

Epidemiology of adult and pediatric Burkitt lymphoma in Canada: sequelae of the HIV epidemic

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ABSTRACT

Background Although the pathogenesis and epidemiology of endemic Burkitt lymphoma (BL) have been extensively studied, the epidemiologic landscape of sporadic and immunodeficiency-associated BL in North America remains poorly understood.

Methods We used 3 distinct population-based cancer registries to retrospectively study BL incidence and mortality in Canada. Data for patient sex; age at the time of diagnosis; and reporting province, city, and forward sortation area (FSA, the first three characters of a postal code) were analyzed.

Results During 1992–2010, 1420 patients with BL in Canada were identified (incidence rate: 2.40 cases per million patient–years), of which 71.1% were male patients. Mean age at diagnosis was 55.5 ± 20.8 years. A bimodal incidence by age distribution was seen in both sexes, with pediatric- and adult-onset peaks. An analysis based on FSAs identified select communities with statistically higher rates of adult BL. Several of those FSAs were located within the 3 major metropolitan areas (Montreal, Vancouver, Toronto) and within self-identified LGBTQ communities. The FSAs with a higher socioeconomic status score were associated with lower rates of BL.

Conclusions Current results highlight the geographic and historic pattern of BL in Canada. The human immunodeficiency virus remains an important risk factor for adult BL.

Key Words Burkitt lymphoma, pediatric; Burkitt lymphoma, adult; incidence in Canada; mortality in Canada; epidemiology in Canada; human immunodeficiency virus; HIV

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INTRODUCTION

Three subtypes of Burkitt lymphoma (BL) are known: endemic, sporadic, and immunodeficiency- or AIDS-associated. Although the pathogenesis of endemic BL is likely polymicrobial and subject to the influence of malaria, arboviruses (for example, Chikungunya virus), and other infectious agents, the better-known and better-studied triggering agent for endemic BL is the Epstein–Barr virus (EBV), although its exact pathobiologic role remains poorly understood¹. In almost all cases of BL, a *MYC/IGH* translocation is found¹. That t(8;14) translocation, likely occurring in the germinal centre in BL, leads to an overexpression of the

MYC gene¹. Thus EBV DNA could be detected in more than 95% of endemic BL, and yet it is found in less than 30% of sporadic BL tumours in Europe and the United States¹. Geographic patterns of EBV seroprevalence likely exist and influence BL epidemiology. For instance, lower rates of EBV infection were reported in children living in towns and rural areas in the United Kingdom². Overcrowded housing and poor socioeconomic conditions might lead to earlier acquisition of EBV carrier status, which might be protective for BL, as argued by certain authors¹. The third subtype of BL, immunodeficiency-associated BL, is most

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frequently diagnosed in patients who are HIV-positive; they are 56 times more likely to develop BL³. Paradoxically, the risk for BL is the lowest when CD4 T lymphocyte counts are very low³. Hence, the incidence of BL does not seem to have been affected by the discovery of antiretroviral therapy and maintenance of normal CD4 counts³.

We aimed to better study time- and space-based distribution of adult and pediatric BL cases in Canada from 1990 through 2010 to assess incidence and mortality rates by calendar year, province, city, and forward sortation area (FSA, the first 3 characters of a postal code). We set out to ascertain whether the Canadian HIV epidemic had influenced the epidemiology of BL over those years and to compare BL epidemiology in Canada with that in the United States and Europe.

METHODS

The present study was conducted in accordance with the CISS-RDC-668035 and 13-SSH-MCG-3749 protocols approved by, respectively, the Social Sciences and Humanities Research Council of Canada and the Québec Inter-University Centre for Social Statistics. Further, in accordance with institutional policy, the study received an exemption from review by the McGill University Research Ethics Board.

We examined data concerning BL incidence and mortality for the period 1992–2010 using the *International Classification of Diseases for Oncology* (3rd edition) and the *International Statistical Classification of Diseases and Related Health Problems* (9th and 10th revisions) codes for

BL lymphoma and leukemia in 3 population-based cancer registries—the Canadian Cancer Registry, the Registre québécois du cancer, and Canadian Vital Statistics—in a manner similar to that previously reported^{4–14}. For further details about the methods, see Methods 1 in the supplementary material.

RESULTS

Incidence and Age Distribution of Adult and Pediatric BL in Canada

We found 1420 patients diagnosed with BL in Canada during 1992–2010. A predisposition for the male sex (71.1% of patients) was observed. Mean age at diagnosis was 55.5 ± 20.8 years.

The average incidence rate for adult and pediatric BL in Canada during 1992–2010 was 2.40 cases per million population per year (Figure 1). We further stratified incidence rates by age groups, as shown in supplementary Table 1(A), revealing 2 incidence peaks. The 1st peak occurred at 0–9 years of age, and the 2nd occurred at 70–79 years of age [Figure 1(A)]. Incidence rates slowly increased from age 10 to age 79. Disease bimodality was conserved when cases occurring in male or female patients were separately analyzed [Figure 1(B)]. We also separately analyzed pediatric incidence trends by year and province (supplementary Text 1). Interestingly, although bimodality was observed in both sexes, the male:female ratio declined significantly with advancing age [Figure 1(D), $p = 0.0002$].

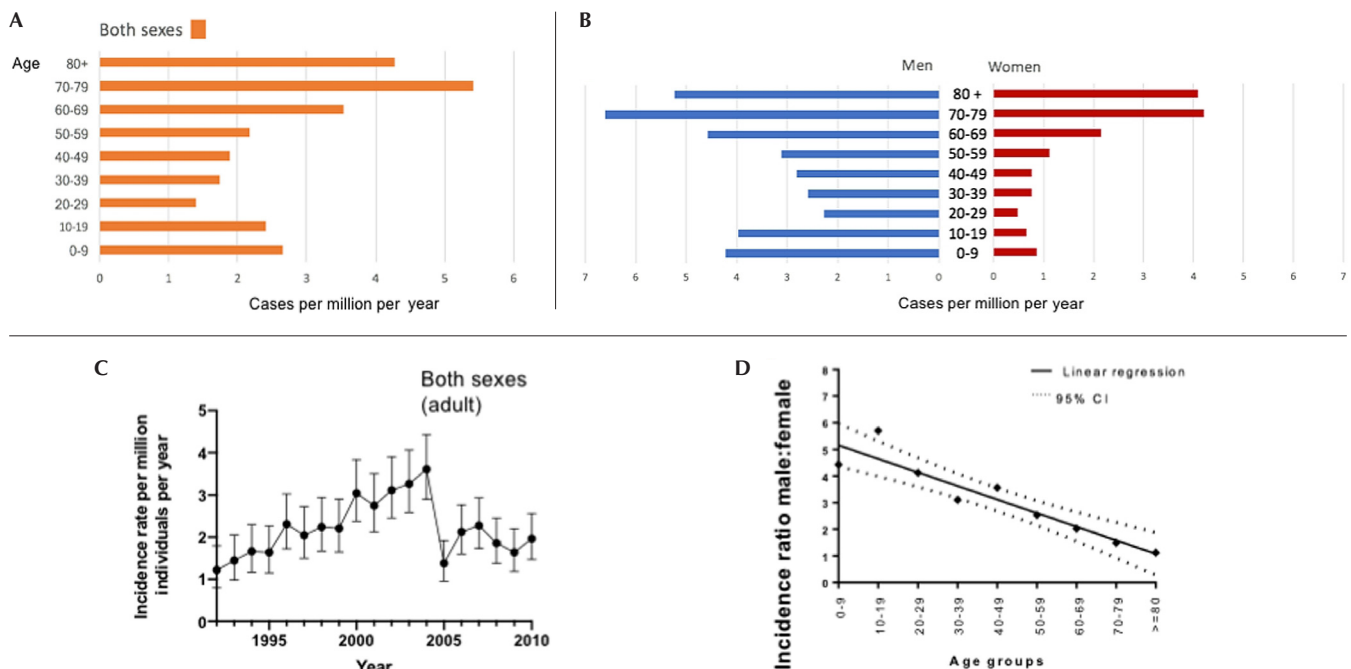


FIGURE 1 (A,B) Incidence rates for Burkitt lymphoma by sex (adult and pediatric), stratified by age group during 1992–2010. (A) Both sexes. (B) Male and female individuals. Bimodality for both sexes is demonstrated, with pediatric and adult incidence peaks. (C) Age-standardized incidence for adult Burkitt lymphoma in both sexes during 1992–2010 (cases per 1 million population per year), with 95% confidence intervals (CIs). (D) Incidence rate ratio (men:women) of Burkitt lymphoma per age group, for all patients diagnosed during 1992–2010, with line of best fit and linear regression analysis of the incidence rate ratio over time [coefficient of determination (R^2) = 0.8811; $p = 0.0002$]. The slope of the line is -0.51 ± 0.07 .

Incidence of Adult BL in Canada

The average age-standardized incidence rate for adult BL in Canada during 1992–2010 was 2.13 cases per million population per year [95% confidence interval (CI): 2.00 cases to 2.27 cases]. Incidence rates for both sexes [Figure 1(C)] increased from 1992 to a peak rate in 2004. From 2004 to 2010 rates stabilized. A similar trend was observed in the rates for male [supplementary Figure 1(B)] and female patients [supplementary Figure 1(C)] when examined separately.

Mortality in Adult BL in Canada During 1992–2010

The average age-standardized mortality rate in adult BL during 1992–2010 was 0.89 deaths per million population per year (95% CI: 0.81 deaths to 0.91 deaths). The mortality rate increased from 1992 to 2003, showing a trend similar to that for the incidence rate [supplementary Figure 2(A)]. The mortality rate for male patients also peaked in 2003 [supplementary Figure 2(B)]. Given that BL predominantly affects male individuals, it was difficult to draw conclusions about the mortality rate for the smaller sample size of female individuals [supplementary Figure 2(C)]. An examination of mortality rates by age group revealed a steady increase from younger to older age, with the peak in disease-specific mortality occurring in the 70–79 age cohort [supplementary Table 1(B)]. Segregating the data by sex revealed similar age-group trends in mortality for male and female patients.

Influence of HIV on Mortality and Provincial Incidence Rates for Adult BL

In contrast to the data for the general population, mortality rates during 2000–2010 for BL in both sexes that is HIV-associated were observed to be decreasing, but did not reach statistical significance [$R^2 = 0.20$, $p = 0.17$, Figure 2(A)]. Data for the HIV-affected population for the years 1992–2000 were not available. When provincial HIV diagnosis rates for the year 2014 (the year for which provincial data from the most provinces were available) were plotted against provincial BL incidence rates, notable trends emerged

[Figure 2(B)]. The Atlantic provinces (Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador) each showed a very low HIV incidence rate and a concurrently low BL rate. Saskatchewan, the province with the highest HIV incidence, also had the highest BL incidence. Those trends were not statistically significant (Spearman correlation $r = 0.48$, $p = 0.17$), but the number of Canadian provinces is small. The observed trends were conserved when HIV prevalence rates for the year 2011 were examined [Figure 2(C), Spearman correlation $r = 0.57$, $p = 0.20$].

Geographic Distribution of Adult BL Cases and Deaths in Canada

The incidence rates for Canadian provinces and cities revealed notable trends [Figure 3, supplementary Table 2(A,B)]. Saskatchewan and Quebec had incidence rates that were significantly higher than the national average [Figure 3(A)]. On the other hand, the Atlantic provinces and Ontario reported lower incidences of BL.

To further corroborate those findings, we analyzed BL-specific mortality. No mortality rate reached statistical significance, and yet the two provinces with the highest incidence rates in the country also had the highest mortality [that is, Saskatchewan and Quebec; Figure 3(B)], and provinces with the lowest incidence rates reported correspondingly lower mortality rates (that is, the Atlantic provinces).

An examination of the incidence of adult BL in Canadian cities showed 12 cities whose incidence rates were statistically significantly lower or higher than the Canadian average [Figure 3(C)]. Of Canada's 3 major metropolitan areas, 2 had a statistically higher incidence of BL—namely, Vancouver and Montreal. Another city, Laval, a large island immediately adjacent to metropolitan Montreal, showed a significantly elevated BL rate. Intriguingly, Toronto and its neighbouring cities in the Greater Toronto Area (Mississauga, Scarborough, Markham, and North York) had lower incidences of BL.

Next, mortality rates at the city level were examined [Figure 3(D)]. A few trends from the city-level incidence

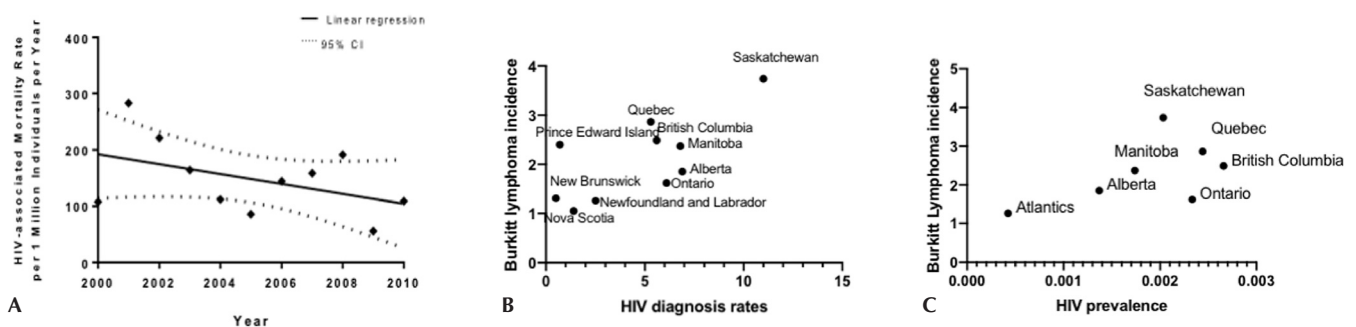


FIGURE 2 (A) The HIV-associated mortality rate for Burkitt lymphoma (BL), both sexes, 2000–2010 (cases per million HIV-positive individuals per year), with line of best fit and linear regression analysis of the mortality rate over time [coefficient of determination (R^2) = 0.20; $p = 0.17$; CI = confidence interval]. The slope of the line is -8.81 ± 5.87 cases per million HIV-positive individuals per year. The average HIV-associated mortality rate for BL in Canada, 2000–2010, in both sexes was 148.33 cases per million HIV-positive individuals per year. (B) Age-adjusted BL incidence rates (adults, cases per million population per year) in both sexes, 1992–2010, by provincial HIV diagnosis rates [per 100,000 population in 2014 (estimates from the Public Health Agency of Canada)]; Spearman correlation coefficient (r) = 0.48, $p = 0.17$. (C) Correlation of BL incidence rates (age-adjusted adult cases per million population per year) with provincial HIV prevalence rates [cases per total population for the year 2011 (estimates from the Public Health Agency of Canada)]; Spearman correlation coefficient (r) = 0.57, $p = 0.20$. “Atlantics” includes Nova Scotia, Newfoundland and Labrador, New Brunswick, and Prince Edward Island.

rates were further supported. Montreal had an elevated mortality rate (2.40; 95% CI: 1.84 to 2.43). The city of Victoria had the highest mortality rate of all jurisdictions analyzed (8.59; 95% CI: 4.28 to 9.18). Vancouver had an elevated mortality rate, correlating with its BL incidence. Ottawa, Edmonton, and London showed elevated mortality, but not incidence, rates.

Incidence Rates for BL by FSA

We used FSAs to examine the BL incidence in Canada by region. The 10 high-incidence FSAs identified are depicted on cartographic maps [Figure 3(E–I)] in various shades of yellow to red, depending on the incidence rate.

Interestingly, 6 of the FSAs (60%) were located within the 3 major metropolitan areas in the country: Montreal⁴, Toronto¹, and Vancouver¹ (Figure 3). Montreal contained the FSA with the highest incidence of BL in Canada [H2L, Figure 3(E)]. Incidentally, H2L is also known as the LGBTQ or gay village of Montreal¹⁵ [Figure 3(E)]. In Toronto, the neighbourhood delimited by Church and Wellesley streets is also a major self-identified LGBTQ village or community in Canada [Figure 3(F)]¹⁶. Its FSA, M4Y, had a high BL incidence. Lastly, the Vancouver metropolitan area showed a high incidence of cases in the downtown core [V6G, Figure 3(I)] immediately adjacent to the short portion of Davie street known as Davie Village, another self-identified LGBTQ community, in the west end of the city¹⁷.

Sociodemographic Characteristics of FSAs with a High Incidence of BL

A significant association between BL incidence rates and socioeconomic status (SES) quintiles was evident. Incidence rates for BL were significantly lower in the highest SES quintile compared with the lowest SES quintile (incidence rate ratio for SES Q5 vs. Q1: 0.16; 95% CI: 0.08 to 0.32).

DISCUSSION

In the present study, we used 3 distinct population-based registries to conduct a detailed analysis of BL incidence and mortality across Canada for the years 1992–2010. The average BL incidence in Canada during 1992–2010 (2.40 cases per million population per year) was slightly higher than the reported BL incidence in Europe (2.2 cases per million population per year)¹⁸. However, when examining only adult BL in Canada and standardizing by age, average rates of BL (2.13 cases per million population per year) were more similar to European trends. The predilection of the disease for male individuals in a 3:1 male:female incidence ratio¹⁸ was seen in the Canadian population. Also, 71.1% of the 1420 identified patients were male. In addition, a study by Mbulaiteye *et al.*¹⁹ of the BL incidence during 1963–2002 on 4 continents, excluding Africa, reported an incidence rate of 1.09 cases per million population per year, with an average age of diagnosis of 33.5 years. For Canada, those authors reported the BL incidence as 1.43 cases per million population per year. However, Mbulaiteye *et al.*¹⁹ studied BL cases for 1963–2002, a vast period that encompasses periods of historically lower BL incidence rates.

An epidemiologic analysis that used the U.S. Surveillance, Epidemiology, and End Results database to examine

population-based BL incidence patterns during 1973–2005 in the United States showed a trimodal (in men) and bimodal (in women) distribution of incidence rates²⁰. By contrast, our study noted two incidence peaks for both sexes, one around 10 years of age, corresponding to pediatric BL, and one around 75 years of age, corresponding to adult-onset BL. Bimodality was observed in both female and male individuals (Figure 1). Indeed, bimodality might indicate a yet-to-be-discovered biologic basis for pediatric BL that is different from that for adult-onset BL²⁰, which is why, in the geographic comparisons, we considered only adult BL so as to not confound risk factors.

Despite advances in BL therapy and excellent 5-year survival for patients less than 20 years of age, the 5-year survival for patients 60 or more years of age was found to be only 33% based in data from the U.S. Surveillance, Epidemiology, and End Results program²¹. However, in our study we observed a trend toward declining mortality for patients with HIV-associated BL between 2000 and 2010, perhaps suggesting prompt access to highly active antiretroviral therapy.

As highlighted throughout this work, HIV is a major risk factor likely to have markedly shaped the geographic landscape of BL in Canada. In Canada, an industrialized country with readily accessible highly active antiretroviral therapy and a universal health care system, variations in HIV prevalence and incidence might have influenced the pattern of BL rates. The higher observed incidence of BL in Saskatchewan, the province with the highest HIV rate in Canada, corresponds with that premise, as do the low BL incidence and mortality rates in the Atlantic provinces, which have notably low HIV incidence rates [Figure 4(B,C)]. Also, the increase in the annual BL incidence and mortality rates from 1992 to 2003 (Figures 2 and 3) mirrors the temporal trends of prevalent and incident HIV infections for the same time period²² (supplementary Figure 3). Indeed, the gradual increase in prevalent HIV infections in Canada since 1981 likely bears witness to the HIV epidemic, with peak incident infections between 1984 and 1990 [supplementary Figure 3(B)]. However, the temporal peak in BL incidence in Canada occurred in about 2003, which might account for a BL latency period in HIV-inoculated individuals from the 1990s, or simply a larger prevalent pool of HIV-affected patients who were BL-susceptible. Finding significantly elevated BL rates in FSAs that map to self-identified LGBTQ communities or gay villages in the cities of Vancouver, Toronto, and Montreal (the 3 largest metropolitan areas of Canada) is also supportive of the influence of HIV on the geographic distribution of BL. Indeed, according to the Public Health Agency of Canada's HIV surveillance update for 1975–2011, it was only in about 1999 that the heterosexual non-endemic and heterosexual endemic exposure categories began to become more represented in the number of incident HIV infections²². Until 1999, most new HIV infections were related to the exposure categories of men who have sex with men or users of intravenous drugs [supplementary Figure 3(C)].

Our study has several limitations. No data in the current Canadian databases reflect race, HIV status, or clinical stage at the time of diagnosis. We also acknowledge that diagnostic criteria for BL have evolved in recent decades and hence misclassification of cases could occur. Because

our incidence and mortality data were consistent with U.S. and European findings, we believe that the risk of misclassification did not affect the validity of our results.

We also acknowledge an inability to analyze additional data because of several federal confidentiality regulations. Finally, corroborating potential individual risk factors for

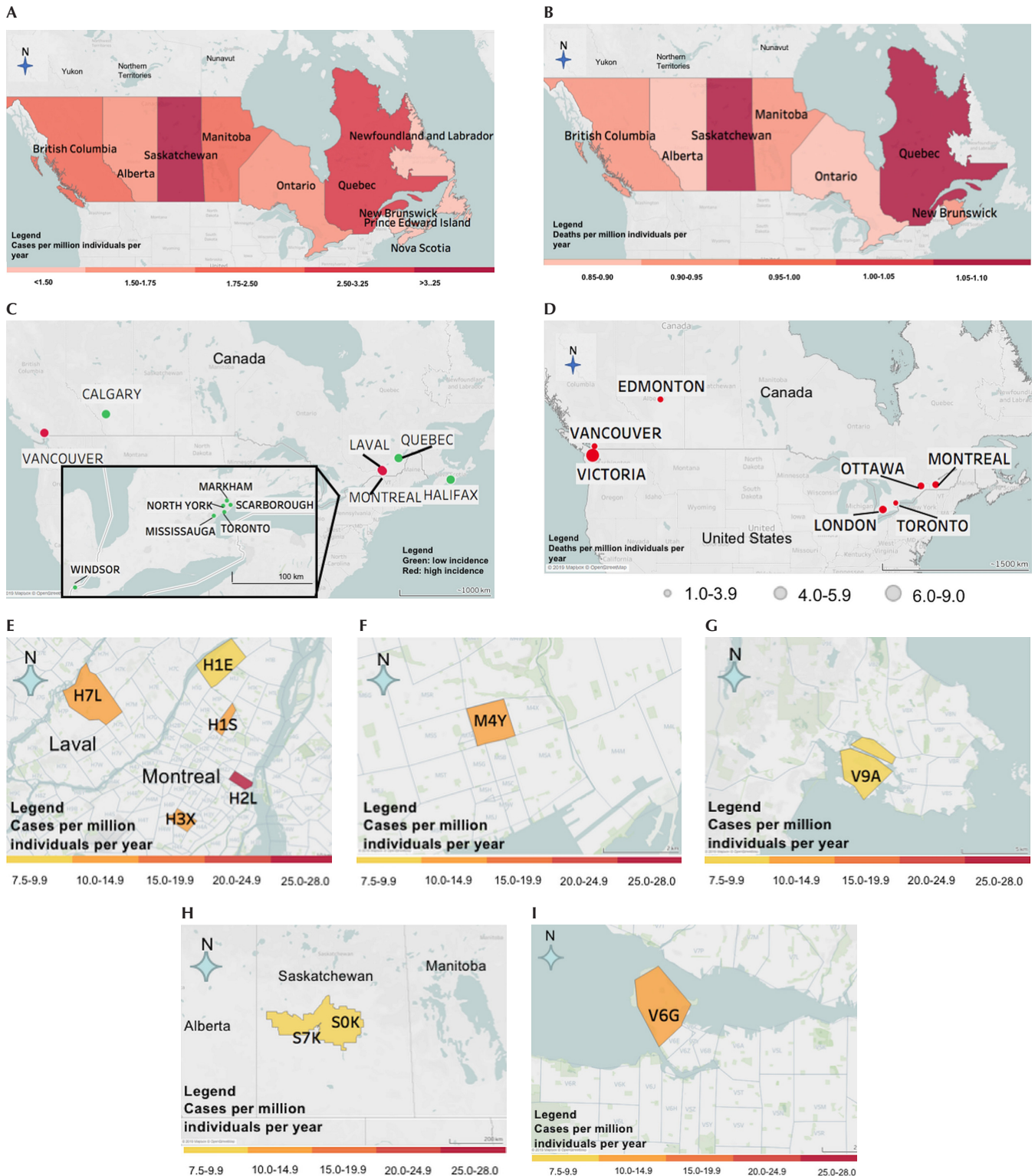


FIGURE 3 Age-adjusted adult Burkitt lymphoma (BL) (A) incidence and (B) mortality trends in Canada. Maps illustrate the distribution of (C) adult BL cases and (D) deaths for Canadian cities with statistically significant high (red) or low (green) incidence rates. (E–I) Forward sortation areas (first three characters of a Canadian postal code) with significantly elevated age-adjusted incidence rates of BL, in various shades of yellow to red.

BL—for example, those proposed by the recent U.K. Clinical Practice Research Datalink case–control study for BL (prior malaria exposure, hepatitis infection, prednisone use, smoking)—was not possible²³.

CONCLUSIONS

We used national cancer registries spanning a period of 19 years to conduct a population-based study that analyzed BL, a rare malignancy, in Canada. That population-based analysis provided the statistical power to calculate incidence and mortality rates at province-wide, city, and FSA scales. We demonstrated bimodality of the disease, peak incidence and mortality rates in the early 2000s, and the HIV geographic and temporal trends that influenced the geographic distribution and yearly epidemiology of BL. Our data are consistent with previously reported Canadian data studying a different time period¹⁹ and with U.S.²⁴ and European trends¹⁸. Understanding the geographic disparity in BL incidence and mortality rates could help to raise disease awareness and lead to timely access to treatment for the populations at risk.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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