



July 15, 2025

Geoffrey Ogram Memorial Research Grant Review Committee
Lung Cancer Canada
401 Bay Street, Suite 1504
Toronto, ON M5H 2Y4

Re: Letter of Intent – 2025 Geoffrey Ogram Memorial Research Grant

Project title: *Vaping, Long-Term Cannabis Use, and Lung-Cancer Risk in Never-Smokers: A Population-Based Cohort Study in Canada*

Principal Investigator: Professor Setor K. Kunutsor, BSc, MB ChB, MPhil, PhD
Evelyn Wyrzykowski Research Chair in Cardiology, University of Manitoba
Email: setor.kunutsor@umanitoba.ca Phone: +1 204-237-3791

1. Purpose and Alignment

Never-smoker lung cancer (NSLC) represents a growing share of Canadian cases, yet the etiologic contribution of non-combustion inhalants - vaping aerosols and cannabis smoke - remains unquantified. This project directly addresses Lung Cancer Canada's priority to elucidate the causes of lung cancer in never-smokers, generating evidence vital for prevention, risk communication, and future screening refinements.

2. Objectives

1. **Quantify risk:** Estimate hazard ratios for incident lung cancer among never-smokers who (a) regularly vape or (b) use cannabis long-term, compared with never-users.
2. **Dose-response & synergy:** Model exposure–response gradients and test for additive and multiplicative interactions between vaping and cannabis.
3. **Population impact:** Calculate the population-attributable fraction of NSLC due to these exposures in Canadians aged 20–85 years.

3. Methods & Feasibility

Design: Retrospective cohort using the 2006 & 2011 Canadian Census Health and Environment Cohorts (CanCHEC) linked to the Canadian Cancer Registry (CCR) (follow-up to 2022).

Population: Approximately 1.5 million self-declared never-smokers, cancer-free at baseline.

Exposures: Self-reported vaping status and cannabis use history captured through linked Canadian Community Health Survey cycles, which are linked to CCR through CanCHEC.

Outcome: First primary lung cancer (ICD-O C34).

Analysis: Cox models with robust adjustment (age, sex, ethnicity, socioeconomic status, second-hand smoke, COPD/asthma, occupational dust). Power calculations indicate >90 % power to detect hazard ratios ≥ 1.3 for exposures with ≥ 5 % prevalence.

Budget (CA \$24,900): Statistics Canada RDC access & server fees (\$6000); data analyst (\$7800); travel to RDC (\$1100); patient partner engagement (\$1000); knowledge-translation products (\$9000).

4. Innovation

- **First national evidence** on vaping/cannabis-related NSLC risk.
- Provides **immediately actionable** risk estimates for clinicians, public-health messaging, and patient advocacy - core to Lung Cancer Canada's mandate.

5. Investigator Team & Environment

I am a clinical epidemiologist with deep expertise in cardiometabolic and chronic disease outcomes, including cancer, and a proven track record in large-scale cohort analysis and causal modelling. I have authored more than 400 peer-reviewed publications in these areas. My multidisciplinary team for this project includes:

1. Diana C. Sanchez-Ramirez, PhD – epidemiology and outcomes research in chronic respiratory diseases, Co-Investigator
2. Dr. Reyhaneh Rikhtehgaran, PhD - advanced survival and causal-inference methods, Statistician
3. Lung Cancer Canada and CancerCare Canada Patient Advisory Group nominee – lived-experience input and KT co-development, Patient-partner

The University of Manitoba provides secure Research Data Centre access and dedicated analyst support, ensuring timely completion within 12 months.

6. Expected Deliverables (1 year)

- Peer-reviewed manuscript (target: *Journal of Thoracic Oncology*).
- Conference presentation (Canadian Lung Cancer Conference 2027).
- Webinar and infographic co-branded with Lung Cancer Canada.

I am enthusiastic about collaborating with Lung Cancer Canada to shed light on emerging inhalational risk factors for never-smoker lung cancer. This study will equip stakeholders with evidence to guide prevention strategies and advocacy campaigns. I have attached a full proposal and am happy to provide any additional information.

Thank you for your consideration.

Yours sincerely,



Setor Kunutsor BSc MB ChB MPhil(cantab) PhD(cantab)
Professor, Evelyn Wyrzykowski Research Chair in Cardiology
PI, Cardiovascular Real-World Evidence (CARDIO-RWE) Research Group
Section of Cardiology
Department of Internal Medicine
Max Rady College of Medicine
Rady Faculty of Health Sciences
University of Manitoba
Saint Boniface Hospital
Winnipeg MB
R2H 2A6, Canada

Title: Vaping, Long-Term Cannabis Use, and Lung-Cancer Risk in Never-Smokers: A Population-Based Cohort Study in Canada

1. Background Information, Literature Review and Rationale

1.1. Problem being addressed: Lung cancer remains the leading cause of cancer death worldwide: in 2022 it accounted for an estimated 2.48 million new cases (12 % of all cancers) and 1.8 million deaths (18.7 % of all cancer deaths).¹ In Canada, it is similarly dominant, with approximately 32,100 new diagnoses and 20,700 deaths projected for 2024, representing one in eight incident cancers and nearly one in four cancer fatalities.² A striking and poorly understood component of this burden is never-smoker lung cancer (NSLC) - disease occurring in people who have never smoked or smoked fewer than 100 cigarettes in their lifetime. Contemporary estimates from high-income settings indicate that 10-20 % of all lung cancers now arise in never-smokers;^{3,4} were it considered a separate tumor, NSLC would rank among the ten most common cancers. NSLC disproportionately affects women, younger adults, and populations of East or South-Asian ancestry, and its incidence is rising even as smoking-related lung cancer declines.^{3,5} Traditional non-tobacco risk factors - radon, second-hand smoke, ambient particulate matter, and some occupational exposures - explain only a fraction of NSLC cases.^{6,7} Attention is therefore shifting to non-combustion inhalational exposures that have expanded rapidly in the last decade and these include vaping and cannabis smoke. National surveillance shows that in 2022, 6% of Canadians aged 15 years and above vaped in the past 30 days, with daily use in 2-3 % and highest prevalence in young adults.⁸ Following nationwide legalization in 2018, more than one-third of adults aged 18-24 (38 %) and one-third of those 25-44 (35 %) reported cannabis use in the previous year (2023).⁹ Both exposures deliver ultrafine particulates, volatile organic compounds, and, in the case of high-temperature vaping devices, novel degradation products whose long-term carcinogenic potential is unknown.^{10,11}

1.2. Review of existing evidence: A focused scoping review of the literature confirms that no population-based study has yet quantified the independent - or joint - contribution of regular vaping and chronic cannabis use to incident lung cancer in adults who have never smoked conventional cigarettes. What evidence does exist comes from small observational studies in which cigarette smoking was statistically adjusted for, but rarely eliminated. With respect to e-cigarettes, a Korean nationwide cohort analysis demonstrated that compared with former cigarette smokers ≥ 5 years since quitting who did not vape, both former cigarette smokers ≥ 5 and < 5 years since quitting who switched to exclusive vaping experienced higher risk of lung cancer and excess lung-cancer mortality.¹² A multi-centre case-control investigation presented at the 2024 American Association for Cancer Research meeting also suggested harm, reporting a three-fold elevation in lung-cancer odds for individuals who both vaped and smoked compared with those who only smoked; however, the numbers of exclusive vapers were too small for stable estimates.¹³ The cannabis literature is similarly inconclusive. In New Zealand, a population-based case-control study (79 cases and 324 controls) of adults aged ≤ 55 years found that heavy cannabis use (≥ 10.5 joint-years) was associated with a five- to six-fold increase in lung-cancer risk even after accounting for tobacco exposure.¹⁴ A Swedish cohort of 49,321 young men followed for 40 years reported that participants with more than fifty lifetime uses of cannabis had twice the lung-cancer hazard of non-users after adjustment for baseline smoking and respiratory comorbidities.¹⁵ In contrast, a Los Angeles case-control investigation¹⁶ and a pooled analysis from the International Lung Cancer Consortium of 2 159 cases drawn from six countries found no significant associations, although both acknowledged limited statistical power among never-smokers.¹⁷ A pooled hospital-based study from North Africa detected an elevated risk, but all cannabis users in that analysis were also tobacco smokers, making it impossible to disentangle independent effects.¹⁸ Taken together, existing studies are hampered by modest sample sizes, short follow-up durations, single-time-point exposure measurement, and persistent confounding from second-hand smoke or concurrent tobacco use. None has examined dose-response gradients, the combined impact of vaping and cannabis, or the population-attributable fraction of never-smoker lung cancer attributable to these rapidly expanding exposures. These limitations underscore the need - and opportunity - for a large, contemporary, population-based Canadian cohort study that can address these unanswered questions.

1.3. Why the research is important: Canada is one of the few high-income nations that has simultaneously legalized recreational cannabis and is witnessing a steep rise in daily vaping, particularly among young adults and women - demographic groups already over-represented in NSLC. Clinicians, public-health officials, and policy-makers therefore need Canadian-specific data on the cancer risk from these new inhalational exposures. Screening with low-dose computed tomography can cut lung-cancer deaths, yet current Canadian Task Force on Preventive Health Care (CTFPHC) guidelines restrict eligibility to heavy current or former smokers (≥ 30 pack-years, aged 55-74).¹⁹ Research shows that multivariable risk-prediction models outperform this smoking-only rule,²⁰ and the Task Force is actively seeking evidence to refine its algorithm. Robust estimates of vaping- and cannabis-related risk could identify high-risk never-smokers who are now

overlooked, making screening more efficient and equitable. This study will deliver the first nationally representative risk and population-attributable fraction estimates for vaping and cannabis in NSLC. These data will ground updated clinical counselling, guide provincial prevention campaigns, and give the Task Force and Lung Cancer Canada the evidence they need to shape smarter, evidence-based screening and regulatory policies.

2. Aims and Objectives

2.1. Aim: To quantify the independent and joint contributions of regular vaping and long-term cannabis use to the development of incident lung cancer among Canadian adults who have never smoked conventional cigarettes.

2.2. Specific objectives

- (1) Estimate the association between current regular vaping and incident lung cancer in never-smokers.
- (2) Estimate the association between long-term cannabis use and incident lung cancer in never-smokers.
- (3) Determine whether combined vaping and cannabis use confers additive or multiplicative risk of lung cancer.
- (4) Characterize the dose-response (frequency and duration) relation of each exposure with lung cancer risk.
- (5) Quantify the population-attributable fraction of never-smoker lung cancer attributable to vaping and/or cannabis use in Canada.

3. Methods

3.1. Study design: Retrospective population-based cohort using secondary data.

3.2. Data Source: Canadian Census Health and Environment Cohorts (CanCHEC) 2006 & 2011 linked to: 1) Canadian Cancer Registry (CCR, follow-up through 2022); 2) Canadian Community Health Survey (CCHS); 3) Discharge Abstract & Vital Stats for competing mortality.

3.3. Study population: Adults 20-85 y who: (i) self-report never having smoked ≥ 100 combustible cigarettes and (ii) have no prevalent cancer at baseline (N ~1.5 million adults).

3.4. Exposures: (i) Vaping status (never / former / current + frequency) and (ii) Cannabis use (never / former / current; duration & frequency) captured through linked CCHS cycles, which can be linked to CCR through CanCHEC.

3.5. Covariates: Age, sex, ethnicity, immigration status, income, province, occupational dust exposure, second-hand smoke, alcohol, body mass index, physician-diagnosed chronic obstructive pulmonary disease/asthma.

3.6. Outcome: First primary malignant neoplasm of bronchus / lung (ICD-O C34) identified via CCR.

3.7. Follow-up: Baseline to earliest of lung-cancer diagnosis, death, emigration, or 31 Dec 2022.

3.8. Data analysis: Age-standardized incidence rates by exposure group will be estimated. Cox proportional hazards regression models will be used to calculate multivariable HRs with 95% confidence intervals for the associations of the exposures with the outcome. Non-linear relationships will be modeled using restricted cubic splines on cumulative vaping-episode-years and cannabis joint-years. We will test for additive and multiplicative interactions between the exposures. With linkage of CanCHEC to the CCR through December 31, 2022, the median follow-up is ~11 years. Based on contemporary Canadian NSLC incidence of 16 per 100,000 person-years, the total events expected is ~2650 NSLC cases. The study is adequately powered to detect modest relative hazards for vaping and cannabis individually and to evaluate their joint (additive or multiplicative) effects (See **Appendix 1. for Full Sample Size Calculations**). In all analyses, two-sided tests with 95% confidence intervals will be used, and a significance level of $p < .05$.

3.9. Project timetable: The project is expected to begin in January 2026 and run for a duration of 12 months (**Appendix 2**).

3.10. Patient engagement plan: A patient partner has not yet been appointed, but within one month of funding we will recruit a lung-cancer survivor through Lung Cancer Canada and CancerCare Manitoba. The partner will receive SPOR-rate honoraria and will (i) review analytic summaries, (ii) co-interpret the findings to highlight patient-centred implications, and (iii) co-create all knowledge-translation products - including the infographic, leaflets, and public webinar - to ensure that the results are clear, actionable, and aligned with patient priorities.

3.11. Knowledge translation plan: Study results will be shared widely through multiple channels. Plain-language summaries, an infographic, and short video clips will be posted on our departmental websites and amplified through institutional and Lung Cancer Canada social-media accounts, with community-engagement events targeting never-smoker audiences. A live, captioned public webinar - co-hosted with Lung Cancer Canada and featuring the patient partner - will present key findings and allow real-time Q&A. Scientific dissemination will include an oral or poster presentation at the Canadian Lung Cancer Conference and a full, open-access paper in a peer-reviewed journal, ensuring rapid uptake by clinicians, researchers, and policy-makers.

Appendix 1. Sample Size Calculations

We based our calculations on the Schoenfeld approximation for time-to-event analyses, assuming a two-sided $\alpha=0.05$, 80% power ($\beta = 0.20$), and a Cox model with a single binary exposure.

The combined 2006 & 2011 Canadian Census Health and Environment Cohorts (CanCHEC) include approximately 1.5 million adults who self-identify as lifetime never-smokers and were cancer-free at baseline. With linkage of CanCHEC to the Canadian Cancer Registry through 31 Dec 2022, the median follow-up is approximately 11 years. Based on a derived contemporary Canadian never-smoker lung cancer (NSLC) incidence of approximately 16 per 100,000 person-years, a total of 2,650 incident NSLC cases is expected. The NSLC value is a derived estimate based on the following Canadian data points:

- The Canadian Medical Association Journal's annual projection report for 2024 estimates 32,100 new lung-cancer diagnoses for a mid-2024 population of about 40.5 million, which translates to approximately 79-80 cases per 100,000 Canadians per year.[1]
- A Dalhousie University-led research project notes that "about one in five Canadians diagnosed with lung cancer are never-smokers." [2]
- Multiplying the overall incidence (80/100,000) by the never-smoker share (20%) yields approximately 16 NSLC cases per 100,000 person-years.

The anticipated exposure prevalence estimates in never-smoker population is 5% for current regular vaping, 15% for long-term cannabis use, and approximately 2% for dual exposure (vaping + cannabis).

References

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2. Dalhousie-led project to study factors that increase lung cancer risk in 'never smokers'. <https://www.halifaxexaminer.ca/health/dalhousie-led-project-to-study-factors-that-increase-lung-cancer-risk-in-never-smokers/>

Events required to detect prespecified hazard ratios

Exposure (prevalence)	Target HR	Events required	Events available	Power
Vaping (0.05)	1.40	1,460	2,650	>90%
Cannabis (0.15)	1.30	895	2,650	>95%
Dual use (0.02)	1.80	1160	2,650	>99%

Appendix 2. Gantt Chart

	2026												2027		
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Ethical approval															
Data access, cleaning and coding															
Data analysis															
Data interpretation and write-up															
Circulation and submission for publication															
Knowledge translation and report writing															

Appendix 3. References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. May-Jun 2024;74(3):229-263. doi:10.3322/caac.21834
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Impact Statement

This project will deliver the first nationally representative, longitudinal evidence quantifying how regular vaping and long-term cannabis use contribute - individually and jointly - to lung cancer in Canadians who have never smoked conventional cigarettes. By filling a critical knowledge gap at the intersection of two rapidly growing inhalational behaviours and a rising cancer subtype, the study is poised to exert a sustained, field-shaping influence in three interconnected domains:

Prevention and incidence reduction (short term, 1-3 years) - Within a year of completion the project will provide precise, sex- and age-stratified risk estimates and population-attributable fractions for never-smoker lung cancer (NSLC). These data will allow Health Canada, provincial cancer agencies, and Lung Cancer Canada to craft evidence-based harm-reduction messages and regulations (e.g., flavor restrictions, device temperature limits, cannabis smoke-free legislation). Even a modest change in uptake or intensity of vaping and cannabis smoking - behaviors disproportionately common among women, young adults, and some immigrant groups that bear a higher NSLC burden - would translate into measurable reductions in incident disease.

Optimized risk stratification and earlier detection (medium term, 2-5 years) - Current low-dose computed tomography (LDCT) screening guidelines such as that of the Canadian Task Force on Preventive Healthcare (CTFPHC), rely almost exclusively on cigarette pack-years, systematically excluding never-smokers. By integrating vaping and cannabis exposure into risk models, the project will potentially inform next-generation, risk-based screening algorithms now under evaluation by the CTFPHC. Earlier detection among high-risk never-smokers promises both mortality reduction and preservation of quality of life through less aggressive treatment.

Catalyzing research and patient-centered care (long term, >5 years) - Solid national evidence will trigger new studies on how heated aerosols and cannabis smoke affect the lungs, support biomarker discovery, and launch trials of quit-programs aimed at vaping and cannabis use. Clear, Canada-specific risk numbers will help clinicians give better advice and enable patients, especially the growing group of NSLC survivors, to shape public discussion and policy.

In sum, by turning an urgent public-health question into solid population data, this project will speed progress in lung-cancer prevention and early detection, cut new cases, boost survival, and improve quality of life for Canadians at risk for, or living with, lung cancer.

Public non-scientific summary

Lung cancer is still the leading cause of cancer death in Canada, and a surprising number of people who have never smoked a cigarette are being diagnosed each year. Two habits that have grown quickly - vaping (e-cigarettes) and cannabis smoking - produce aerosols and smoke that reach deep into the lungs, yet no Canadian study has measured whether they actually raise the risk of lung cancer in never-smokers. Our project will fill that gap.

We will study about 1.5 million Canadian adults who told Statistics Canada they had never smoked conventional cigarettes and who were cancer-free when they first took part in the long-form Census. By securely linking their census answers to national health surveys, we can see who later reported regular vaping or long-term cannabis use. We will then link these records to the Canadian Cancer Registry, which tracks every new cancer diagnosis across the country up to the end of 2022.

Using well-tested statistical methods, we will compare the rate of lung cancer in four groups: people who vape, people who use cannabis, people who do both, and people who do neither. We will account for other factors that can affect lung health, such as age, sex, ethnicity, immigration status, socioeconomic status, province, and prevalent lung disease such as asthma. From these comparisons we will calculate:

- how much vaping or cannabis alone increases lung-cancer risk;
- whether using both together multiplies that risk;
- how the risk changes with heavier or longer use; and
- what share of never-smoker lung cancers in Canada might be prevented if these exposures were avoided.

What will this mean for Canadians?

Within twelve months we will deliver the first solid, Canada-specific numbers that doctors, public-health agencies, and patient advocates can use when talking about the safety of vaping and cannabis. Clear risk estimates can guide smarter regulations (for example, product labelling or marketing restrictions), help refine future lung-cancer screening rules for non-smokers, and support tailored quit programs. Even a small drop in high-risk vaping or cannabis use could translate into hundreds of prevented lung-cancer cases over the coming decade.

Patient engagement is built into the project: a member of Lung Cancer Canada's Never-Smoker Advisory Group will help shape the study materials and co-create an easy-to-understand infographic and public webinar to share the findings.

Timeline and outputs

Months 1-3: Obtain secure data access and build the linked dataset.

Months 4-8: Analyze the data and check results with our patient partner and clinical advisers.

Months 9-12 and beyond: Publish the findings in a medical journal, present them at a national lung-cancer conference, and release the infographic and webinar for the Canadian public.

This study will turn a pressing health question into clear evidence that can cut lung-cancer cases, aid earlier detection, and improve the lives of Canadians affected by the disease.

Budget Justification

Total requested: CAD \$24,900

	Item & Amount (CAD)	Justification
	Research Associate Statistician – \$7,800	A part-time PhD-level statistician (5 h/week × 39 weeks at \$40 /h) will clean, link, and analyze the CanCHEC–Cancer Registry dataset, run models, and prepare reproducible code.
	Statistics Canada RDC access & server fees – \$6,000	Mandatory fees for secure data access, extraction, on-site computing, and storage for the 12-month project, per Statistics Canada tariff.
	Local travel to RDC – \$1,100	Approximately 85 round trips (2-3/week for 8 months) using CRA 2025 mileage rate to ensure cost-effective access to the secure facility.
	Patient-partner engagement – \$1,000	Honoraria and local travel for a lung-cancer survivor collaborator, following SPOR compensation guidelines, ensuring meaningful patient involvement.
	Knowledge-translation materials – \$1,500	Professional design and print of bilingual infographic and 500 color leaflets co-branded with Lung Cancer Canada and University of Manitoba to distil key findings.
	Public webinar – \$1,000	Resources for a national webinar featuring the PI, patient partner, and Lung Cancer Canada moderator.
	Open-access publication – \$3,000	Journal of Thoracic Oncology article-processing charge to ensure free, immediate access to results.
	Conference dissemination – \$3,500	Registration, travel, hotel, and per diem to present at the Canadian Lung Cancer Conference 2027, engaging clinicians and policy-makers.

Name	Role of participant	Primary affiliation
Kunutsor, Setor	Principal Investigator	University of Manitoba
Diana C. Sanchez-Ramirez	Co-Investigator	University of Manitoba
Rikhtehgaran, Reyhaneh	Statistician	University of Manitoba



June 30, 2025

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

Re: Institutional Letter of Support – Professor Setor K. Kunutsor

Dear Review Committee Members,

On behalf of the University of Manitoba, I am pleased to offer full institutional support for Professor **Setor Kunutsor's** application to the **Geoffrey Ogram Memorial Research Grant** entitled **“Vaping, Long-Term Cannabis Use, and Lung-Cancer Risk in Never-Smokers: A Population-Based Cohort Study in Canada.”**

Confirmation of feasibility and resources

1. **Secure data access.** The University hosts an accredited **Statistics Canada Research Data Centre (RDC)** on the Bannatyne Campus. The RDC's secure infrastructure, on-site servers, and trained staff will provide Professor Kunutsor and his team with all necessary access to the linked Canadian Census Health and Environment Cohorts (CanCHEC), Canadian Community Health Survey files, and the Canadian Cancer Registry.
2. **Research environment.** The project will be carried out within the Section of Cardiology, Department of Internal Medicine, Rady Faculty of Health Sciences, which offers dedicated workspace, high-performance computing, biostatistical support, and administrative expertise in data-driven population-health research.
3. **Institutional commitment.** The University affirms that all required facilities, compliance processes, and personnel are in place to enable successful completion of the proposed 12-month study. The project aligns with our institutional priorities of advancing evidence-based prevention and improving the health of Manitobans and Canadians.

We are confident that Professor Kunutsor's project is feasible at the University of Manitoba and will generate impactful, policy-relevant findings that advance lung-cancer prevention and early detection.

Please contact me if additional information is required.

Sincerely,

Ryan Zarychanski MD MSc, FRCPC
Acting Department Head, (for Dr. Nick Hajidiacos, MD)
Department of Internal Medicine,
Max Rady College of Medicine, University of Manitoba
Winnipeg, MB R3T 2N2
Tel: 204-787-7772
Email: nhajidiacos@hsc.mb.ca
ryan.zarychanski@umanitoba.ca