Major Stressful Life Events and Risk of Developing Lung Cancer: A Case-Control Study

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ABSTRACT

BACKGROUND: Lung cancer is the leading cause of cancer-related mortality and is strongly linked with smoking. We sought to determine whether major stressful life events (e.g. divorce) are also a risk factor for developing lung cancers.

METHODS: We performed a matched case-control study. Cases (CA) were lung cancer patients diagnosed within the previous 12 months. Controls (CO) were patients without a prior history of malignancy. Data on major stressful life events were collected using the modified Holmes-Rahe stress scale. The primary endpoint was the odds of having a major stressful life event between CA and CO. A sample of 360 patients (CA = 120, CO = 240) was needed to achieve 80% power to detect an odds ratio (OR) of 2.00 versus the alternative of equal odds using $\chi^2 = 0.05$.

RESULTS: Between May 2015 and December 2016, we enrolled 301 patients (CA = 102, CO = 199), matched for median age (CA = 64.4 years, CO = 63.9 years), sex (CA-Male = 48%, CO-Male = 49.2%), and smoking status (ever smoker, CA = 84%, CO = 85%). There was no difference in lifetime stressful life event rate between CA and CO (95% vs 93.9%; $P = .68$). However, CA were significantly more likely to have had a stressful event within the preceding 5 years than CO (CA = 77.4% vs CO = 65.8%; $P = .03$, OR = 1.78). β-blocker use was significantly higher among CO (CA = 29.4%, CO = 49.7%; $P = .0007$, OR = 0.42), suggesting a protective effect.

CONCLUSION: Patients with lung cancer are significantly more likely to have had a major stressful life event within the preceding 5 years. In addition, use of β-blockers may be protective against lung cancer.

KEYWORDS: stress, lung cancer, smoking, β-blockers, risk factors

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Introduction

Lung cancer is the leading cause of cancer-related death in the United States, as well as worldwide. Lung cancer causes more deaths than colorectal, breast, and prostate cancer combined. More women die each year from lung cancer than from breast cancer.[1,2]

Lung cancer became prevalent concurrent with the widespread practice of smoking at the beginning of the 20th century.[3] Nearly 85% of lung cancer patients have a history of smoking, but not every smoker develops lung cancer. In fact, only 6% to 18% of lifetime heavy smokers (smoking >25 cigarettes/day) will die of lung cancer.[4] Similarly, approximately 15% of lung cancer cases are seen in never/light smokers,[5] pointing to risk factors other than smoking.

Stress has been defined as a state in which our homeostasis is either perceived to be or actually threatened and is re-established by behavioral and physiological adaptive responses. Stressors can be physical, such as extreme heat, or emotional, such as the death of a family member. The stress response involves the release of glucocorticoids through the hypothalamic-pituitary adrenal axis and of epinephrine/norepinephrine through activation of the sympathetic nervous system. These, in turn, cause a variety of physiological and metabolic changes including influencing the inflammatory response and suppressing the immune system.[6]

Stressful life events have been linked with the development of chronic illnesses, including depression, anxiety, diabetes, and heart disease.[7] Studies that have examined the association between stressful life events and cancer have yielded variable results. One large prospective cohort study from Denmark showed no association between stressful life events and risk of cancer.[8] By contrast, a meta-analysis of 165 studies showed that stress-related psychological factors were associated with higher incidence of cancer in a healthy population ($P = .005$).[9]

Similarly, a meta-analysis of 7 studies including nearly 100,000 women showed that stressful life events are linked with the development of breast cancer.[10] The marital status of cancer patients has been linked with outcome—unmarried patients were shown to be more likely to present with metastatic cancer, receive less treatment, and die earlier than a control group of married patients.[11]

Release of cortisol and catecholamine in response to stress can contribute to cancer progression. β-Adrenergic signaling from the sympathetic nervous system has been shown to up-regulate genes that contribute to both tumor progression and metastasis.[12] Xenograft mouse models of non-small-cell lung cancer have shown that social stress promotes lung cancer growth.[13] Flattening of the diurnal cortisol rhythm is a biomarker of early lung cancer mortality.[14]

Epidemiological studies have shown that stressful life events are linked with the development of lung cancer. In one study, bereaved parents who had lost an adult son in an accident had a significantly higher chance of developing lung cancer later in life.[15] Smokers who are also depressed have significant suppression of natural killer (NK) cell activity compared with non-smokers and non-depressed smokers, showing that the combination of smoking and depression can contribute to decreases in NK cell activity.[16]

In this study, we explored the relationship between major stressful life events and the risk of developing lung cancer.

Methods

We performed a matched case-control study. Cases (CA) were patients diagnosed with lung cancer within the preceding 12 months. Cases were enrolled from the outpatient thoracic oncology clinic at The University of Texas/Memorial Hermann Cancer Center, Louisiana State University/Feist Weiller Cancer Center, or admitted at the Memorial Hermann Hospital. Controls (CO) were patients without a prior history of a malignancy. Controls were enrolled from the outpatient pulmonary clinic or those admitted to the hospital at the above-mentioned institutes for reasons other than malignancy. Patients admitted to the intensive care unit, those having ⩾2 prior hospital admissions in the preceding year, or those residing in a nursing home were excluded. Data were collected using a standardized research questionnaire on 12 major stressful life events, filled by the patients using the modified Holmes-Rahe stress scale[17] (see Table 3 for a list of stressful life events). Basic demographic and medical information was obtained from the medical records. Data were stored electronically using the REDCap software.[18]

Cases and CO were matched for age, sex, and smoking status. Smokers had at least a 10 pack-years history of smoking. The primary endpoint was the odds of having a major stressful life event in CA as compared to the CA. A sample of 360 patients (CA = 120 and CO = 240) was needed to achieve 80% power to detect an odds ratio (OR) of 2.00 using the chi-square test with $P = .05$ significance. The study was performed after Institutional Review Board approval was obtained at each institution.

Results

Between May 2015 and December 2016, 324 patients were enrolled into the study and data were analyzed. A total of 23 patients were excluded due to prior cancer history or incomplete information, leaving 301 (CA = 102, CO = 199) patients for the final analysis. The two groups were well matched in median age (CA = 64.4 years, CO = 63.9 years; $P = .72$), sex (CA-Male = 48%, CO-Male = 49.2%; $P = .84$), and smoking status (ever smoker: CA = 84%, CO = 85%; $P = .8$). There was no difference in educational or marital status between the groups. Cases had a significantly lower body mass index ($P < .0001$), which is expected in lung cancer patients. Cases were also significantly more likely to report a family history of lung cancer (CA = 35%, CO = 18%; $P = .001$; Table 1).

There was no difference in the history of chronic obstructive pulmonary disease between the groups ($P = .88$), but CO were significantly more likely to have diabetes (CA = 14.7%, CO = 36.6%; $P \leqslant .0001$) and cardiovascular disease (CA = 23.5%, CO = 47.7%; $P \leqslant .0001$; Table 1).

The two groups showed no difference in the age at which smoking was started (CA = 17.3 years, CO = 17.8 years; $P = .44$) or the number of packs of cigarettes/day smoked ($P = .42$), but CA had significantly longer exposure to smoking (average years of smoking: CA = 42.3 years, CO = 36.5 years; $P = .003$; Table 2).

Over the lifetime, there was no difference in stressful life events between CA and CO (95% vs 93.9%; $P = .68$). However, CA were significantly more likely to have had a major stressful life event within the preceding 5 years than CO (CA = 77.4% vs CO = 65.8; $P = .04$, OR = 1.78). Serious life-threatening illness of an immediate family member ($P = .05$) and retirement ($P = .08$) within the preceding 5 years were noticeably more common among CA (Table 3).

Based on 12 major stressful life events from the modified Holmes-Rahe stress scale, a life event score was calculated. In the preceding 5 years, the stress score of the two groups was higher in men (CA = 86.3, CO = 66.2; $P = .07$) and those >65 years old (CA = 82.4, CO = 57.2; $P = .05$). Patients with squamous histology also had a higher stressful life events score in the preceding 5 years than those with adenocarcinoma histology (adenocarcinoma = 63.4, squamous = 115.6; $P = .005$). Non-smoking lung cancer patients also showed a trend of having a higher stressful life events score in the preceding 5 years, but this was not significantly different than CO, perhaps due to the small sample size (CA = 75.1, CO = 59.9; $P = -.47$; Supplemental Table 1).

We assessed the social situation of both groups using the Duke-UNC functional social support questionnaire.[19] Patients with lung cancer reported having significantly better social support than CO ($P = .01$; Table 1). We also checked the

Table 1. Patient characteristics among study subjects.

CHARACTERISTIC	ALL PATIENTS (N = 301)	CASES (N = 102)(%)	CONTROLS (N = 199)(%)	*P*
Sex				
Male	147	49 (48)	98 (49)	.842
Female	154	53 (52)	101 (51)	
Median age, years	64.1	64.4	63.9	.728
Ethnicity				
African American	106	32 (31)	74 (37)	.400
White	143	54 (53)	89 (45)	
Hispanic, Asian, other	52	16 (16)	36 (18)	
Body mass index, mean	29.2	25.7	31	<.0001*
Maximum education				
High school	152	53 (52)	99 (50)	.742
College	125	40 (39)	85 (43)	
Masters/PhD	20	8 (8)	12 (6)	
Marital status				
Married	154	59 (58)	95 (48)	.100
Single	49	18 (18)	31 (16)	
Separated/divorced/widowed	98	25 (25)	73 (37)	
Medical history				
Family history of lung cancer	72	36 (35)	36 (18)	.001*
Diabetes	88	15 (15)	73 (37)	<.0001*
Hypertension	209	64 (63)	145 (73)	.073
COPD	96	32 (31)	64 (32)	.888
Cardiovascular disease	119	24 (24)	95 (48)	<.0001*
Major depression	39	10 (10)	29 (15)	.237
β-blockers	129	30 (29)	99 (50)	.0007
Metformin	34	9 (9)	25 (13)	.318
Duke-UNC social support score (Max. 40)	34.8	36.2	34.1	.013
Belief system score (Max. 25)	18.3	18.5	18.1	.604

*Significant: chi-square test.

religiosity of the two groups by asking questions regarding the practice of any religion, belief in an after-life, visiting a place of worship, and having friends from a place of worship; there was no significant difference between the two groups ($P = .6$).

β-Blocker use was significantly higher among CO than CA (CO = 50% vs CA = 29%; $P = .0007$; Table 1). We also found that, among lung cancer patients, those with early-stage disease (stage I and II) were more likely to be on β-blockers (44%) than those with late-stage disease (stage III/IV) (26%), although this was not statistically significant ($P = .12$), perhaps because of the small number of β-blocker users. More patients were on selective β_1-blockers among both CA (61%) and CO (56%).

In the univariate logistic regression analysis, number of years smoked (OR = 1.04, 95% confidence interval [CI] = 1.02-1.07, $P = .0005$), family history of lung cancer (OR = 2.45, 95% CI = 1.43-4.23, $P = .001$), and any stressful life events in the past 5 years (OR = 1.78, 95% CI = 1.03-3.09, $P = .039$) were significantly associated with an increased risk of developing lung cancer, and the use of β-blockers (OR = 0.42, 95% CI = 0.25-0.7, $P = .0009$) and diabetes (OR = 0.3, 95%

Table 2. Smoking history of study subjects.

	ALL PATIENT (N = 301)	CASES (N = 102)	CONTROLS (N = 199)	*P*
Ever smoker (%)	256	86 (84)	170 (85)	.797
Current smoker (%)	77	23 (23)	54 (27)	.406
Age at which started smoking, mean	17.6	17.3	17.8	.449
Age at which quit smoking, mean	53.7	58.4	51.2	<.0001*
Average packs/day				
<1	131	46	85	.426
1-2	84	28	56	
3-4	41	12	29	
Smoking exposure, mean packs/year	34.9	39	32.9	.057

*Significant: chi-square test.

Table 3. Major stressful life events in the past 5 years (from Holmes-Rahe stress scale (17).

STRESSFUL EVENT	ALL PATIENTS (N = 301)	CASES (N = 102)	CONTROLS (N = 199)	*P*
Any event (%)	210	79 (77)	131 (66)	.037*
Death of spouse	24	8	16	.952
Death in family	72	27	45	.457
Serious personal illness	58	16	42	.259
Serious illness of a family member	63	28	35	.046
Divorce/separation	14	5	9	.882
Loss of job	27	10	17	.717
Caring for ill family member	32	13	19	.394
Financial difficulties	57	21	36	.600
Relocation	26	8	18	.725
Stress at work	36	17	19	.716
Detention/incarceration	7	2	5	.763
Retirement	44	20	24	.079

*Significant: chi-square test.

CI = 0.16-0.55, *P* = .0001) were associated with a decreased risk (Table 4). In the multivariate logistic regression analysis adjusting for number of years smoked and family history of lung cancer, stressful life events in the preceding 5 years remained significantly associated with an increased risk of developing lung cancer (OR = 2.20, 95% CI = 1.11-4.36, *P* = .02). Similarly, the use of β-blockers (OR = 0.43, 95% CI = 0.23-0.81, *P* = .0014) remained protective against developing lung cancer (Table 4).

Discussion

Measuring stress and its impact on an individual's health in a population-based study can be challenging. We approached the association between stress and lung cancer by focusing on major stressful life events during an individual's lifetime, which are easier to quantify. Even with this approach, a particular stressful life event such as divorce or retirement may elicit a variable response in each individual depending on many other personal factors that are impossible to control. Hence, we focused only on quantifying the number of stressful events instead of on the degree of stress that a patient may attribute to a particular event, which is a subjective assessment. Since lung cancer is strongly linked with smoking, we included CO who were matched for smoking status. To our knowledge, this is the first study to examine the association between stressful life events and lung cancer to have adequately matched CO.

Table 4. Univariate and multi-variable analysis.

	ODDS RATIO (95% CI)	*P*
Univariate analysis		
Smoking exposure in years	1.04 (1.02-1.07)	.0005
Family history of lung cancer	2.45 (1.43-4.23)	.001
Stressful life events, past 5 years	1.78 (1.03-3.09)	.039
Diabetes	0.3 (0.16-0.55)	.0001
β-blockers	0.42 (0.25-0.7)	.0009
Multivariate analysis		
Smoking exposure in years	1.04 (1.02-1.07)	.002
Family history of lung cancer	2.72 (1.42-5.21)	.002
Stressful life events, past 5 years	2.21 (1.11-4.37)	.023
Use of β-blockers	0.44 (0.23-0.81)	.009
Diabetes mellitus	0.35 (0.17-0.73)	.005

Logistic regression analysis.

Over the lifetime of study subjects, there was no difference in rate or number of stressful life events between the two groups. However, lung cancer patients were significantly more likely to have had a major stressful life event in the preceding 5 years than were CO (OR = 1.78). This temporal association shows that when major stressful life events affect an individual's chance of developing lung cancer, the effect happens within months to a few years as opposed to smoking, which can take decades to cause cancer. In the multivariate analysis, after adjusting for smoking exposure and family history of lung cancer, major stressful life events within the preceding 5 years remained significantly associated with an increased risk of developing lung cancer.

The modified Holmes-Rahe stress score was calculated on the basis of 12 major stressful life events. The score was higher in men with lung cancer than in CO, in elderly persons (≥65 years) with lung cancer than in CO, and in lung cancer patients with squamous histology than those with adenocarcinoma. There was no difference in stress score among CA and CO in women and those <65 years old. The higher stress score in elderly men with squamous lung cancer compared with corresponding CO and those with adenocarcinoma histology suggests that major stressful life events as a risk factor for lung cancer affects this subgroup more than others. The exact reason behind this correlation is not known to us. The stress score among non-smoking lung cancer patients was also higher than that of non-smoking CO, although this was not significant, perhaps because of the small sample size of non-smokers. A larger study focusing on stressful life events among non-smoking lung cancer patients should help determine whether stressful life events can be a risk factor for developing lung cancer in this population or whether they contribute only in the setting of smoking exposure. Other studies have shown a similar association between stressful life events and breast cancer, colorectal cancer, and cancers in children.[10,20,21] Stressful life events have also been linked with a shorter disease-free interval in breast cancer patients.[22]

We also examined social support and religiosity between the two groups. Lung cancer patients actually reported better social support according to the Duke-UNC functional support score than CO, perhaps due to more involvement of the family in the care of patients after a cancer diagnosis. There was no difference in measure of religiosity between the two groups.

In terms of the biological effects of major stressful life events, we speculate that these events are linked with suppression of the immune system and activation of the endogenous catecholamine pathway, which have been linked with tumor growth. In a xenograft mouse model of non-small-cell lung cancer, social stress has been linked with significant tumor growth. In these mice, serum and tumor levels of noradrenaline, adrenalin, and cortisol were found to be elevated.[13] In our study, we found that CO were significantly more likely to be receiving β-blockers than patients with lung cancer, and this remained significant in the multivariate analysis after adjusting for other factors. Similarly, early-stage lung cancer patients (Stage I/II) were more likely to be on β-blockers (44%) than were those with advanced stage (Stage III/IV) disease (26%), although this was not statistically significant. This raises the question of whether, by targeting endogenous catecholamine, β-blockers may be protective against the development of lung cancer. Use of β-blockers has been linked with improved survival in patients with locally advanced lung cancer undergoing definitive radiotherapy, as well as in patients with ovarian cancer.[23,24]

Major stressful life events have also been linked with suppression of immune system resulting in diminishing immune surveillance, which is protective against neoplastic growth. In one study, patients who had a troubled early parent-child relationship and also developed a severe stressful life event within the preceding year showed a poor immune response in their basal cell tumors as reflected by lower levels of mRNA for CD25 (an interleukin (IL)-2 receptor), CD3 (total T cells), ICAM-1, and CD68 (macrophages).[25] Stress is also linked with the release of inflammatory cytokines such as IL-6, which plays an important role in tumor growth and progression.[26] It is possible that individuals who are exposed for decades to carcinogens such as smoking are prone to developing cancer during periods of immune suppression triggered by major stressful life events. This hypothesis requires confirmation through biological correlative studies such as measuring NK cell activity or the infiltration of macrophages in the tumor microenvironment in lung cancer patients with a history of recent major stressful events.

Study Limitations

There are several limitations in our study. The two groups were well matched for age, sex, and smoking status, but the duration of smoking exposure was longer in CA than CO, and this could account for the increased chance of developing lung cancer.

Moreover, recall bias could have caused a poor estimation of stressful events among the study subjects. In the univariate and multivariate analyses, diabetes was linked with a decreased risk of developing lung cancer, for which we have no good explanation. The association between diabetes and lung cancer is not very clear in the literature,[27,28] with studies giving conflicting conclusions; this matter requires clarification in future studies. There was no difference in the use of metformin between the two groups. Similarly, higher use of β-blockers among CO may be the result of higher prevalence of hypertension and cardiovascular disease among CO than among lung cancer patients, although their protective effect cannot be ruled out.

Clinical Implications

One obvious clinical implication of this study is to recognize major stressful life events as a risk factor for lung cancer in addition to smoking. Patients can be screened for recent major stressful life events at diagnosis and offered appropriate psychological counseling if needed, just as they are counseled about smoking cessation. Similarly, β-blockers can be used as preventive therapy for high-risk patients. However, before any clinical recommendations are made, further research is needed to validate these findings.

Conclusion

In conclusion, to our knowledge, this is the first case-control study matched for smoking showing that major stressful life events can be a risk factor for developing lung cancer. Moreover, we found that the use of β-blockers may be protective against developing lung cancer. Future studies should be done to validate these findings and to determine biological correlates for the effects of major stressful life events in lung cancer patients and the protective effects of β-blockers.

Authors' Note

Mahran Shoukier is now Leukemia fellow, UT MD Anderson, Houston, Texas and Hazem el-Osta is now affiliated to Baylor college of Medicine, Division of Oncology, Houston, Texas.

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Author Contributions

SHJ designed the study, collected and analyzed the data, and wrote the manuscript. FA, AM, SMH, RH, BA, and HE-O collected and analyzed the data. JW analyzed the data and performed statistical analysis. All authors reviewed the manuscript.

Availability of Data

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Consent to Participate

Written, informed consent was obtained from patients in accordance with the IRB guidelines at each institution.

Ethical Approval

Patients provided written, informed consent to enroll in the study. The study was conducted after getting institutional review board approval from the UTHealth Committee For the Protection of Human Subjects (IRB00004604) and the Louisiana State University Health Sciences Center at Shreveport Institutional Review Board.

SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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