Epidemiologic trends and geographic distribution of esophageal cancer in Canada: A national population-based study

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Abstract

Background: Esophageal cancer can be subdivided into two main histological subtypes with significant variability in their etiology and epidemiology. The incidence of esophageal adenocarcinoma (AC) is increasing across the developed countries, whereas the incidence of esophageal squamous cell carcinoma (SCC) is declining. Several risk factors have been identified in the pathogenesis of each subtype, however, their epidemiologic characteristics and distribution throughout Canada remain poorly understood.

Methods: We performed a retrospective analysis of demographic data across Canada from 1992 to 2010 using two independent population-based cancer registries. The incidence of esophageal cancer, for each subtype, was examined at the levels of provinces/territories, cities, and postal codes.

Results: A total of 19790 patients were diagnosed with esophageal cancer in Canada between 1992 and 2010; 74% were males. The average national incidence rate was 33.5 cases per million individuals per year. Incidence of esophageal AC increased over time, with notable high-incidence rates on the Vancouver Island, the coasts of the Great Lakes, and the coasts of the Northumberland Strait in the Maritimes. The overall incidence of esophageal SCC has decreased. However, high incidence of esophageal SCC was detected in the Vancouver city, rural eastern Québec, and in the Maritimes. We also report clustering for each subtype using postal codes, which sheds light onto new avenues of research for potential environmental etiologies.

Conclusions: This study, for the first time, provides a detailed analysis on the burden of esophageal cancer in Canada, revealing important geographic clustering trends.

KEYWORDS
Barrett’s esophagus, Canada, epidemiology, esophageal adenocarcinoma, esophageal cancer, esophageal squamous cell carcinoma, gastroesophageal reflux disease (GERD), geographic clustering, great lakes, incidence, obesity, pollution, risk factors, smoking
1 | INTRODUCTION

Esophageal cancer has two main histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (AC). Esophageal SCC is the most common of the two, representing 87% of all esophageal neoplasms in 2012. While esophageal SCC is more common in the developing countries, esophageal AC has become much more predominant across the western world. There exist many epidemiological differences between the two subtypes, however, these have not been explicitly defined on a global level until in 2014; a study by Arnold et al investigated worldwide trends of esophageal cancer incidence by histological type, reporting a global esophageal SCC incidence of 52 cases per million individuals per year, with the male predominance of 2.7 to 1. The majority (80%) of cases of esophageal SCC occurred in central and southeast Asia, with only 1.8% of cases reported in North America. The etiology of esophageal SCC is closely linked to alcohol and tobacco use. SEER data for esophageal SCC incidence in the United States examined between 1992 and 2013 demonstrated a decreasing incidence over time, from 51 cases to 26 cases per million individuals per year.

Global esophageal AC affects 7 individuals per million per year with a predilection for the male gender at a ratio of 4.4:1. The majority of cases (22.8%) occurred in the northwestern Europe, with Southeast Asia and North America close behind. Within these regions, the incidence rates were much higher and favored the male gender with 8.5:1 incidence rate ratio. AC originates from Barrett’s esophagus, in which normal squamous mucosa of the lower third of the esophagus undergoes dysplasia and is replaced by columnar cells resembling intestinal mucosa. The two most recognized risk factors for esophageal AC are gastroesophageal reflux disease and obesity. While the incidence rates of several cancers have been decreasing, the incidence rate of esophageal AC has risen sixfold in the United States since 1970. Data from 13 European countries between 1983 and 1997 reported similar trends.

In Canada, there have been limited studies reporting on rising rates of esophageal cancer in Ontario and in British Columbia in recent years. In this study, we conducted an extensive epidemiological analysis on the burden of esophageal cancer for both subtypes across all provinces and territories in Canada during the period 1992-2010. The geographic distribution of these patients was analyzed, with the aim to better understand risk factors related to the pathogenesis of this neoplasm and to identify communities at high vs low risk for esophageal cancer.

2 | METHODS

This study was conducted in accordance with the CISS-RDC-668035 and 13-SSH-MCG-3749-S001 protocols approved by the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Québec Inter-University Centre for Social Statistics (QICSS), respectively. This study was exempt from the McGill University Research Ethics Board review. The data on esophageal cancer incidence was examined using two distinct population-based cancer databases: the Canadian Cancer Registry (CCR) and Le Registre Québécois du Cancer (LRQC) during 1992-2010. International Classification of Disease for Oncology ICD-O-3 codes were used for five subtypes of esophageal AC, and three subtypes of esophageal SCC, similarly as reported in our previous studies. Due to space limitations, detailed methods are provided in the Appendix S1.

3 | RESULTS

A general overview of demographic characteristics for esophageal cancer and its two histologic subtypes are presented in Table 1. In total, 19,790 patients were diagnosed with esophageal cancer. The majority (74%) were males, while 26% were females, with a male:female IRR of 2.9:1.0. The average age of diagnosis was 67.5 ± 0.8 years, with 92% of patients being > 60. The crude annual incidence of esophageal cancer showed a steady upward trend (Figure 1A); in 1992 the incidence rate was of 29.1 cases per million individuals per year; in 2010 this value had risen to 41.5, representing an increase of 43% over 19 years. The average national incidence rate for esophageal cancer between 1992 and 2010 was 33.5 cases per million individuals per year.

Geographic analysis of esophageal cancer trends throughout the country is presented in Figure 1B,C. On the provincial level, Prince Edward Island (PEI), Nova Scotia (NS), New Brunswick (NB), and British Columbia (BC) had significantly higher annual age-standardized incidence rates than that of the national average, of up to 45.7 cases per million individuals in PEI. In contrast, Newfoundland and Labrador and Quebec (QC) had significantly lower incidence rates.

Incidence rates for Canadian cities corroborated these trends and revealed certain clustering of cases throughout the country, as seen in Tables S1A,B and Figure S1. Of the 20 cities with high incidence of esophageal cancer, 10 (50%) were in Ontario (ON), 9 (45%) were in BC, and 1 (5%) was in Saskatchewan (SK). In contrast, of the 20 low-incidence cities in Canada, 11 (55%) were located in QC, which also had a significantly lower provincial incidence rate than the rest of Canada. On further assessment, 8/11 of low-incidence
We were able to observe high incidence areas on the Vancouver Island (BC), and in Southern Ontario, which encompasses Eastern, Central, and Western Ontario (Figure S1A). Subsequently, the distribution of esophageal cancer patients was examined within cities by analyzing individual Forward Sortation Areas (FSAs). Each FSA corresponds to an area where all postal codes share the first three entries (e.g., H4A). There are 1648 FSAs in Canada, 15.7% (258/1648) of which were excluded from this study as their populations were less than 5000, as per Statistics Canada regulations. High concentration of esophageal cancer cases was observed on the Vancouver Island, in Eastern Ontario, Newfoundland’s Avalon Peninsula, and surrounding the Northumberland Strait on the coasts of PEI and Nova Scotia (Table S2B; Figure S1B). The majority of these FSAs were located in Central Ontario and in the Greater Toronto Area (GTA).

### Table 1: Epidemiologic characteristics of esophageal cancer and its two major histological subtypes between 1992 and 2010

**A: Incidence by sex**

| Subtype            | Number of males | % of females | Number of females | % females | Average crude incidence rate (95% confidence intervals) | Average ASIR (95% confidence intervals) |
|--------------------|-----------------|--------------|-------------------|-----------|---------------------------------------------------------|------------------------------------------|
| Esophageal Cancer  | 14635           | 70.01        | 5140              | 25.99     | 33.49 (33.02-33.96)                                     | 23.01 (22.62-23.40)                     |
| Esophageal AC      | 9005            | 84.36        | 1670              | 15.64     | 18.08 (17.74-18.43)                                     | 12.59 (12.30-12.89)                     |
| Esophageal SCC     | 5630            | 61.87        | 3470              | 38.13     | 15.41 (15.09-15.73)                                     | 10.42 (10.16-10.69)                     |

**B: Incidence by age group**

| Subtype            | <30 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90+ | Average age of diagnosis |
|--------------------|-----|-------|-------|-------|-------|-------|-------|-----|--------------------------|
| Esophageal Cancer  | 0   | 3.03  | 13.42 | 38.89 | 85.68 | 144.51| 129.13| 58.88| 67.52 ± 0.76             |
| Esophageal AC      | 0   | 2.31  | 9.32  | 23.16 | 43.95 | 73.65 | 64.50 | 26.44| 66.40 ± 1.01             |
| Esophageal SCC     | 0   | 0.73  | 4.11  | 15.74 | 41.74 | 70.86 | 63.63 | 32.44| 68.30 ± 1.14             |

3.1 Analysis of esophageal adenocarcinoma

Esophageal AC was diagnosed in 10,675 Canadians between 1992 and 2010, of which 84.4% of patients were male and the average age at the time of diagnosis was 66.4 ± 1.0 years. The crude average incidence rate for esophageal AC was 18.1 cases per million individuals per year. In 1992, the incidence rate of esophageal AC was 10.9 cases per million individuals per year. By 2010 this value had risen to 26.8 cases, representing >2-fold increase over 19 years (Table 1). The age-standardized national incidence rate was 12.6 cases per year.
**A**

Incidence of cases per million individuals per y vs. Y of diagnosis.

**B**

| Territory        | Incidence |
|------------------|-----------|
| Canada           | 33.56     |
| Yukon            | 57.85     |
| Nunavut          | 47.28     |
| Prince Edward Island | 45.72   |
| New Brunswick    | 40.75     |
| British Columbia | 40.34     |
| Nova Scotia      | 40.71     |
| Saskatchewan     | 34.83     |
| Ontario          | 34.40     |
| Alberta          | 31.86     |
| Manitoba         | 31.79     |
| New Brunswick*   | 28.23     |
| Quebec*          | 28.22     |
| Northwest Territories | 22.41  |

**C**

Map showing incidence of cases per million individuals per y across different provinces and territories in Canada.
FIGURE 1 Incidence of esophageal cancer throughout Canada between 1992 and 2010 over time and by province (in cases per million individuals per year). A. Changing incidence rates for esophageal cancer between 1992 and 2010. Linear regression analysis of incidence rates over time \([R^2] = 0.86; P = 0.002\). The slope of the line was 0.69 cases per million individuals per year. Dotted lines indicate 95% confidence interval. B. Age-standardized incidence rates of esophageal cancer across Canadian provinces between 1992 and 2010. *Statistically significant lower incidence rates \((P < 0.05)\) compared to the Canadian average. **Statistically significant higher incidence rates \((P < 0.05)\) compared to the Canadian average. C. Esophageal cancer incidence trends by province in Canada. Geographic maps illustrate age-standardized incidence rates of esophageal cancer relative to the national average based on the Canadian Cancer Registry/Le Registre Québecois du Cancer databases.

3.2 Analysis of esophageal squamous cell carcinoma

Esophageal SCC was diagnosed in 9115 Canadians between 1992 and 2010, with 61.9% male patients, and an average age at diagnosis of 68.3 ± 1.1 years (Table 1). The crude average incidence rate for esophageal SCC was 15.4 cases per million individuals per year. In 1992, the incidence rate was 18.2 cases per million individuals per year. In 2010, this value had decreased to 14.7 cases, representing a 19% decrease over 19 years (Figure 2C). The age-standardized national incidence rate was 10.4 cases per year. On the provincial level (Figure 2D), only BC exhibited significantly higher incidence rates than the national average (18.6 cases per million individuals per year). In contrast, QC had a significantly lower incidence rate of 14.4 cases per million individuals per year. Analysis by FSA (Table 3 and Figure 4A) showed a notable high-incidence in V6A postal code, a borough within the Vancouver city, encompassing Strathcona, Chinatown and Downtown Eastside (DTES) with a rate of 63.7 cases per million individuals per year, approximately four times higher than the national average. Significant clusters of esophageal SCC cases were found in the west coast of BC, rural QC and NB, and in the Maritimes. Results at the city and FSA levels are further discussed in Appendix S2 and can be viewed in Figure 4A-D.

4 DISCUSSION

To our best knowledge, no previous study performed has assessed the distribution of esophageal AC or SCC across the entire country and to this level of detail. In this work, we present important national trends corroborating those seen in similar studies from the United States, Europe, and Australia. At the national level, we report a steadily increasing overall burden of esophageal cancer in Canada, with a male predominance. Over 90% of these patients were > 60, reflecting a correlation between Canada's aging population and an increase in the current and projected incidence of cancer across the country.26 The average incidence rate was found to be 33.5 cases per million individuals per year, and the average age-adjusted (to the World Standard Population) incidence rate was 23.0 cases per million individuals per year. This is consistent with worldwide trends:

Wong et al27 reported national age-standardized incidence rates, standardized to the World Standard Population (in cases per million individuals per year) of 27 in Europe, 29 in North America, 34 in South America, and 29 in Australia. The authors additionally report an average male to female incidence ratio of 3:1,27 similar to our findings of 2.9:1.

Regarding the specific subtypes analyzed, we confirmed an important increase in esophageal AC incidence over time that has been seen in many developed countries. Age-standardized esophageal AC incidence rates were reported by Thrift et al3 (in cases per million individuals per year) as 24.5 cases in Australia, 24.5 cases in the United States, and 13.9 cases in Sweden between 1999 and 2003. The proportion of obese Canadians has doubled between the 1980s and 2004.28 This potentially links esophageal AC to the higher rates of obesity seen in countries of a higher socioeconomic status.23,26 With an aging population, patients may experience a longer duration of Gastroesophageal reflux disease (GERD) which would increase the risk of Barrett's esophagus and esophageal AC.30,31 In addition, this increasing rate of esophageal AC may reflect the failure of screening appropriate patients or inadequate surveillance since Barrett's esophagus, GERD and obesity are potentially modifiable risk factors.32,33

In the present study, we also described a decrease in esophageal SCC. The age-standardized esophageal SCC incidence rates reported by Thrift et al3 (in cases per million individuals per year) corroborate our results: 25.1 in Australia, 18.1 in the United States, 14.0 in the Caucasian population of the United States, and 17.2 per in Sweden between 1999 and 2003. A study by Otterstatter et al29 reports an incidence of esophageal SCC in Canada of 13.5 cases per million individuals per year in 2004-2006, reflecting the decreased incidence of esophageal SCC in recent years.29 A decline in tobacco smoking among Canadians may in part explain the decline in esophageal SCC incidence.34 SEER data during the period 1998-2003 also corroborates these results; an overall incidence during that time was documented to be 18
**FIGURE 2** Incidence of esophageal cancer subtypes throughout Canada between 1992 and 2010 over time and by province (in cases per million individuals per year). A. Changing incidence rates for esophageal adenocarcinoma between 1992 and 2010. Linear regression analysis of incidence rates over time \( [R^2] = 0.95; P = .002 \). The slope of the line was 0.87 cases per million individuals per year. Dotted lines indicate 95% confidence interval. B. Age-standardized incidence rates of esophageal adenocarcinoma across Canadian provinces between 1992 and 2010. *Statistically significant lower incidence rate \( (P < .05) \) compared to Canadian average. **Statistically significant higher incidence rates \( (P < .05) \) compared to Canadian average. C. Changing incidence rates for esophageal squamous cell carcinoma between 1992 and 2010. Linear regression analysis incidence rate over time \( [R^2] = 0.74; P = .002 \). The slope of the line was −0.19 cases per million individuals per year. Dotted lines indicate 95% confidence interval. D. Age-standardized incidence rates of esophageal squamous cell carcinoma (per 1 million individuals per year) in the Canadian provinces between 1992 and 2010. *Statistically significant lower incidence rate \( (P < .05) \) compared to Canadian average. **Statistically significant higher incidence rates \( (P < .05) \) compared to Canadian average.
### Table 2: List of Populous Forward Sortation Areas (FSA) in Canada with high crude incidence rates of esophageal adenocarcinoma from 1992 to 2010. All population numbers are rounded to the nearest thousand

| FSA | Province | Cases | Average Population | Crude incidence per million individuals per year | Lower 95% CI | Higher 95% CI |
|-----|----------|-------|---------------------|-----------------------------------------------|--------------|---------------|
| B0E | NS       | 20    | 30 000              | 34.97                                         | 21.36        | 54.01         |
| B0K | NS       | 30    | 38 000              | 41.13                                         | 27.75        | 58.71         |
| B0N | NS       | 30    | 44 000              | 36.15                                         | 24.39        | 51.60         |
| B0T | NS       | 15    | 17 000              | 47.73                                         | 26.71        | 78.73         |
| B0W | NS       | 25    | 33 000              | 39.49                                         | 25.56        | 58.29         |
| B1H | NS       | 10    | 11 000              | 48.78                                         | 23.39        | 89.70         |
| B2N | NS       | 20    | 29 000              | 36.45                                         | 22.26        | 56.29         |
| B2T | NS       | 10    | 14 000              | 38.99                                         | 18.70        | 71.70         |
| B3A | NS       | 15    | 20 000              | 38.62                                         | 21.62        | 63.70         |
| B3N | NS       | 10    | 12 000              | 43.57                                         | 20.89        | 80.13         |
| B3P | NS       | 10    | 8000                | 62.36                                         | 29.90        | 114.68        |
| B3Z | NS       | 10    | 11 000              | 48.96                                         | 23.48        | 90.04         |
| C0A | PEI      | 25    | 43 000              | 30.32                                         | 19.62        | 44.77         |
| C1A | PEI      | 25    | 31 000              | 42.17                                         | 27.29        | 62.26         |
| E1N | NB       | 10    | 11 000              | 47.54                                         | 22.80        | 87.44         |
| E2J | NB       | 20    | 16 000              | 66.71                                         | 40.75        | 103.02        |
| E2M | NB       | 15    | 19 000              | 41.27                                         | 23.10        | 68.07         |
| E3A | NB       | 20    | 27 000              | 38.40                                         | 23.46        | 59.31         |
| E3V | NB       | 10    | 12 000              | 42.17                                         | 20.22        | 77.56         |
| E5N | NB       | 10    | 11 000              | 46.70                                         | 22.39        | 85.88         |
| E7M | NB       | 10    | 10 000              | 54.26                                         | 26.02        | 99.78         |
| G1H | QC       | 20    | 29 000              | 36.41                                         | 22.24        | 56.23         |
| G1M | QC       | 15    | 18 000              | 44.45                                         | 24.88        | 73.32         |
| G6G | QC       | 15    | 20 000              | 38.66                                         | 21.64        | 63.77         |
| J1H | QC       | 20    | 29 000              | 36.88                                         | 22.53        | 56.96         |
| J6S | QC       | 15    | 23 000              | 34.58                                         | 19.35        | 57.04         |
| K0A | ON (Eastern) | 50  | 91 000               | 28.76                                         | 21.35        | 37.92         |
| K0C | ON (Eastern) | 30  | 51 000               | 30.92                                         | 20.86        | 44.14         |
| K0E | ON (Eastern) | 35  | 39 000               | 47.83                                         | 33.32        | 66.53         |
| K0G | ON (Eastern) | 20  | 33 000               | 31.51                                         | 19.24        | 48.66         |
| K0H | ON (Eastern) | 30  | 42 000               | 37.49                                         | 25.29        | 53.51         |
| K0K | ON (Eastern) | 75  | 103 000              | 38.23                                         | 30.07        | 47.93         |
| K0L | ON (Eastern) | 50  | 68 000               | 38.52                                         | 28.59        | 50.78         |
| K0M | ON (Eastern) | 40  | 46 000               | 45.39                                         | 32.43        | 61.81         |
| K2A | ON (Eastern) | 15  | 15 000               | 51.16                                         | 28.64        | 84.39         |
| K6H | ON (Eastern) | 25  | 29 000               | 44.75                                         | 28.96        | 66.07         |
| K6V | ON (Eastern) | 25  | 28 000               | 46.33                                         | 29.98        | 68.39         |
| K7G | ON (Eastern) | 10  | 8000                | 63.03                                         | 30.23        | 115.92        |
| K7K | ON (Eastern) | 20  | 31 000               | 34.46                                         | 21.05        | 53.21         |
| K7L | ON (Eastern) | 15  | 21 000               | 38.12                                         | 21.34        | 62.87         |
| K7M | ON (Eastern) | 35  | 45 000               | 40.76                                         | 28.39        | 56.69         |

(Continues)
| FSA | Province       | Cases | Average Population | Crude incidence per million individuals per year | Lower 95% CI | Higher 95% CI |
|-----|----------------|-------|--------------------|-----------------------------------------------|-------------|--------------|
| K7S | ON (Eastern)   | 10    | 12 000             | 44.57                                         | 21.37       | 81.96        |
| K8N | ON (Eastern)   | 20    | 26 000             | 39.89                                         | 24.36       | 61.60        |
| K8P | ON (Eastern)   | 15    | 20 000             | 38.53                                         | 21.56       | 63.55        |
| K8V | ON (Eastern)   | 20    | 27 000             | 39.17                                         | 23.93       | 60.50        |
| K8H | ON (Eastern)   | 25    | 26 000             | 50.47                                         | 32.66       | 74.51        |
| K9J | ON (Eastern)   | 35    | 45 000             | 41.18                                         | 28.69       | 57.28        |
| K9V | ON (Eastern)   | 20    | 25 000             | 42.41                                         | 25.91       | 65.50        |
| L0K | ON (Central)   | 20    | 33 000             | 32.19                                         | 19.66       | 49.72        |
| L0P | ON (Central)   | 10    | 11 000             | 47.76                                         | 22.90       | 87.83        |
| L2E | ON (Central)   | 15    | 21 000             | 36.87                                         | 20.64       | 60.82        |
| L2N | ON (Central)   | 20    | 32 000             | 33.35                                         | 20.37       | 51.51        |
| L2P | ON (Central)   | 10    | 13 000             | 39.04                                         | 18.72       | 71.80        |
| L3V | ON (Central)   | 25    | 41 000             | 32.01                                         | 20.71       | 47.25        |
| L7N | ON (Central)   | 15    | 13 000             | 61.29                                         | 34.31       | 101.10       |
| L8L | ON (Central)   | 20    | 34 000             | 31.40                                         | 19.18       | 48.50        |
| L8P | ON (Central)   | 15    | 22 000             | 35.79                                         | 20.03       | 59.03        |
| L8T | ON (Central)   | 15    | 19 000             | 40.97                                         | 22.93       | 67.57        |
| L8V | ON (Central)   | 15    | 22 000             | 36.69                                         | 20.53       | 60.51        |
| L9A | ON (Central)   | 15    | 23 000             | 33.71                                         | 18.87       | 55.60        |
| L9H | ON (Central)   | 25    | 31 000             | 42.44                                         | 27.47       | 62.66        |
| N0A | ON (Western)   | 20    | 30 000             | 35.56                                         | 18.47       | 42.14        |
| N0H | ON (Western)   | 25    | 45 000             | 29.32                                         | 21.72       | 54.92        |
| N1A | ON (Western)   | 10    | 12 000             | 44.19                                         | 18.97       | 43.28        |
| N2H | ON (Western)   | 15    | 21 000             | 37.45                                         | 20.96       | 61.77        |
| N3B | ON (Western)   | 10    | 10 000             | 50.85                                         | 24.39       | 93.52        |
| N3Y | ON (Western)   | 15    | 22 000             | 36.03                                         | 20.17       | 59.43        |
| N4N | ON (Western)   | 10    | 9000              | 56.35                                         | 27.02       | 103.63       |
| N4W | ON (Western)   | 10    | 10 000             | 54.15                                         | 25.97       | 99.58        |
| N5C | ON (Western)   | 10    | 14 000             | 38.96                                         | 18.68       | 71.64        |
| N7A | ON (Western)   | 10    | 12 000             | 45.06                                         | 21.61       | 82.87        |
| N7T | ON (Western)   | 20    | 27 000             | 38.91                                         | 23.77       | 60.10        |
| N8S | ON (Western)   | 15    | 23 000             | 34.49                                         | 19.30       | 56.89        |
| P0B | ON (Northern)  | 10    | 8000              | 62.51                                         | 29.97       | 114.95       |
| P1B | ON (Northern)  | 20    | 34 000             | 30.72                                         | 18.77       | 47.45        |
| P2N | ON (Northern)  | 10    | 8000              | 65.87                                         | 31.59       | 121.14       |
| P4N | ON (Northern)  | 20    | 28 000             | 37.04                                         | 22.62       | 57.20        |
| P5A | ON (Northern)  | 10    | 12 000             | 43.39                                         | 20.81       | 79.80        |
| P6B | ON (Northern)  | 15    | 24 000             | 33.42                                         | 18.71       | 55.13        |
| P7B | ON (Northern)  | 25    | 30 000             | 43.67                                         | 28.26       | 64.47        |
| P7C | ON (Northern)  | 25    | 29 000             | 45.23                                         | 29.27       | 66.77        |
| P7E | ON (Northern)  | 15    | 22 000             | 35.79                                         | 20.03       | 59.03        |
| R2Y | MB             | 15    | 20 000             | 39.28                                         | 21.98       | 64.78        |
| S0E | SK             | 20    | 34 000             | 30.56                                         | 18.67       | 47.20        |

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cases per million individuals per year, slightly higher than the Canadian average. Esophageal SCC incidence in Europe tends to be much higher than in North America, likely due to much higher rates of cigarette consumption.

Geographic analysis of esophageal cancer trends throughout the country demonstrated that this malignancy localized more strongly to the Maritimes and BC. The present findings demonstrated clustering of esophageal AC cases in three particular areas of Canada; Vancouver Island, the coasts of the Great Lakes, and the coasts of the Northumberland Strait between NS and PEI. A recent study reported on clustering of esophageal cancer mortality in Caucasian men across the United States, which showed a high mortality from this cancer in the northeastern part of the country, particularly along the coasts of Lakes Michigan, Erie, and Ontario. Further analysis
FIGURE 3  Esophageal adenocarcinoma incidence trends by FSA in Canada. Geographic maps illustrating incidence rates of esophageal adenocarcinoma (cases per million individuals per year) relative to the national average based on the Canadian Cancer Registry/Le Registre Québécois du Cancer databases. A: Esophageal adenocarcinoma incidence trends by FSA in British Columbia (BC). This figure includes the highest incidence FSA, V8L in Sidney, North Saanich, BC. B: Esophageal adenocarcinoma incidence trends by FSA in Ontario. This figure shows high incidence esophageal adenocarcinoma FSAs in Eastern Ontario surrounding Lake Ontario. C: Esophageal adenocarcinoma incidence trends by FSA in the Maritimes. This figure shows high incidence esophageal adenocarcinoma FSAs in Nova Scotia and PEI.
| FSA | Province   | Cases | Average population | Crude incidence per million individuals per year | Lower 95% CI | Higher 95% CI |
|-----|------------|-------|--------------------|-----------------------------------------------|-------------|--------------|
| A0B | NF         | 15    | 23 610             | 33.44                                         | 18.70       | 55.15        |
| A1C | NF         | 10    | 14 280             | 36.86                                         | 17.64       | 67.79        |
| B0C | NS         | 5     | 5300               | 49.65                                         | 16.00       | 115.87       |
| B0K | NS         | 20    | 38 390             | 27.42                                         | 16.74       | 42.35        |
| B1P | NS         | 10    | 16 060             | 32.77                                         | 15.69       | 60.27        |
| B1V | NS         | 5     | 7020               | 37.49                                         | 12.08       | 87.48        |
| B2G | NS         | 10    | 14 080             | 37.38                                         | 17.90       | 68.75        |
| E3A | NB         | 15    | 27 410             | 28.80                                         | 16.11       | 47.51        |
| E7C | NB         | 5     | 5500               | 47.85                                         | 15.42       | 111.66       |
| G0E | QC         | 10    | 11 790             | 44.64                                         | 21.37       | 82.10        |
| G0K | QC         | 10    | 13 200             | 39.87                                         | 19.09       | 73.33        |
| G1J | QC         | 20    | 22 810             | 46.15                                         | 28.18       | 71.28        |
| G1K | QC         | 15    | 18 270             | 43.21                                         | 24.17       | 71.28        |
| G1L | QC         | 15    | 22 920             | 34.44                                         | 19.26       | 56.82        |
| G1R | QC         | 15    | 16 710             | 47.25                                         | 26.42       | 77.93        |
| H1H | QC         | 20    | 34 700             | 30.34                                         | 18.52       | 46.85        |
| H1M | QC         | 15    | 27 510             | 28.70                                         | 16.05       | 47.34        |
| H2H | QC         | 10    | 13 920             | 37.81                                         | 18.10       | 69.54        |
| H2K | QC         | 15    | 27 080             | 29.15                                         | 16.30       | 48.09        |
| H4H | QC         | 15    | 19 480             | 40.53                                         | 22.67       | 66.85        |
| H8N | QC         | 15    | 26 490             | 29.80                                         | 16.67       | 49.16        |
| H8P | QC         | 15    | 22 410             | 35.23                                         | 19.70       | 58.11        |
| H9S | QC         | 15    | 21 540             | 36.65                                         | 20.50       | 60.46        |
| J2K | QC         | 10    | 14 570             | 36.12                                         | 17.29       | 66.44        |
| J7Z | QC         | 15    | 28 270             | 27.93                                         | 15.62       | 46.06        |
| J8X | QC         | 10    | 10 900             | 48.29                                         | 23.12       | 88.81        |
| K0J | ON (Eastern) | 20  | 33 120             | 31.78                                         | 19.41       | 49.09        |
| K2A | ON (Eastern) | 15  | 15 430             | 51.16                                         | 28.62       | 84.39        |
| K2B | ON (Eastern) | 20  | 33 050             | 31.85                                         | 19.45       | 49.19        |
| K2C | ON (Eastern) | 15  | 27 040             | 29.20                                         | 16.33       | 48.16        |
| K2P | ON (Eastern) | 10  | 14 810             | 35.54                                         | 17.01       | 65.36        |
| K6V | ON (Eastern) | 20  | 28 400             | 37.06                                         | 22.63       | 57.25        |
| K7A | ON (Eastern) | 10  | 16 640             | 31.63                                         | 15.14       | 58.17        |
| K7C | ON (Eastern) | 10  | 15 160             | 34.72                                         | 16.62       | 63.85        |
| K7H | ON (Eastern) | 10  | 14 520             | 36.25                                         | 17.35       | 66.67        |
| K8N | ON (Eastern) | 15  | 26 390             | 29.92                                         | 16.73       | 49.34        |
| K9J | ON (Eastern) | 30  | 44 730             | 35.30                                         | 23.81       | 50.39        |
| L2A | ON (Central) | 10  | 16 200             | 32.49                                         | 15.55       | 59.75        |
| L4Y | ON (Central) | 15  | 24 090             | 32.77                                         | 18.33       | 54.06        |
| L6K | ON (Central) | 10  | 12 650             | 41.61                                         | 19.92       | 76.52        |
| L6L | ON (Central) | 15  | 26 320             | 30.00                                         | 16.78       | 49.48        |
| L6T | ON (Central) | 20  | 38 980             | 27.00                                         | 16.49       | 41.71        |

(Continues)
| FSA | Province       | Cases | Average population | Crude incidence per million individuals per year | Lower 95% CI | Higher 95% CI |
|-----|---------------|-------|--------------------|-----------------------------------------------|--------------|--------------|
| L7L | ON (Central)  | 20    | 36 720             | 28.67                                         | 17.50        | 44.28        |
| L7N | ON (Central)  | 10    | 12 880             | 40.86                                         | 19.56        | 75.15        |
| M4G | ON (Toronto)  | 10    | 16 260             | 32.37                                         | 15.50        | 59.53        |
| M4V | ON (Toronto)  | 10    | 16 380             | 32.13                                         | 15.38        | 59.10        |
| M6N | ON (Toronto)  | 25    | 41 110             | 32.01                                         | 20.71        | 47.25        |
| M9N | ON (Toronto)  | 15    | 23 880             | 33.06                                         | 18.49        | 54.53        |
| N0M | ON (Western)  | 30    | 64 370             | 24.53                                         | 16.55        | 35.02        |
| N2G | ON (Western)  | 10    | 13 490             | 39.02                                         | 18.68        | 71.76        |
| N3T | ON (Western)  | 15    | 26 310             | 30.01                                         | 16.78        | 49.49        |
| N5A | ON (Western)  | 20    | 30 420             | 34.60                                         | 21.13        | 53.44        |
| N6A | ON (Western)  | 10    | 10 850             | 48.51                                         | 23.22        | 89.21        |
| N6B | ON (Western)  | 10    | 9970               | 52.79                                         | 25.27        | 97.09        |
| N7A | ON (Western)  | 10    | 11 680             | 45.06                                         | 21.57        | 82.88        |
| N8X | ON (Western)  | 10    | 16 280             | 32.33                                         | 15.48        | 59.46        |
| N9A | ON (Western)  | 20    | 27 120             | 38.81                                         | 23.70        | 59.95        |
| P0H | ON (Northern) | 20    | 34 630             | 30.40                                         | 18.56        | 46.95        |
| P0K | ON (Northern) | 10    | 12 270             | 42.89                                         | 20.54        | 78.89        |
| P0L | ON (Northern) | 15    | 25 130             | 31.42                                         | 17.57        | 51.82        |
| P1H | ON (Northern) | 10    | 14 700             | 35.80                                         | 17.14        | 65.85        |
| P2A | ON (Northern) | 10    | 12 270             | 42.89                                         | 20.54        | 78.89        |
| P3B | ON (Northern) | 10    | 15 010             | 35.06                                         | 16.79        | 64.49        |
| P4N | ON (Northern) | 15    | 28 420             | 27.78                                         | 15.54        | 45.82        |
| P5A | ON (Northern) | 10    | 12 130             | 43.39                                         | 20.77        | 79.80        |
| P6A | ON (Northern) | 20    | 35 850             | 29.36                                         | 17.93        | 45.35        |
| P6B | ON (Northern) | 20    | 23 620             | 44.57                                         | 27.21        | 68.83        |
| R2L | MB            | 10    | 14 680             | 35.85                                         | 17.16        | 65.94        |
| R2W | MB            | 20    | 27 960             | 37.65                                         | 22.99        | 58.15        |
| R3J | MB            | 15    | 27 220             | 29.00                                         | 16.22        | 47.84        |
| R7N | MB            | 10    | 10 090             | 52.16                                         | 24.97        | 95.93        |
| S4P | SK            | 10    | 12 480             | 42.17                                         | 20.19        | 77.56        |
| S6H | SK            | 25    | 29 770             | 44.20                                         | 28.59        | 65.25        |
| T1A | AB            | 20    | 26 160             | 40.24                                         | 24.57        | 62.15        |
| T5B | AB            | 10    | 15 890             | 33.12                                         | 15.86        | 60.92        |
| T6A | AB            | 10    | 14 710             | 35.78                                         | 17.13        | 65.80        |
| T6E | AB            | 15    | 21 600             | 36.55                                         | 20.44        | 60.29        |
| V0H | BC            | 25    | 50 980             | 25.81                                         | 16.70        | 38.10        |
| V0R | BC            | 35    | 64 150             | 28.72                                         | 20.00        | 39.94        |
| V0X | BC            | 15    | 19 960             | 39.55                                         | 22.12        | 65.24        |
| V1R | BC            | 10    | 9950               | 52.90                                         | 25.32        | 97.28        |
| V1Y | BC            | 25    | 31 970             | 41.16                                         | 26.63        | 60.76        |
| V2P | BC            | 20    | 33 490             | 31.43                                         | 19.19        | 48.55        |
| V3M | BC            | 20    | 34 410             | 30.59                                         | 18.68        | 47.25        |
| V5C | BC            | 15    | 23 470             | 33.64                                         | 18.81        | 55.48        |
demonstrated high association of these areas with cigarette use, binge alcohol drinking habit, and obesity. This corroborates SEER data which reports that the highest incidence of esophageal AC is found in the Northeast and Midwest of the United States. In addition, although the heritable nature of esophageal cancer is not as strong as in some other cancers, familial clustering in high incidence areas has been observed in both esophageal cancer subtypes in previous studies.

The data in the present study demonstrate high incidence around several coastal cities of the Great Lakes, with the largest cluster surrounding Lake Ontario. The Great Lakes represent 80% of the fresh water supply in North America, providing drinking water for millions of people. A study by the Great Lakes Environmental Assessment and Mapping Project identified environmental stressors impacting this region, which may in part explain these findings. Their investigations revealed that Lakes Ontario, Erie, and Michigan scored highest on the cumulative stress index (CSI), due to being more populated and developed. Most common “stressors” ranged from toxins such as polychlorinated biphenyls and mercury, to pollution related to high shipping activity and charter, to land run-off such as phosphorous and nitrogen. According to the World Wildlife Foundation’s national assessment of Canada’s freshwater, Vancouver Island, and parts of the NS and PEI were also highly affected by increased pollution related to industrial waste, urban runoff, and pipeline incidents. This accentuates the need to consider environmental exposures as an additional cardinal factor in the pathogenesis of this cancer among Canadians in these industrialized coastal regions.

Analysis of esophageal SCC trends, on the other hand, revealed high incidence in BC, rural eastern QC, and in the Maritimes. A recent report on tobacco use in Canada highlighted the overall decrease in smoking prevalence in the country, which may have contributed to the decrease of incidence of esophageal SCC. The authors reported higher rates of cigarette consumption in NB, PEI, BC, AB, QC, and NL; these provinces happened to show higher incidence of esophageal SCC in the present study. Arnold et al identified a disproportionately high rate of esophageal SCC in central and southeast Asia. Similarly, BC has a large Southeast Asian population that may contribute to the higher incidence of esophageal SCC in that province.

The highest incidence FSA corresponded to downtown Vancouver, specifically the DTES, colloquially referred to as Canada’s “poorest postal code.” This low-income area is known for unusually high rates of unemployment, crime, substance abuse, prostitution, and high incidence of infection with HIV/AIDS and hepatitis C virus. Efforts have recently been placed on providing better access to screening for certain cancers to which the DTES residents appear very vulnerable such as oral and cervical cancer.

This study is not without limitations; in large retrospective studies using databases as those presently employed, there exists a risk of data omission or misclassification. While many other worldwide studies have noted the prevalence of esophageal adenocarcinoma to differ by ethnicity, data concerning ethnic background of Canadian patients was not collected by the CCR and LRQC databases and, hence, was not available for analysis.

It is also important to highlight that as Canada’s healthcare system is a single-tier (payer), which is funded and operated by the government, the data are collected with consistency, where each provincial and territorial cancer registry identifies tumors in its population by combining
information from sources such as: cancer clinic files, radiotherapy and hematology reports, records from in-patient hospital stays, out-patient clinics, pathology and other laboratory/autopsy reports, radiology and screening program reports, medical billing and hospital discharge administrative databases. The CCR/LRQC performs multiple rigorous processes to ensure accuracy including an internal record linkage to identify possible duplicate records. These measures allow for high rates of detection and diagnostic accuracy of incidence data recorded by the registries.

Indeed, several studies investigated the detection rates and accuracy of diagnostic data in the largest provincial branch of the Canadian Cancer Registry: the Ontario Cancer Registry (OCR) which collects data from the most populous province. In fact, a case ascertainment of ~99%, a detection rate (detecting and accurately assigning index tumor site) of 81.4%-96%, and a confirmation rate (correctly assigning tumor site) of 90.9% were documented by several studies, which confirms a high quality of data and detection rates in the examined registries.

In conclusion, this epidemiologic study highlights areas of clustering of esophageal AC and SCC throughout Canada and provides an overview of known and potential risk factors to consider. Future analyses may confirm the existence of putative environmental risk factors presented in the present study. This report also provides the basis for locating and studying the areas of Canada that may benefit from more efforts for education and screening, as well as more focused distribution of healthcare resources in order to decrease incidence, morbidity, and mortality relating to esophageal cancer throughout the country.

CONFLICT OF INTEREST

Authors declare they have no conflict of interest regarding the content of this article.

AUTHOR CONTRIBUTIONS

Leila Cattelan collected and analyzed data and wrote the article. Feras M. Ghazawi analyzed data and co-wrote the article. Michelle Le analyzed data. François Lagacé performed statistical analyses. Evgeny Savin performed statistical analyses. Andrei Zubarev performed statistical analyses. Jennifer Gantchev co-wrote the paper. Marcel Tomaszewski co-wrote the paper. Denis Sasseville collected data, designed and supervised the study, and co-wrote the article. Kevin Waschke collected data, designed and supervised the study, and co-wrote the article. Ivan V. Litvinov collected and analyzed the data, designed and supervised the study, and co-wrote the article.

DATA AVAILABILITY STATEMENT

All original data is publicly available through Canadian Cancer Registry, Quebec Cancer Registry and Canadian Vital Statistics databases from Statistics Canada.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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