Second Hand Smoke Exposure and Survival in Early-Stage Non–Small-Cell Lung Cancer Patients

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Abstract

Purpose: Second hand smoke (SHS) exposure is associated with higher risk of lung cancer. However, the role of SHS in lung cancer survival is not clear.

Experimental Design: We examined the association between self-reported SHS exposure before diagnosis and overall survival and recurrence-free survival in 393 early-stage non–small-cell lung cancer patients. SHS exposure was analyzed by both duration and location of exposure using log-rank test and Cox proportional hazard models, adjusting for covariates including pack-years of smoking.

Results: The median follow-up time was 66 months (range, 0.2-140 months). There were 135 recurrences and 213 deaths. The 5-year overall survival rates were 71% [95% confidence interval (95% CI), 62-81%], 61% (51-72%), 49% (38-60%), and 47% (37-58%), respectively, for patients with the lowest to highest quartile of SHS exposure durations ($P < 0.001$, log-rank test), with the adjusted hazard ratio (AHR) of 1.57 (95% CI, 1.02-2.41) for the highest versus lowest quartile of SHS exposure durations ($P_{trend} = 0.04$). For different SHS exposure locations, a stronger association was found for SHS exposure at work (AHR of the highest versus lowest quartile, 1.71; 95% CI, 1.12-2.61; $P_{trend} = 0.03$) than for exposure at home (AHR, 1.26; 95% CI, 0.86-1.86; $P_{trend} = 0.20$) or leisure places (AHR, 1.28; 95% CI, 0.83-1.95; $P_{trend} = 0.16$). Similar associations were observed when SHS exposure durations were dichotomized into two or three groups and between SHS exposure and recurrence-free survival.

Conclusions: SHS exposure is associated with worse survival in early-stage non–small-cell lung cancer patients, especially for SHS exposure at the work.

Lung cancer remains the leading cause of cancer death among both men and women in the United States. The association between active cigarette smoking [mainstream smoke (MSS)] or second hand smoke (SHS) exposure and the risk of non–small-cell lung cancer (NSCLC) has been well established. However, little is known about the effect of smoking, particularly SHS exposure, on the prognosis of NSCLC patients. Higher "dose" exposure to carcinogens has been associated with higher levels of both DNA-adducts and somatic aberrations in cancer cells (1), and higher levels of somatic aberrations have been directly associated with worse clinical prognosis in lung cancer (2). Thus, increased exposure to carcinogens may lead to accumulation of genetic abnormalities that result not only in the evolution into cancer but also in the progression towards biologically aggressive cancers. Epidemiologic studies have suggested that cumulative MSS (measured in pack-years) is related directly to the clinical prognosis of lung cancer patients (3, 4).

SHS is composed of emissions from cigarettes, pipes, and cigars, as well as exhaled materials from MSS, which contains thousands of chemicals including over 50 known carcinogens (1, 5). The concentration of carcinogens in SHS is much higher than in MSS, and the smaller particles in SHS are more likely to be deposited in the lung (1, 5). SHS may induce DNA adducts, sister chromosome exchanges (6), oxidative DNA damage (7, 8), and increased number of *p53* mutations in lung cancer (9, 10), suggesting a similar etiologic mechanism for cases exposed to SHS and to MSS.

SHS exposure may occur at different locations including home (including childhood exposure and exposure from spouse or other family members), work (occupational exposure), and leisure places (exposure at public places other than work). The exposure intensity or frequency in work places is generally higher than that of at home or leisure places (11), and a previous study has suggested that SHS exposure at work places may have a stronger effect on NSCLC risk than exposure at

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home or leisure places (12). We hypothesized that SHS exposure is associated with worse survival in NSCLC patients, before and after adjusting for cumulative MSS exposure. Furthermore, SHS exposure at work places may have stronger effect on NSCLC survival than exposure at home or leisure places. We tested these a priori hypotheses in a large cohort of early-stage NSCLC patients.

Materials and Methods

Study population. This study began in 1992 and was approved by the Human Subjects Committee of Massachusetts General Hospital and Harvard School of Public Health. Eligible subjects were histologically confirmed and consecutively recruited NSCLC patients at the Massachusetts General Hospital who were >18 years old. More than 85% of eligible patients participated in this study and 96% were Caucasians. Details of this case population have previously been reported (13).

In this population, we first identified 558 incident early-stage (stages IA-IIB) NSCLC patients recruited between 1992 and 2002, ensuring a follow-up time of at least 3 years. We excluded 16 patients who did not have complete treatment or MSS information (pack-years of smoking) and 149 patients with missing SHS exposure information, leaving the subset of 393 incident patients with histologic diagnoses confirmed at Massachusetts General Hospital, who had their surgical resection at Massachusetts General Hospital, and who had outpatient records available. The demographic (including pack-years of smoking), clinical, and treatment characteristics of subjects not included in the analysis were similar to those of the included subjects.

Data collection. A modified version of detailed American Thoracic Society health questionnaire was completed for each patient at the time of recruitment (soon after the diagnosis), including demographic and detailed MSS information. SHS exposure information before the diagnosis was obtained using a separate questionnaire. Patients were asked whether they were regularly exposed to SHS at home (including childhood), work (including on the way to and back from wok), or leisure places, respectively. If patients answered "yes" to any of the above locations for exposure, further questions including the start and the end year of each SHS exposure at different periods of time were asked. The duration of SHS exposure at home, work, or leisure places was the sum of the exposure years at different periods, respectively. The average total SHS exposure time was defined as the sum of SHS exposure durations at home, work, and leisure places as previously reported (14–16), divided by three.

Overall survival (OS) was the primary outcome of this study and was calculated from the date of surgery to the date of last follow-up, or death from any cause. Recurrence-free survival (RFS) was the secondary outcome of this study and was defined as the time from the date of surgery to the first date of recurrence of cancer, or death from any cause. Details of the verification of dates of death and dates of recurrence have previously been described (13). For those 14% of patients who had their primary follow-up outside of the Massachusetts General Hospital system, we contacted the primary physician to obtain follow-up information. Median follow-up time for this cohort was computed among subjects who were still alive.

Statistical analysis. To investigate the associations between SHS exposure and NSCLC survival, we dichotomized the population into four groups based on quartiles of total SHS exposure duration. Demographic and clinical information was compared across different SHS exposure groups using Pearson χ^2 tests (for categorical variables) and Kruskal-Wallis tests (for continuous variables), where appropriate. The associations between SHS exposure and OS and RFS were estimated using the method of Kaplan and Meier and assessed using the log-rank test. Cox proportional hazards models were used as our primary analyses, controlling for multiple possible covariates simultaneously, including age, gender, stage, pack-years of smoking, smoking status, and histologic cell types. Trend tests were based on the integer scores of different SHS exposure levels (from 1 to 4 based on quartiles of SHS exposure). In addition to the effect of total SHS exposure, we also investigated the associations between SHS exposure at home, work, and leisure places and the survival of NSCLC patients, respectively.

In the secondary analysis, we classified the population into two groups (by median of SHS exposure) or three groups (by the bottom 75%, the next 15%, and the top 10% of SHS exposure; or by the bottom 75%, and the next two groups were divided by median), as suggested in the previous literature (12), because a urinary cotinine study has shown that misclassification of questionnaire-based SHS exposure is greater in the three lowest quartiles of the distribution than in the top quartile (17). We also did subgroup analyses by age, gender, histologic cell type, stage, and pack-years of smoking. All reported P values are from two-sided tests. $P < 0.05$ was considered statistically significant. All statistical analyses used SAS software version 8 (SAS, Cary, NC).

Results

Patient, stage, and treatment characteristics. Among the 393 NSCLC patients, median age was 69 years (range, 31-89 years), and 49% were women. Never-smokers, ex-smokers, and current smokers were 8%, 57%, and 35%, respectively. Median pack-years of smoking in ever-smokers was 54 (range, 0.5-204) and median years since smoking cessation in ex-smokers was 12 (range, 1-59). Adenocarcinoma, squamous cell, large-cell, and bronchioloalveolar carcinoma represented 48%, 28%, 5%, and 13% of the tumor histologies, respectively. Fifty-three percent were stage IA, 29% were stage IB, and 18% stage IIA/IIB. All patients had surgical resection as the initial treatment, including wedge (26%), lobectomy (62%), bilobectomy (3%), pneumonectomy (5%), sleeve lobectomy (4%), and lobectomy plus wedge (1%). Additionally, 32 (8%) patients received postoperative radiation and 5 (1%) patients received adjuvant chemotherapy. There were 135 recurrences and 213 deaths, including 110 (52%) deaths without recurrence and 32 (18%) recurrence without death. The median follow-up time was 66 months (range, 0.2-140 months).

The majority of the patients reported having been exposed to SHS, including 356 (91%) exposed at home, 323 (82%) exposed at work, 359 (91%) exposed at leisure places, and 287 (73%) exposed at all of the above locations. One hundred seventy-eight (45%) patients were exposed to SHS within 1 year of the time of diagnosis (current SHS exposure). The demographic, clinical, treatment, and smoking information on patients by quartiles of SHS exposure durations is shown in Table 1. Compared with patients with the lowest quartile of SHS exposure, patients with the highest quartile of SHS exposure were older, more likely to be male, have squamous cell carcinoma, and be heavy smokers. No statistically significant differences were found for stage, treatment, smoking status, or years since smoking cessation among patients with different SHS exposure durations.

SHS exposure and OS. From Kaplan-Meier curves and log-rank test, we observed that SHS exposure was associated with statistically significant worse survival ($P < 0.001$; Table 2; Fig. 1A); the 5-year OS rates of the lowest to higher quartile of SHS exposure durations were 71% (52-81%), 61% (51-72%), 49% (38-60%), and 47% (37-58%), respectively.

In the univariate analysis of the Cox proportional hazard model where each variable was treated as categorical variable (age, pack-years of smoking, and SHS exposure durations were

Table 1. Demographic, clinical, and treatment characteristics for patients with different SHS exposure durations

Characteristic	<28 y	28-37 y	38-46 y	>48 y	P*
	n = 99	n = 99	n = 99	n = 96	
Age*	67 (31-88)	69 (46-89)	68 (50-86)	73 (57-87)	<0.001
Gender, female†	65 (66%)	53 (54%)	40 (40%)	36 (38%)	<0.001
Histologic cell type†					0.02
Adenocarcinoma	52 (53%)	55 (56%)	44 (44%)	38 (40%)	
Squamous cell carcinoma	17 (17%)	28 (28%)	33 (33%)	32 (33%)	
Large-cell carcinoma	5 (5%)	5 (5%)	3 (3%)	8 (8%)	
Bronchioloalveolar	21 (21%)	7 (7%)	10 (10%)	11 (11%)	
Others	4 (4%)	4 (4%)	9 (9%)	7 (7%)	
Stage†					0.75
IA	56 (57%)	52 (53%)	49 (49%)	50 (52%)	
IB	31 (31%)	28 (28%)	31 (31%)	26 (27%)	
IIA/IIB	12 (18%)	19 (19%)	19 (19%)	20 (21%)	
Surgery type†					0.54
Wedge	22 (22%)	28 (28%)	21 (21%)	31 (32%)	
Lobectomy	66 (67%)	60 (61%)	65 (66%)	52 (54%)	
Others	11 (11%)	11 (11%)	13 (13%)	13 (14%)	
Radiation/chemotherapy†	6 (6%)	8 (8%)	8 (8%)	10 (10%)	0.74
Smoking status†					0.10
Never-smokers	14 (14%)	7 (7%)	5 (5%)	4 (4%)	
Ex-smokers	56 (57%)	55 (56%)	61 (62%)	52 (54%)	
Current smokers	29 (29%)	37 (37%)	33 (33%)	40 (42%)	
Pack-years among smokers*	40 (1-162)	49 (2-159)	59 (8-204)	65 (0.5-169)	<0.001
Years of quit smoking among ex-smokers*	12 (2-47)	12 (1-41)	11 (1-41)	12 (1-59)	0.66

NOTE: The durations were the average SHS exposure years (total SHS exposure years divided by 3).
*Median, tested by Kruskal-Wallis test.
†Frequency, tested by χ^2 test.

dichotomized by quartiles), older age, male gender, more advanced stage, squamous cell type, heavier smoking, current smoking status, current SHS exposure status, and heavier SHS exposure were associated with statistically significantly worse OS or RFS, and bronchioloalveolar cell type was associated with improved OS and RFS. However, histology, smoking status, and current SHS exposure status were not statistically significant after adjusting for age and stage and were excluded in the analysis. In the adjusted Cox proportional hazard model, SHS exposure was associated with statistically significant higher risk of death, with an adjusted hazard ratio (AHR) of 1.57 [95% confidence interval (95% CI), 1.02-2.41] for the highest versus lowest quartile of SHS exposure (P_{trend} = 0.04; Table 2). When SHS exposures at home, work, and leisure places were analyzed separately, statistically significant associations were found for SHS exposure at work places, but not for exposure at home or leisure places; the AHRs for the highest versus lowest quartile of SHS exposure durations were 1.71 (95% CI, 1.12-2.61; P_{trend} = 0.03) for work exposure, 1.26 (95% CI, 0.86-1.86; P_{trend} = 0.20) for home exposure, and 1.28 (95% CI, 0.83-1.95; P_{trend} = 0.16) for leisure exposure, respectively. Similar associations were found when home, work, and leisure SHS exposures were analyzed in the same model (Table 2) and when SHS exposure was dichotomized into two or three groups.

SHS exposure and RFS. Similar to the results of OS, SHS exposure was associated with statistically significant worse RFS in Kaplan-Meier curves and log-rank test (P = 0.004, log-rank test; Table 3; Fig. 1B): the 5-year RFS rates of the lowest to higher quartile of SHS exposure durations were 58% (47-68%), 54% (53-64%), 43% (32-53%), and 39% (29-50%), respectively. In Cox proportional hazard model, SHS exposure was associated with borderline significantly higher risk of death/recurrence, with an AHR of 1.38 (95% CI, 0.94-2.03) for the highest versus lowest quartile of SHS exposure (P_{trend} = 0.10). When SHS exposures at different locations were analyzed separately, stronger associations were found for SHS exposure at work places than at home or leisure places, with AHRs of the highest versus lowest quartile of exposure of 1.60 (95% CI, 1.08-2.37; P_{trend} = 0.07) for work exposure, 1.15 (95% CI, 0.81-1.65; P_{trend} = 0.34) for home exposure, and 1.19 (95% CI, 0.81-1.76; P_{trend} = 0.16) for leisure exposure. Similar associations were found when home, work, and leisure SHS exposures were adjusted in the same model (Table 3) and when SHS exposure was dichotomized into two or three groups.

SHS exposure and OS in subgroup analyses. In the subgroup analyses by age, gender, histologic cell type, stage, and pack-years of smoking, stronger associations between SHS exposure and OS were observed for subjects of ages <69 years (by median; AHR of highest versus lowest quartile of exposure, 2.38; 95% CI, 1.19-4.74; P_{trend} = 0.02), adenocarcinoma patients (AHR, 2.34; 95% CI, 1.28-4.30; P_{trend} = 0.01), stage IA patients (AHR, 1.69; 95% CI, 0.93-3.08; P_{trend} = 0.04), and heavier smokers (by median; pack-years ≥54; AHR, 2.23; 95% CI, 1.11-4.47; P_{trend} = 0.05), when compared with corresponding subgroups of older subjects (age >69 years), squamous cell carcinoma patients, stage IB/IIA/IIB patients, and lighter smokers (Table 4). Similar differences were observed for RFS in the subgroup analyses as well (data not shown).

Discussion

Our results suggested that SHS exposure before diagnosis is associated with worse OS and RFS among early-stage NSCLC patients. The associations were consistent in different models where subjects were classified into different subgroups, and when important covariates including cumulative MSS exposure were adjusted. The results supported the hypothesis that SHS has a similar etiologic mechanism for cases exposed to MSS. Although cigarette smoking has been banned in public and work places in more and more cities around the world, SHS exposure and associated risks are not totally eliminated, and exposure to SHS is still possible for those working where smoking is allowed and for those working where smoke may migrate from outdoor areas (18). Therefore, SHS exposure remains a common public health hazard that is entirely preventable.

Approximately 3,000 lung cancer deaths occur each year among adult nonsmokers in the United States as a result of exposure to SHS (19). A number of epidemiologic studies have investigated the associations between SHS exposure and lung cancer mortality, especially for SHS exposure at home. A U.S. female never-smoker study suggested that SHS exposures at home, work, and leisure places were associated with lifetime excess risk of death from lung cancer (20). A European study suggested that in 1990, at least hundreds of lung cancer deaths were attributable to exposure to a spouse's SHS in the European Union (21); this was echoed by the American Cancer Society Cancer Prevention Study, which suggested a 20% higher mortality among women whose husbands ever smoked compared with women married to never-smokers (22). However, one study suggested that SHS exposure from spouse is not associated with mortality of coronary heart disease, lung cancer, or chronic obstructive pulmonary disease, although the authors did not rule out a small effect (23). Our results suggest nonstatistically significantly higher HRs for SHS exposure at home or leisure places.

SHS exposure at work places is also termed "occupational" SHS exposure. It is suggested that working in a smoke-filled environment has about the same long-term effect on a person's health as smoking 10 cigarettes per day (24). A Finnish study suggested that SHS exposure at work accounts for ~0.9% of the total mortality in the relevant disease and age categories, including lung cancer, chronic obstructive pulmonary disease, asthma, ischemic heart disease, and cerebrovascular stroke (25). Consistent with our finding, SHS exposure at work has been shown to be associated with higher risk of lung cancer (12), respiratory symptoms (26), and acute coronary syndromes (11), compared with the exposure at home or leisure places. One possible explanation is that the exposure intensity or frequency of SHS is generally higher in work places than that of home (11) because environmental monitoring studies suggest that for many groups of workers, occupational exposure may involve a higher density of smokers in the immediate

Table 2. Five-year OS rates (95% CI) and AHRs for SHS exposure

Location	Quartile of SHS exposure (duration, y)				*P**
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total exposure (y)	<28	28-37	38-46	>48	
N/deaths	99/41	99/50	99/58	96/64	
5-y survival rate (%)	71 (62-81)	61 (51-72)	49 (38-60)	47 (37-58)	<0.001
Crude HR	1.00	0.98 (0.66-1.46)	1.60 (1.09-2.35)	1.84 (1.24-2.73)	<0.001
AHR	1.00	1.19 (0.78-1.82)	1.26 (0.83-1.92)	1.57 (1.02-2.41)	0.04
Home exposure (y)	<22	22-36	37-53	>53	
N/deaths	103/52	93/44	100/56	97/61	
5-y survival rate (%)	61 (52-71)	63 (52-74)	56 (46-67)	49 (39-60)	0.18
Crude HR	1.00	0.93 (0.62-1.39)	1.18 (0.81-1.73)	1.37 (0.94-1.98)	0.05
AHR model 1†	1.00	1.04 (0.69-1.57)	1.18 (0.79-1.76)	1.26 (0.86-1.86)	0.20
AHR model 2‡	1.00	1.05 (0.68-1.63)	1.22 (0.81-1.85)	1.16 (0.76-1.77)	0.48
Work exposure (y)	<7	7-30	31-42	>42	
N/deaths	101/40	95/51	104/55	93/67	
5-y survival rate (%)	71 (61-81)	52 (41-64)	60 (50-70)	45 (34-56)	<0.001
Crude HR	1.00	1.50 (0.99-2.28)	1.38 (0.92-2.07)	2.38 (1.61-3.53)	<0.001
AHR model 1†	1.00	1.36 (0.89-2.09)	1.20 (0.78-1.83)	1.71 (1.12-2.61)	0.03
AHR model 2‡	1.00	1.37 (0.88-2.14)	1.04 (0.66-1.64)	1.71 (1.09-2.67)	0.06
Leisure exposure (y)	<36	36-48	49-60	>60	
N/deaths	99/47	95/46	106/63	93/57	
5-y survival rate (%)	66 (56-76)	68 (58-78)	48 (37-58)	49 (38-60)	<0.001
Crude HR	1.00	0.94 (0.63-1.42)	1.59 (1.09-2.32)	1.84 (1.25-2.73)	<0.001
AHR model 1†	1.00	0.86 (0.57-1.31)	1.12 (0.75-1.68)	1.28 (0.83-1.95)	0.16
AHR model 2‡	1.00	0.77 (0.49-1.18)	1.01 (0.66-1.53)	1.06 (0.67-1.68)	0.40

NOTE: In all of the analyses, the quartile 1 group was treated as the reference group, and age, gender, stage, and pack-years of smoking were included in the adjusted Cox proportional hazard model (all treated as categorical variables) where appropriate.
*The *P* values were for log-rank test or trend test in Cox models, respectively.
†Home, work, and leisure exposures were analyzed in separate models.
‡Home, work, and leisure exposures were analyzed in the same model.

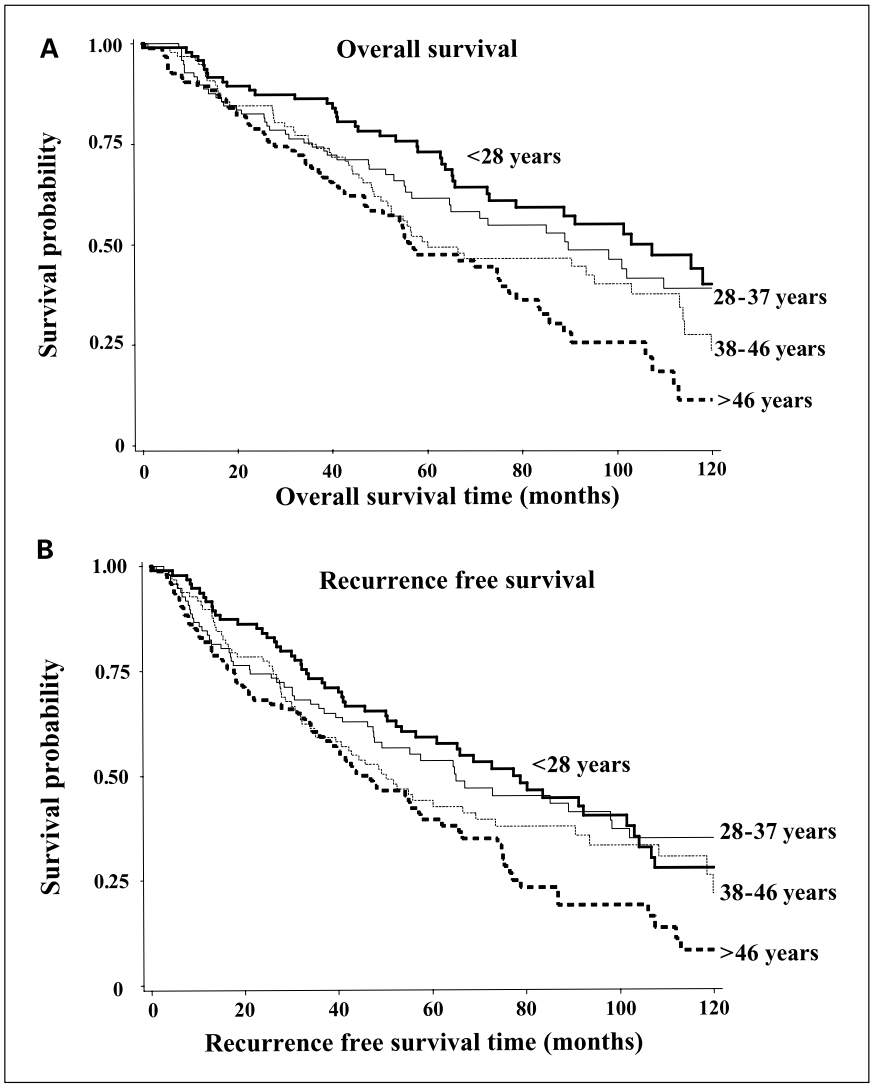

Fig. 1. Kaplan-Meier curves of SHS exposure (by quartiles of average exposure durations) in OS (*A*; $P < 0.001$, log-rank test) and RFS (*B*; $P = 0.004$, log-rank test). Log-rank test was based on the full data of 393 NSCLC patients.

environment (27, 28). Additionally, many individuals spend more time at work than in the company of their spouses at home or at the leisure places. Because many subjects were reported to be exposed to SHS at all of the above locations, it may be difficult to differentiate the effects of SHS exposure at different locations. We did observe consistent and similar results when all of the SHS exposures were adjusted in the same model (Tables 2 and 3).

In the subgroup analysis by different covariates, we expected that the effect of SHS would be stronger among younger subjects, adenocarcinoma patients, and stage IA patients because they are less likely to be associated with MSS or have fewer years of smoking. Therefore, the effect of SHS may be easier to detect among these subgroups. Interestingly, we observed a stronger effect of SHS among heavier smokers than light smokers, which suggests that, in addition to its independent effect on NSCLC survival, SHS exposure may have joint effects with MSS exposure. A previous study has also suggested a stronger effect of SHS exposure on the risk of respiratory diseases and lung cancer among former smokers than never-smokers (29). One possible explanation is that heavier smokers may be more susceptible to SHS exposure because they may have more mutations or are sicker than light smokers. We observed similar effects of SHS exposure between women and men, although our data did suggest that women have better survival than men as reported in a recent report (30).

The strengths of this study include large sample size, a relatively homogeneous population, and complete clinical, treatment, and follow-up information. However, there are a number of limitations. First, recall bias may have affected our results. SHS exposure history was collected by questionnaire and patients' recall and not validated biochemically. However, the smoking information was collected at the time of diagnosis, and it is unlikely that the prognosis of NSCLC patients would be related to statements about the SHS exposure. We observed similar and consistent results in different models. Second, there is missing information. A total of 149 patients have missing information on the SHS exposure. However, the distributions of demographic, clinical, and treatment characteristics between subjects with and without SHS exposure data are very similar; therefore, the results are unlikely to be biased because of the missing information. We also investigated the associations between cumulative SHS exposure (accounting for both SHS exposure durations and intensity) and NSCLC survival among

Table 3. Five-year RFS rates (95% CI) and AHRs for SHS exposure

Location	Quartile of SHS exposure (duration, y)				P*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
All exposures (y)	<28	28-37	38-46	>46	
N/deaths	99/54	99/57	99/62	96/72	
5-y survival rate (%)	58 (47-68)	54 (53-64)	43 (32-53)	39 (29-50)	0.004
Crude HR	1.00	1.10 (0.76-1.60)	1.33 (0.93-1.92)	1.82 (1.27-2.59)	<0.001
AHR model	1.00	1.03 (0.70-1.50)	1.08 (0.74-1.58)	1.38 (0.94-2.03)	0.10
Home exposure (y)	<22	22-36	37-53	>53	
N/deaths	103/63	93/52	100/61	97/69	
5-y survival rate (%)	50 (40-60)	55 (44-66)	48 (37-58)	42 (32-52)	0.25
Crude HR	1.00	0.85 (0.59-1.23)	1.06 (0.75-1.51)	1.23 (0.88-1.73)	0.14
AHR model 1†	1.00	0.90 (0.61-1.31)	1.05 (0.72-1.53)	1.15 (0.81-1.65)	0.34
AHR model 2‡	1.00	0.95 (0.64-1.41)	1.12 (0.76-1.64)	1.13 (0.77-1.67)	0.62
Work exposure (y)	<7	7-30	31-42	>42	
N/deaths	101/49	95/63	104/62	93/71	
5-y survival rate (%)	59 (49-70)	40 (29-51)	55 (45-65)	37 (27-47)	<0.001
Crude HR	1.00	1.60 (1.10-2.32)	1.25 (0.86-1.82)	2.15 (1.45-3.11)	<0.001
AHR model 1†	1.00	1.37 (0.93-2.01)	1.09 (0.74-1.60)	1.60 (1.08-2.37)	0.07
AHR model 2‡	1.00	1.45 (0.97-2.18)	1.08 (0.72-1.62)	1.66 (1.09-2.52)	0.13
Leisure exposure (y)	<36	36-48	49-60	>60	
N/deaths	99/57	95/52	106/72	93/64	
5-y survival rate (%)	55 (44-65)	59 (49-70)	40 (30-50)	41 (30-51)	0.002
Crude HR	1.00	0.86 (0.59-1.25)	1.46 (1.030-2.06)	1.58 (1.10-2.27)	0.001
AHR model 1†	1.00	0.77 (0.52-1.14)	1.16 (0.81-1.67)	1.19 (0.81-1.76)	0.16
t1AHR model 2‡	1.00	0.67 (0.45-1.01)	1.00 (0.68-1.48)	0.96 (0.63-1.48)	0.38

NOTE: In all of the analyses, the quartile 1 group was treated as the reference group, and age, stage, and pack-years of smoking were included in the adjusted Cox proportional hazard model (reference category).
*The *P* values were for log-rank test or trend test in Cox models, respectively.
†Home, work, and leisure exposures were analyzed in separate models.
‡Home, work, and leisure exposures were analyzed in the same model.

the 283 NSCLC patients with complete SHS exposure information, and found similar results for SHS exposure at work places (AHR, 1.73; 95% CI, 1.08-2.78 of highest versus lowest quartile; P_{trend} = 0.03). We did not collect the data of SHS after the diagnosis of NSCLC. Because SHS exposure is not totally controlled by patients themselves, it may be very difficult to change the exposure status of SHS even after the diagnosis of lung cancer, especially before smoking in public and work places was banned (July 2004 in Massachusetts). Third, residual confounding may exit for the data. We observed a stronger effect of SHS exposure among heavy smokers as compared with light smokers, which may partly be due to

Table 4. AHRs of OS for SHS exposure among different subgroups (need to be modified)

	<28 y		28-37 y		38-46 y		>46 y		P*
	N/death	AHR	*N*/death	AHR	*N*/death	AHR	*N*/death	AHR	
Age ≤69 y	56/18	1.00	52/23	1.20 (0.63-2.31)	52/28	1.45 (0.76-2.78)	31/24	2.38 (1.19-4.74)	0.02
Age >69 y	43/23	1.00	47/27	1.11 (0.63-1.96)	47/30	0.79 (0.44-1.44)	65/40	1.12 (0.65-1.94)	0.58
Female	65/25	1.00	53/24	0.84 (0.46-1.53)	40/22	1.64 (0.90-2.97)	36/20	1.28 (0.68-2.40)	0.18
Male	34/16	1.00	46/26	1.92 (1.00-3.70)	59/36	1.10 (0.59-2.06)	60/44	1.70 (0.88-3.26)	0.35
Adenocarcinoma	52/22	1.00	55/27	1.29 (0.72-2.30)	44/24	1.38 (0.74-2.57)	38/28	2.34 (1.28-4.30)	0.01
Squamous cell	17/9	1.00	28/18	1.29 (0.56-2.97)	33/23	0.90 (0.39-2.11)	32/22	0.94 (0.39-2.23)	0.66
Stage IA	56/21	1.00	52/23	1.09 (0.60-1.99)	49/28	1.64 (0.92-2.92)	50/31	1.69 (0.93-3.08)	0.04
Stage IB/IIA/IIB	43/20	1.00	47/27	1.34 (0.73-2.45)	50/30	0.99 (0.53-1.84)	46/33	1.34 (0.72-2.52)	0.53
Pack-years <54	70/29	1.00	65/27	1.03 (0.60-1.76)	42/21	1.26 (0.69-2.30)	30/17	1.28 (0.67-2.44)	0.36
Pack-years ≥54	29/12	1.00	34/23	1.93 (0.93-4.02)	57/37	1.64 (0.81-3.30)	66/47	2.23 (1.11-4.47)	0.05
No current smokers	70/26	1.00	62/28	1.13 (0.65-1.96)	66/38	1.15 (0.67-1.99)	56/35	1.41 (0.79-2.49)	0.26
Current smokers	29/15	1.00	37/22	1.11 (0.56-2.20)	33/20	1.19 (0.57-2.49)	40/29	1.89 (0.89-4.03)	0.09

NOTE: In all of the analyses, the quartile 1 group was treated as the reference group, and age, gender, stage, and pack-years of smoking were included in the adjusted Cox proportional hazard model where appropriate.
*The *P* values were for trend test in Cox proportional hazard models.

residual confounding. However, the associations were consistent in different subgroups of pack-years of smoking and smoking status (current smokers and noncurrent smokers), and we adjusted for pack-years of smoking 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. Fourth, the survival data could not distinguish between the death from lung cancer and from other causes, and we could not control for comorbid illness; therefore, we assessed the all-cause deaths instead of lung cancer–specific death. Because the 5-year OS rates in this population were 65%, 54%, 43%, and 40%, respectively, for stages IA to IIB, the vast majority of these patients likely died from lung cancer. Fifth, because SHS exposure may be associated with stage, performance status, or grade of NSCLC, one may argue that the effect of SHS exposure may be due the effect of stage or performance status. However, all of the patients in this cohort were surgical early-stage patients, and we adjusted for stages in all of the analyses. Lastly, recurrence data were collected retrospectively and patients were not on a prescribed surveillance schedule. However, this will not affect our results of OS.

To our knowledge, this is the first epidemiologic study to suggest that SHS exposure is independently associated with worse OS and RFS among early-stage NSCLC patients, particularly for SHS exposure at work places. The results, together with the previous findings of SHS exposure on lung cancer risks and mortalities, support the importance and efforts of banning smoking in public places and work places.

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