking and non-smoking pairs when exposed under the age of 15 years ($p < 0.05$). In a similar study in Taiwan, Lee et al. [22] found that environmental tobacco smoke exposure occurring in childhood increased the effect of high doses of exposure in adult life in the development of lung cancer. In women exposed to greater than 20 smoker-years, compared to never exposed, the risk of lung cancer was 1.8 (1.2—2.9). When the exposure was greater than 40 years the risk was 2.2 (1.4—3.7). In addition, when smoker-years was treated as a continuous variable, the increased risk associated with a one-unit increase larger for childhood exposure compared to adulthood (1.35 vs.1.27). In a population-based case—control study of lung cancer among lifetime non-smoking women and with measured lifetime residential and workplace environmental tobacco smoke, the odds ratio for women with passive exposure as a child and as an adult was 1.63 (0.8—3.5) and for those exposed only as an adult 1.20 (0.5—3.0). Although no increase was observed with childhood exposure only, there were just two cases in that category.

SHS exposure and associated risks are increasingly becoming a major source of uncontrolled exposure in younger individuals, especially in children without the ability to negotiate a smoke-free environment at home, work or leisure. A worldwide study among students aged 13—15 years [58], showed that nearly half of never smokers were

Table 1 Demographic characteristics (by smoking status) of study subjects

	Never smokers		Ex-smokers		Current smokers		Whole population	
	Cases ($n = 138$)	Controls ($n = 466$)	Cases ($n = 894$)	Controls ($n = 570$)	Cases ($n = 637$)	Controls ($n = 227$)	Cases ($n = 1669$)	Controls ($n = 1263$)
Age[a]	62 (13)	57 (13)	68 (9)	61 (10)	61 (10)	54 (11)	65 (10)	59 (12)
Cigarette smoking								
Pack—years			53 (36)	29 (27)	64 (37)	38 (27)	53 (38)	20 (27)
Years since quit			15 (12)	20 (12)			8 (11)	9 (13)
Gender[b]								
Male	56 (41)	177 (38)	512 (57)	290 (51)	321 (50)	86 (38)	889 (53)	553 (44)
Female	82 (59)	289 (62)	382 (43)	280 (49)	316 (50)	141 (62)	780 (47)	710 (56)
Race								
White	129 (97)	451 (96)	871 (98)	561 (98)	610 (96)	220 (97)	1610 (97)	1232 (97)
Non-white	9 (3)	15 (4)	23 (2)	9 (2)	27 (4)	7 (3)	59 (3)	31 (3)
Histology								
Adenocarcinoma	72 (54)		374 (42)		252 (40)		698 (42)	
Squamous cell	10 (8)		189 (21)		140 (22)		339 (21)	
Other	51 (38)		324 (37)		240 (38)		615 (37)	
Stage								
I and II	57 (43)		460 (53)		286 (46)		803 (50)	
III and IV	75 (57)		409 (47)		331 (54)		815 (50)	

[a] Entries are mean (S.D.).
[b] Entries are counts(%); some subjects have incomplete data on stage and histology.

Table 2 Distribution of SHS variables for all subjects

	Non-smokers + <15cigarette pack—years		Non-smokers		Ex-smokers		Current smokers		Whole population	
	Cases (*n* = 267)	Controls (*n* = 732)	Cases (*n* = 138)	Controls (*n* = 466)	Cases (*n* = 894)	Controls (*n* = 570)	Cases (*n* = 637)	Controls (*n* = 227)	Cases (*n* = 1669)	Controls (*n* = 1263)
Exposure at all ages										
Home										
No	42 (16)	115 (16)	24 (17)	73 (16)	76 (9)	78 (14)	21 (3)	15 (7)	121 (7)	166 (13)
Yes	25 (84)	617 (84)	114 (83)	393 (84)	818 (91)	492 (86)	616 (97)	212 (93)	1548 (93)	1097 (87)
Work										
No	85 (32)	306 (42)	53 (38)	200 (43)	117 (13)	159 (28)	84 (13)	66 (29)	254 (15)	425 (34)
Yes	182 (68)	426 (58)	85 (62)	266 (57)	777 (87)	411 (72)	553 (87)	161 (71)	1415 (85)	838 (66)
Leisure										
No	64 (24)	178 (24)	39 (28)	129 (28)	118 (13)	82 (14)	84 (13)	20 (9)	241 (14)	231 (18)
Yes	203 (76)	554 (76)	99 (72)	337 (72)	776 (87)	488 (85)	553 (87)	207 (91)	1428 (86)	1032 (82)
Exposure after age 25										
Home										
No	14 (25)	52 (29)	9 (26)	32 (25)	20 (26)	37 (40)	8 (17)	9 (36)	37 (23)	78 (32)
Yes	41 (75)	126 (71)	25 (74)	96 (75)	58 (74)	55 (60)	38 (83)	16 (64)	121 (77)	167 (68)
Work										
No	39 (71)	129 (72)	25 (74)	91 (71)	49 (63)	61 (66)	26 (57)	20 (80)	100 (63)	172 (70)
Yes	16 (29)	49 (28)	9 (26)	37 (29)	29 (37)	31 (34)	20 (43)	5 (20)	58 (37)	73 (30)
Leisure										
No	45 (82)	137 (77)	31 (91)	100 (78)	54 (69)	62 (67)	35 (76)	14 (56)	120 (76)	176 (72)
Yes	10 (18)	41 (23)	3 (9)	28 (22)	24 (31)	30 (33)	11 (24)	11 (44)	38 (24)	69 (28)
Exposure up to age 25										
Home										
No	28 (13)	63 (11)	15 (14)	41 (12)	56 (7)	41 (9)	13 (2)	6 (3)	84 (6)	88 (9)
Yes	184 (87)	491 (89)	89 (86)	297 (88)	760 (93)	437 (91)	578 (98)	196 (97)	1427 (94)	930 (91)
Work										
No	46 (22)	177 (32)	28 (27)	109 (32)	68 (8)	98 (21)	58 (10)	46 (23)	154 (10)	253 (25)
Yes	166 (78)	377 (68)	76 (73)	229 (68)	748 (92)	380 (79)	533 (90)	156 (77)	1357 (90)	765 (75)
Leisure										
No	19 (9)	41 (7)	8 (8)	29 (9)	64 (8)	20 (4)	49 (8)	6 (3)	121 (8)	55 (5)
Yes	193 (91)	513 (93)	96 (92)	309 (91)	752 (92)	458 (96)	542 (92)	196 (97)	1390 (92)	963 (95)

Table 3 Adjusted odds ratio (95% CI) of SHS duration at work and leisure places and lung cancer risk[a]

All subjects (1669 cases, 1261 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities[b]	0.66 (0.21—1.57)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.30 (1.08—1.57)
Non-smokers + < 15cigarette pack—years (272 cases and 740 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities	0.94 (0.31—2.80)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.30 (0.96—1.76)
Non-smokers (138 cases and 766 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities	0.87 (0.22—3.38)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.29 (0.82—2.02)
Ex smokers (894 cases and 570 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities	1.03 (0.10—10.20)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.55 (0.94—2.56)
Current smokers (693 cases and 227 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities	4.29 (0.153—119.99)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.08 (0.76—1.53)
Current and ex smokers combined (1587 cases and 797 controls)	
Exposure after age 25	
SHS at one or no activity	Referent
SHS at two activities	0.66 (0.15—2.85)
Exposure up to age 25	
SHS at one or no activity	Referent
SHS at two activities	1.28 (1.04—1.58)

[a] Logistic regression models were used, adjusting for age, gender, active cigarette Smoking (smoking status, pack—years, years since cessation), and smoking cigar/pipe.

[b] Exposure at home was excluded from further analysis since there was little variability by outcome status (most subjects reported exposure from birth).

exposed to SHS at home (46.8%), and a similar percentage were exposed in places other than the home (47.8%). Never smokers exposed to SHS at home were 1.4—2.1 times more likely to be susceptible to initiating smoking than those not exposed. Students exposed to SHS in places other than the home were 1.3—1.8 times more likely to be susceptible to initiating smoking than those not exposed, especially for SHS exposure at home.

The strengths of this study include large sample size, relatively homogeneous population, and almost complete demographic and smoking information. However, we acknowledge several limitations to our study. As expected of a case—control study, recall bias may have affected our results. Smoking and SHS exposure history were collected by questionnaire and patients' recall and are not validated biochemically. However, given the nature of controls (friends and non-blood-related family) the impetus to recall would be similar (non-differential) across case status, with controls possibly as affected by diagnosis of friend or family member. Non-differential misclassification biases to the null making the odds ratio a conservative estimate of the actual magnitude of association.

We also observed similar and consistent results in different smoking categories. To ensure that control selection was representative we compared the smoking habits of our controls to the smoking habits of the general Massachusetts population and found no significance differences. It is most likely that these controls would have been referred to MGH for treatment, if they were to become cases as they were either their spouses or friends. Residual confounding may be another limitation that exists for the results in our study. We observed a slightly stronger effect of SHS exposure among smokers as compared to non-smokers, which may be explained partly by residual confounding. However, the associations were consistent in different subgroups of smoking status (past, current and non-smokers), and we adjusted for pack—years of smoking and years since cessation (for past smokers) in all of the analysis. Residual confounding may bias the magnitude of the association but it is unlikely to change the direction of the association. In our analysis we did not adjust for the duration or the amount of SHS exposure.

To conclude, results from this epidemiological study support the evidence that individuals first exposed to SHS before age 25 have a higher lung cancer risk compared to those for whom first exposure occurred after age 25 years. These results need to be confirmed by other independent studies and further studies are needed to more accurately assess the SHS exposure and fully investigate the SHS-age of exposure interaction and to what extent this is influenced by the duration or the amount of SHS exposure.

Conflict of interest statement

None.

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