BCCA FAN#: 7109 FAS #: F25-04706	DATE RECEIVED

Due date: 25/09/30

Office of Research Administration
BC Cancer Research Centre
15th Floor, 675 West 10th Ave

GRANT APPLICATION COVER SHEET- Form 101

BC Cancer PRINCIPAL INVESTIGATOR: Surname, Given Name(s)
Rafael Meza

(NPA) Nominated Principal Applicant? ☒ Yes ☐ No

BC Cancer TITLE
Distinguished Scientist

E-MAIL ADDRESS
rmeza@bccrc.ca

BC Cancer DEPARTMENT
Population Health Sciences

Project Manager/Administrative Contact Sukhinder Khattra
email: skhattra@bccancer.bc.ca Phone Number: 604-675-8089

TITLE OF PROJECT:
Environmental Exposures on Lung Cancer Risk in Light Ex-Smokers and Non-Smokers

TRAINEE NAME: Yixian (Crystal) Chen, PhD
DEGREE STATUS: Postdoctoral Fellow

FUNDING AGENCY/COMPANY (no acronyms)
Lung Cancer Canada

Program Name:
Geoffrey Ogram Memorial Research Grant

Additional sponsors or program partners

HOST INSTITUTION (if other than BC Cancer)

TYPE OF GRANT/AGREEMENT: ☒ Operating ☐ Equipment ☐ Collaborative ☐ Service Agreement ☐ Scholarship (Faculty) ☐ Fellowship (Student/PDF) ☐ Other (Specify):

CO-INVESTIGATORS/Co App/Collaborators: (Affiliation) **Indicate NPA if not the BCC PI, only list those with Scientific Appointment(s)**

AMOUNTS REQUESTED:

Year 1: $ 25000	Year 2:$	Year 3:$	Year 4:$
Year 5: $	Year 6:$	Year 7:$	Total: $ 25000

☐ **OVERHEAD / INDIRECT COSTS:** ☐ In accordance with policy **BCC Policy FIN 100**: _____%
☐ $ Rate different than stipulated in the policy: _____% $ Justification:

TO BE APPLIED FOR WHEN FUNDED:

Human Subjects **Will** be used ☒ Yes ☐ No Certificate # H23-03784

Human biospecimen **Will** be used (if yes, is registration required?) ☐ Yes ☒ No Registration #

Animal Subjects **Will** be used ☐ Yes ☒ No Certificate #

Biohazardous Materials **Will** be used ☐ Yes ☒ No Certificate #

Radioactive Materials **Will** be used ☐ Yes ☒ No Certificate #

LOCATION(S) WHERE RESEARCH WILL BE CARRIED OUT:

☒ CRC ☐ VCC ☐ DRC ☐ VICC ☐ ABCC ☐ FVCC ☐ CCSI ☐ PGCC ☐ OTHER: _____

SPACE- Is additional space/resources required by the department? ☒ **No** ☐ Yes (if yes, include a brief description)

	PRINTED NAME	SIGNATURE	DATE
BC Cancer Principal Investigator	Rafael Meza		Sept 19, 2025
BC Cancer Dept Head	Tim Lee		Sept 19, 2025
Sr. Executive Director,Research	Karen Lemmen		Sept 24, 2025

Please note that all applications/co-applications/proposals/competative letters of intent (LOI's) are to be approved by our office, Research Admin(ORA)using a BC Cancer Grant Coversheet(Form 101) and accompany a copy of the application signature package for ORA records. We strongly recommend that applicants allow sufficient lead-time for processing signature packages i.e. 5 business days prior to funder deadline. NOTE: The ORA signature package in required prior to e-Submission or paper submission by the applicant to the funding agency.

BC CANCER RESEARCH
Provincial Health Services Authority

September 19, 2025

Lung Cancer Canada
133 Richmond St. W., Suite 208
Toronto, ON
M5H 2L3

Re: Letter of Intent 2025 Geoffrey Ogram Memorial Research Grant

Dear Grant Review Committee,

We are writing to formally express our intention to apply for the 2025 Geoffrey Ogram Memorial Research Grant (GOMRG), with our research proposal, "Environmental Exposures on Lung Cancer Risk in Light Ex-Smokers and Non-Smokers."

This project is responsive to the GOMRG's objective #2, which aims to support research on understanding the etiology of lung cancer in different populations, specifically focusing on the groups of light ex-smokers and non-smokers. Our research strives to examine the impact of long-term environmental exposures, such as air pollutants and residential radon, on lung cancer incidence within these understudied populations with a growing lung cancer burden.

By employing extensive data from three large prospective cohorts and leveraging advanced statistical and machine learning models, we seek to build a more accurate and inclusive lung cancer risk prediction framework. This research builds on the work we are conducting to assess the impact of air pollution on never smoking, leveraging existing resources and ensuring the feasibility of our proposal. Our goal is to generate useful data that can inform public health strategies and enhance early detection for individuals who are not protected by existing smoking-based lung cancer screening criteria.

Our study has the potential to lessen the burden of lung cancer in Canada. Our research proposal, impact statement, budget, and other documentation are enclosed with our full application.

Thank you for your time and consideration. We look forward to the opportunity to continue contributing to the advancement of lung cancer research through the support of Lung Cancer Canada.

Sincerely,

Rafael Meza, PhD
Distinguished Scientist, Department of Population Health Sciences
BC Cancer Research Institute
675 W 10th Ave, Vancouver, BC V5Z 0B4
rmeza@bccrc.ca

Title: Environmental Exposures on Lung Cancer Risk in Light Ex-Smokers and Non-Smokers

This project will examine the effects of long-term exposure to air pollution and residential radon on lung cancer incidence in light ex-smokers and non-smokers. These populations are a growing but understudied lung cancer patient group. Using data from three large cohorts in Canada, the US, and the UK, we will build a comprehensive and accurate risk prediction framework through robust statistical and machine learning models. The findings will offer insights into lung cancer etiology, pinpoint key exposure windows for carcinogenesis, and inform forthcoming public health strategies for prevention and early detection in populations not currently targeted by smoking-based screening.

Background and Significance

Lung cancer remains the most fatal cancer in Canada, responsible for 25% of cancer deaths.[1] While national public health interventions have led to promising declines in overall incidence and mortality rates,[1] a challenge persists: 28% of lung cancers were not attributed to smoking.[2] These cases are no longer rare and represent a unique clinical and etiological conundrum. As the population who smoke heavily (≥25 cigarettes per day) declines,[3] the share of lung cancers occurring in light ex-smokers and non-smokers will rise, necessitating a shift in research focus beyond traditional tobacco-centric models. The Geoffrey Ogram Memorial Research Grant (GOMRG) prioritizes identifying the etiology of lung cancer in these specific populations, which this proposal aims to address directly.

Evidence strongly indicates that environmental exposures are primary drivers of lung cancer in these groups. Residential radon is a naturally occurring radioactive gas produced from the decay of uranium in soil and rock, and it is the leading cause of lung cancer among non-smokers.[4] Long-term exposure to ambient fine particulate matter ($PM_{2.5}$) from traffic, industry, and other sources was classified as a Group 1 human carcinogen by the International Agency for Research on Cancer.[5] Large-scale cohort studies have consistently linked $PM_{2.5}$ exposure to higher lung cancer risk and mortality.[6,7] Foundational work by Cheng et al.[8] has established a clear association between traffic-related air pollutants and lung cancer incidence within the Multiethnic Cohort (MEC), a key data source for this proposal.

Despite this progress, knowledge gaps persist, hindering the development of effective risk stratification and prevention strategies. First, the risk profile for light ex-smokers is inadequately assessed.[9] This knowledge gap stems from a common methodological practice where this diverse group is often combined with heavy ex-smokers in analyses, obscuring the unique risks and potential interactions relevant to individuals with low cumulative tobacco exposure. This directly results in current, tobacco-centric lung cancer screening criteria excluding these individuals. The 2021 US Preventive Services Task Force (USPSTF) guidelines exclude ex-smokers who quit over 15 years ago and those with a lighter smoking history.[10] Validated risk prediction models, like the PLCOm2012, are valuable tools; however, environmental factors' independent risk is not incorporated. Characterizing the risk from environmental exposure for ex-smokers and light smokers separately is essential to fully understand lung cancer etiology and to develop inclusive and effective screening strategies.

Second, the synergistic interaction between air pollution and smoking is a knowledge gap, despite a strong biological rationale based on a "two-hit" model of carcinogenesis.[11] Tobacco smoke initiates direct DNA damage, while subsequent long-term $PM_{2.5}$ exposure promotes chronic inflammation, exacerbating the proliferation of these damaged cells.[12] We hypothesize that this leads to a synergistic risk, and this proposal will formally test this interaction effect in large cohort studies focusing on light ex-smokers.

Finally, prior research faced key methodological limitations. Many studies rely on time-invariant exposure metrics that can result in misclassification; in contrast, the method used by Vanoli et al. (2025) shows the advantage of using time-varying exposure to precisely model disease latency.[13] Furthermore, conventional statistical models do not effectively capture complex non-linear dose-response relationships. As a recent systematic review by Teshale et al. (2024) shows, machine learning models outperform traditional models in time-to-event predictions by learning complex data patterns.[14]

This project will tackle these three critical gaps leveraging data from three cohorts: BC Generations Project (BCGP)[19], the Multiethnic Cohort (MEC),[15] and the UK Biobank.[16] Together, these cohorts provide a diverse dataset directly relevant to Canada's multicultural population. Results from the proposed study will provide crucial evidence on lung cancer etiology, inform targeted public health strategies for air quality and radon mitigation, and establish a foundation for accurate, personalized risk prediction models to enhance early detection.

Approach

This study employs a coordinated analysis involving three extensive prospective cohorts. Our study populations will consist of participants from BCGP (~ 30,000 British Columbians), MEC (>215,000 residents of California and Hawaii), and UK Biobank (~500,000 British adults). We will define our analysis groups as light ex-smokers (e.g., ≤10 pack-years and quit ≥15 years ago) and non-smokers. Sensitivity analyses will systematically adjust the pack-year (≤5, ≤15) and years-since-quit (≥10, ≥20) thresholds to verify the result consistency.

A key innovation lies in the study's detailed longitudinal exposure assessment. For each participant, we will reconstruct time-varying exposure histories by linking their complete residential histories to validated high-resolution spatiotemporal models for $PM_{2.5}$, PM_{10}, NO_X, NO_2, and residential radon. This method adheres to the best practices demonstrated by Vanoli et al., thereby reducing exposure misclassification.[13] Following a coordinated analysis protocol, each cohort will be analyzed independently. Effect estimates will then be pooled using random-effects meta-analysis to generate summary estimates of risk.

Aim 1: Quantify the independent and synergistic effects of long-term environmental exposures on lung cancer incidence.

Extended Cox proportional hazards models will be used to assess the relationship between time-varying exposures and incident lung cancer in separate models for non-smokers, light ex-smokers, and both groups combined. To assess confounding, we will build models with three adjustment sets: 1) a crude model; 2) a base model that adjust for age, sex, race/ethnicity, and education; and 3) a full model that further adjusts for body mass index, previous personal cancer, family history of lung cancer, and detailed smoking history (in light ex-smokers). In the full model applied specifically to the light ex-smoker cohort, effect modification will be tested by including a product term between the environmental exposure and continuous pack-years (e.g., $PM_{2.5}$ x pack-years).

Aim 2: Identify key exposure windows and characterize the dose-response relationship.

We will model exposure metrics, including running average, running cumulative, average of the past 12 months, peak of the past 12 months, and cumulative max. These metrics will be assessed over multiple discrete lag durations (1-, 3-, 5-, 7-, and 9-years) to determine critical exposure windows of etiological significance. Furthermore, we will explore the shape of the dose-response curve for each environmental exposure by testing linear, quadratic, and other nonlinear forms using restricted cubic splines.

Aim 3: Enhance risk prediction using advanced machine learning models.

To capture complex, high-order interactions and non-linearities, we will develop and validate time-to-event models using two algorithms: Random Survival Forest (RSF)[17] and DeepSurv.[18] The predictive performance of these models, using the optimal exposure parameters and adjustment sets identified in Aims 1 and 2, will be compared against the final Cox model from Aim 1. Model performance will be evaluated using a 10-fold cross-validation strategy, with the C-index (discrimination) and calibration plots as the primary metrics for identifying the most accurate and generalizable risk prediction model.

References

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14. Teshale AB, Htun HL, Vered M, Owen AJ, Freak-Poli R. A Systematic Review of Artificial Intelligence Models for Time-to-Event Outcome Applied in Cardiovascular Disease Risk Prediction. *J Med Syst*. 2024;48(1):1-18. doi:10.1007/s10916-024-02087-7
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Impact Statement: Environmental Exposures on Lung Cancer Risk in Light Ex-Smokers and Non-Smokers

The Problem: Lung cancer remains the most lethal cancer in Canada. A critical public health challenge has emerged due to an increasing number of diagnoses recorded in individuals who have a light smoking history or have never smoked. Existing lung cancer screening programs are intended exclusively for individuals with a heavy smoking history. This results in a growing at-risk population without a pathway for early detection, which frequently leads to diagnosis at later, less manageable stages and contributes to poor patient outcomes. The lack of clear evidence on the environmental drivers of their cancer hinders the development of comprehensive and effective prevention and screening strategies.

Our Solution: This initiative will provide the solution by directly quantifying the lung cancer risk from long-term exposure to air pollution and residential radon in light ex-smokers and non-smokers. By leveraging comprehensive and reliable health and residential history data from three large international cohorts and implementing advanced statistical and machine learning models, our research will generate a robust, evidence-based risk prediction framework that accounts for these critical environmental factors.

Beneficiaries and Outputs: The findings will be utilized to benefit specific groups. The primary beneficiaries are Canadian light ex-smokers and non-smokers, who are currently underserved by publicly funded screening programs. Our outputs, including validated risk prediction models, peer-reviewed publications, and a public-facing summary distributed through Lung Cancer Canada, will directly support policymakers and public health agencies (e.g., Canadian Partnership Against Cancer, provincial screening programs) by supplying the necessary evidence to enhance national screening guidelines. Clinicians, including oncologists and primary care physicians, will be equipped with new knowledge to improve risk assessment for their patients.

Sustained Impact: This research is designed to exert a lasting and powerful influence by advancing the understanding, prevention, and detection of lung cancer in Canada.

- Short- to Medium-Term Impact (Improved Patient Care and Reduced Mortality): In the short term, this project will expedite the application of scientific findings to optimize patient care. Our effort will enhance the understanding of risk, empowering clinicians to identify high-risk individuals who are currently overlooked. This results in improved early detection, which is the most effective way for reducing lung cancer mortality and improving patient quality of life.
- Long-Term Impact (Reduced Incidence and Burden): In the long term, our research will provide the foundational evidence to transform clinical practice and public health policy. Through the integration of environmental exposures into risk assessment, we seek to enhance the criteria for screening eligibility. This initiative will alleviate the burden of late-stage lung cancer in Canada and create a more equitable, inclusive, and effective prevention strategy for all, ensuring that an individual’s lung cancer risk is determined by factors beyond smoking history.

Public Summary: Understanding Lung Cancer in Light Ex-Smokers and Non-Smokers

Lung cancer is the leading cause of cancer-related deaths in Canada. Although we usually associate it with smoking, more people who have never smoked or have only smoked a little are being diagnosed. This indicates that other factors are responsible for this serious disease, but we lack a complete understanding of what they are. Current lung cancer screening programs focus on heavy smokers, neglecting other at-risk individuals.

Our research project seeks to address this important need. We aim to learn how long-term exposure to environmental factors, particularly air pollution and radon gas, influences the risk of lung cancer in individuals who have never smoked and those who smoke lightly. Radon is a natural radioactive gas that can accumulate in homes and is the main cause of lung cancer in non-smokers. Air pollution from traffic and industry is a recognized cause of cancer.

We will examine health information from more than 700,000 individuals involved in major health studies in Canada, the United States, and the United Kingdom. We will examine where they lived over the years and connect this to data on local air pollution and radon levels. We will use computer models to find out how much these environmental factors increase a person's risk of lung cancer.

Our study aims to improve the prediction of individuals at high risk for lung cancer, going beyond smoking history. The results may lead to new screening guidelines for individuals exposed to high levels of air pollution or radon. Understanding the real causes of lung cancer in this increasing group of patients allows us to develop better prevention strategies and enhance early detection, which can save lives.

Budget Modules

Personnel	salary	FTE	Months	Salary Requested	Fringe	Total
Research Methodologist	82,000	8%	1	$6,560.00	$1,476.00	$8,036.00
Research Assistant	56,000	24.70%	3	$13,832.00	$3,112.20	$16,944.20
Total Personnel						$24,980.20
Consumables						
Publications						$0.00
Total Consumables						$0.00
Grand Total						**$24,980.20**

Budget Justification

A. Personnel

- **Research Methodologist (Total Cost: $8,036.00)**
    - To support data curation, management of large-scale cohort data, and preliminary statistical analysis. (Based on 8% of an $82,000/year salary + 22.5% fringe benefits).
- **Research Assistant (Total Cost: $16,944.80)**
    - To support a summer student for a 3-month term to assist with implementing machine learning models under the supervision of Dr. Meza. (Based on 24.7% of a $56,000/year salary + 22.5% fringe benefits).

B. Other

- **Travel & Publications: $0.00**
    - No funds are requested for travel or publication fees.

Personnel	salary	FTE	Months	Salary Requested	Fringe	Total
Research Methodologist	82,000	8%	1	$6,560.00	$1,476.00	$8,036.00
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Total Personnel						$24,980.20
Consumables						
Publications						$0.00
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Grand Total						$24,980.20

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B. Other

- **Travel & Publications: $0.00**
    - No funds are requested for travel or publication fees.

BC CANCER RESEARCH
Provincial Health Services Authority

September 19, 2025

Geoffrey Ogram Memorial Research Grant (GOMRG) Grant Review Committee
Lung Cancer Canada
133 Richmond St. W., Suite 208
Toronto, ON
M5H 2L3

Subject: Letter of Institutional Support for Dr. Rafael Meza, 2025 GOMRG Application

Dear Members of the GOMRG Grant Review Committee,

I am pleased to express my full support for the grant proposal titled "Environmental Exposures on Lung Cancer Risk in Light Ex-Smokers and Non-Smokers" submitted by Dr. Rafael Meza. As the Interim Head of the Department of Population Health Sciences and a Distinguished Scientist at BC Cancer Research Institute, I believe that Dr. Meza and his team are the ideal team to conduct this work.

Dr. Meza is an internationally recognized leader in Cancer Epidemiology, Prevention, and Policy Analytics, with a track record of publications in highly regarded journals such as *JAMA*, *New England Journal of Medicine,* the *Journal of Thoracic Oncology*, and *Annals of Internal Medicine*. His leadership of major research consortia, such as the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working Group and the Center for the Assessment of Tobacco Regulations (CAsToR), demonstrates his ability to generate impactful lung cancer research that shapes national and international health policies. Dr. Meza's extensive body of work on lung cancer epidemiology, risk prediction and the real-world impact of lung cancer screening guidelines provides a solid foundation for this proposal. His research into tobacco control has lent him a unique perspective on the promising decline of cigarette use, which motivates his interest in studying the etiology of lung cancer in light ex-smokers and non-smokers, a growing yet understudied population in Canada and globally. His mathematical modeling skills make him uniquely qualified to investigate this understudied demographic and its environmental risk factors. We were thrilled to have him join our institution back in 2022, and this project is exactly the kind of high-quality research we aim to support.

The proposed research aligns perfectly with the core objectives of the Geoffrey Ogram Memorial Research Grant. By focusing on the environmental etiology of lung cancer in understudied populations of light ex-smokers and never-smokers, this project addresses a key and widening gap in cancer prevention. The use of robust statistical methods and innovative machine learning approaches provides a solid technical foundation for this complex challenge. The findings have the potential to inform more inclusive, personalized lung cancer screening strategies, which would significantly improve the health of many Canadians.

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BC CANCER RESEARCH
Provincial Health Services Authority

I confirm that Dr. Meza and his team have our institution's full and unwavering support. The project is not only feasible but also set for success within our research environment. We will provide all necessary administrative oversight and have the infrastructure required for this work. Furthermore, our institution fosters an inclusive cross-functional setting where experts in epidemiology, biostatistics, environmental health, and clinical oncology collaborate, providing a nurturing ground for this project to develop.

In summary, this proposal brings together an exceptional principal investigator, a highly skilled research team, a crucial research question, and a fully supportive research institute. I am confident that this research will result in fruitful scientific results that will benefit Canadians and will be a valuable investment for Lung Cancer Canada.

Thank you for considering this excellent application.

Sincerely,

Dr. Tim Lee, PhD
Interim Department Head, Distinguished Scientist
Department of Population Health Sciences
BC Cancer Research Institute
675 W 10th Ave, Vancouver, BC V5Z 1L3
(604) 675-8053
tlee@bccrc.ca