EXPOSURE TO STRESSFUL LIFE EVENTS AND LUNG CANCER RISK

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ÉCOLE DE SANTÉ PUBLIQUE DE L'UNIVERSITÉ DE MONTRÉAL

MÉMOIRE PRÉSENTÉ À LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES
EN VUE DE L'OBTENTION DU GRADE
MSc SANTÉ PUBLIQUE

DÉCEMBRE 2015

Résumé

Objectif: Examiner l'association entre l'exposition aux évènements stressants de la vie et le cancer du poumon.

Méthodes: Les données proviennent d'une étude cas-témoins, menée chez les hommes et les femmes vivant dans la région métropolitaine de Montréal entre 1996 et 2001. Le cancer du poumon d'un cas éligible devait être confirmé histologiquement à l'un des 18 hôpitaux de cette région. Les témoins ont été sélectionnés aléatoirement de la liste électorale du Québec et ont été appariés au cas par fréquence de groupes d'âge et par sexe. Un questionnaire a été administré en entrevue pour recueillir les données, dont l'évaluation de huit évènements stressants de la vie par le participant. Si le participant avait vécu un évènement stressant ciblé durant les six dernières années, il devait aussi coter cet évènement sur une échelle de trois points. La régression logistique non conditionnelle a été utilisée pour estimer les rapports de cotes ainsi que leurs intervalles de confiance à 95%. Des analyses par sexe, niveau de tabagisme et par type histologique ont été réalisées. Nous avons aussi analysé l'association entre le cancer du poumon et le nombre total d'évènements, les évènements de perte et les évènements socioéconomiques, ainsi que chaque évènement individuellement. Les analyses des scores d'impact autoévalués et avec un score externe de perception, ont également été menées.

Résultats: La population de ce projet comprend 1061 cas et 1422 témoins, âgés de 35 à 70 ans. Les participants inclus avaient répondu aux sections du questionnaire portant sur les facteurs de style de vie et sur l'historique de tabagisme. Dans l'ensemble, nous n'avons pas observé d'association entre le cancer du poumon et l'exposition aux évènements stressants de la vie. Nous avons observé une diminution du risque pour les évènements socioéconomiques autoévalués comme peu stressants (RC=0,50; IC 95%= 0,31 - 0,81).

Conclusion: Nos résultats suggèrent que les évènements socioéconomiques sont associées à un risque réduit si ces évènements sont considérés comme peu stressant.

Mots-clés : Épidémiologie, cas-témoin, cancer du poumon, évènements stressants de la vie, stress psychosociale.

Abstract

Objective: To examine exposure to stressful life events in relation to lung cancer risk.

Methods: Our research used data from a case-control study conducted in Montreal from 1996 to 2001. Cases were diagnosed with histologically confirmed incident lung cancer at one of 18 Montreal-area hospitals. Controls were randomly selected from the Quebec electoral list and frequency matched to the distribution of cases by sex and 5 year age groups. Data was collected on sociodemographic characteristics, lifetime smoking, and lifestyle factors including 8 stressful life events. Participants indicated the stressful life events they experienced over the past six years, and an appraisal of their level of stress due to each event on a three-point scale. Unconditional logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals. Each stressful life event was analyzed individually as well as in grouped variables measuring total number of events, loss events and socioeconomic events. Analyses of self-appraised impact scores were also conducted; additionally an external perceived stress score was also employed.

Results: 1061 cases and 1422 population controls were included in the analyses. Overall, we observed no association between lung cancer and stressful life events. A decrease in risk for socioeconomic events self-appraised as not very stressful was observed (OR, 0.50; 95% CI, 0.31, 0.81), which included job loss, increase in debt, and move to another city.

Conclusion: Our results suggest that socioeconomic events, deemed not very stressful, may reduce the risk of lung cancer.

Keywords: epidemiology, case-control, lung cancer, stressful life events, psychosocial stress.

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Abbreviations

4DCT: Four-dimensional Computed Tomography

8-OH-dG: 8-hydroxydeoxyguanosine

BMI: Body Mass Index

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CSI: Comprehensive Smoking Index

CT: Computed Tomography

DNA: Deoxyribonucleic Acid

EBRT: External Beam Radiation Therapy

EGFR: Epidermal Growth Factor Receptor

GWAS: Genome Wide Association Studies

IARC: International Agency for Research on Cancer

K-RAS: Kirsten Rat Sarcoma Viral Oncogene Homolog

LCU: Life Change Unit

MLCS: Montreal Lung Cancer Case-Control Study

NK: Natural Killer

NOS: Not Otherwise Specified

OR: Odds Ratio

PET: Positron Emission Tomography

PSS: Perceived Stress Scale

PTEN: Phosphatase and Tensin Homolog

RR: Risk ratio

SAS: Statistical Analysis Software

SNS: Sympathetic Nervous System

SRRS: Social Readjustment Rating Scale

TERT: Telomerase Reverse Transcriptase

Acknowledgements

I must express my deep gratitude and appreciation to my supervisor Dr. Anita Koushik for her mentorship, patience and consistent support. I have gained precious knowledge and epidemiologic research skills during my time as her student, and I am grateful to her for all the constructive criticism and valuable feedback.

I would like to thank Dr. Jack Siemiatycki for his time and valued feedback on the analytical plan of this thesis, and for sharing a wonderful dataset with me. Thank you to Lesley Richardson and all members of the Environmental Epidemiology and Population Health Research Group at the CrCHUM for their time and feedback on analyses and oral presentations. Special thank you to Romain Pasquet and Dr. Vikki Ho for their optimism and willingness to share their epidemiology acumen. Thank you to my classmates at the University of Montreal for their encouragement and continued collaboration.

I would also like to thank my professors in the Department of Social and Preventive Medicine for interesting class discussions, inspiration and encouragement. Many thanks to the Faculté des études supérieures et postdoctorales for the funding they provided me to complete this project.

I would like to acknowledge the participants who completed the questionnaires as a part of this case-control study – thank you for your time.

Finally, thank you to my family for their love, encouragement and understanding. This accomplishment would not have been possible without their unwavering support. Thank you!

1.0 Introduction

Lung cancer is a malignant tumour that arises from uncontrolled cell growth in the epithelial layer of the lungs and respiratory tract.[1] Numerous histological subtypes exist, which vary in pathogenesis, genetic etiology and growth rate.[2] The principal malignant subtypes can be categorized into small cell lung carcinomas and non-small cell carcinomas; the latter including adenocarcinoma, squamous cell carcinoma, large cell carcinoma.[3]

Doll and Hill, in their landmark epidemiologic study first suggested the link between lung cancer and cigarette smoking in 1950.[4-6] Today, it is widely accepted that tobacco smoking is the most important risk factor for lung cancer.[7] However 10-15% of lung cancer deaths occur in non-smokers, and only 15% of smokers develop lung cancer.[8] This suggests a gap within the causal pie for lung cancer,[9] whereby other etiological factors may be important. Further research is required to examine suspected and novel risk factors for lung cancer.

Epidemiologic and environmental studies have implicated psychosocial stress in neoplasm development. "Stressful life events" are employed as a measure of the acute physiologic response to environmental stressors; distinct from adaptations to chronic and daily stress.[10] Acute physiologic demands of stressful life events may lead to changes in the immune system, changes in the endocrine system, dysfunction in cellular self-regulation and increased generation of reactive oxygen species, resulting in enhanced opportunity for lung tumour growth.[11-18]

Using data from a case-control study carried out in Montreal, the association between lung cancer risk and exposure to stressful life events in the 6 years prior to date of diagnosis or recruitment was examined. Exposure to eight individual stressful life events, and total number of events, was investigated. Because the human response to stressors varies between individuals, we also examined each stressful life event weighted according to perceived stressfulness of the event. One weighting scheme was based on self-appraisal of each event, assessed in the same

questionnaire, while the other weighting scheme was developed and updated external to this study.[19] Crucial confounding factors such as smoking, ethnicity and socioeconomic status were included in the analyses. Stressful life events grouped according to "loss events" and "socioeconomic events" were also analyzed.

Background on known risk factors for lung cancer, as well as a summary of the current literature on the association between psychosocial stress and lung cancer promotion is included in Chapter 2, followed by the main objective of this thesis in Chapter 3. The methodology, primary and secondary analysis plans are described in detail in Chapter 4. Results are presented in Chapter 5, the interpretations of which along with the context in current literature and methodological considerations are discussed in Chapter 6. Conclusions and their implications in the Canadian public health landscape are discussed in Chapter 7.

2.0 Background and Rationale

2.1 Descriptive Epidemiology

Lung cancer is a major Canadian public health concern, as it is the leading cause of death due to cancer in Canada and worldwide.[19] The Canadian Cancer Society estimates that 20,900 Canadians will die from Lung Cancer in 2015.[20] Among Canadian women, the mortality rate for this deadly disease has continued to climb, increasing by approximately 0.6% every year since 2000.[21] Moreover, primary lung tumors are the second most frequently diagnosed cancer among all Canadians.[19] While the incidence rate is higher among males (60 per 100,000), incidence rates of lung cancer among Canadian females have been increasing since 1982 with a yearly increase of 1.1% between the years 1998 to 2007, reaching 51 per 100,000 person-years in 2007.[21] In both men and women, the incidence of lung cancer is low before age 40, and increases up to at least age 70.[22]

Geographical patterns of lung cancer incidence are determined by tobacco consumption.[22] In 2015, the Canadian Cancer Society estimated Quebec to have the highest lung cancer incidence rate in Canada, and British Columbia to have the lowest.[21] This discrepancy is strongly linked to differences in smoking prevalence and distribution of socioeconomic classes.[23] Temporal patterns are similarly dictated by smoking patterns, with a decrease in the prevalence of squamous cell carcinoma since the 1970s, following the introduction of filtered cigarettes in the United States and a subsequent change in inhalation of tobacco smoke.[23]

2.2 Clinical Care

Chest X-rays and computed tomography (CT) scans are performed to screen for lung cancer, but the sensitivity of this screening practice varies with histological subtype, tumour size and location in the lungs and respiratory tract.[22] Therefore small tumours in their early stages,

when they are most curable, are often missed.[24] Consequently, most cases of lung cancer are diagnosed at a later stage, and five year survival rates are between 5% and 15%.[25] In fact, 40% of patients with non-small cell lung cancer have metastasis at presentation.[26] Initial diagnosis of a primary lung tumour is made on the basis of an asymptomatic lesion discovered on X-ray, with confirmation from histological analysis of a biopsy.[22] Symptoms vary depending on tumour subtype and location, but may include chest pain, fatigue, decreased physical activity, weight loss, persistent cough or labored breathing.[22] Radiograph screening carries adverse risks, consequently the Canadian Taskforce on Preventive Healthcare has recommended against screening asymptomatic people for lung cancer using radiography.[27]

Surgery to resect the tumour remains the standard treatment in stage 1 and 2 non-small cell lung cancer.[28] Chemoradiotherapy, usually given concurrently to surgery, has been shown to improve long-term survival in patients with advanced non-small cell lung cancer.[28] With respect to small cell lung cancer, surgery is rarely used as the main treatment, as it grows quickly and has spread to other organs before it is found. Chemotherapy is the main treatment for small cell lung cancer, followed by external beam radiation therapy (ERBT).[29] Progress in the overall survival of patients is enabled by the introduction of targeted therapies which exploit genomic alterations and histological subtypes, the use of endoscopic ultrasound for less invasive prognosis and staging, PET scans used as a compliment to CT scans for the improved detection of metastasis, and real-time tumour imaging using four-dimensional computed tomography (4DCT) which allows radiation to be delivered more precisely to the tumour.[28,29]

2.3 Risk Factors

Lung cancer etiology had been studied since the mid-twentieth century; therefore there exists a wide range of risk factors that have been identified as contributing to the incidence of this disease. The International Agency for Research on Cancer (IARC) classifies tobacco smoking,[30] secondhand tobacco smoke,[30] indoor and outdoor air pollution,[31] and several occupational exposures as Group 1 lung cancer carcinogenic agents,[32] which means there is "sufficient evidence in humans" to establish them as harmful to humans.[32] Additional modifiable risk and protective factors that have been identified in previous studies include dietary and

lifestyle factors. Finally, there is evidence that supports an association between lung cancer risk and certain genetic and socioeconomic factors.

2.3.1 Tobacco Smoking

Tobacco smoking, including environmental tobacco smoke (or secondhand smoke), is the primary risk factor for lung cancer and has been recognized as such by public health authorities since 1964.[33] Duration of smoking is the dominant factor contributing to this effect, however other aspects of tobacco smoking including age at initiation, time since quitting, average daily consumption and inhalation pattern, also contribute to the overall effect.[22,34]

When compared to never-smokers, male ever-smokers have an 8 to 15 fold increased risk of lung cancer and female ever-smokers have a 2 to 10 fold increase.[22] There is an elevated risk of lung cancer associated with increasing pack-years of cigarettes smoked, and a stronger increase in risk associated with duration of smoking vs. daily consumption of cigarettes.[22,35] Inhalation patterns may decrease risk with an observed reduction in risk for smokers of filtered cigarettes compared to unfiltered cigarette smokers.[22] Current and former smokers are at an increased risk when compared to never smokers, however the risk for former smokers decreases with a longer time since smoking cessation, and with a greater benefit to those quitting at a younger age.[36,37] Never smokers can also be affected by tobacco smoking; if residing with a smoker, never smokers have a 24% increased risk of lung cancer.[38]

Men and women living in high-income countries smoke at nearly the same rate.[39] Interestingly, since 1992 lung cancer incidence rates have been on the decline among males, but on the rise among females.[40] While this may be attributed, in part, to an increase in smoking cessation among males, it has been suggested that female ever-smokers may be more susceptible to certain histological subtypes of lung cancer, when compared to male ever-smokers. [35]

2.3.2 Occupational Exposures

Occupational exposures to carcinogens are important risk factors for lung cancer because they are modifiable and preventable. Asbestos has been identified as the most important occupational risk factor, contributing to 7% of all lung cancer cases.[43,44] Today, exposure to asbestos predominantly occurs through inhalation of fibrous crystals while directly handling the material, with maintenance workers most often exposed.[45] There is a 77% increase in mortality among asbestos-exposed workers when compared to non-exposed workers, and evidence that asbestos exposure and smoking may work synergistically to increase risk of lung cancer.[46] Other occupational carcinogens classified as group1 by IARC include: radon, arsenic, silica dust (bricklayers), chromium compounds, chloromethyl ethers (painters), nickel and welding fumes (welders).[32]

2.3.3 Environmental Exposures

Outdoor air pollution has only recently become recognized as a risk factor for lung cancer, classified as a group 1 carcinogen in October 2013. Outdoor air pollution is primarily made up of particulate matter (large, fine and ultrafine matter), diesel engine exhaust, solvents and dust.[47] Particulate matter has been recognized as a risk factor for lung cancer, on its own. A recent meta-analysis has shown an increase in adenocarcinoma risk associated with exposure to particulate matter, with risks increasing as the size of particulate decreases: 29% increased risk per 10μg/m^3 exposure to large particulates, and a 40% increased risk per 10μg/m^3 exposure to fine particulates.[48] Indeed, an increase in lung cancer risk was observed for people living close to major roads compared to those living farther.[49] Outdoor air pollution has a particular public health importance due to the scale of exposure and large amount of people exposed daily.

Exposure to air pollution can also occur in the home. Sources of indoor pollution are emissions resulting from residential heating and cooking.[31,50] A recent meta-analysis has shown a doubling of risk for people, primarily in China, using coal in the home for cooking or heating.[50] Of note, coal composition varies worldwide and risks may be geographically specific. Indeed, a European case-control study did not find an association between coal use in the home and lung

cancer risk.[51] Our Montreal population-based case-control study has suggested that cooking fuels may confer an increased risk in women, with no association in men.[52]

2.3.4 Socioeconomic Factors

Socioeconomic status is commonly measured as a combination of education, income and job title. Several epidemiologic studies have suggested an inverse relationship between socioeconomic status and lung cancer incidence and mortality.[53] However, it has been proposed that this relationship may be due, in part, to incomplete adjustment for smoking.[54] Epidemiologic studies have also provided "moderate support" for the association between race or ethnicity and risk of lung cancer.[55] It has been proposed that black smokers have an increased risk of lung cancer when compared to Caucasian smokers.[56] However, smoking, via socioeconomic status, may explain this variation due to the lack of biologic evidence.[57] Evidence suggests that on a global scale, low SES groups have higher smoking rates because they are more likely to try smoking, become regular smokers, and are less likely to quit.[58] Furthermore, tobacco consumption varies by socioeconomic status in that smokers with low SES smoke more cigarettes per day and smoke each cigarette more heavily and therefore extract more nicotine (and therefore tar) per cigarette.

2.3.5 Genetic Factors

Family history can increase the risk of lung cancer development, with varying magnitudes, dependent on smoking status. Smokers with a positive family history of lung cancer are at twice the risk of developing cancer themselves, while non-smokers have a 1.5-fold increased odds ratio of developing the disease.[59] These risks are additionally increased if a family member was diagnosed at an early age and if numerous family members are affected.[59,60] The genetic component to the pathogenesis of lung cancer could relate to the host's susceptibility to lung cancer; either through mutagen sensitivity or genomic instability.[59,60] Genome wide association studies (GWAS) have been conducted to identify the responsible polymorphisms. Examples of candidate genes include: glutathione-S transferases and cytochrome P450 enzymes,

which are involved in the metabolism of tobacco smoke compounds, and cholinergic nicotinic receptor subunits that may influence nicotine dependence[59] and cell signaling pathway mutations (eg. EGFR, K-Ras, PTEN, TERT). The extent to which a candidate gene is carcinogenic can be assessed by using DNA adducts as biomarkers.[60] The results have been mixed and the specific genes involved have not been identified.[60] Current studies aim to examine gene-gene interactions.

2.3.6 Dietary and Anthropometric Factors

In 2007, the World Cancer Research Fund conducted an international panel review of the evidence for the association between dietary factors, physical activity and cancer.[61] The evidence for lung cancer was based on 561 included articles. The panel concluded that there was convincing evidence that arsenic in drinking water and beta-carotene supplements increase the risk of lung cancer in current smokers. Additionally, the evidence was considered probable that consumption of fruits and carotenoid-containing food decrease the risk of lung cancer.[61] The mechanism of action proposed for carotenoids, is their ability to capture reactive oxygen species, and thus counterbalance the formation of free radical cell damage that and has been linked to cancer.[62] In particular, increased vitamin A (fat-soluble vitamin) and beta-carotene (carotenoid) intake has been shown to have a protective effect, while low serum concentrations of antioxidants have been linked to an increased risk.[59,60] Two large randomized controlled trials,[63,64] one of which was cut short,[64] concluded that alpha-tocopherol, beta-carotene and vitamin A supplement use resulted in increased mortality and incidence of lung cancer.[60,63,64] Given the protective effect conferred by carotenoid rich foods, this result was unexpected. As a result of the findings in these trials, taking beta-carotene and vitamin A supplements is discouraged.[60] However, there is criticism of the implications of these findings, due to the enrollment of heavy and longtime smokers in the trials which may have confounded the relationship between lung cancer and supplement use.[65]

An additional risk reduction was proposed for a diet rich in fruits and vegetables when consumed raw, since cooking can destroy these important micronutrients.[60] Epidemiologic studies have indicated the possibility of an increased lung cancer risk associated with red and processed meat, however the evidence was judged as limited and inconsistent.[61] It was recently

suggested that occasional consumption of coffee was inversely associated with lung cancer, while drinking black tea for more than 50 years was associated with a slight increase in risk for adenocarcinoma.[66]

Obesity in smokers has been positively associated with lung cancer when measured by waist circumference,[67] but inversely associated with BMI.[68] The latter can be attributed to effect modification by cigarette smoking.[69,70] It follows that among never smokers, BMI has been shown to have no association with lung cancer,[69] however positive associations have been suggested by some studies.[68]

2.3.7 Summary of Risk Factors for Lung Cancer

A complex network of modifiable and non-modifiable factors, as well as their interactions with one another, influences the absolute risk of developing lung cancer within a lifetime. Figure 1 provides a graphical representation of sections 2.3.1 to 2.3.6, inclusive. While socioeconomic status has been reported to be associated with an increase in risk of lung cancer, it is understood that this is likely via known and unknown pathways and mediators. Thus, it is likely that air pollution and dietary factors act as mediators for this last association. Few studies have estimated the proportion of lung cancer cases attributable to the factors presented in Figure 1 (population attributable risk). However, there is some consensus with respect to cigarette smoking; Alberg[71] reported that active smoking is responsible for 90% of lung cancer cases, while Chyou reported that 85% of lung cancer cases could have been avoided if the cases had been non-smokers.[72]

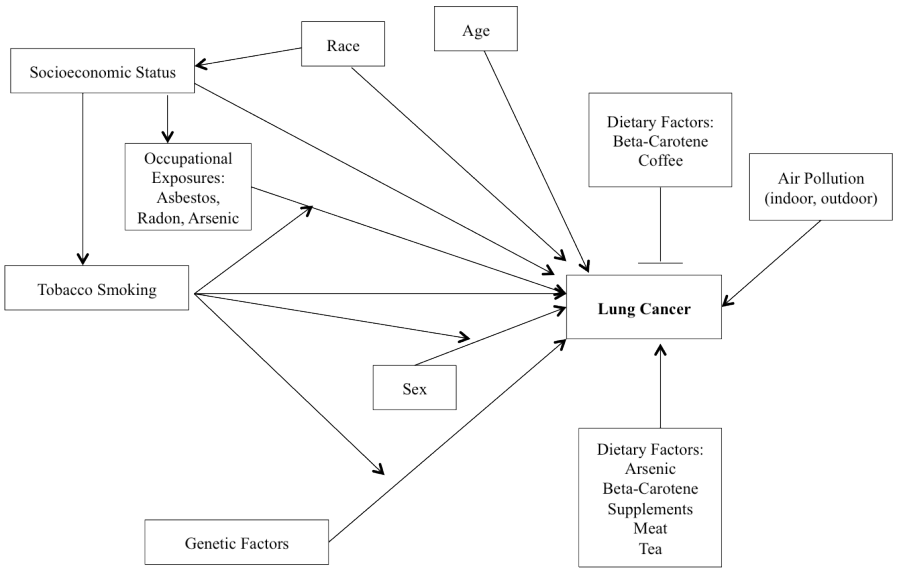


Figure 1: Risk Factors for Lung Cancer

2.4 Psychosocial Factors are Suspected Risk Factors

2.4.1 Psychosocial Stress

There is a long-standing discussion about the association between psychosocial stress and neoplasms. Hans Selye first described the physiological response, or alarm reaction, to external "stressful" stimuli in 1936.[73] This response-based, biological stress theory has been used as the primary framework for clinical research aimed at investigating the role of stress in physiological illness. Under Selye's conceptual theory, environmental conditions eliciting physiological reactions are termed stressors, and the resulting adaptive (stress) response is a probabilistic and nonspecific feature of the stressor.[74-76] It has since been accepted that cognitive appraisal, personality and emotional response may act as coping mechanisms and effect measure modifiers between stressor and stress reaction, shaping the differential human response to environmental stressors.[77,78]

Stressful life events are an "objective" way to measure environmental stressors. It has been widely accepted in psychological literature to employ measurements of life events as

indicators of stress, due to the probabilistic stress feature of particular events.[79] However it is possible that it is the meaning of the events and perception of stress to the individual, rather than the events themselves, that are important. Richard Lazarus first proposed the idea that the impact of exposure to these events is determined, in part, by a person's perception of the stressfulness of any event, whether it be positive or negative.[80] In this way, humans can adapt to the effect of specific circumstances that change over time. Susan Kune proposes a model (Figure 2) of the pathway from stressful life event to immunosuppression, via perception of stress.[81] In this way, the event is a catalyst for the stress response, which is ultimately in the control of the individual.[81]

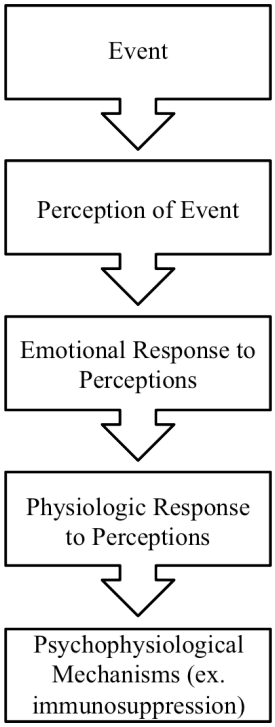


Figure 2: Kune model depicting the way in which stressful life events may lead to illness.[81]

Thomas Holmes and Richard Rahe attempted to quantify the perception of stress associated with 43 common life events in their 1967 landmark study, when they proposed their Social Readjustment Rating Scale (SRRS).[82] 394 men and women were administered questionnaires and asked to determine if each life event was "indicative of more or less readjustment than marriage," which was assigned a score of 500.[82] Social readjustment refers to the participants' estimation of the intensity and length of time required to adapt their life to the life event proposed. Of note, only 223 of 394 participants were married at the time of interview,

illustrating the fact that assessment of the adjustment required was not always based on personal experience of the event.[82] The degree of readjustment eventually came to be known as a Life Change Unit (LCU), and the scale was adapted with additional life events and larger samples on two separate occasions; most recently in 1995 by Mark Miller and Richard Rahe.[19]

The use of stressful life events as a measure for psychosocial stress when investigating the link with physical illness has clear advantages. First, it presents an easily identifiable event that can be objectively measured. Second the measurement procedure is simple and can be easily included within a larger questionnaire. Third, the chance for variation and subjective bias in the reporting of the events is low. On the other hand, the implication that the inherent stressfulness of the event causes physiologic changes in the human body disregards the appraisal of stressfulness for each event, along with the ability to cope, in the assessment of the exposure. Gold standard instruments aimed to measure perceived stress in a population have been developed since the SRRS was first presented. One such tool, the Perceived Stress Scale (PSS), is a 14 item questionnaire intended to measure the degree of a participant's perception of life stress.[80] However, these instruments are not commonly used in studies aimed at examining the link between stress and cancer. Current studies aim to validate the reliability of a four-item version of the PSS for telephone interviews.

2.4.2 Mechanism for Hypothesized Association with Lung Cancer

Stressful life events provoke an acute physiological response distinct from physiologic reactions to chronic and daily stress.[10] While acute stress results from events or situations that may leave a person with a sense of lack of control in the short term (eg. an automobile accident, loss of an important contract), chronic stress occurs through long-term attrition and may leave a person with a sense of misery in the face of unrelenting demands and pressures (eg. sexual assault, war).[83] Stressful life events are commonly believed to decrease immunity or resistance to disease, which may allow for individuals to more easily succumb to illness, including cancer.[81,84] Indeed, in a prospective study where healthy participants were assessed for stress and subsequently experimentally exposed to different cold viruses, Cohen showed that psychological stress was associated in a dose-response manner with increased infection of acute respiratory

illness.[84] Sklar and Anisman have suggested that stressful events may have effects on physiology that may influence the course of neoplastic disease.[85]

There is evidence from experimental and clinical studies, that psychosocial stress may be involved in the initiation of tumours,[18,86] progression[11,85,86] and recurrence of cancer.[11] Although stress may have a role in the initiation of the tumour, it has been more compellingly demonstrated as having a role in the progression or recurrence of cancer.[87] Stress can affect important pathways such as the deregulation of antiviral defenses, DNA repair, NK cell function and cellular aging.[11] These defects encourage the multiplication of cancer cells, which in turn can result in cancer growth and metastasis. Animal models have provided compelling evidence regarding the effects of stress on the sympathetic nervous system (SNS), the "fight or flight" response, and lung tumorigenesis.[11,12] Application of psychological stressors (spatial disorientation,[13] isolation[14] and rotational stress[15]) to murine models resulted in increased lung tumour metastasis and incidence. Similarly at the hormonal level, beta-adrenergic agonists, which simulate activation of the SNS, show dose dependent increases in lung tumour metastasis.[16] Pharmacological inhibition of this pathway has shown to reduce lung tumour metastasis.[17] The acute physiological stress response to stressful life events could present an interesting target for intervention and prevention of lung tumours. There have been attempts to reduce progression and recurrence of disease, including breast cancer, by psychosocial interventions.[87-92]

2.4.3 Epidemiologic Evidence

The link between stressful life events and cancer has been examined in several epidemiologic studies.[93-96] Studies have observed an increased risk of large bowel cancer, breast cancer, colorectal cancer and lung cancer associated with stressful life events.[81,88,95-97] Given that this association has been observed for different organs and therefore different cell types, it is likely that the effect of stressful life events are not specific to one type of cancer.[81] Epidemiologic investigations into stressful life events and colorectal cancer, another cancer of the epithelial layer, suggest that relatively recent life events occurring five to ten years before date of diagnosis are most influential.[81,96]

A literature review aimed at summarizing the epidemiological evidence examining exposure to stressful life events and lung cancer risk was conducted. The search strategy, inclusion and exclusion criteria are outlined in Appendix section A.1. In summary, 14 articles were found that examined exposures varying from environmental stressors, stress prone personality and emotional response in relation to lung cancer and unspecified cancers. Six studies focused specifically on lung cancer and stressful life events (or major life events) and were therefore retained for this literature review.

2.4.3.1 Case-Control Studies

From 1978 to 1980, Blohmke[98] conducted a case-control study among male current smokers. 419 cases had a diagnosis of malignant lung carcinoma confirmed morphologically, histologically or by bronchoscopy at one of seven specialized lung hospitals in Germany as well as one in Austria. 419 healthy controls were randomly sampled in the same time period, and from the same regions of Germany where the hospitals were located, and matched to cases according to age and social stratum. A 203-item, self-reported, biographical questionnaire proposed by Bahson, was used to assess psychosocial factors and personality traits. Blohmke aimed to test seven hypotheses, one is relevant to this literature review, and states that experiences of loss do not occur more frequently in cases than in controls. The authors observed a statistically significant higher number of reported changes in the conditions of life among cases than controls ($p=0.001$). Sensitivity analyses aimed at minimizing the effect of stress associated with hospital stay was conducted using 169 hospitalized controls instead of the 419 population controls. The observed results in sensitivity analyses were not different to the primary analyses. This study suffers from a few limitations. First, the authors do not report the number of respondents and non-respondents, and therefore the potential for non-response bias cannot be evaluated. Second, there is a potential for information bias as a result of non-differential misclassification due to the possibility that cases and controls report trivial life events as a "change in life", thus classifying them as exposed when they may be unexposed. This would result in an underestimation of the hypothesized relationship between changes in life and lung cancer. Furthermore, changes throughout the lifetime are being assessed, which may increase the potential for recall bias. Finally, participants' perceptions of the changes in life are not considered in this study, thereby contributing to the non-differential misclassification discussed above. Despite these limitations, the study has a few strengths. First, the participants were unaware of their malignant diagnosis at the time of response to the questionnaire. Thus, information bias as a result differential misclassification where cases may report more changes in life based on cultural belief that stress may have caused cancer, is minimized. Another strength is that the study was done with adjustment for age and SES, which minimized residual confounding as a result of unmeasured confounders, and analyses was restricted to men and current smokers. However, generalizability may be an issue in that the results may not apply to non-smokers or women.

In 1995, Jahn[99] conducted a case-control study in Germany with the objective of investigating the association between lung cancer risk and voluntary/involuntary job loss in addition to job stability among males. Results reported for outcomes pertaining to job stability are outside the scope of this literature review and will not be presented in detail. 391 incident histologically or cytologically confirmed primary lung cancer cases were recruited from three clinics in Germany. Controls were randomly sampled from regional municipal records and matched to cases by region and age. Jahn reported a 76.4% response rate for controls. Trained interviewers spent 1.5 hours, administering a structured questionnaire with closed questions obtaining information on job history, occupational exposure, smoking, and medical history among others. Voluntariness of job loss was measured by asking the question "Can you please tell me the reason for this change (of work, of company, of occupation)?" Items were assigned a score of voluntariness, established a priori, that ranged from -3 (very involuntary) to +3 (very voluntary). Conditional logistic regression was used to report odds ratios and 95% confident intervals, adjusted for smoking, asbestos exposure and socioeconomic status. Overall, Jahn et al reported a tendency for an increase in risk of lung cancer for ever exposure to job loss deemed a priori as "involuntary", though not statistically significantly. However, there was a general tendency for ever exposure to job loss deemed a priori as "voluntary" to be associated with a decrease in risk of lung cancer, though not statistically significantly. Of note, two statistically significant estimates were observed: job loss deemed "moderately voluntary" due to the conclusion of an apprenticeship (OR=0.48 (95% CI: 0.26, 0.89)) and job loss deemed "very voluntary" due to the demands or advantages of the new job (OR=0.53 (95% CI: 0.36, 0.78)). Similar trends were reported for cumulative measures of lifetime job loss, with "neutral" job loss serving as the reference category. This study suffers from a few limitations. First, the potential for selection bias is unclear because the lung cancer catchment of the clinics from which incident lung cancer cases were recruited, is unreported. Of note, there is a high response rate for the participating controls. Second, reporting of lifetime job history may result in recall bias due to a long period of time over which the participants must recall reasons for job loss. Furthermore, there is a potential for information bias due to differential misclassification as a result of cases reporting more involuntary reasons for job loss due to belief that psychosocial factors associated with involuntary job loss may have caused their lung cancer. This would result in either the

underestimation or overestimation of the reported association. Finally, there is a potential for non-differential misclassification, as a result of unmeasured perceptions of stress in relation to job loss, and voluntariness based on a scale determined by authors a priori. This may have resulted in an underestimation of the hypothesized association. A major strength of this study is the quality of the adjustment for important confounders, and restriction to males.

Kvikstad et al published two nested case-control studies, in 1994 and 1996, based on the same population of females in Norway.[100,101] In 1994,[100] Kvikstad investigated the potential association between cancer risk and widowhood and divorce, with site-specific analysis of lung cancer. 361 incident lung cancer cases were obtained from the Norwegian Cancer Registry. Controls were selected from the general population and were frequency matched to cases (2:1) by age. Logistic regression was performed to estimate odds ratios and the Mantel-Haenszel chi-squared statistics were used to calculate 95% confidence intervals. A statistically significant increase in risk of lung cancer was reported for divorce (OR=1.53 (95% CI: 1.18, 1.99)). No association was reported for widowhood and lung cancer (OR=1.17 (95% CI: 0.62, 2.21)). In 1996,[101] Kvikstad investigated the risk and prognosis of cancer in women experiencing the death of a child. 358 lung cancer cases and 1309 controls were included in the analysis. The authors observed a tendency for an increase in risk associated with death of a child and lung cancer (OR = 1.32 (95% CI: 0.85, 2.05)), though not statistically significant. The results from both publications should be interpreted in light of some limitations. First, there is potential for information bias due to non-differential misclassification of the exposure as a result of the lack of information on marital changes between 1985 and 1990, thus all cases and controls divorced or widowed in this time window would be classified as married. This may result in an underestimation of the hypothesized association. Furthermore, although problems in marriage were measured in order to investigate the period of life preceding life changes, the participants' perception of the stressfulness of the events were not measured. Finally, there was a lack of adjustment of important confounding variables, including smoking. Therefore, the observed increased risk associated with divorce may have been confounded by smoking. The primary strength of the two studies is the restriction to females, and data on exposure and outcome not collected by self-report, and therefore potential for recall bias is minimal. Second, the authors

report that the Norwegian Cancer Registry is practically complete due to mandatory reporting of cancer diagnosis, thus selection bias as it pertains to cases is likely minimal.

In 1979, Horne and Picard[102] published a case-control study in the United States. The objective of the study was to investigate psychological indicators and their association with pulmonary malignancies. Physicians from two Veterans Administration Hospitals selected participants for inclusion based on chest x-ray and the presence of a visible lung lesion. In total, 44 malignant male cancer cases and 66 male controls with benign lung disease participated. Control groups were patients with X-rays showing no lung disease, including COPD. Data on job history and recent (within 5 years) life changes was collected via interview assisted with semi-structured questionnaire. Horne and Picard reported that recent significant loss statistically significantly predicted diagnosis of malignant lung cancer ($p<0.001$). This result should be interpreted in light of a few limitations. First, there is a possibility of information bias as a result of differential misclassification of the outcome among controls, owing to the fact that controls were hospitalized and had radiological findings consistent with lung disease; which is problematic due to the potential effect of stress on the expression of various types of disease.[81] Furthermore, there is possible confounding due to age because the median age of those with benign tumours was lower than the participants with malignant lung tumour diagnosis, and there was no adjustment for age. Finally, the results of this study may only be generalizable to male veterans, and not to the general male population.

2.4.3.2 Cohort Studies

Levav (2000)[103] investigated the possible association between bereavement and cancer incidence, with site specific analysis, using a prospective cohort study design conducted in Israel. Bereavement was classified into two groups: death of a son during the Yom-Kippur war in 1973 (n=4469), or death of a son by accident between 1970 and 1977 (n=1815). Incident cancer cases were identified by the Israel Cancer Registry, which captures 95% of all cancer cases diagnosed. Controls were Israelis born before 1945, as identified by census. Bereavement exposed parents were identified through The Ministry of Defense or the Census Bureau of Statistics. Multiple logistic regression analysis was conducted and the following variables were adjusted: age, sex,

period of immigration, and region of birth. The model was additionally adjusted for secular changes through the study period. There was a statistically significant increase in risk for respiratory cancer associated with death of a son from an accident (OR=1.50 (95% CI: 1.07, 2.11)). This positive association was stronger among females (OR=2.78 (95% CI: 1.06, 7.29)) than among males (OR=1.84 (95% CI: 1.28, 2.65)). For death of a child from war, there was an overall tendency for an increased risk or respiratory cancer (OR=1.06 (95% CI: 0.84, 1.34)), though not statistically significant, however this result differed by sex and there was a statistically significant increased risk among females (OR=1.86 (95% CI: 1.19, 2.92)) and no observed association among males (OR=1.11 (95% CI: 0.85, 1.46)). When lung cancer (including cancer of trachea, bronchus and lung) was the outcome of interest, there was a statistically significant increase in risk associated with accident bereavement (OR=1.54 (95% CI: 1.02, 2.31)), while no association was observed for bereavement due to war (OR=1.14 (95% CI: 0.87, 1.48)). These results should be interpreted in light of some limitations. First, there is potential for information bias as a result of differential misclassification of controls considered lung cancer cases, due to the definition of the outcome, which included cancer of trachea and bronchus along with lung cancer. Similarly, the definition of respiratory cancer was not defined, although categorized in a rigorous review as a lung cancer outcome,[11] the authors do not explicitly define this outcome as exclusively cancer of the lung. This may have resulted in the underestimation or overestimation of the observed association. Second, there is a risk of information bias due to non-differential misclassification of exposed parents as unexposed, due to the loss of a daughter rather than a son. This may have resulted in an underestimation of the reported association between death of a child and lung cancer. The authors state that the death of a child is the most stressful event among Israelis, and although the participants' perceptions of the stressfulness of the events were not measured, death of a child is likely an extremely stressful life event. Finally, the estimates were not controlled for smoking, which may severely confound and the observed estimates may overestimate the true association. Furthermore familial factors that may predispose sons to an accident, or the good health of parents of perfectly healthy sons enlisted in the army, may further confound the reported results. A major strength of the study is the low risk for recall bias due to exposure to death of a son ascertained through registry information.

2.4.4 Summary of Evidence

The relationship between potentially stressful life events and lung cancer has been examined in three case-control studies,[98,99,102] two nested case-control studies,[100,101] and one prospective cohort study.[102,103] One Chinese[104] and one German study were excluded, however based on the abstracts; these may have been included if written in English. Included studies were conducted in Norway,[100,101] Israel,[103] Germany,[98,99] and the United States[102] (Table A1). Studies examining exposure to emotional response and stress prone personality were excluded because these exposures are outside the scope of this literature review. The literature of stressful life events and lung cancer risk contains predominantly sex-specific results: two study populations consist only of women,[100,101] three only of men,[98,99,102] and the last conducted additional sex-specific analysis.[103] All six studies investigated merely one or two stressful life event exposures, a stark contrast to epidemiologic studies investigating the association between stressful life events and other cancer sites, which generally investigate upwards of four different types of life events.[93-96] Furthermore, the choice of stressful life event under study was inconsistent across the literature: only one study each investigated divorce,[101] job loss[99] and general changes in the conditions of life,[98] while four studies investigated death (of a child or spouse).[100-103] None of the studies considered the participants' self-appraised perception of the stressfulness of each event.

Overall, the findings in the literature suggest that exposure to stressful life events may have a tendency to increase risk of lung cancer, although many observed estimates were not statistically significant. Risk of lung cancer was statistically significantly increased with exposure to divorce among women (OR=1.53 (95% CI: 1.17, 1.98)),[101] death of a child as a result of an accident (OR=1.54 (95% CI: 1.02, 2.31)),[103] changes in the conditions of life among males ($p=0.001$),[98] and recent significant loss among males ($p<0.0001$).[102] Four studies reported no association between lung cancer for death of a spouse (OR=1.17 (95% CI: 0.62, 2.19)),[100] death of a child (OR=1.32 (95% CI: 0.85, 2.05)),[101] death of a child from war (OR=1.14 (95% CI: 0.87, 1.48))[103] and involuntary job loss,[99] although the direction of all the estimates are positive. Of note, Jahn has reported inverse associations between voluntary job loss and lung cancer risk, two of which were statistically significant (OR=0.48 (95% CI: 0.26, 0.89); OR=0.53

(0.36, 0.78)).[99] A significant methodological flaw of the literature on stressful life events and lung cancer risk is the inadequate control for possible confounding factors. One study did not adjust for any covariates,[102] only one study adjusted for smoking, education and occupational exposure to asbestos,[99] one study adjusted for period of immigration and region of birth,[103] and three studies accounted for age.[100,101,103] Overall, there is a paucity of literature examining the association between stressful life events and lung cancer risk. The existing literature reports inconsistent results, inadequately controls for possible confounding factors including smoking status, and fails to take into account the individual perception of the stressful life events measured.

Studies examining the association between lung cancer risk and stress prone personality and emotional response were not included in this review. However data extracted from these eight studies is included in the appendix (Table A1). Three cohort studies examined the association between stress prone personality and lung cancer risk. Overall, there does not seem to be an association between stress prone personality and lung cancer risk. Two of the three studies controlled for smoking, while all studies adjusted for age, alcohol, SES and BMI. Four cohort studies and one case-control study investigated the association between lung cancer risk and emotional response. Generally, there does not seem to be an association between emotional response and lung cancer. However, White reported a statistically significant hazard ratio for negative affect (HR=1.24 (95% CI: 1.01, 1.52)),[105] and Kneckt reported an increased RR associated with high levels of depression, albeit with wide confidence intervals (RR=2.89 (95% CI: 1.18, 7.08)).[106] Five of the six studies controlled for smoking status, while all studies adjusted for sex, and most adjusted for age, alcohol, and SES.

3.0 Research Question and Objective

The aim of this study was to answer the research question: is exposure to stressful life events associated with an increased risk of lung cancer?

The objective of this study was to investigate lung cancer risk in relation to exposure to stressful life events experienced in the previous six years. Analyses were conducted for (1) each individual life event separately, (2) total number of life events experienced, (3) total number of

loss and socioeconomic events experienced, as well as (4) the self-appraised impact and (5) Miller and Rahe impact scores for both individual and total number of stressful life events.

4.0 Methodology

The etiology of lung cancer was the object of study; therefore a population-based case-control study, which was economical in terms of time and cost, was an appropriate study design. Montreal, Canada was a favorable locale to carry out this study because the population is 3.1 million.

4.1 The Study

This project was conducted on data from a case-control study carried out in Montreal from 1996 to 2001. The primary goal of the original study was to determine the association between a large number of occupational exposures and lung cancer risk, however several non-occupational factors were also assessed. The source population for this study was the 3.1 million people living in metropolitan Montreal during the study period. Subjects eligible to be a part of the study population were men and women, who were Canadian citizens, aged 35-70 years and residents of the island of Montreal, Laval, and the South Shore of Montreal; a suburb of Montreal in the Quebec administrative region of Montérégie made up of four regional county municipalities (Marguerite-D'Youville, La Vallée-du-Richelieu, Champlain, et Roussillon) during the study period.[107]

4.1.1 Ethical Considerations

This project is an add-on to an existing research project, which was funded by several national funding agencies. Ethics approval was obtained for each of the 18 Montreal hospitals where incident lung cancer cases were recruited. Informed consent was received from all

subjects, and the data was stored under password protection on a secure network at the Centre de Recherche du Centre Hospitalier de l'Université de Montréal.

4.1.2 Cases

Participant recruitment took place between 1996 and 2001. Cases were Canadian citizens that were diagnosed with incident, histologically confirmed lung cancer at one of the 18 Montreal-area hospitals. This catchment area captures over 98% of all lung cancers diagnosed in the area, as discovered through previous communication with Michel Beaupré from the Quebec Tumor Registry.[52] New cases were histologically confirmed by hospital pathologists according to the classifications put forth by the International Agency for Research on Cancer.[66,108] Under this classification, invasive lung tumours are categorized as ICD-O-3, while lung tumours with "uncertain behavior" (borderline or pre-invasive tumours) are categorized as ICD-O-1. Both types of lung tumours are included in the hospital tumour registry. However, benign lung tumours are coded as ICD-O-0 and are not registered. This classification of lung tumours was discovered through personal communication with Sharon Wei from the Adult Tumour Registry at the MUHC. Incident cases were identified through hospital tumour registries, and active monitoring of pathology and medical department records. Study staff obtained physician authorization to contact 1429 eligible cases for inclusion into the study. 1202 eligible cases accepted to participate and completed the questionnaire, resulting in an 84.1% response rate. In total, 737 male and 465 female eligible cases completed the study questionnaire, which translates to a response rate of 83.4% among men and 81.3% among women. For participants who died before interview or were too ill to participate, interviews were conducted with a proxy respondent, which was their closest next of kin. A proxy response was obtained for 21% of subjects in this study, 25% among cases and 8% among controls.

4.1.3 Controls

Quebec electoral lists for Montreal were used as the sampling frame for the population controls. Controls were sampled randomly from this frequently updated list, and were frequency matched to cases by sex, by five-year age group. Three possible control participants were

selected and matched to each case, however only eligible controls were contacted, and thus not all three controls selected at the outset were contacted. Research staff began by assessing eligibility of the first control. If the control was not eligible, or refused to participate in the study, research staff would then move on to the second control, and so on until an eligible control agreed to participate in the study. Thus, 2179 eligible controls were contacted, of which 1513 (69.5%) accepted to participate and completed the questionnaire. Of these, 899 were males and 614 were females, corresponding to response rates of 69.5% and 69.2%, respectively.

4.2 Exposure Assessment

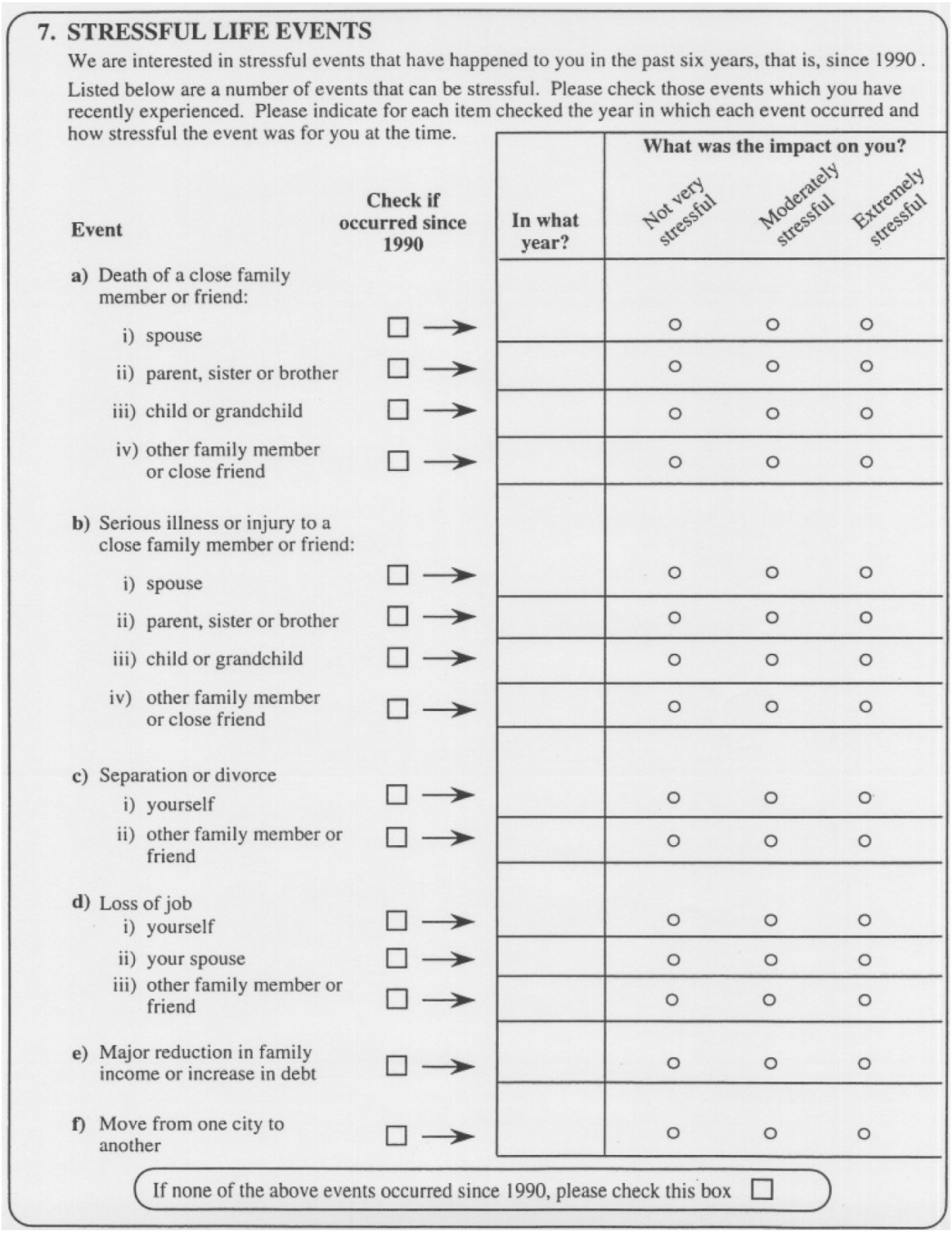
4.2.1 Data Collection

Eligible participants were invited to participate via mail. A short self-administered questionnaire included with a letter of invitation, consisted of items confirming address, phone number, birth date and place, date of entry into Canada, and a short section on occupational history. After obtaining informed consent, computer-assisted face-to-face interviews were conducted with all participating cases and controls by trained, bilingual interviewers. Interviewers were not blinded to the lung cancer status of the participants. These two-hour interviews consisted of two parts. The first part was structured questionnaires that collected data on sociodemographic characteristics, complete smoking history, medical and residential histories, and included a section on lifestyle factors and exposure to stressful life events. This was followed by a semi-structured questionnaire that recorded a detailed lifetime occupational history, including specific tasks held by the participants and the presence of known carcinogens in the work environment.

4.2.2 Assessment of Stressful Life Events

During the structured face-to-face interview, participants were provided with a list of 15 stressful life events and were asked to check the events they had experienced in the previous six years, or since 1990 (Figure 3). Afterward, participants were asked to indicate the year in which each event occurred, and to indicate the impact it had made on them at that time. In this way,

exposure to an environmental stressor (stressful life event) was measured – these environmental stressors were the experiences of death, serious illness, divorce, job loss, increase in debt or move from one city to another (Figure 3). In addition to the environmental stressors, the perception of stress due to exposure to environmental stressors was measured using the participants' self-appraised assessment of the impact each event had on them, on a three-point scale (not very stressful, moderately stressful, extremely stressful). Participants were asked to check a box if none of the above events occurred since 1990.



7. STRESSFUL LIFE EVENTS

We are interested in stressful events that have happened to you in the past six years, that is, since 1990 . Listed below are a number of events that can be stressful. Please check those events which you have recently experienced. Please indicate for each item checked the year in which each event occurred and how stressful the event was for you at the time.

Event	Check if occurred since 1990	In what year?	What was the impact on you? Not very stressful	Moderately stressful	Extremely stressful
a) Death of a close family member or friend:					
i) spouse	☐ →		○	○	○
ii) parent, sister or brother	☐ →		○	○	○
iii) child or grandchild	☐ →		○	○	○
iv) other family member or close friend	☐ →		○	○	○
b) Serious illness or injury to a close family member or friend:					
i) spouse	☐ →		○	○	○
ii) parent, sister or brother	☐ →		○	○	○
iii) child or grandchild	☐ →		○	○	○
iv) other family member or close friend	☐ →		○	○	○
c) Separation or divorce					
i) yourself	☐ →		○	○	○
ii) other family member or friend	☐ →		○	○	○
d) Loss of job					
i) yourself	☐ →		○	○	○
ii) your spouse	☐ →		○	○	○
iii) other family member or friend	☐ →		○	○	○
e) Major reduction in family income or increase in debt	☐ →		○	○	○
f) Move from one city to another	☐ →		○	○	○

If none of the above events occurred since 1990, please check this box ☐

Figure 3: Question 7 structured questionnaire section on lifestyle factors: checklist of stressful life events

4.3 Statistical Analyses

4.3.1 Participants Included in the Analysis

Analysis for this project was restricted to cases and controls with complete questionnaire data. In particular, completion of the question pertaining to stressful life events was mandatory for inclusion in the analysis (Figure 3). Specifically, participants must have indicated a date for each event that was checked as having occurred, or a checked box indicating that none of the listed events had occurred. Of the 1202 cases and 1513 controls that were eligible and had completed the face-to-face interview, 60 cases and 45 controls did not complete the lifestyle factor portion of the questionnaire and thus were missing data on exposures to stressful life events. An additional 79 cases and 39 controls indicated exposure to at least one stressful life event, but were missing data on the year in which a given event occurred. Finally, 2 cases and 7 controls were excluded from analyses owing to missing data on smoking, a crucial potential confounding factor. In total, 1061 cases (88% of interviewed cases) and 1422 controls (94% of interviewed controls) were included in the analysis (Figure 4).

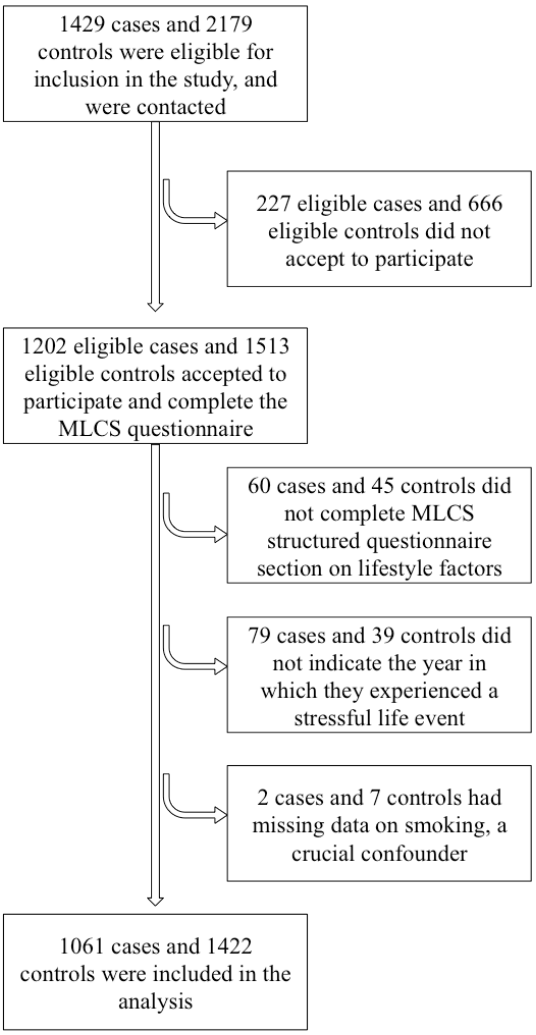


Figure 4: Flowchart of participant inclusion steps

4.3.2 Outcome Variable

Lung cancer was the primary variable of interest. The variable was binary and coded as 0 for controls and 1 for incident cases of histologically confirmed incident lung cancer.

It has been shown that there is variation between different lung cancer histological subtypes, in terms of aetiology.[22] Given that associations between stressful life events and some cancer sites have been observed, but not with others,[11] there is reason to believe that the effect of exposure to stressful life events varies for different types of lung tumours. Secondary analyses were conducted by redefining cases based on histological subtype (i.e. adenocarcinoma,

squamous cell carcinoma, small cell carcinoma, the most prevalent subtypes). The same series of controls were compared to cases of each of the three histological subtypes.

4.3.3 Exposure Variables

Stressful life events were operationalized in five different ways for analysis: (1) individual stressful life events, (2) total number of life events, (3) total number of loss and socioeconomic events, (4) self-appraised impact score, and (5) Miller and Rahe impact score. Stressful life events occurring to "other family member or close friend" (7aiv, 7biv, 7cii, 7diii in Figure 3) were not considered as exposures in the analysis, owing to the ambiguous nature of the question. In particular, this category spans a broad spectrum of individuals connected indirectly to the participant, and is likely interpreted with great variation among the study population. Similarly, the event of a serious illness or injury is open to interpretation, and may not indicate an acute stressful event as defined for this thesis, such as in the event of a prolonged state of disease or rehabilitation. As stressful life events were considered as indicators of acute stress in this study, questions 7bi through 7biv, were not considered as exposures in the analysis. Ultimately, only eight individual stressful life events on the checklist (Figure 3) were considered. Cases and controls were considered exposed to a stressful life event if they indicated at least one event occurring in the six years prior to date of diagnosis (or date of interview for controls). Our questionnaire focused on this 6 year period because we hypothesized that the role of exposure to stressful life events is in the promotion of lung cancer. In order to adhere to this time frame, those participants that reported events occurring beyond a threshold of six years were re-categorized as unexposed. To determine this threshold, the date of occurrence of each stressful life event was subtracted from the date of interview or diagnosis. This difference corresponded to the number of years, prior to interview, the event had occurred. Since neither day nor month was given for the time of stressful life event occurrence, a date (December 31st) was assigned to all years. To account for the dates of diagnosis or interview occurring on the 31st of December, and therefore to minimize the incorrect exclusion of events occurring six years prior, events whose differences were lesser than or equal to seven years were considered exposed. It follows that events occurring greater than seven years from date of diagnosis or interview were re-categorized as unexposed.

Cases and controls that did not indicate the impact of a stressful life event were included only in analyses that did not require this information, and thus excluded from self-appraised impact score analysis.

4.3.3.1 Environmental Stressors

Individual Stressful Life Events

The individual stressful life events that were examined included: (1) death of a spouse, (2) death of a parent, sister or brother, (3) death of a child or grandchild, (4) separation or divorce, (5) loss of job, (6) loss of job of spouse, (7) major reduction in family income or increase in debt, and (8) move from one city to another (Figure 3). Exposure to each of these individual stressful life events was analyzed separately. For each event, a binary variable was created to define participants having experienced the event as "ever exposed" to the event (coded as 1), and those that had not experienced the life event as "never exposed" (coded as 0). Of note, for a given stressful life event, exposure to another life event did not preclude a participant from being defined as "never exposed" to that event. For example, if a participant did not experience the loss of a job, they were defined as "never exposed" to loss of job, regardless of exposure to any of the seven other stressful life events.

Total Number of Life Events

To analyze the effect of cumulative exposure to stressful life events, among those who have experienced more than one stressful life event, ever exposure to the eight individual stressful life events was summed to create a new variable. The range of exposure to "total number of life events" was from 0 to 8. The distribution of this variable among controls that experienced at least one event was used to create three categories, based on approximate tertiles. The three categories for total number of life events exposed in the 6 years prior were: zero, one and greater than or equal to two. Additionally, this variable was analyzed as a binary variable of "ever" or "never" exposure to any stressful life events.

Total Number of Loss Events and Socioeconomic Events

Studies examining stressful life events and colorectal cancer risk have observed differences between exposure to loss events and socioeconomic events.[96] Given that cancers of both the colon and lungs are epithelial cancers, it was of interest to examine this difference in lung cancer. Thus, the total number of life events was separated into two cumulative measures: "total number of loss events" and "total number of socioeconomic events". Loss events consisted of ever exposure to (1) death of a spouse, (2) death of a parent, sister or brother, (3) death of a child or grandchild, and (4) divorce or separation. Socioeconomic events consisted of (1) loss of job, (2) loss of job of spouse, (3) major reduction in family income or increase in debt, and (4) move from one city to another. Using the same cut points as in the previous variable, participants were separated into three categories: 0, 1 and ≥ 2. Additionally, this variable was analyzed as a binary variable of "ever" or "never" exposed to any loss or socioeconomic event.

4.3.3.2 Impact of Stressful Life Events

Self-Appraised Impact Score

The association between self-appraised impact of stressful life events and lung cancer risk was analyzed using a categorical variable. In order to develop this variable, participants who had experienced a stressful life event were assigned different weights according to their answer to the question "what was the impact [of the experience of this stressful life event] on you?". Participants were assigned an impact score of 1 for each answer of "not very stressful", a score of 2 for "moderately stressful" and a score of 3 for "extremely stressful". This scoring system was applied to individual stressful life events, total number of stressful life events, and total number of loss and socioeconomic events. For each of the eight individual life events, the range of the self-appraised impact score was from 0 to 3. Death of a spouse, death of a parent, sister or brother and death of a child or grandchild were combined to form "death of a family member". Similarly, loss of job and loss of job of spouse were combined to form "loss of job". The ranges for self-appraised impact scores corresponding to these two new exposures were 0 to 9, and 0 to 6, respectively. With respect to the total number of life events, the self-appraised impact scores for all eight stressful life events were summed in order to create a cumulative score for self-

appraised impact, for each participant. This score ranged from 0 to 24. The scores were categorized into approximate tertiles based on the distribution among controls who had experienced at least one event. A score between 1 and 2 inclusive reflected a "low" level of self-appraised impact for a stressful life event, "medium" impact was defined as a score of 3 and "high" impact was defined as having a score of ≥ 4. These cut points were applied to all variables. With respect to death of a family member, low numbers in the "medium" and "high" impact levels forced a merging of the two categories, resulting in three levels of impact: "none", "low" for those with a score between 1 and 2 inclusive, and "medium/high" for those with a score ≥ 3.

Miller and Rahe Impact Score

The Holmes and Rahe Score, as previously described in section 2.4.1, has been widely used to quantify perceived stress in the investigation of stressful life events and health outcomes, including cancer.[96,110,111] The updated 1995 version proposed by Miller and Rahe included a more recent re-assessment of the original 43 events first assessed in 1967, as well as the inclusion of 44 additional events. 239 women and 131 men were assigned Life Change Units (LCUs) to 87 stressful life events, using the stressfulness of marriage as a benchmark to estimate if an event would require more or less adjustment in their lives.[19] The mean gender-specific Miller and Rahe derived LCU score was applied to the three cumulative measures in our analysis (i.e. total number of life events, number of loss events and number of socioeconomic events). The Miller and Rahe score was not applied to individual stressful life events because all exposed participants would have had the same score. For all stressful life events that were measured and analyzed, a comparable event was selected from the Miller and Rahe 1995 scale (Appendix Table A2). All events, except loss of job of spouse, matched to an event in the Miller and Rahe scale. Some of the stressful life events measured in our study were separated in the Miller and Rahe scale; for instance, death of a parent and death of sibling events were pooled into one question in our study. In these circumstances, an average of the LCU scores was used for the stressful life event in our study (Table 1). To create the three cumulative measures for each participant, LCU scores were summed across seven life events. Loss of job of spouse was not included in the analyses of Miller and Rahe impact score attributed to cumulative measures, and therefore participants exposed to loss of job of spouse were re-categorized as unexposed. The

distribution of the Miller and Rahe scores across exposed controls was categorized into tertiles, resulting in four categories: "none", "low stress", "medium stress" and "high stress". With respect to loss and socioeconomic events, the numbers were small which necessitated the merging of "medium stress" and "high stress" categories.

Table 1: Miller and Rahe LCU Score Equivalency Table

Stressful Life Events[2]	**Life Events Assessed by Experts (Miller and Rahe, 1995)**	**Women**	**Men**
Death of a spouse	Death of a spouse	122	113
Death of a parent, sister or brother[1]	Death of a sibling	111	87
	Death of a parent	105	90
Death of a child or grandchild	Death of a child	135	103
Separation or divorce – yourself[1]	Divorce	102	85
	Separation for marital problems	79	70
Loss of Job – Yourself[1]	Fired from work	85	69
	Laid off from work	73	59
Major reduction in family income or increase in debt[1]	Decreased income	66	49
	Investment/credit problems	62	46
	Foreclosure	62	51
	Change financial state	58	48
Move from one city to another	Move from one city to another	52	39

[1] Average values were calculated in the event where more than one Miller and Rahe event score was used to create an equivalent event score for stressful life events in our study

[2] The following stressful life event did not have a comparable life event appraised by the experts: Loss of job of your spouse.

4.3.4 Covariates

Certain variables which may have been potential confounders in the relation between stressful life events and lung cancer risk were included in the models as covariates.

4.3.4.1 Demographic Characteristics

Age, sex, and ethnicity were selected due to the variables' association with lung cancer risk ascertained from past publications of data. Age was considered as a continuous variable, and sex was considered as a binary categorical variable (male coded as 0, female coded as 1) based on participants' self-report. There were 14 different ethnic groups represented in the study population, however, 77% of cases and 66% of controls were of French Canadian descent,

therefore the remaining 13 ethnic groups were pooled to create an "other" ethnicity category since there were too few participants in each individual ethnic group to include them as individual categories.

4.3.4.2 Comprehensive Smoking Indicator (CSI)

Smoking is the most important risk factor for lung cancer,[59] and has been shown to be a coping mechanism capable of decreasing a person's experience of stress.[112] Smoking history is a multifaceted variable, and is a crucial confounding variable in any etiologic study of lung cancer. The comprehensive smoking index is a measure of smoking history, first suggested by Hoffman[113] and subsequently adapted for data by Leffondré,[114] which combines duration of smoking in years, time since smoking cessation in years, and the natural logarithm of the average intensity of smoking in cigarettes per day into one parsimonious measure. This measure has been shown to be an effective way to control for confounding by smoking in data.[114] Thus, CSI was calculated for each participant based on self-report, and considered as a continuous variable in analyses.

4.3.4.4 Socio-economic Factors

Socioeconomic status has been observed to be associated with lung cancer in Canada,[53] and has also been shown to be associated with acute stress hormone levels.[115] Two covariates that measure different aspects of socioeconomic status were included in the analysis. The first is education level, categorized into three groups based on number of school years attended: less than 7 years, 7 years up to twelve years, and twelve years or more. The mean census tract family income was also included, and categorized into tertiles based on the distribution among controls resulting in three categories "low", "medium", and "high".

4.3.4.5. Other Stressful Life Events

For a given individual stressful life event, analyses were adjusted for all other individual life events, which were operationalized as binary categorical yes/no variables.

4.3.4.6 Respondent Status

In the analysis based on the whole study population, more cases than controls were represented by proxy respondents. This may result in differential misclassification as a result of proxy respondents being more prone to error in reporting the number of stressful life events having occurred in the timeframe specified, as well as the impact of those events on the participants. Respondent status was included as a binary covariate variable (self coded as 0 and proxy coded as 1) in order to shift the misclassification to non-differential and decrease risk of information bias. As described below in section 4.3.6, analyses were also restricted to self-respondents, but with the objective of establishing a cleaner comparison for analyses of self-appraised impact scores.

4.3.5 The Logistic Regression Model

Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for the association between stressful life events, and lung cancer risk. The probability of lung cancer risk, a binary dependent variable, was modeled as a logistic function of multiple independent variables, i.e. exposure to stressful life events and covariates. The precision, or amount of uncertainty, and statistical significance of the estimated odds ratios was inferred from 95% Wald confidence intervals. The Wald confidence interval is based on large sample normality assumptions, and accounts for the variability in point estimates. That is to say that out of one hundred tests, the confidence interval for 95 tests will contain the true value of the parameter. The narrower the confidence interval, the more precise the point estimate, or odds ratio. Logistic regression analyses were carried out using Statistical Analysis System (SAS) 9.3.

4.3.6 Main Analysis

Five exposure variables were analyzed in the main analysis, grouped into (1) environmental stressors (individual stressful life events, total number of stressful life events, total number of loss and socioeconomic events), and (2) impact of the environmental stressors, or stressful life events (self-appraised impact score, Miller and Rahe impact score). These variables were analyzed using unconditional logistic regression in the Statistical Analysis System (SAS) 9.3. The analyses were adjusted for by the following variables: age, sex, ethnicity, stressful life

events, respondent status, smoking history and socioeconomic factors. These covariates have been well described in the literature, and thus were forced into the model as they were assessed as being the best covariates for the model. Figure 5 illustrates the conceptual framework for the association between stressful life events and lung cancer, under the hypothesis that an inflammatory response at the cellular level, independent of other risk factors, underlies this relationship. The interplay between risk factors for lung cancer and stressful life events is complex and while many causal pathways have been proposed within this network, figure 5 illustrates the framework that reflects the hypotheses for this investigation of exposure to stressful life events and promotion of lung tumours. Risk factors from figure 1 judged as confounders of the association between stressful life events and lung cancer were included in figure 5, and those factors with no evidence of associations with stressful life events were excluded. While indoor and outdoor air pollution may have confounded this association, exposure variables were not measured in this study, and thus socioeconomic status was considered a proxy. The final model was adjusted for 8 covariates, including self-respondent status which is not a confounder and thus not presented in figure 5. Inclusion of self-respondent status as a covariate is justified in section 4.3.4.6.

Of the 1061 cases and 1422 controls, 62% and 92% were self-respondents, respectively. Although proxy respondents were the closest next of kin, it is difficult for people who are not directly experiencing a stressful life event, to accurately and precisely appraise the impact of the experience of a stressful life event, for another person. For this reason, the main analysis was repeated in its entirety, while restricting to self-respondents: 657 cases and 1313 controls. While restriction to self-respondents decreases the number of participants included in analysis and lowers power, a cleaner comparison between those exposed and not exposed is achieved for self-appraised impact score analyses.

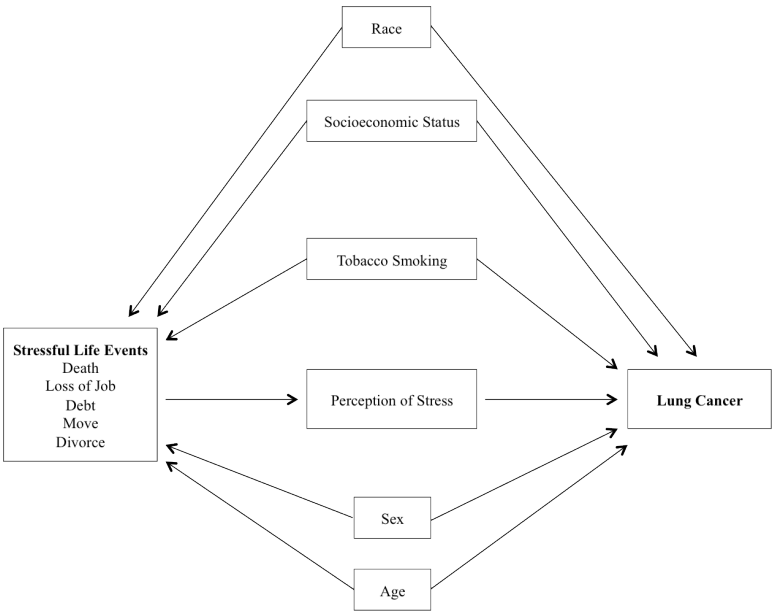


Figure 5: Conceptual framework for main analysis

4.3.7 Secondary Analyses

Stratification by Sex

Of the six included studies in the literature review, all but one restricted the study population to either sex. The one study that included both sexes in the analysis[103] observed differences among males and females in sex-specific analysis of death of a child due to war; with females having a higher relative risk of respiratory cancer. Therefore, we hypothesized that the effect of exposure to stressful life events on lung cancer risk will vary with sex. In order to analyse the role of sex as an effect measure modifier for this association, stratified analyses were conducted. Stratification by sex was restricted to environmental stressors, and was not conducted for self-appraised impact scores due to small numbers. A p-value for interaction < 0.05 was considered as statistically significant.

Stratification by Smoking Status

Smoking status has a predominant role in the risk of incident lung cancer. Therefore, further investigation to better define this role in the context of exposure to stressful life events was conducted. Participants were categorized into "Never-Light Smokers" and "Heavy Smokers" based on their comprehensive smoking indicator (CSI). Models were additionally

adjusted for CSI within groups. In order to separate cases and controls into the two groups of smokers, the median CSI value was calculated (1.928) and light smokers were defined as having a CSI less than or equal to the median, whereas heavy smokers had CSI values higher than this threshold. Few cases (n=46) were never-smokers and therefore were merged with the light smoker category. As was the case for sex, analyses were restricted to ever exposure to individual stressful life events, total number of stressful life events, and total number of loss and socioeconomic events. We determined a significant interaction if p-value for interaction < 0.05.

Analysis by Histological Subtype.

The effect of exposure to stressful life events varies for among different cancer sites.[11] Thus, it is possible that variation exists for different subtypes of lung tumours. Lung cancer cases can be categorized into six major subtypes: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, carcinoma NOS and other epithelial tumours. The proportion of cases in our study population with the last three histological subtypes is 9%, 3% and 2%, respectively. Thus, only adenocarcinoma, squamous cell carcinoma and small cell carcinoma had enough cases to be analyzed. Analyses were restricted to ever exposure to individual stressful life events, total number of stressful life events, and total number of loss and socioeconomic events. Analysis by histological subtype was not conducted for self-appraised impact scores due to small numbers.

Restriction to Stressful Life Events Occurring Three Years Prior

In order to further explore our hypothesis that exposure to stressful life events acts as a promoter of lung cancer, we replicated all main and secondary analyses while restricting exposures to three years priors to date of interview or diagnosis. In order to accomplish this, the seven-year threshold was divided in two, and events occurring greater than 3.5 years before interview or diagnosis were re-categorized as unexposed. Our survey did not collect data for all participants on exposures to stressful life events occurring greater than six years prior to diagnosis. Thus, additional investigation of a longer incubation period for the promotion of lung cancer by exposure to stressful life events was not possible to undertake.

5.0 Results

5.1 Selected Characteristics of the Study Population

The distributions of eight selected characteristics of the total study population are shown in table 2. The study population was predominantly male (63% of cases and 60% of controls) and between the ages of 66 and 75 years old (50% of cases and 52% of controls). The majority of all participants were French Canadian, while more cases (78%) than controls (66%) were of this ethnic origin. The majority of cases (48%) and controls (38%) attended 7 to 12 years of schooling, while more controls (40%) than cases (26%) attained a level of education beyond 12 years. Similarly, controls (33%) had a higher mean census tract family income than cases (24%). Only 4% of cases reported never smoking, while 31% of controls had never smoked. The prevalence of smoking was higher among cases (69%) than controls (26%). 38% of cases used proxy respondents to answer the structured questionnaire in their place, while only 8% of controls did the same. Lung cancer cases were categorized into six different histological subtypes; adenocarcinoma (38%), squamous cell carcinoma (30%) and small cell carcinoma (17%) were the most prevalent subtypes.

5.1.3 Missing Data

141 cases (11.7% of interviewed cases) and 91 controls (6% of interviewed controls) were excluded from analyses as a result of missing data on smoking and incomplete information on their exposure to stressful life events (Figure 4). While excluding participants with missing data decreases the sample size, the percentage of missing data is relatively low; therefore it is not likely that the removal of these participants has influenced the analyses results. Overall, the distribution of selected characteristics for the excluded participants is similar to the distributions observed in the study population (Table 2). Thus, missing participants were not apparently directly related to other variables and therefore were not selectively missing; the excluded population is a random subsample of the original study sample.

5.2 Selected Characteristics of the Self-Respondent Study Population

The distributions of the eight selected characteristics shown in table 2 are shown for the self-respondent study population in table 3. Overall, the trends observed among the self-respondents are similar to those observed in the total study population. Specifically, the self-respondent population was predominantly male (48% cases and 52% controls), French Canadian (77% cases and 67% controls) and between the ages of 66 and 75 years old (48% of cases and 52% controls). Controls (42%) attained a higher level of schooling than cases (27%), and a greater proportion of controls (33%) have a high mean census tract family income when compared to cases (24%). Cigarette smoking was more prevalent among cases (67%) than controls (26%), with more controls (31%) than cases (5%) reporting never smoking. Similar to the total study population, the three predominant histological subtypes of lung cancer were adenocarcinoma (40%), squamous cell carcinoma (32%) and small cell carcinoma (14%).

Table 2: Selected characteristics of the study population

	Study Population		Participants excluded owing to missing data	
	Cases, n=1061 N (%)	**Controls, n=1422 N (%)**	**Cases, n= 141 N (%)**	**Controls, n= 91 N (%)**
Age				
≤55 years	175 (17%)	253 (18%)	37 (26%)	8 (9%)
56-65 years	351 (33%)	424 (30%)	52 (37%)	24 (26%)
66-75 years	535 (50%)	745 (52%)	52 (37%)	59 (65%)
Sex				
Women	396 (37%)	565 (40%)	68 (48%)	49 (54%)
Men	665 (63%)	857 (60%)	73 (52%)	42 (46%)
Ethnic Origin				
French Canadian	824 (78%)	939 (66%)	112 (79%)	61 (67%)
Other	237 (22%)	483 (34%)	29 (21%)	30 (33%)
Years of Schooling				
<7 years	275 (26%)	313 (22%)	31 (22%)	8 (9%)
7-12 years	515 (48%)	537 (38%)	79 (56%)	40 (44%)
≥12 years	271 (26%)	572 (40%)	31 (22%)	43 (47%)
Mean Census Tract Family Income				
Low	472 (44%)	479 (34%)	70 (50%)	27 (30%)
Middle	339 (32%)	473 (33%)	38 (27%)	31 (34%)
High	250 (24%)	470 (33%)	33 (23%)	33 (36%)
Cigarette Smoking				
Never	47 (4%)	440 (31%)	3 (2%)	27 (33%)
Former (quit 10+ years ago)	178 (17%)	485 (34%)	16 (12%)	26 (31%)
Former (quit 2-<10 years ago)	103 (10%)	122 (9%)	14 (10%)	9 (11%)
Current	733 (69%)	375 (26%)	105 (76%)	3 (25%)
Missing	0	0	3[1]	8[1]
Respondent Status				
Self	657 (62%)	1313 (92%)	92 (65%)	82 (90%)
Proxy	404 (38%)	109 (8%)	49 (35%)	9 (10%)
Histological Subtype				
Adenocarcinoma	403 (38%)	-	55 (39%)	-
Squamous cell carcinoma	318 (30%)	-	33 (23%)	-
Small cell carcinoma	178 (17%)	-	29 (21%)	-
Large cell carcinoma	99 (9%)	-	15 (11%)	-
Carcinoma NOS	37 (3%)	-	6 (4%)	-
Other epithelial tumours	26 (2%)	-	3 (2%)	-

[1] While 2 cases and 7 controls were excluded for missing data on smoking, one control and one case excluded for missing data on lifestyle factors also were missing data on smoking.

Table 3: Selected characteristics of the self-respondents

	Cases, n=657 N (%)	**Controls, n=1313 N (%)**
Age		
≤55 years	116 (18%)	240 (18%)
56-65 years	222 (34%)	395 (30%)
66-75 years	319 (48%)	678 (52%)
Sex		
Women	263 (40%)	541 (41%)
Men	394 (60%)	772 (59%)
Ethnic Origin		
French Canadian	503 (77%)	882 (67%)
Other	154 (23%)	431 (33%)
Years of Schooling		
<7 years	169 (26%)	270 (21%)
7-12 years	307 (47%)	496 (38%)
≥12 years	181 (27%)	547 (42%)
Mean Census Tract Family Income		
Low	285 (43%)	432 (33%)
Middle	212 (32%)	444 (34%)
High	160 (24%)	437 (33%)
Cigarette Smoking		
Never	33 (5%)	413 (31%)
Former (quit 10+ years ago)	121 (18%)	448 (34%)
Former (quit 2-<10 years ago)	65 (10%)	110 (8%)
Current	438 (67%)	342 (26%)
Histological Subtype		
Adenocarcinoma	267 (40%)	-
Squamous cell carcinoma	211 (32%)	-
Small cell carcinoma	93 (14%)	-
Large cell carcinoma	46 (7%)	-
Carcinoma NOS	20 (3%)	-
Other epithelial tumours	20 (3%)	-

5.3 Exposure to Individual Stressful Life Events in the Previous 6 Years

5.3.1 Death of a family member

Multivariate adjusted odds ratios (ORs) indicated a slight increased relative risk of lung cancer associated with ever exposure to death of a family member, although with no statistical significance (OR=1.20 (0.96, 1.49)) (table 4). Further examination of the association, with respect to the participants' specific relationship with the departed, revealed similar positive, though statistically non-significant, associations. The odds ratios ranged from 1.08 to 1.28.

Given that for a given event, the perception of stress may vary by individual, we also analyzed self-appraised impact of the event in relation to incident lung cancer. For ever exposure to death of a family member, the magnitude of the estimates observed for low impact and medium/high impact death of a family member were similar, and were not different from the OR observed when self-appraised impact was not considered. When examining associations with respect to the participants' specific relationship with the departed, a similar trend was observed for death of a parent or sibling, where the associations for low and medium/high impact did not appreciably differ from each other. For death of a spouse or death of a child or grandchild, the number of cases and controls that self-appraised the impact as 'low' was very small, thus, the observed ORs had very wide confidence intervals (table 4).

Given that appraisal of impact of a stressful life event is more likely to be reliable from self-respondents than proxy respondents, analyses restricted to self-respondents were also conducted for each variable. For the variables related to death of a family member, restriction to self-respondents generally revealed similar self-appraised impact OR estimates to that observed in the total study population.

5.3.2 Separation or divorce

Ever exposure to separation or divorce (table 5) was shown to be non-statistically significantly positively associated with incident lung cancer (OR=1.21 (0.71-2.06)). An OR suggesting a protective effect was observed for low impact exposure (OR=0.66 (0.23-1.93)), while an increased risk was observed for medium/high impact exposure (OR=1.59 (0.84-3.01)).

Both of these results were statistically non-significant. With respect to self-respondents, the overall pattern of the observed estimates was similar to those observed among all participants.

5.3.3 Loss of job

Losing a job was inversely associated, though not statistically significantly, with lung cancer risk (OR=0.76 (0.56, 1.03)) (table 6). The majority of participants experiencing job loss had experienced loss of their own job (95% of exposed cases and controls), versus loss of a spouse's job. The observed relative risk for ever exposure to loss of own job was similar to the global loss of job estimate (OR=0.74 (0.55, 1.01)). There was no association observed for loss of a spouse's job and lung cancer (OR=0.95 (0.41, 2.21)).

Interestingly, a strong statistically significant protective association was observed for job loss appraised to have a low impact (OR=0.50 (0.31, 0.80)). This protective effect was attenuated, and no longer statistically significant, as the impact scores increased (i.e. as the impact of the event was perceived to be more highly stressful). When considering loss of own job and loss of spouse's job, generally, the observed estimates for self-appraised impact followed a similar trend, though the numbers for loss of a spouse's job were very small. A statistically significant protective effect was observed for job loss self-appraised to be of low impact (OR=0.56 (0.38, 0.83)). When these analyses were restricted to self-respondents, the results were generally similar.

5.3.4 Decrease in income or increase in debt

Ever exposure to a decrease in income or increase in debt was not shown to be associated with lung cancer risk (OR=0.98 (0.70, 1.39)) (table 7). A protective odds ratio was observed for self-appraised low impact events (OR=0.77 (0.31, 1.88)), though statistical significance was not reached. Medium and high impact events were similar to the estimate for ever exposure to decrease in income or increase in debt. The observed results were not different when restricted to self-respondents.

5.3.5 Move from one city to another

Ever exposure to a move from one city to another was shown to be positively associated with lung cancer risk (OR=1.63 (0.77, 3.43)), albeit not with statistical significance and with wide confidence intervals, due to small numbers (table 8). The result did not differ when analysis was restricted to self-respondents. Further categorizing exposure to a move from one city to another with respect to self-appraised impact, the numbers in each category were even smaller, thus confidence intervals were wide. Nonetheless, a statistically significant increased relative risk was observed for individuals that appraised a move as having a high impact of stress (OR=5.06 (1.63, 15.65)). Numbers were even smaller when restricted to self-respondents; however, the pattern of results was similar as that seen with everyone included.

Table 4: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with death in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Death of a family member								
No	694	996	1.00 (referent)	1.00 (referent)	424	911	1.00 (referent)	1.00 (referent)
Yes	367	426	1.26 (1.06, 1.49)	1.20 (0.96, 1.49)	233	402	1.26 (1.03, 1.54)	1.13 (0.90, 1.43)
Self-Appraised Impact Score[2]								
None	694	996	1.00 (referent)	1.00 (referent)	424	911	1.00 (referent)	1.00 (referent)
Low	86	127	0.99 (0.74, 1.32)	1.21 (0.84, 1.72)	58	121	1.04 (0.75, 1.46)	1.13 (0.77, 1.67)
Medium/High	277	295	1.37 (1.13, 1.66)	1.20 (0.94, 1.53)	172	278	1.35 (1.08, 1.68)	1.13 (0.87, 1.47)
Death of a spouse								
No	993	1359	1.00 (referent)	1.00 (referent)	621	1252	1.00 (referent)	1.00 (referent)
Yes	68	63	1.53 (1.07, 2.19)	1.28 (0.81, 2.02)	36	61	1.24 (0.81, 1.90)	1.08 (0.66, 1.78)
Self-Appraised Impact Score								
None	993	1359	1.00 (referent)	1.00 (referent)	621	1252	1.00 (referent)	1.00 (referent)
Low	6	12	0.71 (0.27, 1.90)	0.51 (0.14, 1.83)	2	11	0.39 (0.09, 1.75)	0.41 (0.08, 2.20)
Medium/High	62	50	1.77 (1.20, 2.60)	1.50 (0.92, 2.46)	34	49	1.45 (0.92, 2.28)	1.24 (0.73, 2.11)
Death of a parent/sibling								
No	756	1063	1.00 (referent)	1.00 (referent)	460	973	1.00 (referent)	1.00 (referent)
Yes	305	359	1.21 (1.01, 1.44)	1.19 (0.95, 1.49)	197	340	1.23 (1.00, 1.52)	1.11 (0.87, 1.42)
Self-Appraised Impact Score								
None	756	1063	1.00 (referent)	1.00 (referent)	460	973	1.00 (referent)	1.00 (referent)
Low	91	118	1.10 (0.82, 1.47)	1.32 (0.92, 1.88)	58	113	1.09 (0.78, 1.53)	1.20 (0.81, 1.77)
Medium/High	210	238	1.25 (1.02, 1.54)	1.14 (0.87, 1.48)	136	225	1.28 (1.01, 1.63)	1.07 (0.80, 1.42)
Death of a child/grandchild								
No	1038	1406	1.00 (referent)	1.00 (referent)	643	1300	1.00 (referent)	1.00 (referent)
Yes	23	16	1.98 (1.04, 3.77)	1.08 (0.49, 2.38)	14	13	2.22 (1.03, 4.74)	1.56 (0.65, 3.71)
Self-Appraised Impact Score								
None	1038	1406	1.00 (referent)	1.00 (referent)	643	1300	1.00 (referent)	1.00 (referent)
Low	1	2	0.68 (0.06, 7.57)	0.56 (0.04, 7.51)	1	2	1.00 (0.09, 11.06)	0.65 (0.05, 8.58)
Medium/High	22	13	2.33 (1.16, 4.65)	1.33 (0.56, 3.13)	13	10	2.68 (1.17, 6.15)	2.11 (0.81, 5.50)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

[2] 4 cases and 4 controls were missing appraisal information and were not included in the self-appraised impact score analysis

Table 5: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with separation or divorce in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Separation or divorce								
No	1021	1376	1.00 (referent)	1.00 (referent)	629	1270	1.00 (referent)	1.00 (referent)
Yes	40	46	1.16 (0.75, 1.80)	1.21 (0.71, 2.06)	28	43	1.29 (0.79, 2.12)	1.23 (0.69, 2.19)
Self-Appraised Impact Score[2]								
None	1021	1376	1.00 (referent)	1.00 (referent)	629	1270	1.00 (referent)	1.00 (referent)
Low	8	17	0.64 (0.27, 1.49)	0.66 (0.23, 1.93)	5	17	0.59 (0.22, 1.62)	0.53 (0.16, 1.76)
Medium/High	30	27	1.48 (0.87, 2.53)	1.59 (0.84, 3.01)	21	25	1.66 (0.91, 3.02)	1.65 (0.83, 3.27)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, death of a child or grandchild, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

[2] 2 cases and 2 controls were missing appraisal information and were not included in the self-appraised weighting analysis

Table 6: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with loss of job in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Loss of Job								
No	905	1207	1.00 (referent)	1.00 (referent)	557	1114	1.00 (referent)	1.00 (referent)
Yes	156	215	0.93 (0.74, 1.17)	0.76 (0.56, 1.03)	100	199	0.98 (0.75, 1.28)	0.74 (0.53, 1.02)
Self-Appraised Impact Score[2]								
None	905	1207	1.00 (referent)	1.00 (referent)	557	1114	1.00 (referent)	1.00 (referent)
Low	40	87	0.58 (0.39, 0.86)	0.50 (0.31, 0.80)	31	80	0.75 (0.49, 1.16)	0.57 (0.35, 0.93)
Medium	21	37	0.73 (0.43, 1.27)	0.66 (0.34, 1.27)	12	34	0.70 (0.36, 1.35)	0.59 (0.28, 1.25)
High	95	90	1.37 (1.01, 1.86)	1.12 (0.74, 1.68)	57	84	1.32 (0.92, 1.89)	1.00 (0.64, 1.57)
Loss of job, yourself								
No	913	1217	1.00 (referent)	1.00 (referent)	563	1124	1.00 (referent)	1.00 (referent)
Yes	148	205	0.924 (0.73, 1.17)	0.74 (0.55, 1.01)	94	189	0.97 (0.73, 1.27)	0.72 (0.51, 1.00)
Self-Appraised Impact Score								
None	913	1217	1.00 (referent)	1.00 (referent)	563	1124	1.00 (referent)	1.00 (referent)
Low	61	118	0.66 (0.47, 0.91)	0.56 (0.38, 0.83)	43	108	0.77 (0.53, 1.13)	0.59 (0.38, 0.90)
Medium/High	87	86	1.30 (0.95, 1.79)	1.04 (0.69, 1.59)	51	80	1.23 (0.85, 1.79)	0.92 (0.58, 1.47)
Loss of job, your spouse								
No	1047	1402	1.00 (referent)	1.00 (referent)	648	1294	1.00 (referent)	1.00 (referent)
Yes	14	20	0.94 (0.47, 1.87)	0.95 (0.41, 2.21)	9	19	0.93 (0.42, 2.08)	0.98 (0.39, 2.47)
Self-Appraised Impact Score								
None	1047	1401	1.00 (referent)	1.00 (referent)	648	1293	1.00 (referent)	1.00 (referent)
Low	5	12	0.55 (0.19, 1.56)	0.43 (0.11, 1.63)	2	11	0.35 (0.08, 1.61)	0.43 (0.08, 2.28)
Medium/High	9	8	1.54 (0.59, 4.02)	1.71 (0.56, 5.26)	7	8	1.73 (0.62, 4.83)	1.60 (0.50, 5.20)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a family member, separation/divorce, increase in debt, and move.

[2] 1 control is missing impact information and was not included in the self-appraised impact analysis

Table 7: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with a major reduction in family income or increase in debt in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Decreased income/increased debt								
No	929	1278	1.00 (referent)	1.00 (referent)	576	1182	1.00 (referent)	1.00 (referent)
Yes	132	144	1.25 (0.97, 1.61)	0.98 (0.70, 1.39)	81	131	1.25 (0.93, 1.69)	1.05 (0.72, 1.54)
Self-Appraised Impact Score[2]								
None	929	1278	1.00 (referent)	1.00 (referent)	576	1182	1.00 (referent)	1.00 (referent)
Low	9	24	0.51 (0.24, 1.11)	0.77 (0.31, 1.88)	8	23	0.71 (0.32, 1.59)	0.83 (0.33, 2.07)
Medium	20	33	1.37 (1.04, 1.79)	0.98 (0.47, 2.01)	11	31	1.31 (0.95, 1.81)	0.90 (0.40, 2.06)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, separation or divorce, loss of job, loss of spouse's job, and move from one city to another.
[2] 4 cases and 1 control were missing impact information and were not included in the self-appraised impact analysis

Table 8: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with a move from one city to another in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Move from one city to another								
No	1037	1397	1.00 (referent)	1.00 (referent)	644	1290	1.00 (referent)	1.00 (referent)
Yes	24	25	1.33 (0.75, 2.34)	1.63 (0.77, 3.43)	13	23	1.14 (0.57, 2.27)	1.61 (0.69, 3.73)
Self-Appraised Impact Score[2]								
None	1037	1397	1.00 (referent)	1.00 (referent)	644	1290	1.00 (referent)	1.00 (referent)
Low	3	12	0.34 (0.09, 1.19)	0.25 (0.05, 1.33)	2	10	0.40 (0.09, 1.82)	0.71 (0.12, 4.24)
Medium	5	7	2.16 (1.07, 4.38)	0.94 (0.19, 4.69)	1	7	1.72 (0.76, 3.88)	0.34 (0.03, 3.62)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, death of a child or grandchild, separation or divorce, loss of job, loss of spouse's job, and major reduction in family income or increase of debt.
[2] 1 case was missing impact information and was not included in the self-appraise impact analysis

5.4 Total Number of Stressful Life Events Experienced in the Previous 6 Years

In addition to analyzing individual stressful life events, we also examined exposure to stressful life events in the previous six years in totality, both as having ever experienced any event (regardless of event), as well as cumulative exposure to number of events, thus considering the total number of stressful life events exposed to. Ever exposure to any stressful life event (table 9) was observed to have no association with lung cancer risk (OR=0.99 (0.81, 1.22)). Similar to ever exposure to any stressful life event, there was no apparent association between lung cancer risk and exposure to one (OR=0.97 (0.77, 1.23)) or more (OR=1.04 (0.78, 1.40)) stressful life events compared to never having experienced a stressful life event. For both of these measures, the results were similar when restricted to self-respondents.

The impact of cumulative exposure to stressful life events according to self-appraisal and an external appraisal (Miller and Rahe) was also examined. When the cumulative exposure to stressful life events was self-appraised as low, a statistically significant protective association was observed (OR=0.71 (0.52, 0.99)). An increased risk, though statistically non-significant, was observed for medium self-appraised impact (OR=1.17 (0.90, 1.52)), and no association was observed for high self-appraised impact (OR=1.02 (0.75, 1.38)). When restricted to self-respondents, the results were generally similar. Overall, estimates observed for the Miller and Rahe impact score tended to show a greater magnitude of increased relative risk for lung cancer, when compared to the self-appraised impact score analysis, though none reached statistical significance. The odds ratios ranged from 1.23 to 1.36. The observed Miller and Rahe estimates did not differ greatly upon restriction to self-respondents.

5.5 Total Number of Loss and Socioeconomic Events Experienced in the Previous 6 Years

We further categorized cumulative exposure to stressful events in two groups: loss events of socioeconomic events. There was an observed increased risk of lung cancer associated with ever exposure to any loss events (OR=1.18 (0.95, 1.45)), albeit not statistically significant (table 10). The majority of cases and controls that had experienced a loss event had experienced only one event versus two or more loss events. The observed estimate for exposure to one event was similar to ever exposure to any loss event. An increase in risk was observed for exposure to at

least two loss events (OR=1.83 (0.99-3.40)), though statistical significance was no achieved due to small numbers in this category.

Self-appraised impact scores for loss events were generally similar to estimates observed for exposure to any loss event, in magnitude and statistical significance, with odds ratios ranging from 1.11 to 1.21. Estimates observed from the Miller and Rahe impact score analysis showed an increased relative risk associated with both low stress (OR=1.38 (0.96, 1.98)) and medium/high stress (OR=1.81 (1.03, 3.16)). The latter was statistically significant. When restricted to self-respondents, the results were generally not different, but in all cases the confidence intervals widened.

For socioeconomic events, there was a decreased relative risk of lung cancer associated with ever exposure (OR=0.83 (0.65, 1.06)), albeit statistically non-significant (table 10). ORs were similar to each other whether exposed to only one or at least two socioeconomic events. A statistically significant protective association was observed for low self-appraised impact of cumulative exposure to socioeconomic events (OR=0.50 (0.31, 0.81)). No association was observed for medium and high self-appraised impact scores. Overall, estimates observed from the Miller and Rahe impact score analyses showed a statistically non-significant decrease in risk associated with low stress and medium/high stress, similar to the results observed for ever exposure to a socioeconomic event. When restricted to self-respondents, the results were generally similar

Table 9: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to any stressful life events in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Any Stressful Life Event								
No	553	790	1.00 (referent)	1.00 (referent)	342	719	1.00 (referent)	1.00 (referent)
Yes	508	632	1.15 (0.98, 1.35)	0.99 (0.81, 1.22)	315	594	1.11 (0.92, 1.34)	0.93 (0.74, 1.16)
Total Number of Stressful Life Events								
0	553	790	1.00 (referent)	1.00 (referent)	342	719	1.00 (referent)	1.00 (referent)
1	328	443	1.06 (0.89, 1.27)	0.97 (0.77, 1.23)	201	420	1.01 (0.82, 1.25)	0.89 (0.70, 1.14)
≥ 2	180	189	1.35 (1.07, 1.71)	1.04 (0.78, 1.40)	114	174	1.36 (1.04, 1.79)	1.00 (0.73, 1.38)
Self-Appraised Impact Score[2]								
None	553	790	1.00 (referent)	1.00 (referent)	342	719	1.00 (referent)	1.00 (referent)
Low	101	200	0.72 (0.56, 0.94)	0.71 (0.52, 0.99)	63	190	0.70 (0.51, 0.95)	0.64 (0.45, 0.91)
Medium	236	265	1.29 (1.04, 1.58)	1.17 (0.90, 1.52)	146	252	1.22 (0.96, 1.56)	1.09 (0.82, 1.44)
High	160	160	1.42 (1.11, 1.82)	1.02 (0.75, 1.38)	97	147	1.38 (1.03, 1.84)	0.96 (0.68, 1.34)
Miller and Rahe Impact Score[3]								
None	856	1166	1.00 (referent)	1.00 (referent)	520	1065	1.00 (referent)	1.00 (referent)
Low stress	30	43	1.10 (0.67, 1.83)	1.26 (0.67, 2.38)	19	41	1.05 (0.58, 1.88)	1.21 (0.61, 2.42)
Medium stress	97	127	1.24 (0.90, 1.70)	1.36 (0.91, 2.03)	122	67	1.28 (0.89, 1.84)	1.29 (0.84, 1.98)
High stress	78	86	1.46 (1.03, 2.09)	1.23 (0.79, 1.93)	51	85	1.39 (0.93, 2.08)	1.12 (0.70, 1.80)

[1] Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other).

[2] 11 cases and 7 controls were missing impact information and were not included in the self-appraised impact analysis

[3] Refer to table 1 for assigned Life Change Unit values. Stressful life events assigned an expert assessed stress appraisal value include job loss (self), increase in debt, move from one city to another, death (spouse, sibling, child), and divorce.

Table 10: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to total number of loss and socioeconomic events in the previous 6 years

	All Participants				Self-Respondents			
	Cases (n=1061)	**Controls (n=1422)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Age and Sex Adjusted OR (95%CI)**	**Multivariate Adjusted OR (95% CI)**
Any Loss Event[2]								
No	672	963	1.00 (referent)	1.00 (referent)	409	880	1.00 (referent)	1.00 (referent)
Yes	389	459	1.23 (1.04, 1.46)	1.18 (0.95, 1.45)	248	433	1.24 (1.02, 1.51)	1.13 (0.90, 1.42)
Total Number of Loss Events								
0	672	963	1.00 (referent)	1.00 (referent)	409	880	1.00 (referent)	1.00 (referent)
1	344	435	1.15 (0.97, 1.37)	1.13 (0.91, 1.41)	222	410	1.18 (0.96, 1.44)	1.10 (0.87, 1.39)
≥ 2	45	24	2.73 (1.65, 4.53)	1.83 (0.99, 3.40)	26	23	2.45 (1.38, 4.36)	1.58 (0.82, 3.06)
Self-Appraised Impact Score[3]								
None	672	963	1.00 (referent)	1.00 (referent)	409	880	1.00 (referent)	1.00 (referent)
Low	89	138	0.94 (0.71, 1.25)	1.11 (0.78, 1.58)	60	132	0.99 (0.71, 1.37)	1.05 (0.72, 1.54)
Medium/High	294	316	1.35 (1.12, 1.63)	1.21 (0.95, 1.53)	183	298	1.33 (1.07, 1.66)	1.14 (0.89, 1.47)
Miller and Rahe Impact Score[4]								
None	883	1212	1.00 (referent)	1.00 (referent)	534	1109	1.00 (referent)	1.00 (referent)
Low stress	126	169	1.21 (0.91, 1.61)	1.38 (0.96, 1.98)	87	164	1.27 (0.92, 1.77)	1.32 (0.90, 1.94)
Medium/High stress	52	41	2.10 (1.35, 3.28)	1.81 (1.03, 3.16)	36	40	2.21 (1.35, 3.63)	1.70 (0.95, 3.06)
Any Socioeconomic Event[5]								
No	832	1124	1.00 (referent)	1.00 (referent)	514	1036	1.00 (referent)	1.00 (referent)
Yes	229	298	1.02 (0.83, 1.24)	0.83 (0.65, 1.06)	143	277	1.02 (0.81, 1.29)	0.82 (0.62, 1.07)
Total Number of Socioeconomic Events								
0	832	1124	1.00 (referent)	1.00 (referent)	514	1036	1.00 (referent)	1.00 (referent)
1	148	209	0.94, 0.75, 1.18)	0.83 (0.62, 1.10)	95	198	0.95 (0.73, 1.25)	0.79 (0.58, 1.08)
≥ 2	81	89	1.20 (1.87, 1.65)	0.84 (0.57, 1.24)	48	79	1.19 (0.82, 1.74)	0.87 (0.56, 1.35)
Self-Appraised Impact Score								
None	832	1124	1.00 (referent)	1.00 (referent)	514	1036	1.00 (referent)	1.00 (referent)
Low	34	84	0.53 (0.35, 0.79)	0.50 (0.31, 0.81)	27	80	0.66 (0.42, 1.04)	0.55 (0.33, 0.91)
Medium	118	145	1.09 (0.84, 1.41)	0.94 (0.68, 1.31)	70	136	1.02 (0.75, 1.40)	0.88 (0.61, 1.26)
High	72	67	1.42 (1.00, 2.02)	0.92 (0.61, 1.41)	42	59		0.95 (0.59, 1.53)
Miller and Rahe Impact Score								
None	1002	1332	1.00 (referent)	1.00 (referent)	622	1225	1.00 (referent)	1.00 (referent)
Low stress	33	52	0.88 (0.56, 1.40)	0.85 (0.48, 1.52)	19	51	0.72 (0.42, 1.26)	0.73 (0.39, 1.38)
Medium/High stress	26	38	0.94 (0.56, 1.59)	0.75 (0.39, 1.44)	16	37	0.83 (0.45, 1.53)	0.75 (0.37, 1.51)

[1] Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other).
[2] Loss events include death (spouse, sibling, child) and divorce.
[3] 11 cases and 7 controls were missing impact information and were not included in the self-appraised impact score analysis
[4] Refer to table 1 for assigned Life Change Unit values. Stressful life events assigned an expert assessed stress appraisal value include job loss (self), increase in debt, move from one city to another, death (spouse, sibling, child), and divorce.
[5] Socioeconomic events include job loss (self), increase in debt, and move from one city to another.

5.6 Secondary Analyses

5.6.1 Stratification by Sex

With respect to individual stressful life events, we generally did not observe differences in RRs when stratifying by sex (table 11). However, for decrease in income or increase in debt, exposed females were protected from lung cancer (OR=0.57 (0.32, 1.00) while exposed males had an increase in relative risk (OR=1.32 (0.87, 2.01)). It is important to note, however, that neither of the observed estimates were statistically significant. Although we did not observe statistically significant interaction at the alpha level of 0.05, we did observe different RRs for death of a family member, by sex. A statistically significant positive association was observed among females (OR=1.49 (1.06, 2.08)) while no association was observed among males (OR=1.03 (0.78, 1.37)).

With respect to cumulative exposures (table 12), RRs differed by sex; an inverse association for exposure to any stressful life event was observed among males (OR=0.85 (0.66, 1.10)), while a positive association was observed among females (OR=1.29 (0.93, 1.78)). Similarly, RRs for total number of stressful life events were different for females than for males: a positive association was observed among females exposed to one stressful life event (OR=1.36 (0.96, 1.95)), while a protective association was observed for males (OR=0.77 (0.57, 1.03)). For exposure to at least two stressful life events, no association was observed among males or among females.

Overall, loss events were positively associated with lung cancer risk among both males and females, however RRs were slightly higher and reached statistical significance among females (OR=1.48 (1.06, 2.05)) when compared to males (OR=1.01 (0.77, 1.33)). Socioeconomic events were inversely associated with lung cancer and RRs did not differ between males and females.

5.6.2 Stratification by Smoking

When stratifying by smoking status (table 13), we did not observe any difference in RRs between never-light smokers and heavy smokers. With respect to cumulative exposures (table 14), no significant differences in RRs were observed in the association between total number of stressful life events, total number of loss and socioeconomic events, and lung cancer risk, with respect to smoking status. Similarly, no significant differences in RRs were observed in the association between ever exposure to any stressful life event, loss event or socioeconomic event and lung cancer risk. However, an inverse association was observed for 1 socioeconomic event among heavy smokers (OR=0.66 (0.36, 1.22)), while no association was observed among never-light smokers, albeit not statistically significant at the alpha level of 0.05.

5.6.3 Analysis by histological subtype

Generally, the observed estimates for individual stressful life events did not vary greatly between histological subtypes (table 15). The observed estimates for adenocarcinoma were generally similar to those observed for ever exposure to individual stressful life events (tables 4 to 8), likely because the majority of exposed cases (38%) were diagnosed with this tumour subtype. For some individual stressful life events, there were low numbers, specifically for exposure to death of a child or grandchild, loss of a job of spouse, and move from one city to another.

With respect to the association between ever exposure to any stressful life event and lung cancer risk, there was no difference in RRs between adenocarcinoma, squamous cell carcinoma and small cell carcinoma (table 16). Similarly, when total number of stressful life events was examined, no difference in RRs between subtypes was observed. Furthermore, no differences in RRs were observed, among histological subtypes, for loss events (table 16). Generally, no differences in RRs were observed for socioeconomic events, however, exposure to at least two socioeconomic events resulted in slight differences in RRs among the three subtypes; a positive association for adenocarcinoma (OR=1.76 (0.46, 1.27)), a slight positive association for squamous cell carcinoma (OR=1.10 (0.67, 1.84)) and an inverse association for small cell carcinoma (OR=0.67 (0.33, 1.35)).

Table 11: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to each stressful life event in the previous 6 years, stratified by sex

	Males			Females			p-value (interaction)
	Cases (n=665)	Controls (n=857)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=396)	Controls (n=565)	Multivariate Adjusted[1] OR (95% CI)	
Death of a family member							
No	465	623	1.00 (referent)	229	373	1.00 (referent)	0.10
Yes	200	234	1.03 (0.78, 1.37)	167	192	1.49 (1.06, 2.08)	
Death of a spouse							
No	631	826	1.00 (referent)	362	533	1.00 (referent)	0.55
Yes	34	31	1.12 (0.60, 2.10)	34	32	1.48 (0.76, 2.87)	
Death of a parent/sibling							
No	497	658	1.00 (referent)	259	405	1.00 (referent)	0.23
Yes	168	199	1.06 (0.79, 1.42)	137	160	1.40 (0.99, 2.00)	
Death of a child/grandchild							
No	653	847	1.00 (referent)	385	559	1.00 (referent)	0.48
Yes	12	10	0.84 (0.29, 2.40)	11	6	1.50 (0.44, 5.06)	
Separation or divorce							
No	646	833	1.00 (referent)	375	543	1.00 (referent)	0.57
Yes	19	24	1.04 (0.48, 2.22)	21	22	1.40 (0.67, 2.92)	
Loss of Job							
No	538	686	1.00 (referent)	367	521	1.00 (referent)	0.99
Yes	127	171	0.76 (0.55, 1.06)	29	44	0.76 (0.41, 1.42)	
Loss of Job, yourself							
No	539	687	1.00 (referent)	374	530	1.00 (referent)	0.74
Yes	126	170	0.76 (0.55, 1.06)	22	35	0.67 (0.33, 1.34)	
Loss of Job, spouse							
No	658	849	1.00 (referent)	389	553	1.00 (referent)	0.94
Yes	7	8	0.99 (0.27, 3.67)	7	12	0.92 (0.31, 2.78)	
Decreased income/increased debt							
No	570	779	1.00 (referent)	359	499	1.00 (referent)	0.01
Yes	95	78	1.32 (0.87, 2.01)	37	66	0.57 (0.32, 1.00)	
Move from one city to another							
No	656	848	1.00 (referent)	381	549	1.00 (referent)	0.49
Yes	9	9	1.18 (0.36, 3.80)	15	16	2.00 (0.78, 5.15)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 12: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with groups of stressful life events in the previous 6 years, stratified by sex

	Males			Females			p-value (interaction)
	Cases (n=665)	Controls (n=857)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=396)	Controls (n=565)	Multivariate Adjusted[1] OR (95% CI)	
Any Stressful Life Event							
No	363	483	1.00 (referent)	190	307	1.00 (referent)	0.05
Yes	302	374	0.85 (0.66, 1.10)	206	258	1.29 (0.93, 1.78)	
Total Number of Stressful Life Events							
0	363	483	1.00 (referent)	190	307	1.00 (referent)	0.05
1	179	252	0.77 (0.57, 1.03)	149	191	1.36 (0.96, 1.95)	
≥ 2	123	122	1.00 (0.70, 1.42)	57	67	1.11 (0.67, 1.83)	
Any Loss Event							
No	454	608	1.00 (referent)	218	355	1.00 (referent)	0.08
Yes	211	249	1.01 (0.77, 1.33)	178	210	1.48 (1.06, 2.05)	
Total Number of Loss Events							
0	454	608	1.00 (referent)	218	355	1.00 (referent)	0.23
1	190	234	0.98 (0.74, 1.29)	154	201	1.41 (1.00, 1.98)	
≥ 2	21	15	1.51 (0.65, 3.53)	24	9	2.36 (0.94, 5.91)	
Any Socioeconomic Event							
No	496	654	1.00 (referent)	336	470	1.00 (referent)	0.63
Yes	169	203	0.86 (0.64, 1.15)	60	95	0.76 (0.49, 1.18)	
Total Number of Socioeconomic Events							
0	496	654	1.00 (referent)	336	470	1.00 (referent)	0.63
1	106	144	0.82 (0.59, 1.16)	42	65	0.83 (0.50, 1.40)	
≥ 2	63	59	0.94 (0.59, 1.48)	18	30	0.61 (0.29, 1.31)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 13: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with each stressful life event in the previous 6 years, stratified by smoking status

	Never-Light Smokers			Heavy Smokers			p-value (interaction)
	Cases (n=358)	Controls (n=1125)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=703)	Controls (n=297)	Multivariate Adjusted[1] OR (95% CI)	
Death of a family member							
No	232	795	1.00 (referent)	462	201	1.00 (referent)	0.52
Yes	126	330	1.28 (0.95, 1.71)	241	96	1.11 (0.81, 1.52)	
Death of a spouse							
No	336	1077	1.00 (referent)	657	282	1.00 (referent)	0.78
Yes	22	48	1.37 (0.73, 2.56)	46	15	1.20 (0.63, 2.29)	
Death of a parent/sibling							
No	255	845	1.00 (referent)	501	218	1.00 (referent)	0.84
Yes	103	280	1.21 (0.89, 1.65)	202	79	1.16 (0.83, 1.62)	
Death of a child/grandchild							
No	353	1117	1.00 (referent)	685	289	1.00 (referent)	0.20
Yes	5	8	2.10 (0.60, 7.40)	18	8	0.76 (0.30, 1.91)	
Separation or divorce							
No	337	1083	1.00 (referent)	684	293	1.00 (referent)	0.33
Yes	21	42	1.05 (0.56, 1.96)	19	4	1.97 (0.63, 6.13)	
Loss of Job							
No	316	973	1.00 (referent)	589	234	1.00 (referent)	0.91
Yes	42	152	0.75 (0.48, 1.15)	114	63	0.77 (0.52, 1.14)	
Loss of Job, yourself							
No	320	982	1.00 (referent)	593	235	1.00 (referent)	0.83
Yes	38	143	0.72 (0.46, 1.12)	110	62	0.76 (0.51, 1.13)	
Loss of Job, spouse							
No	353	1108	1.00 (referent)	694	294	1.00 (referent)	0.69
Yes	5	17	0.83 (0.28, 2.49)	9	3	1.20 (0.29, 4.87)	
Decreased income/increased debt							
No	319	1022	1.00 (referent)	610	256	1.00 (referent)	0.99
Yes	39	103	0.98 (0.61, 1.58)	93	41	0.98 (0.62, 1.53)	
Move from one city to another							
No	350	1103	1.00 (referent)	687	294	1.00 (referent)	0.95
Yes	8	22	1.59 (0.64, 3.97)	16	3	1.67 (0.45, 6.10)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 14: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with groups of stressful life events in the previous 6 years, stratified by smoking status

	Never-Light Smokers			Heavy Smokers			p-value (interaction)
	Cases (n=358)	Controls (n=1125)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=703)	Controls (n=297)	Multivariate Adjusted[1] OR (95% CI)	
Any Stressful Life Event							
No	184	642	1.00 (referent)	369	148	1.00 (referent)	0.36
Yes	174	483	1.08 (0.82, 1.43)	334	149	0.90 (0.67, 1.21)	
Total Number of Stressful Life Events							
0	184	642	1.00 (referent)	369	148	1.00 (referent)	0.49
1	121	344	1.10 (0.81, 1.49)	207	99	0.84 (0.60, 1.17)	
≥ 2	53	139	1.06 (0.70, 1.60)	127	50	1.02 (0.67, 1.53)	
Any Loss Event							
No	220	763	1.00 (referent)	452	200	1.00 (referent)	0.84
Yes	138	362	1.20 (0.90, 1.60)	251	97	1.15 (0.84, 1.57)	
Total Number of Loss Events							
0	220	763	1.00 (referent)	452	200	1.00 (referent)	0.91
1	126	346	1.16 (0.87, 1.55)	218	89	1.12 (0.80, 1.52)	
≥ 2	12	16	2.08 (0.86, 5.01)	33	8	1.63 (0.70, 3.76)	
Any Socioeconomic Event							
No	289	911	1.00 (referent)	543	213	1.00 (referent)	0.58
Yes	69	214	0.89 (0.63, 1.25)	160	84	0.78 (0.57, 1.08)	
Total Number of Socioeconomic Events							
0	289	911	1.00 (referent)	543	213	1.00 (referent)	0.13
1	50	149	1.04 (0.70, 1.55)	98	60	0.66 (0.45, 0.97)	
≥ 2	19	65	0.66 (0.36, 1.22)	62	24	0.99 (0.58, 1.68)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 15: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to each stressful life event in the previous 6 years, by histological subtype

		Adenocarcinoma		Squamous Cell Carcinoma		Small Cell Carcinoma	
	Controls (n=1422)	Cases (n=403)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=318)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=178)	Multivariate Adjusted[1] OR (95% CI)
Death of a family member							
No	996	261	1.00 (referent)	205	1.00 (referent)	119	1.00 (referent)
Yes	426	142	1.22 (0.93, 1.60)	113	1.24 (0.93, 1.67)	59	1.09 (0.74, 1.58)
Death of a spouse							
No	1359	380	1.00 (referent)	297	1.00 (referent)	166	1.00 (referent)
Yes	63	23	1.18 (0.67, 2.09)	21	1.30 (0.72, 2.35)	12	1.32 (0.62, 2.79)
Death of a parent/sibling							
No	1063	280	1.00 (referent)	225	1.00 (referent)	130	1.00 (referent)
Yes	359	123	1.26 (0.95, 1.67)	93	1.21 (0.89, 1.64)	48	1.03 (0.69, 1.53)
Death of a child/grandchild							
No	1406	396	1.00 (referent)	310	1.00 (referent)	175	1.00 (referent)
Yes	16	7	1.01 (0.37, 2.75)	8	1.31 (0.49, 3.49)	3	0.80 (0.20, 3.19)
Separation or divorce							
No	1376	388	1.00 (referent)	309	1.00 (referent)	172	1.00 (referent)
Yes	46	15	1.17 (0.60, 2.30)	9	1.30 (0.58, 2.90)	6	1.31 (0.50, 3.46)
Loss of Job							
No	1207	350	1.00 (referent)	261	1.00 (referent)	151	1.00 (referent)
Yes	215	53	0.73 (0.51, 1.05)	57	0.92 (0.63, 1.33)	27	0.76 (0.46, 1.24)
Loss of Job, yourself							
No	1217	353	1.00 (referent)	262	1.00 (referent)	154	1.00 (referent)
Yes	205	50	0.72 (0.49, 1.04)	56	0.91 (0.63, 1.33)	24	0.67 (0.40, 1.13)
Loss of Job, spouse							
No	1402	399	1.00 (referent)	314	1.00 (referent)	174	1.00 (referent)
Yes	20	4	0.65 (0.20, 2.05)	4	1.11 (0.33, 3.68)	4	1.69 (0.49, 5.82)
Decreased income/increased debt							
No	1278	354	1.00 (referent)	278	1.00 (referent)	153	1.00 (referent)
Yes	144	49	0.89 (0.60, 1.33)	40	0.97 (0.63, 1.49)	25	0.93 (0.55, 1.57)
Move from one city to another							
No	1397	396	1.00 (referent)	310	1.00 (referent)	175	1.00 (referent)
Yes	25	7	1.16 (0.43, 3.15)	8	2.17 (0.82, 5.76)	3	1.27 (0.31, 5.15)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another

Table 16: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to groups of stressful life events in the previous 6 years, by histological subtype

		Adenocarcinoma		Squamous Cell Carcinoma		Small Cell Carcinoma	
	Controls (n=1422)	Cases (n=403)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=318)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=178)	Multivariate Adjusted[1] OR (95% CI)
Any Stressful Life Event							
No	790	209	1.00 (referent)	163	1.00 (referent)	95	1.00 (referent)
Yes	632	194	1.02 (0.79, 1.32)	155	1.05 (0.79, 1.38)	83	0.91 (0.63, 1.30)
Total Number of Stressful Life Events							
0	790	209	1.00 (referent)	163	1.00 (referent)	95	1.00 (referent)
1	443	130	1.01 (0.76, 1.35)	97	0.99 (0.72, 1.35)	51	0.86 (0.57, 1.30)
≥ 2	189	64	1.03 (0.71, 1.49)	58	1.17 (0.79, 1.73)	32	1.00 (0.61, 1.63)
Any Loss Event							
No	963	251	1.00 (referent)	201	1.00 (referent)	116	1.00 (referent)
Yes	459	152	1.22 (0.93, 1.59)	117	1.22 (0.91, 1.63)	62	1.07 (0.74, 1.55)
Total Number of Loss Events							
0	963	251	1.00 (referent)	201	1.00 (referent)	116	1.00 (referent)
1	435	137	1.18 (0.90, 1.55)	103	1.16 (0.86, 1.56)	55	1.04 (0.71, 1.53)
≥ 2	24	15	1.83 (0.87, 3.89)	14	2.15 (0.99, 4.67)	7	1.55 (0.58, 4.16)
Any Socioeconomic Event							
No	1124	323	1.00 (referent)	245	1.00 (referent)	134	1.00 (referent)
Yes	298	80	0.79 (0.57, 1.09)	73	0.88 (0.63, 1.24)	44	0.95 (0.62, 1.45)
Total Number of Socioeconomic Events							
0	1124	323	1.00 (referent)	245	1.00 (referent)	134	1.00 (referent)
1	209	52	0.80 (0.55, 1.16)	42	0.77 (0.52, 1.16)	32	1.12 (0.69, 1.81)
≥ 2	89	28	1.76 (0.46, 1.27)	31	1.10 (0.67, 1.84)	12	0.67 (0.33, 1.35)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

5.6.4 Restriction of exposures to the three years prior to date of interview or diagnosis

5.6.4.1 Individual Stressful Life Events

Based on the hypothesis that exposure to stressful life events acts on the lung tumour promotion pathway, exposures were restricted to those having occurred in the three years prior to date of interview or diagnosis, and the results were compared to the primary analysis. With respect to experience of death of a family member (table 17), when compared to the number of participants exposed in the six years prior to interview, fewer participants were exposed to a low impact death of a family member in the three years prior to interview. Overall, the magnitude, direction and statistical significance of the observed associations were similar between analyses of exposures in the three-year time window and six-year time window. However, there was a statistically non-significant stronger positive association between ever exposure to death of a child or grandchild and lung cancer (OR=1.72 (0.68, 4.31)) occurring in the three years prior to interview, when compared to exposures occurring six years prior to interview.

Results were generally similar in the primary analyses when compared to exposures occurring three years prior to interview for ever exposure to separation or divorce (table 18). Restriction to self-respondents revealed a stronger increased relative risk associated with ever exposure, in the three-year time window (OR=1.37 (0.60, 3.13)) when compared to the null association observed in the six-year time window (OR=1.21 (0.58, 2.56)). With respect to self-appraised impact scores, positive associations were stronger when exposures were restricted to three years prior to interview.

The inverse association between ever exposure to loss of job and lung cancer risk observed in the primary analysis was attenuated when exposures were restricted three years prior to interview (OR=1.06 (0.71, 1.56)) (table 19). Low and medium self-appraised impact estimates remained protective but were attenuated in the three year time window when compared to the six year time window, however the high impact estimate showed a statistically significant stronger increased relative risk (OR=1.95 (1.11, 3.41)) when exposures were restricted to three years prior to interview, when compared to the primary analysis. A similar trend was observed for exposures to loss of own job and loss of spouse's job, though the majority of participants experienced their own job loss versus that of their spouse. Restriction to self-respondents did not appreciably change the observed results.

The observed estimate for the association between ever exposure to decrease in income or increase in debt and lung cancer was null in the primary analysis, however a protective, albeit not statistically significant, estimate was observed when exposure were restricted to the three years prior to interview (OR=0.79 (0.50, 1.26)) (table 20). This change in observed estimates is most prominent in the low self-appraised impact exposure category (OR=0.46 (0.13, 1.60)), although there were low numbers. Observed results did not differ when the analyzed population was restricted to self-respondents.

Overall, the observed estimates for the association between move from one city to another and lung cancer in the primary analysis were similar to those observed when exposures were restricted to three years prior to interview (table 21). In some cases, there were low numbers and comparisons could not be made.

5.6.4.2 Total Number of Stressful Life Events

Generally, there was no difference in the observed estimates for total number of stressful life events experienced and lung cancer risk when comparing the primary analyses to the analyses of exposures occurring three years prior to interview (table 22). However, a slight attenuation of the protective effect associated with low self-appraised impact was observed when exposures were restricted to three years prior to interview (OR=0.86 (0.60, 1.24)) compared to the primary analysis (OR=0.71 (0.52, 0.99)) (table 9). Conversely, a stronger increase in risk was observed for the high self-appraised impact score (OR=1.20 (0.80, 1.81)) when exposures were limited to those occurring three years prior to interview, when compared to the primary analysis (OR=1.02 (0.75, 1.38)) (table 9). When restricted to self-respondents, the results did not differ appreciably.

5.6.4.3 Total Number of Loss and Socioeconomic Events

Overall, observed estimates among for exposures occurring three years prior to interview were not different to those observed in the primary analyses (table 23). However, a stronger suggestion of a positive association between exposure to at least 2 loss events and lung cancer risk was observed among those exposed three years prior to interview (OR=2.39 (0.99, 5.80)), albeit with lower numbers, compared to the estimate observed in the primary analysis (OR=1.83

(0.99, 3.40)) (table 10). Secondly, a change in direction was observed for the suggestive protective association for high self-appraised impact score of socioeconomic events observed in the primary analysis (OR=0.92 (0.61, 1,41)) (table 10) when exposures were restricted to those occurring three years prior to interview (OR=1.35 (0.77, 2.38)). Results were not different when restricted to self-respondents.

5.6.4.4 Stratification by sex

When stratifying by sex, with respect to individual stressful life events, the overall trends observed in the primary analyses were similar to those observed upon restriction of exposures to three years prior to interview. However, RRs for decrease in income or increase in debt were different among males and females, but were not appreciably different in the primary analyses when compared to the estimates observed for exposures restricted to three years prior to interview.

The RRs for total number of stressful life events, total number of loss events and total number of socioeconomic events (table 25), did not differ between males and females, when exposures were restricted to those occurring three years prior to interview. The observed suggestive increase in risk for any stressful life event, and total number of stressful life events observed in the primary analysis, were attenuated when exposures were restricted to three years prior to interview.

5.6.4.5 Stratification by Smoking

No significant differences were observed in the association between ever exposure to individual stressful life events and lung cancer risk, with respect to smoking status (table 26), when comparing exposures restricted to three years prior to interview and the primary analysis.

With respect to cumulative exposures (table 27), no significant differences in RRs between never-light smokers and heavy smokers were observed for total number of stressful life events, and for total number of loss and socioeconomic events. Similarly, no significant differences in RRs were observed for ever exposure to any stressful life event, loss event or socioeconomic event, with respect to smoking status. These observations were not different in the primary analyses when compared to estimates observed when exposures occurred only in the three years prior to interview or date of diagnosis.

5.6.4.6 Analysis by Histological Subtype

Overall, as in the primary analyses, there were no observed differences in RRs between the three histological subtypes (adenocarcinoma, squamous cell carcinoma, small cell carcinoma) for individual stressful life events, total number of stressful life events and total number of loss events; when exposures were restricted to three years prior to interview. In some cases, there were lower numbers. With respect to the association between socioeconomic events, and histological subtype, the observed estimates among analyses restricted to exposures occurring three years prior to interview were largely attenuated when compared to the primary analyses (table 29).

5.6.4.7 Sensitivity Analysis for Loss of Job in the Previous 6 Years

In order to minimize the risk of reverse causality bias, from participants losing jobs due to early symptoms of lung cancer, a sensitivity analysis eliminating exposures in the year prior to interview or diagnosis, was conducted (table 30). Overall, the observed results were similar to those observed in the primary analyses (table 6).

Table 17: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with death in the previous 3 years

	All Participants			Self-Respondents		
	Cases (n=1058)	**Controls (n=1418)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Death of a family member						
No	819	1145	1.00 (referent)	498	1048	1.00 (referent)
Yes	242	277	1.15 (0.90, 1.46)	159	265	1.10 (0.85, 1.42)
Self-Appraised Impact Score[2]						
None	819	1145	1.00 (referent)	498	1048	1.00 (referent)
Low	52	83	1.05 (0.68, 1.62)	39	80	1.07 (0.68, 1.68)
Medium/High	187	190	1.20 (0.91, 1.58)	118	182	1.11 (0.82, 1.50)
Death of a spouse						
No	1015	1380	1.00 (referent)	631	1272	1.00 (referent)
Yes	46	42	1.30 (0.76, 2.22)	26	41	1.11 (0.62, 2.00)
Self-Appraised Impact Score						
None	1015	1380	1.00 (referent)	631	1272	1.00 (referent)
Low	3	6	0.43 (0.07, 2.47)	1	6	0.25 (0.03, 2.46)
Medium/High	43	35	1.52 (0.86, 2.70)	25	34	1.33 (0.72, 2.47)
Death of a parent/sibling						
No	867	1191	1.00 (referent)	527	1092	1.00 (referent)
Yes	194	231	1.09 (0.84, 1.42)	130	221	1.05 (0.79, 1.39)
Self-Appraised Impact Score						
None	867	1191	1.00 (referent)	527	1092	1.00 (referent)
Low	54	76	1.14 (0.73, 1.78)	38	73	1.16 (0.73, 1.84)
Medium/High	137	152	1.08 (0.79, 1.47)	90	146	0.99 (0.71, 1.38)
Death of a child/grandchild						
No	1042	1412	1.00 (referent)	645	1304	1.00 (referent)
Yes	19	10	1.72 (0.68, 4.31)	12	9	2.01 (0.76, 5.29)
Self-Appraised Impact Score						
None	1042	1412	1.00 (referent)	645	1304	1.00 (referent)
Low	1	2	0.56 (0.04, 7.45)	1	2	0.61 (0.05, 8.05)
Medium/High	18	8	2.04 (0.75, 5.57)	11	7	2.47 (0.85, 7.16)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

[2] 3 cases and 4 controls were missing stress impact information and were not included in the self-appraised impact score analysis

Table 18: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with separation or divorce in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Separation or divorce						
No	1039	1401	1.00 (referent)	643	1294	1.00 (referent)
Yes	22	21	1.21 (0.58, 2.56)	14	19	1.37 (0.60, 3.13)
Self-Appraised Impact Score[2]						
None	1039	1401	1.00 (referent)	643	1294	1.00 (referent)
Low	3	9	0.47 (0.09, 2.31)	2	9	0.40 (0.07, 2.32)
Medium/High	18	10	2.09 (0.81, 5.38)	11	9	2.37 (0.84, 6.66)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, death of a child or grandchild, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

[2] 1 cases and 3 controls were missing stress impact information and were not included in the self-appraised impact score analysis

Table 19: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with loss of job in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Loss of Job						
No	969	1317	1.00 (referent)	597	1214	1.00 (referent)
Yes	92	105	1.06 (0.71, 1.56)	60	99	1.01 (0.66, 1.54)
Self-Appraised Impact Score[2]						
None	969	1317	1.00 (referent)	597	1214	1.00 (referent)
Low	24	44	0.61 (0.33, 1.12)	18	40	0.69 (0.36, 1.32)
Medium	11	18	0.75 (0.30, 1.84)	6	16	0.64 (0.23, 1.79)
High	57	42	1.95 (1.11, 3.41)	36	42	1.69 (0.93, 3.07)
Loss of job, yourself						
No	975	1323	1.00 (referent)	601	1220	1.00 (referent)
Yes	86	99	1.01 (0.68, 1.52)	56	93	0.97 (0.63, 1.50)
Self-Appraised Impact Score						
None	975	1323	1.00 (referent)	601	1220	1.00 (referent)
Low	32	59	0.63 (0.37, 1.07)	23	53	0.67 (0.38, 1.18)
Medium/High	54	39	1.83 (1.03, 3.25)	33	39	1.56 (0.85, 2.87)
Loss of job, your spouse						
No	1052	1411	1.00 (referent)	652	1302	1.00 (referent)
Yes	9	11	1.20 (0.40, 3.66)	5	11	1.03 (0.30, 3.53)
Self-Appraised Impact Score						
None	1052	1411	1.00 (referent)	652	1302	1.00 (referent)
Low	5	6	0.77 (0.16, 3.67)	2	6	0.57 (0.09, 3.66)
Medium/High	4	5	1.84 (0.40, 8.44)	3	5	1.70 (0.33, 8.74)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, major reduction in family income or increase of debt, and move from one city to another.

[2] 1 controls was missing stress impact information and were not included in the self-appraised impact score analysis

Table 20: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with a major reduction in family income or increase in debt in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Decreased income/increased debt						
No	1001	1343	1.00 (referent)	615	1238	1.00 (referent)
Yes	60	79	0.79 (0.50, 1.26)	42	75	0.81 (0.49, 1.33)
Self-Appraised Impact Score						
None	1001	1343	1.00 (referent)	615	1238	1.00 (referent)
Low	4	13	0.46 (0.13, 1.60)	4	14	0.54 (0.15, 1.91)
Medium	11	20	0.81 (0.31, 2.14)	6	20	0.66 (0.22, 1.97)
High	44	43	0.84 (0.49, 1.46)	31	40	0.89 (0.49, 1.61)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, separation or divorce, loss of job, loss of spouse's job, and move from one city to another.

[2] 1 case and 3 controls were missing stress impact information and were not included in the self-appraised impact score analysis

Table 21: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with a move from one city to another in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Move from one city to another						
No	1048	1407	1.00 (referent)	647	1299	1.00 (referent)
Yes	13	15	1.74 (0.69, 4.40)	10	14	1.76 (0.65, 4.78)
Self-Appraised Impact Score[2]						
None	1048	1407	1.00 (referent)	647	1299	1.00 (referent)
Low	2	7	0.39 (0.05, 2.71)	2	6	0.80 (0.12, 5.58)
Medium	-	3	-	-	3	-
High	10	5	4.36 (1.26, 15.08)	8	5	3.67 (0.98, 13.75)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: death of a spouse, death of a parent, sister or brother, death of a child or grandchild, separation or divorce, loss of job, loss of spouse's job, and major reduction in family income or increase of debt.

[2] 1 case was missing stress impact information and was not included in the self-appraised impact score analysis

Table 22: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with all stressful life events in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Any Stressful Life Event						
No	721	1013	1.00 (referent)	437	924	1.00 (referent)
Yes	340	409	1.05 (0.84, 1.30)	220	389	0.99 (0.78, 1.25)
Total Number of Stressful Life Events						
0	721	1013	1.00 (referent)	437	924	1.00 (referent)
1	255	327	1.03 (0.81, 1.30)	164	311	0.97 (0.75, 1.25)
≥ 2	85	82	1.12 (0.76, 1.65)	56	78	1.06 (0.70, 1.60)
Self-Appraised Impact Score[3]						
None	721	1013	1.00 (referent)	437	924	1.00 (referent)
Low	76	136	0.86 (0.60, 1.24)	55	131	0.84 (0.57, 1.23)
Medium	177	200	1.11 (0.84, 1.47)	108	190	1.02 (0.75, 1.38)
High	81	66	1.20 (0.80, 1.81)	53	63	1.14 (0.74, 1.75)
Miller and Rahe Impact Score[2]						
None	929	1257	1.00 (referent)	564	1151	1.00 (referent)
Low stress	20	34	0.98 (0.47, 2.04)	12	34	0.81 (0.36, 1.81)
Medium stress	68	84	1.34 (0.86, 2.10)	53	81	1.42 (0.89, 2.26)
High stress	44	47	1.13 (0.66, 1.96)	28	47	1.06 (0.59, 1.88)

[1] Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other).

[2] Refer to table 1 for assigned Life Change Unit values. Stressful life events assigned an expert assessed stress appraisal value include job loss (self), increase in debt, move from one city to another, death (spouse, sibling, child), and divorce.

[3] 6 cases and 7 controls were missing stress impact information and were not included in the self-appraised impact score analysis

Table 23: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with a loss events and socioeconomic events in the previous 3 years

	All Participants			Self Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Any Loss Event[3]						
No	805	1127	1.00 (referent)	491	1032	1.00 (referent)
Yes	256	295	1.12 (0.89, 1.43)	166	281	1.09 (0.84, 1.41)
Total Number of Loss Events						
0	805	1127	1.00 (referent)	491	1032	1.00 (referent)
1	231	286	1.07 (0.84, 1.37)	150	272	1.04 (0.80, 1.35)
≥ 2	25	9	2.39 (0.99, 5.80)	16	9	2.18 (0.87, 5.43)
Self-Appraised Impact Score						
None	805	1127	1.00 (referent)	491	1032	1.00 (referent)
Low	55	90	1.00 (0.66, 1.53)	41	87	1.01 (0.65, 1.58)
Medium/High	197	200	1.19 (0.91, 1.56)	122	191	1.11 (0.83, 1.48)
Miller and Rahe Impact Score						
None	948	1294	1.00 (referent)	575	1188	1.00 (referent)
Low stress	79	105	1.22 (0.81, 1.85)	59	102	1.29 (0.84, 1.99)
Medium/High stress	34	23	1.88 (0.94, 3.73)	23	23	1.77 (0.87, 3.61)
Any Socioeconomic Event[4]						
No	936	1263	1.00 (referent)	576	1161	1.00 (referent)
Yes	125	159	0.90 (0.66, 1.22)	81	152	0.83 (0.60, 1.16)
Total number of events						
0	936	1263	1.00 (referent)	576	1161	1.00 (referent)
1	85	118	0.83 (0.58, 1.19)	51	115	0.72 (0.48, 1.07)
≥ 2	40	41	1.08 (0.63, 1.83)	30	37	1.16 (0.66, 2.04)
Self-Appraised Impact Score						
None	936	1263	1.00 (referent)	576	1161	1.00 (referent)
Low	22	48	0.56 (0.30, 1.02)	16	47	0.52 (0.27, 0.99)
Medium	62	78	0.90 (0.59, 1.38)	35	74	0.80 (0.49, 1.28)
High	39	31	1.35 (0.77, 2.38)	29	29	1.36 (0.75, 2.47)
Miller and Rahe Impact Score						
None	1030	1367	1.00 (referent)	639	1258	1.00 (referent)
Low stress	16	35	0.57 (0.27, 1.21)	9	35	0.45 (0.19, 1.04)
Medium/High stress	15	20	0.91 (0.38, 2.17)	9	20	0.87 (0.35, 2.19)

[1] Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other).
[2] Refer to table 1 for assigned Life Change Unit values. Stressful life events assigned an expert assessed stress appraisal value include job loss (self), increase in debt, move from one city to another, death (spouse, sibling, child), and divorce.
[3] Loss events include death (spouse, sibling, child) and divorce.
[4] Socioeconomic events include job loss (self), increase in debt, and move from one city to another.

Table 24: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to each stressful life event in the previous 3 years, stratified by sex

	Males			Females			p-value (interaction)
	Cases (n=665)	Controls (n=857)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=396)	Controls (n=565)	Multivariate Adjusted[1] OR (95% CI)	
Death of a family member							
No	531	696	1.00 (referent)	288	449	1.00 (referent)	0.11
Yes	134	161	0.98 (0.71, 1.34)	108	116	1.45 (0.99, 2.13)	
Death of a spouse							
No	640	832	1.00 (referent)	375	548	1.00 (referent)	0.25
Yes	25	25	1.00 (0.50, 2.01)	21	17	1.91 (0.81, 4.47)	
Death of a parent/sibling							
No	555	724	1.00 (referent)	312	467	1.00 (referent)	0.31
Yes	110	133	0.98 (0.70, 1.37)	84	98	1.29 (0.85, 1.94)	
Death of a child/grandchild							
No	657	851	1.00 (referent)	385	561	1.00 (referent)	0.61
Yes	8	6	1.36 (0.37, 4.95)	11	4	2.19 (0.57, 8.34)	
Separation or divorce							
No	650	850	1.00 (referent)	388	551	1.00 (referent)	0.12
Yes	14	7	2.41 (0.74, 7.87)	8	14	0.72 (0.26, 1.98)	
Loss of Job							
No	589	774	1.00 (referent)	380	543	1.00 (referent)	0.95
Yes	76	83	1.06 (0.69, 1.62)	16	22	1.03 (0.44, 2.42)	
Loss of Job, yourself							
No	592	776	1.00 (referent)	383	547	1.00 (referent)	0.77
Yes	73	81	1.04 (0.68, 1.59)	13	18	0.89 (0.34, 2.31)	
Loss of Job, spouse							
No	659	852	1.00 (referent)	393	559	1.00 (referent)	0.77
Yes	6	5	1.44 (0.28, 7.49)	3	6	1.03 (0.22, 4.81)	
Decreased income/increased debt							
No	623	818	1.00 (referent)	378	525	1.00 (referent)	0.04
Yes	42	39	1.15 (0.64, 2.05)	18	40	0.44 (0.21, 0.92)	
Move from one city to another							
No	659	852	1.00 (referent)	389	555	1.00 (referent)	0.86
Yes	6	5	1.92 (0.45, 8.17)	7	10	1.62 (0.49, 5.41)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 25: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to groups of stressful life events in the previous 3 years, stratified by sex

	Males			Females			p-value (interaction)
	Cases (n=665)	**Controls (n=857)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=396)**	**Controls (n=565)**	**Multivariate Adjusted[1] OR (95% CI)**	
Any Stressful Life Event							
No	457	614	1.00 (referent)	264	399	1.00 (referent)	0.36
Yes	208	243	0.97 (0.74, 1.27)	132	166	1.19 (0.84, 1.69)	
Total Number of Stressful Life Events							
0	457	614	1.00 (referent)	264	399	1.00 (referent)	0.13
1	148	196	0.88 (0.65, 1.19)	107	131	1.31 (0.89, 1.91)	
≥ 2	60	47	1.29 (0.80, 2.09)	25	35	0.86 (0.45, 1.64)	
Any Loss Event							
No	522	690	1.00 (referent)	283	437	1.00 (referent)	0.20
Yes	143	167	0.99 (0.73, 1.35)	113	128	1.35 (0.93, 1.96)	
Total Number of Loss Events							
0	522	690	1.00 (referent)	283	437	1.00 (referent)	0.27
1	129	163	0.93 (0.68, 1.27)	102	123	1.33 (0.91, 1.94)	
≥ 2	14	4	3.26 (0.92, 11.50)	11	5	1.77 (0.52, 6.03)	
Any Socioeconomic Event							
No	571	755	1.00 (referent)	365	508	1.00 (referent)	0.20
Yes	94	102	1.02 (0.71, 1.47)	31	57	0.66 (0.37, 1.17)	
Total Number of Socioeconomic Events							
0	571	755	1.00 (referent)	365	508	1.00 (referent)	0.45
1	63	76	0.95 (0.62, 1.46)	22	42	0.60 (0.31, 1.18)	
≥ 2	31	26	1.20 (0.64, 2.24)	9	15	0.83 (0.30, 2.26)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 26: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to each stressful life event in the previous 3 years, stratified by smoking status

	Never-Light Smokers			Heavy Smokers			p-value (interaction)
	Cases (n=358)	Controls (n=1125)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=703)	Controls (n=297)	Multivariate Adjusted[1] OR (95% CI)	
Death of a family member							
No	282	912	1.00 (referent)	537	233	1.00 (referent)	0.98
Yes	76	213	1.14 (0.82, 1.60)	166	64	1.15 (0.81, 1.63)	
Death of a spouse							
No	345	1093	1.00 (referent)	670	287	1.00 (referent)	0.89
Yes	13	32	1.25 (0.59, 2.66)	33	10	1.35 (0.62, 2.94)	
Death of a parent/sibling							
No	297	947	1.00 (referent)	570	244	1.00 (referent)	0.93
Yes	61	178	1.08 (0.75, 1.55)	133	53	1.10 (0.76, 1.61)	
Death of a child/grandchild							
No	353	1119	1.00 (referent)	689	293	1.00 (referent)	0.55
Yes	5	6	2.30 (0.62, 8.57)	14	4	1.34 (0.40, 4.46)	
Separation or divorce							
No	347	1107	1.00 (referent)	692	294	1.00 (referent)	
Yes	11	18	1.11 (0.45, 2.74)	11	3	1.53 (0.39, 5.95)	0.69
Loss of Job							
No	334	1052	1.00 (referent)	635	265	1.00 (referent)	0.91
Yes	24	73	1.03 (0.59, 1.81)	68	32	1.07 (0.65, 1.78)	
Loss of Job, yourself							
No	336	1058	1.00 (referent)	639	265	1.00 (referent)	0.99
Yes	22	67	1.01 (0.56, 1.81)	64	32	1.01 (0.61, 1.68)	
Loss of Job, spouse							
No	355	1114	1.00 (referent)	697	297	1.00 (referent)	0.97
Yes	3	11	0.70 (0.17, 2.88)	6	-	-	
Decreased income/increased debt							
No	338	1070	1.00 (referent)	663	273	1.00 (referent)	0.51
Yes	20	55	0.92 (0.49, 1.74)	40	24	0.70 (0.38, 1.26)	
Move from one city to another							
No	353	1112	1.00 (referent)	695	295	1.00 (referent)	0.88
Yes	5	13	1.64 (0.52, 5.18)	8	2	1.91 (0.38, 9.55)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 27: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to groups of stressful life events in the previous 3 years, stratified by smoking status

	Never-Light Smokers			Heavy Smokers			p-value (interaction)
	Cases (n=358)	Controls (n=1125)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=703)	Controls (n=297)	Multivariate Adjusted[1] OR (95% CI)	
Any Stressful Life Event							
No	251	813	1.00 (referent)	470	200	1.00 (referent)	0.90
Yes	107	312	1.03 (0.77, 1.39)	233	97	1.06 (0.78, 1.45)	
Total Number of Stressful Life Events							
0	251	813	1.00 (referent)	470	200	1.00 (referent)	0.98
1	80	254	1.01 (0.72, 1.39)	175	73	1.05 (0.75, 1.48)	
≥ 2	27	58	1.14 (0.66, 1.97)	58	24	1.10 (0.65, 1.89)	
Any Loss Event							
No	277	895	1.00 (referent)	528	232	1.00 (referent)	0.66
Yes	81	230	1.07 (0.77, 1.48)	175	65	1.19 (0.84, 1.69)	
Total Number of Loss Events							
0	277	895	1.00 (referent)	528	232	1.00 (referent)	0.21
1	72	226	0.98 (0.70, 1.38)	159	60	1.18 (0.83, 1.69)	
≥ 2	9	4	5.02 (1.37, 18.41)	16	5	1.30 (0.44, 3.84)	
Any Socioeconomic Event							
No	321	1011	1.00 (referent)	615	252	1.00 (referent)	0.93
Yes	37	114	0.91 (0.59, 1.42)	88	45	0.89 (0.59, 1.33)	
Total Number of Socioeconomic Events							
0	321	1011	1.00 (referent)	615	252	1.00 (referent)	0.97
1	25	86	0.86 (0.51, 1.46)	60	32	0.80 (0.49, 1.31)	
≥ 2	12	28	1.12 (0.51, 2.45)	28	13	1.04 (0.51, 2.10)	

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 28: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to each stressful life event in the previous 3 years, by histological subtype

		Adenocarcinoma		Squamous Cell Carcinoma		Small Cell Carcinoma	
	Controls (n=1422)	Cases (n=403)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=318)	Multivariate Adjusted[1] OR (95% CI)	Cases (n=178)	Multivariate Adjusted[1] OR (95% CI)
Death of a family member							
No	1145	312	1.00 (referent)	240	1.00 (referent)	132	1.00 (referent)
Yes	277	91	1.16 (0.85, 1.57)	78	1.28 (0.92, 1.77)	46	1.38 (0.92, 2.09)
Death of a spouse							
No	1380	386	1.00 (referent)	305	1.00 (referent)	169	1.00 (referent)
Yes	42	17	1.36 (0.70, 2.65)	13	1.17 (0.56, 2.41)	9	1.51 (0.63, 3.62)
Death of a parent/sibling							
No	1191	328	1.00 (referent)	254	1.00 (referent)	141	1.00 (referent)
Yes	231	75	1.12 (0.81, 1.55)	64	1.24 (0.87, 1.75)	37	1.28 (0.82, 1.99)
Death of a child/grandchild							
No	1412	396	1.00 (referent)	312	1.00 (referent)	175	1.00 (referent)
Yes	10	7	1.88 (0.63, 5.55)	6	2.01 (0.64, 6.30)	3	1.62 (0.37, 7.01)
Separation or divorce							
No	1401	397	1.00 (referent)	312	1.00 (referent)	174	1.00 (referent)
Yes	21	6	0.84 (0.30, 2.33)	6	1.53 (0.54, 4.36)	4	1.49 (0.44, 5.05)
Loss of Job							
No	1317	370	1.00 (referent)	285	1.00 (referent)	163	1.00 (referent)
Yes	105	33	0.99 (0.62, 1.57)	33	1.15 (0.72, 1.83)	15	0.89 (0.47, 1.67)
Loss of Job, yourself							
No	1323	372	1.00 (referent)	286	1.00 (referent)	165	1.00 (referent)
Yes	99	31	0.97 (0.60, 1.55)	32	1.14 (0.71, 1.83)	13	0.79 (0.40, 1.54)
Loss of Job, spouse							
No	1411	400	1.00 (referent)	316	1.00 (referent)	175	1.00 (referent)
Yes	11	3	0.97 (0.24, 4.00)	2	1.10 (0.20, 5.93)	3	2.36 (0.51, 11.01)
Decreased income/increased debt							
No	1343	377	1.00 (referent)	303	1.00 (referent)	166	1.00 (referent)
Yes	79	26	0.93 (0.55, 1.56)	15	0.69 (0.37, 1.28)	12	0.90 (0.45, 1.82)
Move from one city to another							
No	1407	402	1.00 (referent)	312	1.00 (referent)	177	1.00 (referent)
Yes	15	1	0.37 (0.05, 3.00)	6	3.22 (1.03, 10.05)	1	1.10 (0.12, 9.70)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 29: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with exposure to groups of stressful life events in the previous 3 years, by histological subtype

		Adenocarcinoma		Squamous Cell Carcinoma		Small Cell Carcinoma	
	Controls (n=1422)	**Cases (n=403)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=318)**	**Multivariate Adjusted[1] OR (95% CI)**	**Cases (n=178)**	**Multivariate Adjusted[1] OR (95% CI)**
Any Stressful Life Event							
No	1013	276	1.00 (referent)	213	1.00 (referent)	115	1.00 (referent)
Yes	409	127	1.05 (0.80, 1.39)	105	1.12 (0.84, 1.51)	63	1.23 (0.85, 1.79)
Total Number of Stressful Life Events							
0	1013	276	1.00 (referent)	213	1.00 (referent)	115	1.00 (referent)
1	327	95	1.03 (0.76, 1.39)	76	1.07 (0.77, 1.49)	47	1.24 (0.82, 1.87)
≥ 2	82	32	1.14 (0.70, 1.85)	29	1.30 (0.78, 2.16)	16	1.21 (0.64, 2.30)
Any Loss Event							
No	1127	306	1.00 (referent)	238	1.00 (referent)	130	1.00 (referent)
Yes	295	97	1.14 (0.84, 1.53)	80	1.23 (0.89, 1.69)	48	1.33 (0.89, 2.00)
Total Number of Loss Events							
0	1127	306	1.00 (referent)	238	1.00 (referent)	130	1.00 (referent)
1	286	89	1.10 (0.81, 1.49)	71	1.15 (0.83, 1.61)	43	1.28 (0.84, 1.94)
≥ 2	9	8	2.17 (0.75, 6.28)	9	2.88 (1.00, 8.25)	5	2.58 (0.73, 9.05)
Any Socioeconomic Event							
No	1263	358	1.00 (referent)	279	1.00 (referent)	155	1.00 (referent)
Yes	159	45	0.88 (0.59, 1.31)	39	0.94 (0.62, 1.44)	23	0.96 (0.56, 1.64)
Total Number of Socioeconomic Events							
0	1263	358	1.00 (referent)	279	1.00 (referent)	155	1.00 (referent)
1	118	30	0.82 (0.51, 1.31)	24	0.80 (0.48, 1.34)	17	1.00 (0.54, 1.83)
≥ 2	41	15	1.04 (0.53, 2.05)	15	1.31 (0.66, 2.59)	6	0.86 (0.33, 2.25)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, loss of job, loss of spouse's job, major reduction in family income or increase of debt, and move from one city to another.

Table 30: Multivariate odds ratios (95% confidence intervals) for lung cancer associated with loss of job in the previous 6 years, with exclusion of the previous year

	All Participants			Self-Respondents		
	Cases (n=1061)	**Controls (n=1422)**	**Multivariate Adjusted OR (95% CI)**	**Cases (n=657)**	**Controls (n=1313)**	**Multivariate Adjusted OR (95% CI)**
Loss of Job						
No	954	1239	1.00 (referent)	590	1143	1.00 (referent)
Yes	107	183	0.62 (0.44, 0.86)	67	170	0.58 (0.40, 0.83)
Self-Appraised Impact Score [2]						
None	954	1239	1.00 (referent)	590	1143	1.00 (referent)
Low	29	75	0.44 (0.26, 0.75)	23	70	0.49 (0.28, 0.84)
Medium	16	28	0.63 (0.29, 1.33)	9	26	0.56 (0.24, 1.32)
High	62	79	0.82 (0.52, 1.29)	35	73	0.69 (0.41, 1.15)
Loss of job, yourself						
No	963	1247	1.00 (referent)	597	1151	1.00 (referent)
Yes	98	175	0.58 (0.41, 0.81)	60	162	0.53 (0.37, 0.77)
Self-Appraised Impact Score						
None	963	1247	1.00 (referent)	597	1151	1.00 (referent)
Low	43	98	0.48 (0.31, 0.75)	31	91	0.50 (0.31, 0.81)
Medium/High	55	76	0.72 (0.45, 1.15)	29	70	0.58 (0.34, 0.99)
Loss of job, your spouse						
No	1050	1409	1.00 (referent)	649	1301	1.00 (referent)
Yes	11	13	1.13 (0.43, 3.01)	8	12	1.27 (0.44, 3.64)
Self-Appraised Impact Score						
None	1050	1409	1.00 (referent)	649	1301	1.00 (referent)
Low	3	8	0.45 (0.09, 2.23)	2	7	0.66 (0.11, 3.88)
Medium/High	8	5	2.20 (0.58, 8.38)	6	5	1.97 (0.49, 7.99)

1 Adjusted for age (continuous), respondent status (self, proxy), comprehensive smoking indicator, sex (male, female), number of school years (<7, 7-12, 12+), mean census tract family income (low, medium, high), ethnic group (French Canadian, other), stressful life event (yes, no). Stressful life events include: separation or divorce, major reduction in family income or increase of debt, and move from one city to another.

[2] 1 control is missing impact information and was not included in the self-appraised impact analysis

6.0 Discussion

6.1 Summary of Key Findings

6.1.1 Individual Stressful Life Events

We first analyzed each of the individual stressful life events assessed on the questionnaire. Overall, exposure to individual stressful life events in the past six years was not associated to lung cancer risk. This lack of overall association was consistent when taking into account self-appraised impact scores and when restricted to self-respondents. Analyses restricting exposures to three years prior to date of diagnosis (or interview) were not appreciably different to the primary analyses. Generally, there were no differences among RRs when stratified by sex, smoking status or in analyses by histological subtype.

However, an increased risk associated with ever exposure to death of a family member was observed, largely driven by ever exposure to death of a parent or sibling. Upon stratification by sex, we did not observe a statistically significant interaction at the alpha level of 0.05, but we saw a stronger increase in risk among females when compared to males, among whom a null association was observed.

In the primary analyses, we observed an inverse association for loss of job, which was attenuated upon restriction to more recent events occurring in the three years prior to interview or date of diagnosis. These associations were largely driven by loss of own job. One possible explanation for this observed attenuation could be that by excluding participants with proxy respondents, the most aggressive cases of lung cancer have been excluded from the analyses since proxy respondents were used for only those cases that had died prior to interview or were too sick to respond themselves. Thus, the self-respondent population is restricted to less aggressive lung cancer cases, and the observed estimate may underestimate the parameter observed in the study population. In primary analyses, we observed an inverse association for not very stressful job loss events and no association for extremely stressful job loss events. With

restriction to events occurring in the three years prior to interview or date of diagnosis, not very stressful events were consistently associated with a decrease in risk, while we observed an increase in RR for extremely stressful loss of job events. There was no difference in the observed RRs when exposures in the year prior to interview were considered unexposed, in order to account for possible reverse causality, that is early symptoms of lung cancer having potentially contributed to the participant's loss of job.

We also observed differences between men and women in the RRs for decreased income or increased debt; exposure to the event was protective among females, while the RR was increased among males.

Finally, a move from one city to another that was self-appraised as having had a high impact was associated with an increased lung cancer risk, though with very wide confidence intervals.

6.1.2 Total Number of Stressful Life Events

We then analyzed total exposure to stressful life events. Having been exposed to any stressful life event during the past six years was not associated with lung cancer risk. Similarly, the total number of stressful life events was not associated with lung cancer risk. Analyses stratified by sex and smoking status did not reveal any differences, nor was there evidence of differences by histological type. We did not observe any appreciable differences between RRs observed in the primary analyses that included a 6 year window before diagnosis/interview and the RRs observed when exposures were restricted to three years prior to date of diagnosis or interview.

When the total number of stressful life events was self-appraised to have had a low impact, a protective association was observed. Relative risks resulting from analyses using Miller and Rahe impact scores generally had wide confidence intervals. Overall, the point estimates were slightly stronger and positive when Miller and Rahe impact scores were used, when compared to self-appraised impact scores.

6.1.3 Total Number of Loss Events and Socioeconomic Events

Finally, we divided total exposure to stressful life events into two groups: loss events and socioeconomic events.

An increased risk associated with exposure to any loss event was observed, largely driven by ever exposure to death of a parent or sibling. Total number of loss events was not associated to lung cancer risk. Overall, we did not observe any differences in RRs when stratified by sex, smoking status, analyses by histological subtype, or restriction to exposures occurring more recently in the three years prior to interview or date of diagnosis. However, we observed a slightly higher RR for any loss event among females, when compared to males, though the interaction was not significant. An increase in relative risk was observed for high impact exposure to loss events on the Miller and Rahe Impact scale. Similarly, an increase in risk was observed for self-appraised high impact loss events and lung cancer risk. Of note, the point estimates were generally higher among the Miller and Rahe Impact score estimates when compared to the self-appraised impact score estimates.

Exposure to any socioeconomic event was not associated with lung cancer risk. Similarly, there was no association between total number of socioeconomic events and lung cancer. There were no differences in RRs when self-appraised impact or Miller and Rahe impact scores were considered. Generally, we did not see any differences in RRs when participants were restricted to self-respondents. Overall, the observed associations were not modified by sex or smoking status, nor did they differ by histological subtype. However, when the total number of socioeconomic events was self-appraised to have a low impact, an inverse association with lung cancer risk was observed.

6.2 Comparison with the Literature

Although two recent meta-analyses have concluded that stressful life events are not associated with overall cancer incidence,[88,116] there has been some indication in the literature that total number of stressful life events was associated with breast cancer risk,[97,117] colorectal cancer risk[96] and a few also suggestive of lung cancer risk.[98,100-103] Overall, six studies have investigated stressful life events and lung cancer risk.[98,100-103] Of these, one studied cumulative exposures to

stressful life events,[98] four studied individual stressful life events,[99-101,103] and the last studied both cumulative measures of loss events in addition to individual stressful life events.[102]

Three studies investigated death of a family member,[100,101,103] including child[101,103] and spouse,[100] where increased risks were suggested with death of a child in two studies,[101,103] which was statistically significant in one.[103] We did not observe similar findings, though death of a child and death of a spouse were rare events in our population.

One study reported that divorce was associated with a statistically significant 50% increase in lung cancer risk.[100] We did not observe an association between divorce or separation and lung cancer in our study. Prevalence of divorce in our study was 3.5% while the prevalence of divorce in Kvikstad's study was 19.7%, suggesting that statistical power in our study may not have been high enough to observe an association.

One case-control study examined cumulative exposures to a wide range of stressful life events and lung cancer risk.[98] In that study it was reported that among male smokers, lung cancer cases claim to have more changes in the conditions of life when compared to controls[98]. In contrast, we observed no overall association with cumulative exposures examined as total number of stressful life events and exposure to any stressful life event. The null relationship that we observed likely reflects the grouping of all stressful life events together that had different directions of relationship with lung cancer risk. For instance, when we considered perception of stress to the life event, we observed a suggestive decrease in risk for total number of life events that were self-appraised as low stress. A 2007 meta-analysis indicated psychosocial factors, including stress-prone personality and unfavorable coping styles, were associated with a higher incidence of lung cancer[88], suggesting that perception is important to take into consideration. We also used an external scale to rate the level of stress, that is the Miller and Rahe scale. In contrast to our result using self-appraised level of stress, we observed no association between total number of life events with a low score on the Miller and Rahe scale and lung cancer risk. However, it may be problematic to use the external Miller and Rahe impact score, as it assumes that the perception of stressfulness of each event is the same for all participants and it does not take into account variability among individuals. Given that the findings for Miller and Rahe impact scores and self-appraised impact scores differ, if our self-appraised impact score results

are better able to estimate associations, then perhaps the Miller and Rahe scale would be most useful in studies that were not able to measure perception of stress variables.

We also refined our measure of cumulative exposure to stressful life events into two subgroups: loss events and socioeconomic events. Horne examined recent significant loss, which was a cumulative measure of death of a family member, loss of job and loss of prestige.[102] Horne has suggested that a high score for recent (past 5 years) significant loss was a predictor for a malignant lung tumour diagnosis among males.[102] This was akin to our observation of a suggestive slight increase in risk for any loss event; particularly those rated as extremely stressful events, as per both the Miller and Rahe score and self-appraised impact score. However the latter was merely a suggestive increase in risk, and the point estimate indicated a weaker increase in risk when compared to the Miller and Rahe score. Upon stratification by sex, we observed an increase in risk only among females, and no association among males, which differs from what Horne previously reported among males. This difference may be due to Horne's lack of adjustment for smoking, which may have resulted in an overestimation of the predictive value of recent loss for lung cancer in the Horne study. Considerable adaptation to a change in life circumstance would be expected to follow an extremely stressful loss event, especially when there is no conceivable opportunity for closure.[74] It has been reported that depression is not associated with lung cancer risk,[88] therefore the effect of exposure to stressful life events may occur via another mechanism. Perhaps exposure to extremely stressful loss events is an indicator of poor stress coping strategies, which has been linked to an increase in oxidative DNA damage that could result in lung cancer.[18]

No study has investigated socioeconomic events in relation to lung cancer risk, however a positive dose-response association between socioeconomic events and colorectal cancer has been reported.[96] We observed a statistically significant association with socioeconomic events when we took into consideration the self-appraised impact of the event. However, we observed a decreased risk, opposite to what was expected, particularly when total number of socioeconomic events self-appraised as not very stressful. This inverse association for the accumulation of socioeconomic events rated as low stress was likely driven by the inverse association between loss of job rated as low stress and lung cancer, since socioeconomic events included job loss, increase in debt and move from one city to another.

The inverse relationship observed for lung cancer and loss of job self-appraised as not very stressful, likely underpins the inverse relationships observed for not very stressful socioeconomic events and total number of events self-appraised as low stress. One previous study observed that job loss occurring five years prior to date of diagnosis was a predictor for malignant lung tumour diagnosis,[102] opposite to our findings. It is possible that this difference could be due to the inclusion of females in our study, and therefore different types of occupations included in our analyses. On the other hand, perception of stress was not assessed in the previous study.[102]

Perhaps our finding of an inverse association with not very stressful loss of job, could be attributed to job loss being more positive, such as a financial resolution or a transition to a healthier environment. Alternatively, job loss may have resulted in a long-term improvement in quality of life. Interestingly, when job loss was appraised as extremely stressful and the job loss occurred three years prior to diagnosis or interview, the association with lung cancer risk was increased. Although no previous study has examined the participants' perception of the stressfulness of each job loss event, Jahn examined the voluntariness of job loss events and lung cancer risk among males, and reported non-statistically significant inverse associations for voluntary job loss events and an increase in lung cancer risk for involuntary job loss events.[99] Since it is reasonable to consider voluntary or positive job loss events as analogous to not very stressful impact appraisal, and a similar equivalence for involuntary job loss and extreme stress, the tendencies reported by Jahn mirror our observations. Job loss events are likely followed by either a gain in job or a period of unemployment. Events appraised as not very stressful could have been experienced in order to make a life change for a seemingly better suited situation to a healthier life. As such, job loss could be directly linked to another more positive event, which could be responsible for the protective effect for lung cancer. Although we don't know why the participants of our study lost their job, the self-appraised stress score can shed some light onto their outlook of the event.

While the event of losing job may be positive (and thus not very stressful) as described above, it is also possible that a person's personality influences the way they perceive the stressfulness of an event. Indeed, it has been suggested that individuals with increased hardiness; the ability to perceive life changes as less stressful or the capability to better cope with life changes, may be less likely to become ill than those with less hardiness.[118,119] To date, there have

not been any published studies examining the link between hardiness and lung cancer to explore this hypothesis (Table A1). Associations between lung cancer risk and loss of job merit further investigation, and future studies should aim to consider the occupational history of the participant in order to understand the context of the job loss in terms of job stability, in addition to the level of hardiness of the participant.

To our knowledge, this is the first lung cancer study to take into consideration a participant's self-appraised perception of a life event's impact. With the exception of total stressful life events, socioeconomic events, loss of job and move from one city to another, analyses using self-appraised impact scores did not show different results. However, this analysis did allow us to uncover differences among those that had experienced a loss of job.

There is evidence from experimental and clinical studies, that stress may be involved in initiation, progression and recurrence of cancer[86,87]. It is generally believed that stress acts on cancer promotion, rather than initiation of tumours[11]. Investigations into stressful life events and colorectal cancer, another cancer of epithelial cells, suggest that relatively recent life events occurring five to ten years before date of diagnosis are most influential[81,96]. Restriction of exposures to three years prior to date of diagnosis or interview generally did not appreciably change our RRs observed in the primary analysis. Although the effect of exposure to stressful life events differs between different types of cancer, we did not observe differences in RRs with sub-analyses by histological subtype, suggesting that the mechanism of action may be similar among all three subtypes. No other previous study examined associations by lung cancer histological type.

6.3 Methodological Considerations

6.3.1 Precision

This study consisted of 1061 cases and 1422 population controls, and was larger than most other studies examining stressful life events and lung cancer risk. However, as a result of the rare occurrence of certain stressful life events in the study population, the overall precision of the estimates presented was reduced. A majority of cases and controls did not experience death

of a spouse, death of a child, loss of job of spouse, separation or divorce, and move from one city to another. Furthermore, in secondary analyses, the number of cases and controls in each category (males/females, never-light smokers/heavy smokers, adenocarcinoma/squamous cell carcinoma/small cell carcinoma) was further reduced. The implication of low precision is that we present our observed results with decreased certainty that they are the true value of the association measured.

6.3.2 Selection Bias

In this study, the response rates were high at 84.1% for cases and 69.2% for controls. However, we must consider the potential for selection bias, or the risk to internal validity due to differences between respondents and non-respondents. Cases were histologically confirmed incident lung cancer cases selected from a group of hospitals, which made up 98% of the lung cancer catchment area in Montreal. It is possible that lung cancer cases that did not participate were diagnosed with more advanced lung cancer, or other co-morbidities, such that the cases that responded were slightly healthier than those that did not respond. If a more severe disease status influenced sampling in this way, then the exposure-outcome relationships observed in our study would be representative of a less severe form of lung cancer. With respect to population controls, it is possible that controls that did not participate in the study may have refused as a result of poor health (eg. depression) caused by elevated exposure to recent stressful life events. Thus, controls that participated may have a slightly lower number of recent stressful life event exposures than those that did not participate, which would result in an underestimation of the results observed for individual and cumulative measures of stressful life events. The difference in response rates between cases and controls reflects the differences in how representative cases and controls are of their source population. Specifically, controls are less representative of the general population when compared to cases which are more representative of lung cancer cases in Montreal. This difference may be a result of the methodology used to recruit cases and controls; it may be more difficult or less efficient to recruit controls from electoral lists when compared to recruitment of cases from hospital records and tumour registries.[120]

Furthermore, there is a greater potential of ascertainment bias with respect to the analyses conducted with restriction to self-respondents. The cases included in these analyses may be less

aggressive than those who were excluded due to use of a proxy respondent, and may not represent the cases of the population. Thus, the observed estimates may over or under-estimate the parameter in the population.

6.3.3 Information Bias

Recall Bias

Although literature on the association between stressful life events and lung cancer risk is insufficient to establish a relationship, there is a cultural belief that illness can be attributed to stress.[80] It has also been suggested that lung cancer cases are more likely to report more stressful experiences than controls, in retrospective studies.[121] Thus, there is a potential for differential recall in our study, as a diagnosis of lung cancer may affect reporting of exposure information because cases may be more prone to incorrectly report life events, due to false memory, depressed mood[99] or cultural bias and belief that stress has caused their cancer. However in our study, participants are provided a checklist of life events, and memory aid procedures have been shown to reduce errors when reporting life events,[122] when compared to open ended questionnaires. Furthermore, saliency of life events is associated with accuracy of life event reporting and the stressful life events proposed in our interview are largely severe.[123,124] Additionally, participants were asked about events occurring in a period of six years prior to interview, which is a relatively short period over which one would have to recall such salient events. These strengths of the interview structure may reduce the reporting differences between cases and controls.

Misclassification

Differential misclassification due to the unequal distribution of proxy respondents between cases and controls (38% and 8% respectively) is another potential source of information bias. In particular, the probability of misclassification may be higher for cases than controls, if the next of kin was unable to completely and accurately answer the interview questions on behalf of the study subject. This is especially important when proxies answer the self-appraised impact of the stressful life events reported, given that one can never be certain of someone else`s appraisal of something. The Miller and Rahe score is potentially useful in decreasing this type of

misclassification resulting from situations with uneven distribution of proxy respondents among cases and controls. Nonetheless, restriction to self-respondents generally did not appreciably change our results, indicating that the influence on our results of differential misclassification as a result of more cases using proxy respondents than controls is low.

There is potential for information bias due to non-differential misclassification of stressful life event exposure. Participants may not report an event as stressful if they perceive an event as "distressful", "unexpected", "serious", "demanding" but not "stressful".[126] However, the potential for information bias is low versus studies that employ self-administered questionnaires, because participants are able to clarify the question and secure a better understanding through discussion with a knowledgeable individual during surveys administered by interview. Thus, interview based measures are better suited for distinguishing between life events that are truly stressful vs. trivial. Gold standard interview questionnaires for measurement of stress (Interview with Life Events and Difficulties Scale questionnaire)[127] and perceived stress (Perceived Stress Scale)[128] do exist, but their use would have been out of the scope of the original study.

Finally, another source of possible differential misclassification is the interviewers' knowledge of the participants' case/control status at the time of data collection. The absence of blinding may have affected the behavior of the interviewers, their influence on the participants, and how they gathered subjective outcome measures, which may have differed between cases and controls; resulting in more extreme or "abnormal" data collected for cases or interviewers trying harder to gather exposure information for cases versus controls.[125] However, the risk for observer bias is decreased by the interviewers' blinding to the study's hypotheses.

6.3.4 Confounding

As stated in Chapter 2, one of the main limitations of the literature examining stressful life events and lung cancer risk is the lack of adjustment for smoking. Smoking is a crucial variable in studies aimed at investigating the etiology of lung cancer, as it is considered the primary cause of lung cancer.[22] Our study controlled for smoking history using a comprehensive

smoking index (CSI), though residual confounding may be possible if the validity of the index was reduced as a result of the use of inaccurate data when building the CSI. Additionally, our analyses adjusted for SES, ethnicity, respondent status, age and sex. There remains a potential for residual confounding due to unmeasured variables that we were unable to include in our model For instance, exposures to adverse childhood events have been linked to lung cancer risk, and may modify a person's coping abilities in the face of stressful life events occurring in adulthood.[129] Controlling for these unmeasured covariates may have resulted in a shift of our observed estimated toward the null.

6.3.5 Multiple Testing

Multiple comparisons, or testing many hypotheses, can result in a greater probability that some true null hypotheses are rejected by chance alone; a type I error.[130] The higher the number of hypotheses tested, the greater the chance of making a type I error by the following formula:[130]

$$1 - (1 - \alpha)^n$$

where n is the number of comparisons made. The alpha level of significance selected as the cutoff for this study was 0.05. While a large number of analyses were conducted in this study, they were all aimed to understand one association established a priori; that of exposure to stressful life events and lung cancer risk. Therefore, adjustment for multiple comparisons may not be appropriate. Furthermore, the opportunity cost of this adjustment is an increase in frequency of type II error.[130]

6.3.6 Strengths

One of the great advantages of a case-control study design, compared to a cohort study, is that it offers a less expensive approach to examining exposure to environmental stress and allows for observation of a large number of lung cancer cases over a shorter period of time. Another advantage of case-control studies is the ability to quickly produce results and contribute to the current knowledge in the field of psychosocial stress and lung cancer risk. An advantage of this protocol is the detailed smoking history collected for all participants, which allows for

adjustment of smoking status by taking into consideration three aspects of smoking history. The stressful life event exposure metrics employed in this study are an improvement over those used in the literature, because they take into account a retrospective measure of individual appraisal of stressfulness for each stressful life event along with the objective exposure.

7.0 Conclusion

Overall, we observed no statistically significant association between lung cancer risk and individual stressful life events. Analyses with cumulative measures of stressful life events revealed a decrease in risk associated with total number of stressful life events and socioeconomic events self-appraised as low stress; this was mainly driven by the inverse association observed for loss of job events self-appraised as not very stressful. Conversely, loss events appraised with Miller and Rahe scale as extremely stressful were associated with an increase in risk of lung cancer. Recent (last three years) job loss events were associated with an increase in lung cancer risk when self-appraised as extremely stressful. Observed results did not appreciably differ when stratified by sex, smoking status and analyses by histological subtype. However, we did observe modification by sex for death of a family member, increase in debt or decrease in income, and any loss event.

Generally, analyses with self-respondents were not different to results observed in the total population. Given that our results have shown that the inclusion of proxy respondents when assessing a participant's perception of stress, does not seem to appreciably change the observed results, future surveys, including the Canadian Community Health Survey, can continue to include proxy respondents' reports on perceived life stress. Future studies should use the gold standard questionnaires to measure stress and perceived stress, and better incorporate the context of certain stressful life events, for example job stability and marital history.

7.1 Implications in Public Health

Given that exposure to stressful life events themselves is not modifiable, the perception of the stressfulness of the event, or the self-appraised impact score is the most interesting in

terms of implications in public health. Although we cannot rule out the potential modifying or mediating effects of personality, self-appraised perception of stress captures an aspect of the participants' coping abilities. This study has found, in the case of loss of job specifically, that not events self-appraised as not very stressful have a protective effect with respect to lung cancer risk. This may be explained by the positive nature of the loss of job event, or the increased hardiness of a person who perceives the event as less stressful, or is better equipped to cope with life change. While a person's personality trait is not amenable to modification, a person's state of mind, which has been implicated in health outcomes,[81] can be changed. A person's mindset may be an interesting target for illness prevention, however this may not apply to lung cancer given that this study did not observe an association between exposure to stressful life events and lung cancer risk. Nevertheless, the opportunity for people to tap into an aspect of their mind for overall health prevention should not be ignored.

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Appendix

A.1 Search Strategy

A literature review investigating and evaluating epidemiological studies aimed at understanding the link between exposure to stressful life events and lung cancer risk was conducted. The following key words and medical subject bases (MeSH) were used in a search for peer-reviewed articles in Google Scholar, Medline, PubMed, Scorpus and WorldCat.
"lung neoplasm/epidemiology", "lung neoplasm/etiology", "lung neoplasm/carcinoma", "adenocarcinoma/etiology", "adenocarcinoma/epidemiology", "psych", "stress", "psychosocial", "life event", "negative life event", "neoplasms/psychology", "stress/psychology", "life change events", "environmental stressor", "stressor". The reference lists of identified studies and reviews were also used to guide the literature review.

6 articles, 1 meta-analysis and 2 review articles on related topics were found and consulted for the literature review.

The following exclusion criteria were used:

- Biochemical studies
- Articles investigating survival among lung cancer patients
- Studies investigating all cancers as the outcome, with no site specific (lung) analysis
- Articles investigating the emotional response, stress-prone personality factors and psychological illness as exposure variables (these were included for background information)
- Articles investigating chronic stress or daily stress as exposure variables
- Articles written in a language other than English (1 Chinese and 1 German article were excluded)
- Articles where stressfulness was the outcome measured (Tas et al 2012)

The following inclusion criteria was used:

- Lung Cancer
- Stressful Life Events, Major Life Events

Table A1: Summary of Results from Studies Investigating Stress and Lung Cancer Risk

Reference, Country	Study Design	Sex, N Cases / N Controls	Exposure Measurement	Results (95% CI)	Adjusted Variables
Stress Related Psychosocial Factor: Environmental Stressor					
Kvikstad A (1994)[100] Norway	Nested Case-Control	Females, 361/874	Death of a spouse	OR=1.17 (0.62, 2.19)	Age
		Females, 361/4739	Divorce	OR=1.53 (1.17, 1.98)	Age
Kvikstad A (1996)[101] Norway	Nested Case-Control	Females, 358/1309	Death of a Child	OR=1.32 (0.85, 2.05)	Age
Levav I (2000)[103] Israel	Prospective Cohort	Males and Females, 34/17511	Death of a child (accident)	OR=1.54 (1.02, 2.31)	Age, Sex, Period of immigration, Region of birth
		Males and Females, 73/17511	Death of a child (war)	OR=1.14 (0.87, 1.48)	Age, Sex, Period of immigration, Region of birth
Blohmke (1984)[98] Germany	Case-Control	Males, 419/419	Changes in the conditions of life	Cases have more changes in conditions of life than controls (p=0.001)	All participants were current smokers. Controls matched to cases by age and social stratum.
Jahn (1995)[99] Germany	Case-Control	Males, 391/391	Job loss	*Conclusion of an Apprenticeship:* OR=0.48 (0.26, 0.89); *Advantages of new job:* OR=0.53 (0.36, 0.78)	Smoking, asbestos exposure, socioeconomic status, age, region.
Horne et al (1979)[102] United	Case-Control	Male Veterans, 44/66	Recent significant loss (death of a family member, loss of job,	Recent significant loss is a predictor for malignant lung cancer (p<0.001)	None

Reference, Country	Study Design	Sex, N Cases / N Controls	Exposure Measurement	Results (95% CI)	Adjusted Variables
States			loss of prestige)		
Stress Related Psychosocial Factor: Stress Prone Personality					
White (2007)[105] United States	Prospective Cohort	Males and Females, 88	Anger Control	HR=1.19 (0.97, 1.46)	Sex, Alcohol, BMI, SES, Physical Activity
Hansen PE (2005)[131] Sweden	Twin Cohort	Males and Females, 65	High Extroversion	HR=1.19 (0.72, 1.99)	Age, Smoking, Alcohol, BMI, Physical activity, Drugs, SES, Parity
		Males and Females, 65	Low Neuroticism	HR=0.74 (0.42, 1.32)	Age, Smoking, Alcohol, BMI, Physical Activity, Drugs, SES, Parity
Nakaya (2003)[132] Japan	Prospective Cohort	Males and Females, 108	High Extroversion	RR=1.70 (0.30, 1.20)	Age, Sex, Smoking, Alcohol, BMI, SES, Family History
		Males and Females, 108	Low Neuroticism	RR=1.00 (0.56, 2.00)	Age, Sex, Smoking, Alcohol, BMI, SES, Family History
		Males and Females, 108	High-lie	RR=1.30 (0.70, 2.40)	Age, Sex, Smoking, Alcohol, BMI, SES, Family History
		Males and Females, 108	Psychoticism	RR=1.30 (0.70, 2.40)	Age, Sex, Smoking, Alcohol, BMI, SES, Family History

Reference, Country	Study Design	Sex, N Cases / N Controls	Exposure Measurement	Results (95% CI)	Adjusted Variables
Stress Related Psychosocial Factor: Emotional Response					
Gallo JJ (2000)[133] United States	Prospective Cohort	Males and Females, 32	Depression	HR=1.00 (0.10, 7.70)	Age, sex, smoking, alcohol
White (2007)[105] United States	Prospective Cohort	Males and Females, 88	Negative Affect	HR=1.24 (1.01, 1.52)	Sex, alcohol, BMI, SES, physical activity
Nagano (2001)[134] Japan	Case-Control	Males and Females, 95/694	Hopelessness and Depression	*2nd tertile:* OR=0.95 (0.55, 1.62), *3rd tertile:* OR=0.54 (0.28-1.05)	Age, sex, job status, education level, smoking status
		Males and Females, 95/694	Anger, Hostility and Depression	*2nd tertile:* OR=1.58 (0.82, 3.04), *3rd tertile:* OR=1.61 (0.81, 3.20)	Age, sex, job status, education level, smoking status
Pennix B (1998)[135] United States	Prospective Cohort	Males and Females, 56	Chronic Depressive Mood	HR=2.10 (0.49, 8.92)	Age, sex, race, smoking, alcohol
Kneckt P (1996)[106] Finland	Prospective Cohort	Males, 70	Depression	*2nd tertile:* RR=1.24 (0.63, 2.44), *3rd tertile:* RR=2.89 (1.18, 7.08)	Age, smoking, alcohol, BMI, serum cholesterol, physical activity, antidepressant, SES, marital status, leisure-time exercise

Table A2: Miller and Rahe 1995 Life Change Units by Gender

Table III.—1995 LCU values by gender

Men				Women		
Mean	99% conf. int.	SD	Life event	Mean	99% conf. int.	SD
103	79.1–126.9	105	Death of child[a]	135	105.0–164.3	177
113	83.5–141.6	126	Death of spouse	122	96.2–148.6	155
87	68.7–104.8	79	Death of sibling	111	85.1–136.8	154
90	69.9–109.6	87	Death of parent	105	82.7–127.6	133
85	63.9–105.6	91	Divorce	102	79.1–125.8	139
78	63.6– 93.3	65	Death of family member	96	75.9–116.1	120
69	56.1– 81.6	56	Fired from work	85	67.1–103.4	108
74	53.1– 94.3	90	Separation from spouse	82	62.6–102.1	117
64	47.8– 80.2	71	Major injury or illness	79	58.0–100.4	126
70	49.2– 90.6	91	Separation for marital problems	79	59.2– 98.5	117
71	62.1– 79.5	38	Jail term	78	61.4– 93.7	96
55	48.5– 62.3	30	Pregnancy[a]	74	57.5– 89.7	96
51	43.3– 57.9	32	Miscarriage/abortion[a]	74	54.5– 92.6	113
64	51.1– 76.5	55	Death of close friend	73	59.1– 87.7	84
59	47.0– 70.4	51	Laid-off from work	73	55.1– 90.5	105
54	47.5– 61.3	30	Adoption of child	71	53.9– 88.3	102
56	48.4– 63.0	32	Birth of child	71	53.9– 88.1	102
47	41.6– 53.4	26	Business readjustment	67	46.0– 88.7	127
49	42.7– 55.0	27	Decreased income[a]	66	49.7– 82.1	97
52	43.1– 60.4	38	Parents' divorce	63	50.9– 74.9	72
53	44.4– 61.9	38	Relative moving in	62	50.2– 74.5	72
46	40.1– 51.5	25	Investment/credit problems[a]	62	48.4– 75.7	81
51	44.9– 57.2	27	Foreclosure	62	48.8– 74.6	77
48	42.9– 54.1	25	Marital reconciliation	61	45.5– 75.9	90
50	43.3– 56.0	28	Health change family member	58	46.2– 70.6	73
52	46.5– 58.0	25	Gain of family member	58	48.7– 67.5	56
48	43.9– 52.8	19	Change financial state	58	48.0– 67.5	58
41	35.8– 47.0	24	Change in arguments	55	38.1– 71.5	99
48	42.4– 54.2	26	Retirement	54	45.3– 63.6	55
46	37.6– 54.0	36	Major decision (re: future)	54	41.7– 65.8	72
38	32.3– 44.3	26	Accident	53	37.4– 68.3	92
54	33.8– 74.7	89	Separation due to work	53	37.2– 67.8	91
45	36.0– 53.2	38	Remarriage of a parent	52	40.6– 64.0	70
39	33.4– 43.6	22	Move (different town)[a]	52	39.4– 64.2	74
50	43.8– 55.6	26	Change to different work	51	44.6– 57.8	39
41	35.0– 46.4	25	"Falling out" of a relationship	50	38.2– 62.0	71
50	—	0	Marriage	50	—	0
38	28.8– 47.6	41	Spouse changes work	50	36.1– 63.3	81
34	26.2– 40.8	32	Birth of a grandchild	48	29.5– 67.4	112
38	32.6– 42.8	22	Child leaves home (other)	48	35.9– 61.0	75
37	32.7– 42.0	20	Child leaves home	48	36.7– 59.3	67
35	29.7– 40.0	23	Property loss or damage[a]	47	36.4– 57.8	64
42	37.2– 45.9	19	Engagement to marry	47	34.7– 59.0	72
39	32.2– 45.4	29	Moderate injury or illness	47	35.3– 58.2	68
35	29.8– 40.0	22	Mortgage >$10,000	46	34.4– 57.8	70
36	30.9– 41.0	22	Child leaves home (marriage)	44	33.0– 55.7	68
34	29.5– 38.3	19	Child leaves home (college)	44	32.8– 55.4	67
37	32.7– 41.8	20	Change in living conditions	44	30.9– 56.9	77
44	37.5– 49.7	27	Sexual difficulties	44	36.8– 50.6	41
39	33.9– 44.6	23	Demotion at work	44	38.1– 49.2	33

(continued)

Table III.—1995 LCU values by gender (*continued*)

Men				Women		
Mean	99% conf. int.	SD	Life event	Mean	99% conf. int.	SD
30	25.9– 34.4	19	Increased income[a]	43	30.4– 55.7	75
37	32.9– 41.7	19	Change work responsibilities	43	37.3– 48.4	33
34	29.7– 38.5	19	Relationship problems	42	31.3– 53.6	66
40	33.0–46.1	28	Change in residence	41	31.8–50.2	54
33	26.7–40.0	29	Trouble with in-laws	41	31.0–50.6	58
33	22.5–43.2	45	Major purchase	40	28.5–51.4	68
35	28.4–40.6	26	Begin/end school or college	40	27.6–52.2	73
34	29.4–38.6	20	New relationship	39	27.8–50.2	67
33	27.5–37.9	23	Outstanding achievement	38	31.1–45.3	42
32	26.8–36.9	22	Trouble with coworkers	37	31.6–41.6	30
31	26.5–36.2	21	Change in schools[a]	37	31.8–41.2	28
32	27.4–36.5	20	Change in work hours	36	31.1–41.7	32
34	27.7–39.4	26	Trouble with supervisees	35	30.8–39.8	27
31	26.2–36.1	22	Transfer at work	33	28.5–37.2	26
29	25.1–33.3	18	Promotion at work	33	28.1–37.0	27
27	21.9–32.9	24	Change in religious beliefs	31	20.3–41.0	62
25	19.8–30.5	23	Christmas	30	25.1–35.0	30
29	22.3–36.1	30	More work responsibilities	29	25.4–33.6	24
23	19.0–26.9	17	Change in eating habits	29	22.8–35.8	38
29	24.4–33.2	19	Trouble with boss	29	25.4–32.8	22
21	17.3–25.6	18	Mortgage <$10,000[a]	29	22.2–35.9	41
27	21.7–32.9	24	Work troubles (other)	29	24.8–33.3	25
28	23.4–31.7	18	Change in recreation	29	22.6–35.1	37
24	20.2–27.5	16	Change in social activities	29	18.5–38.5	60
23	18.8–27.1	18	Change in sleep[a]	28	24.6–31.9	22
20	16.8–23.9	16	Change in get-togethers	28	18.2–37.0	56
24	19.9–28.1	18	Change in personal habits	27	23.4–31.2	23
21	17.8–24.4	15	Move (within same town)[a]	27	23.5–31.0	22
23	18.0–27.9	21	Major dental work	27	22.5–31.8	28
20	16.1–24.1	17	Vacation[a]	26	20.4–31.3	33
21	16.9–25.1	18	Change in political beliefs	26	14.4–36.8	67
17	13.1–20.4	16	Minor injury or illness	22	11.4–33.3	65
18	14.5–20.8	14	Moderate purchase	22	15.6–28.4	38
21	16.8–24.3	16	Fewer responsibilities at work	22	18.6–24.8	19
20	16.2–24.5	18	Change in church activities	21	17.9–24.3	19
19	15.5–23.1	16	Minor violation of law	20	17.0–23.7	20
16	12.8–18.7	13	Correspondence course	19	15.7–21.4	17
42	36.8–47.7	24	Grand mean[a]	51	44.0–57.4	20

[a] Significant at $p<0.01$.