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Cancers attributable to infections in Canada

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ABSTRACT

Infections are estimated to cause approximately 15% of the world's cancers with large geographic variations. Yet, Canadian estimates for specific cancer-causing infections are not available. To estimate the number of infection-associated cancers diagnosed among Canadian adults in 2015, we calculated population attributable risks (PARs) and the number of attributable cases for seven carcinogenic infections and their 20 associated cancers. A systematic literature search was performed for each infection to obtain data on infection prevalence in the population and the relative risk or odds ratio associated with the cancer it causes. When mechanistic evidence suggested that detection of a given infection within cancer tissue was sufficient to attribute the cancer to the infection, prevalence among cancer cases was used to approximate the PAR. Data from 61 studies formed the basis of our analyses. The estimated number of infection-attributable cancer cases for 2015 was: 3828 for human papillomavirus (HPV), 2052 for *Helicobacter pylori*, 578 for Epstein-Barr virus, 509 for hepatitis B and C viruses (HBV, HCV), 100 for human herpesvirus type 8, and 30 cases for human T-cell lymphotropic virus type 1. These seven infections were responsible for 3.7% of cancers diagnosed among Canadian adults in 2015; 3.5% among men and 4.0% among women. The infections with the highest number of attributable cases are largely preventable or treatable through vaccination (HBV and HPV), antibiotic therapy (*H. pylori*), or a combination of interventions (HCV), thereby representing an important target for reducing the infection-caused cancer burden among Canadians.

1. Introduction

Numerous infectious viruses and bacteria are established risk factors for certain cancers (International Agency for Research on Cancer, 2012). Many carcinogenic infections are strongly associated with specific cancers (e.g., *Helicobacter pylori* (*H. pylori*) and non-cardia gastric cancer, hepatitis B virus (HBV) and hepatitis C virus (HCV) and hepatocellular carcinoma) (Helicobacter and Cancer Collaborative Group, 2001; Cho et al., 2011), while several others are necessary causes for cancer development (e.g., human papillomavirus (HPV) and cervical cancer, human herpesvirus type 8 (HHV-8) and Kaposi sarcoma) (Franco et al., 1999; Mesri et al., 2010).

Globally, almost one-sixth of cancers were attributable to infections with large geographical variations observed (de Martel et al., 2012; Parkin, 2006; Plummer et al., 2016). The proportion of infection-attributable cancers in 2012 varied from a high 31.3% in Sub-Saharan Africa to a low 4.0% in North America (Plummer et al., 2016). Although the latter constitutes a relatively smaller percentage, there is an

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opportunity to lower the Canadian cancer burden with currently available interventions. Specifically, primary preventive interventions include vaccination against HBV and HPV, along with secondary prevention measures such as direct-acting antivirals for chronic HCV infection and antibiotic therapy to treat *H. pylori* infection (De Flora and Bonanni, 2011; Falade-Nwulia et al., 2017; Kohli et al., 2014). The prolonged latency associated with HCV and *H. pylori* provides an opportunity to treat them prior to cancer development (Lingala and Ghany, 2015).

Although, to date, no study has estimated the impact of the different infections on cancer incidence in Canada, a global study reported that 3.9% of incident cancers in Canada were attributable to infections overall in 2012 (Plummer et al., 2016). The global analysis combined infection prevalence for regions comprising many countries; for example, low, medium and high infection incidence areas. Since infection prevalence varies geographically, region-specific data based on more recent evidence from the scientific literature and population-based studies are necessary to obtain accurate estimates of the impact of infections on cancer incidence. Additionally, estimating individually the proportion of cancers attributable to each infection provides essential assessment of the cancer burden due to infections with modifiable prevalence.

Estimates of the impact of each infection on cancer incidence will contribute to the evidence needed to prioritize strategies aimed at reducing the prevalence of certain carcinogenic infections and initiating treatment for others. We estimated, among individuals 18 years and older, the proportion and number of cancers diagnosed in Canada in 2015 that were attributable to infections, by sex and age whenever possible.

2. Methods

The current analysis is part of the ComPARe (Canadian population attributable risk of cancer) Study, which estimates the current and future burden of cancer due to modifiable risk factors in Canada. Here, we estimated the current burden of cancers caused by infections.

2.1. Infections and cancer sites selection

We considered infections classified by the International Agency for Research on Cancer (IARC) as established, Group 1, carcinogens (Table 1). Infections with extremely low prevalence in Canada (*Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma haematobium*) were excluded. We also did not include human immunodeficiency virus

Table 1
Overview of the carcinogenic infections and associated cancer sites.[a]

Infection	Main transmission route(s)	Main factor(s) for transmission	Carcinogenic mechanism(s)[b] *From Bouvard 2009*	Gold standard for detection	Cancers with *sufficient* evidence[c]	Cancers with *limited* evidence[c]
Hepatitis B virus (HBV), *chronic infection*	Sera and other body fluids	Reusing needles, sexual intercourse	Inflammation Liver cirrhosis Chronic hepatitis	HBsAg	Hepatocellular carcinoma	Cholangiocarcinoma, non-Hodgkin lymphoma
Hepatitis C virus (HCV), *chronic infection*	Sera	Reusing needles	Inflammation Liver cirrhosis Liver fibrosis	HCV RNA	Hepatocellular carcinoma, non-Hodgkin lymphoma	Cholangiocarcinoma
Helicobacter pylori (*H. pylori*)	Oral/fecal	Crowding, contaminated water	Inflammation Oxidative stress Altered cellular turn-over and gene expression Methylation Mutation	Immunoblot	Non-cardia gastric carcinoma, low-grade B-cell MALT gastric lymphoma	None
Epstein-Barr virus[d] (EBV)	Oral/saliva	Pre-chewing food for babies, sharing utensils, kissing	Cell proliferation Inhibition of apoptosis Genomic instability Cell migration	EBER ISH LMP1 IHC for Hodgkin lymphoma (Gulley and Tang, 2008)	Burkitt lymphoma, Hodgkin lymphoma, extranodal natural killer T-cell lymphoma - nasal type, nasopharyngeal carcinoma, immune suppression-related non-Hodgkin lymphoma	Gastric carcinoma, lymphoepithelioma-like carcinoma
Human papillomavirus (HPV), type 16	Skin-to-skin/ mucosal	Sexual contact including oral sex and open mouth kissing	Immortalisation Genomic instability Inhibition of DNA damage response Anti-apoptotic activity	PCR alone or with p16 for anogenital cancers E6 and/or E7 mRNA for head and neck cancers	Cancers of the cervix, anus, penis, vagina, vulva, oropharynx, tonsil, and oral cavity	Laryngeal carcinoma
Human herpesvirus, type 8[e] (HHV-8)	Oral/saliva	Sexual contact including oral sex and open mouth kissing	Cell proliferation Inhibition of apoptosis Genomic instability Cell migration	IFA	Kaposi sarcoma, primary effusion lymphoma	Multicentric Castleman's disease
Human T-cell lymphotropic virus, type 1 (HTLV-1)	Sera and other body fluids, including breast milk	Breast-feeding, sexual intercourse, and reusing needles (Goncalves et al., 2010)	Immortalisation and transformation of T cells	PCR	Adult T-cell leukemia/ lymphoma	None

Abbreviations: HBsAg = Hepatitis B surface antigen, RNA = ribonucleic acid, mRNA = messenger ribonucleic acid, EBER ISH = Epstein-Barr virus encoding region in situ hybridization, LMP1 = latent member protein 1, IHC = immunohistochemistry, PCR = polymerase chain reaction, IFA = immunofluorescent assays, MALT = mucosa-associated lymphoid tissue.

[a] Included infections have been categorized by IARC as Group 1 carcinogens.

[b] Carcinogenic mechanisms were taken from Bouvard 2009 (Bouvard et al., 2009).

[c] Cancer sites were categorized by IARC as having *sufficient* or *limited* evidence.

[d] Epstein-Barr virus is also referred to as human herpesvirus, type 4.

[e] Human herpesvirus, type 8 is also referred to as Kaposi sarcoma virus.

(HIV) because HIV acts indirectly through immunosuppression, thereby amplifying the carcinogenic effects of co-infections such as Epstein-Barr virus (EBV), HCV, and HPV, infections that are already included in our analysis. Table 1 also enumerates the cancers for which there was 'sufficient' evidence for the role of infections in carcinogenesis, as concluded by IARC (International Agency for Research on Cancer, 2012). There was one exception; we estimated the impact of HPV16 on laryngeal cancer incidence because more data have accumulated since the last IARC monograph publication on HPV in support of an etiologic role of HPV in laryngeal cancer (Li et al., 2013; Torrente et al., 2011).

2.2. Population attributable risk calculations

To estimate the proportion of cancer incidence that could have been avoided had the infection been eliminated, we calculated population attributable risks (PARs). The three equations below can estimate PARs for binary exposures (infected or not). The first formula requires the infection prevalence in the general population (Pe) and the relative risk (RR) or odds ratio (OR) associated with the cancer (Levin, 1953). When Pe is not known, the second formula can estimate PARs using prevalence in cases (Pc) in place of Pe (Miettinen, 1974). The third formula is used when the attributable risk in the exposed approaches 1.0 (i.e., RRs are very high), such that the prevalence in cases approximates the PAR.

1. $PAR = \frac{Pe(RR-1)}{1+Pe(RR-1)}$ 2. $PAR = Pc\frac{(RR-1)}{RR}$ 3. $PAR = Pc$

Since we were able to obtain population-based data for HBV, HCV, and *H. pylori* prevalence, the first formula was used for estimating PARs for HBV, HCV, and *H. pylori*. The PARs for the remaining infections, EBV, HPV, HHV-8 and human T-cell lymphotropic virus type 1 (HTLV-1) were estimated with the third formula because they either demonstrate strong relationships with their associated cancers or mechanistic evidence exists for the role of the infection in cancer thus allowing for the PAR to be approximated by the prevalence in cancer cases (International Agency for Research on Cancer, 2012; Plummer et al., 2016; D'Souza et al., 2007).

2.3. Data collection and selection

The data needed to estimate PARs were identified by reviewing IARC monographs (International Agency for Research on Cancer, 2012, 1997, 2007), PAR analyses from other regions (de Martel et al., 2012; Plummer et al., 2016; Antonsson et al., 2015; Parkin, 2011), the Catalan Institute of Oncology HPV Information Centre reports for Canada and the United States (Bruni et al., 2017a; Bruni et al., 2017b), and results of our systematic literature reviews. A systematic literature search was conducted for each infection (details in Supplementary Table 1, S1) to extract data on the infection prevalence and identify meta-analyses on infection-associated cancers. Since the most recent IARC meeting that reviewed each infectious agent considered data published to the end of 2007, we searched for records published in English or French from January 1, 2008 to the search date of June 20, 2017. When data were sparse, we performed more targeted searches in PubMed and contacted experts in their respective fields. Ethics approval was granted for this project by the Health Research Ethics Board of Alberta - Cancer Committee (HREBA.CC-14-0220_REN4), and McGill Univeristy exempted this study from Research Ethics Board review.

Cancers for which the infection is a necessary cause or part of the diagnostic criteria for a given cancer were: cervical cancer, extranodal natural killer T-cell lymphoma - nasal type, Kaposi sarcoma, primary effusion lymphoma, and adult T-cell leukemia/lymphoma, 100% were attributable to their associated infection and therefore inclusion criteria were not required. For all other infections and cancers, the inclusion criteria were: adult population (defined as age 15 and older), North American study population, non-specialized population (e.g. studies performed in exclusively HIV-positive participants were excluded), 10 or more cancer cases, and use of the gold standard method to detect the infection. The inclusion criteria specific to each infection-cancer pair are noted in the tables of included studies (Supplementary Tables 2–13).

When the prevalence in cancer cases approximated the PAR (formula 3), the infection had to be detected in the cancer tumor, such as in a biopsy or surgical specimen. To extrapolate prevalence estimates to recent cancer incidence, rather than incorporating a latency period, the aim was to select studies conducted closer to the timeframe when cancer incidence data were collected. For this reason, studies had to be published in 1995 or later. Specifically, the prevalence of any HPV in the oropharynx has increased over time in the USA; pre-1990 HPV prevalence was 20.9% and from 2000 to 2013 it rose to 65.4% (Stein et al., 2014), further emphasizing the importance of utilizing more recent studies.

The prevalence of HBV and *H. pylori* were derived from North American population-based serosurveys, and HCV prevalence was extracted from a study that modeled chronic HCV prevalence in the Canadian population (Trubnikov et al., 2014). Due to limited data on the measures of association for *H. pylori* associated cancers, a posteriori decision was made to consider studies conducted among European populations and studies that used the detection method that preceded the current gold standard method (we corrected to the new standard).

The chosen detection method for assessing the presence of infection was crucial to the PAR estimation. Selecting studies that utilized the gold standard detection method was prioritized over other factors such as having a Canadian population or sex and age-specific results leading to sparser data.

2.4. Estimating infection prevalence in the Canadian population

Below is a brief description of how we adjusted population-based data to obtain sex- and age-specific estimates of HBV, HCV, and *H. pylori* prevalence for the Canadian population. The prevalence estimates and further details are provided in supplementary Tables S2–S5.

2.5. Hepatitis B virus

The Canadian Health Measures Survey (CHMS) was the first population-based survey to provide estimates of HBV and HCV prevalence for the Canadian population (Rotermann et al., 2013). Data from two cycles of the CHMS (Statistics Canada, n.d.), collected from 2007 to 2009 and 2009 to 2011, were combined for the analysis. The combined participation rate for those providing direct health measures after sample strategy adjustments was 52.8% for the two cycles (Rotermann et al., 2013). Sera from CHMS participants aged 14–79 testing positive for hepatitis B core antigen (anti-HBc) were then tested for hepatitis B surface antigen (HBsAg). Chronic HBV infection is defined as the presence of HBsAg six months after a positive HBV test (National Notifiable Diseases Surveillance System, 2012). Given the cross-sectional design of the CHMS, we assumed that HBsAg positivity at one time point represented chronic HBV infection. Privacy restrictions limited HBsAg results to either sex or broad age groups (14–49 and 50–79), yet sex and age effect HBV prevalence. To obtain Canadian age-specific prevalence estimates, we used the HBsAg 10-year age-group prevalence from two merged cycles of the weighted National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention, 2009, 2011) to partition the CHMS estimates by 10-year age groups. The first two cycles of the CHMS were collected from 2007 to 2011, resulting in a six-year latency. This time period does not correspond to the prolonged latency for hepatocellular carcinoma (El-Serag, 2012), yet it is still plausible as the CHMS measured prevalent not incident HBV infection.

2.6. Hepatitis C virus

The CHMS is a household-based survey of non-institutionalized populations (Statistics Canada, 2010). Thus, groups with higher HCV prevalence, namely intravenous drug users, were underrepresented by excluding those who were homeless or in prison. Moreover, although a diagnosis of either HBV or HCV in Canada are reported to national public health agencies (Public Health Agency of Canada, 2018), many of these infections remain undiagnosed and therefore uncaptured in this data source. We thus obtained the modeled chronic HCV prevalence by birth cohort from Trubnikov, Yan and Archibald who accounted for high-risk groups and undiagnosed infections in their analyses (Trubnikov et al., 2014). To obtain chronic HCV prevalence by sex, we partitioned the estimates using the sex distribution of HCV prevalence from another study that modeled HCV prevalence in Canada in 2007 (Remis, 2010). Since the latency period between initial HCV infection and hepatocellular carcinoma is 25–30 years (Lingala and Ghany, 2015), we used the midpoint of a 15-year latency in our estimates.

We did not estimate a PAR for HBV and HCV coinfection and hepatocellular carcinoma because data on coinfection prevalence were not available. To estimate the combined impact of HBV and HCV on hepatocellular carcinoma, we combined their PARs with the following equation: 1 – (1-HBV PAR) * (1-HCV PAR) (Miettinen, 1974).

2.7. Helicobacter pylori

Few studies have assessed *H. pylori* prevalence in Canadian populations. Although most of these studies were conducted with specialized populations (Cheung et al., 2014; Sethi et al., 2013), one study included 1306 residents aged 50–80 in Canada's most populous province, Ontario (Naja et al., 2007). As population-based data covering a broad age range were required, we opted to utilize other data. *H. pylori* serostatus was assessed in one NHANES cycle collected from 1999 to 2000 (Centers for Disease Control and Prevention, 2001) which resulted in a 15–16 year latency period. The weighted NHANES data were re-weighted by sex, five-year age groups, and race/ethnicity (Black, Latin American, White, and Other) to better reflect the composition of the Canadian population in 2001 (the closest year for which Canadian census ethnicity data were available). Missing *H. pylori* results, accounting for 5.0–6.6% of the reweighted data, were assumed to be missing completely at random and excluded. Additionally, half of the 1–2% 'equivocal' results, which were the results of IgG levels between the cut-offs for positive and negative results, were re-assigned as positive or negative. NHANES used enzyme-linked immunosorbent assay (ELISA) to detect *H. pylori*. ELISA has a sensitivity of 95.6% and specificity of 92.6% (Monteiro et al., 2001). We corrected our reweighted prevalence data according to these reported diagnostic accuracy measures (Franco, 1992).

Since immunoblot is more sensitive than ELISA for the detection of *H. pylori* in gastric cancer cases (Gonzalez et al., 2012; Mitchell et al., 2008), we also corrected the association measures from matched case-control studies that used ELISA by deriving a formula used to adjust the OR, (Franco, 1992) and calculating sensitivity and specificity parameters. The latter were derived by pooling the sensitivity and specificity from three studies (Gonzalez et al., 2012; Mitchell et al., 2008; Peleteiro et al., 2010), that directly compared ELISA and immunoblot in the same patients.

2.8. Estimating infection prevalence in cancer cases

The PARs for EBV- and HPV- associated cancers were approximated by pooling studies that provided data on the prevalence of the infectious agent as detected in cancer tissues. For anogenital cancers, we considered an infection with at least one high-risk type (HPVs 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, and 97) to indicate that the cancer was due to HPV. Head and neck cancers were considered attributable to HPV if genotype 16 was found via the detection of E6 and/or E7 oncoproteins which indicates viral activity and replication.

2.9. Cancer incidence

To determine the number of cases attributable to a given infection, the calculated PAR is multiplied by the number of incident cases. Incident cancer data were obtained from the Canadian Cancer Registry for 2015, which was the most recent year available. When data were requested for rare or subsite cancers, they were aggregated to maintain privacy; for example, cancer incidence counts were combined into two age groups (ages < 50, and ≥ 50), instead of five-year age groups. To preserve the granularity in the incidence data, we estimated the proportion of liver cancer estimated to be hepatocellular carcinoma. A study using SEER (Surveillance, Epidemiology, and End Results) data reported that there were 55,344 primary liver cancers diagnosed from 1978 to 2007, of which 44,080 were hepatocellular carcinoma (Altekruse et al., 2011). We applied the ensuing proportion of 0.797 (44,080/55,344) to liver cancer incidence to get the estimated number of hepatocellular carcinoma cases.

For the province of Quebec, the most recent year for which cancer incidence data were available was 2010. Quebec's 2015 cancer incidence was estimated in one of two ways. For cancers with fewer cases (< 500 in Canada in 2015), the last five years of available incidence data for Quebec, 2006–2010, were averaged and applied to Quebec's 2015 population. For other cancers, Quebec's 2015 incidence was imputed by fitting a Poisson regression on Canada's 2008–2015 incidence.

2.10. Statistical analysis

To obtain the prevalence of a given infection in its associated cancer, individual studies were pooled with a random effects model; a fixed effect model was adopted if the index of consistency (I^2) was $<$ 25% and if the test for heterogeneity was not statistically significant ($p > 0.05$). To pool the proportions and measures of association, we used the commands *metaprop* (Nyaga et al., 2014) and *metan* (Harris et al., 2008), respectively. To calculate 95% confidence intervals (CIs) for the pooled proportions, the exact method was used with the command "cimethod (exact)". When studies were excluded by the software because of inadmissible 95% CIs (e.g. proportions of 1.0 can yield CIs over 1.0), the Freeman-Tukey double arcsine transformation was enabled to calculate admissible 95% CIs bounded by 0.0–1.0 (stata command is: "ftt"). All meta-analyses were conducted in Stata v14 (StataCorp., College Station, TX, USA). R was used to calculate PARs via formula 1 (R Foundation for Statistical Computing [Internet], 2017). For infections where the PAR was approximated by the prevalence of the infection in cancer cases, no additional calculations were necessary after pooling the prevalence. The CIs for PARs calculated via formula 1 were calculated as previously described (Brenner et al., 2018; Brenner et al., 2019).

3. Results

A summary of the overall methods and findings for HBV, HCV, *H. pylori* is presented in Table 2, and for infections where the prevalence in cases approximated the PAR in Table 3. Specific results and tabulations on the characteristics of included studies as well as forest plots, are provided under the respective infection and cancer sites (Supplementary Tables 6–13 and Figs. 1–8).

Table 2 shows that the prevalence of chronic HBV infection in the Canadian population was $< 1.0\%$ across all age and sex groups whereas chronic HCV prevalence ranged from 0.1 to 1.9%. The prevalence of *H. pylori* was notably lower among those younger than 50 years (12.8% for men and 9.8% for women) compared to those aged 50 years and over (27.9% for men and 29.6% for women). Between 1.6 and 15.3% of

Table 2
Infections for which the attributable risk was estimated using the prevalence in the population and measures of association.

Infection cancer (ICD-03 code)	Method of infection measurement	Source of prevalence data	Range of prevalence estimates by sex	Data used to estimate measure of association	Odds ratio (95% CI)
Helicobacter pylori					
Stomach, non-cardia (C16.1–16.9)	Serology with ELISA or immunoblot detection	NHANES (1999–2000) data reweighted by Canada's sex, age, and race/ethnicity distribution.	Men: 12.8% (aged < 50) to 27.9% (aged ≥50)	Pooled unadjusted ORs from matched case-control studies with fixed effects: 3 corrected studies that used ELISA and 3 studies that used immunoblot	9.4 (6.5–13.4)
Stomach, MALT lymphoma (9699)	Serology with ELISA detection	Estimates were corrected for sensitivity and specificity.	Women: 9.8% (aged < 50) to 29.6% (aged ≥50)	One study of 33 cases matched to 134 controls (Parsonnet et al., 1994)	6.3 (2.0–19.9)
Hepatitis B virus					
Hepatocellular carcinoma (C22.0, 817)	Serology with HBsAg detection	CHMS HBsAg data (2007–2011) partitioned with NHANES HBsAg 10-year age group distribution (2007–2010)	Men: 0.1% (aged 70–79) to 0.9% (aged 30–39) Women: 0.1% (aged 70–79) to 0.7% (aged 30–39)	Meta-analysis with pooled estimate from 3 case-control studies conducted in the USA and 1 cohort study from Australia (Cho et al., 2011)	20.3 (11.3–36.5)
Hepatitis C virus					
Hepatocellular carcinoma (C22.0, 817)	Estimates from modeling studies (Trubnikov et al., 2014; Remis, 2010)	Chronic HCV prevalence modeled for the Canadian population by five-year birth cohorts, partitioned with the sex distribution from another modeling study	Men: 0.2% (aged 16–20) to 1.9% (aged 46–50) Women: 0.1% (aged 16–20) to 1.2% (aged 46–50)	Pooled from seven studies from the USA and Australia (Cho et al., 2011)	23.8 (16.9–33.5)
Non-Hodgkin lymphoma (9591)				Adjusted OR calculated from SEER Medicare data with 33,940 cases matched to controls on sex, age, and year of diagnosis (Anderson et al., 2008)	1.35 (1.06–1.73)

Abbreviations: CI = confidence interval, MALT = mucosa-associated lymphoid tissue, NHANES = National Health and Nutrition Examination Survey, CHMS = Canadian Health Measures Survey, HBsAg = Hepatitis B surface antigen, SEER = Surveillance, Epidemiology, and End Results (United States).

Table 3
Methods used for the infections where population attributable risks were estimated using the prevalence of infection in cancer cases.

Infection cancer (ICD-03 code)	Method of infection measurement	Source of prevalence estimates[d]	Cases used to estimate PAR, n	Sex/age group	PAR (prevalence of infection in cancer cases)	
					Estimate (%)	95% CI
Epstein-Barr virus						
Burkitt lymphoma (9687)	EBER ISH	1 study	30	< 50 years old	40.0	22.7–59.4
			21	≥50 years old	28.6	11.3–52.2
ENKTL, nasal type (9719)			–	All	100.0	–
Hodgkin lymphoma (C81)	EBER ISH and/or LMP1 IHC	4 studies	560	Men	43.0	28.4–57.7
			583	Women	26.6	12.1–41.1
Nasopharynx (C11)	EBER ISH	2 studies	172	All	69.4	61.9–76.9
Human papillomavirus, high-risk types,[a] anogenital tract cancers						
Anus (C21)	PCR detection with genotyping of at least HPV 16 and 18	5 studies	154	Men	87.6	76.4–95.8
			250	Women	94.6	89.3–98.3
Cervix (C53)		Necessary cause	–	Women	100.0	–
Penis (C60)		6 studies	311	Men	39.3	21.8–56.9
Vagina (C52)		2 studies	85	Women	72.2	62.7–81.7
Vulva (C51)		2 studies	43	< 50 years old	76.8	64.2–89.4
		3 studies	201	≥50 years old	43.2	13.9–72.5
Human papillomavirus, type 16, head and neck cancers						
Oropharynx[b] (C01.9, C02.8, C02.4, C05.1, C05.2, C14.2, C09, C10)	PCR with E6 and/or E7 for HPV16	16 studies	1396	All	60.2	51.8–68.5
Oral cavity[c] (C00.4–0.5, C00.9, C02.0–C02.9, C03, C04, C05.0, C05.8, C05.9, C06, C14.8)		9 studies	733	All	8.2	3.6–14.2
Larynx (C32)		5 studies	194	All	12.7	3.7–25.4
Human herpesvirus, type 8						
Kaposi sarcoma (9140)	IFA	Necessary cause	–	All	100.0	–
Primary effusion lymphoma (9678)	IFA	Part of diagnostic criteria	–	All	100.0	–
Human T-cell lymphotropic virus, type 1						
Adult T-cell leukemia and lymphoma (9827)	PCR	Necessary cause	–	All	100.0	–

Abbreviations: EBER ISH = EBV-encoded RNA in situ hybridization, PCR = polymerase chain reaction, LMP1 = latent member protein 1, IHC = immunohistochemistry, CI = confidence interval, PAR = population attributable risk, ENKTL = extranodal natural killer T-cell lymphoma, IFA = immunofluorescent assays.

[a] High-risk HPV types include types classified by the International Agency for Research on Cancer as Group 1 (16, 18, 31, 33, 35, 39, 45, 51, 56, 58 and 59), Group 2A (68) and Group 2B (34, 53, 66, 70 and 73) carcinogens. HPV types 52 and 97 were also considered high-risk types.

[b] Oropharynx subsites: base of the tongue (C01.9), overlapping lesion of tongue (C02.8), lingual tonsil (C02.4), soft palate (C05.1), uvula (C05.2), Waldeyer ring (C14.2), tonsil (C09), oropharynx (C10).

[c] Oral cavity subsites: mucosa of lip (C00.4–0.5) and lip NOS (C00.9), other and unspecified parts of tongue (C02.0–C02.9), gum (C03), floor of mouth (C04), palate - hard, overlapping lesion, NOS (C05.0, C05.8, C05.9), other and unspecified parts of mouth (C06) and overlapping lesion of lip, oral cavity and pharynx (C14.8).

[d] Included studies can be found in the supplement under their respective infection and cancers.

hepatocellular carcinomas were attributable to chronic HBV infection (Supplement, Table S2). Chronic HCV had higher attributable percentages than HBV, ranging from 2.5 to 30.0% (Supplement, Table S4). However, the percent of non-Hodgkin lymphoma attributable to HCV was negligible (< 0.7%) for each age and sex group.

As shown in Table 3, the proportion of cancer attributable to high-risk HPV types in anogenital cancers was lowest for penile cancer (39.3%) and highest for cervical cancer (100.0%). The presence of HPV16 in head and neck cancers was 60.2% for the oropharynx, 12.7% for the larynx and 8.2% for the oral cavity.

Table 4 demonstrates that HPV infections were the causative agent for most infection-associated cancers (3828, 95% CI: 3190–4425), followed by *H. pylori* (2052, CI: 1473–2395), and EBV (578, CI: 286–604). More than half (54.0%) of the infection-caused cancers diagnosed in 2015 were related to HPV, then *H. pylori* (28.9%), EBV (8.1%), HBV/HCV (7.2%), HHV-8 (1.4%), and finally HTLV-1 (0.4%) (data not shown). The cancers with the highest number of attributable cases were: non-cardia stomach (n = 1730), cervix (n = 1375), oropharynx (n = 1083), anus (n = 589), and hepatocellular carcinoma (n = 480) (Table 4). A total of 7097 cancers were attributable to infections, representing an estimated 3.7% of the cancers diagnosed among those ≥18 years old in 2015. The proportion of incident cancers attributable to infections was higher among women (4.0%) than men (3.5%).

4. Discussion

The proportion of attributable cancers in Canada in 2015 ranged from a low of 0.4% for HCV in non-Hodgkin lymphoma to a high of 100.0% for HPV in cervical cancer. Cervical cancer was one of five cancers where all cases are attributable to an infection. With few exceptions (HCV in non-Hodgkin lymphoma, and HPV in the oral cavity and larynx), all the calculated PARs exceeded 25.0%, thereby demonstrating the important role that infections play in certain malignancies.

We found that the burden of infection-caused cancers was higher among women (4.0%) than men (3.5%), largely because of HPV's role in cervical and other anogenital cancers. Estimates for the United Kingdom also demonstrated a higher attributable proportion among women than men (3.7% versus 2.5%, respectively) in 2011 (Parkin, 2011) and a similar finding was found in Australia where 2.4% of cancers diagnosed among men in 2010 were attributed to infections and 3.7% among women (Antonsson et al., 2015). In contrast, an analysis for the USA found that 3.3% among both men and women were attributable to infections in 2014 (Islami et al., 2018).

As PAR estimates assume causality between the exposure and outcome, we included only established carcinogens and cancers where the evidence for the role of the infection was deemed 'sufficient' by the IARC (except for HPV16 in laryngeal cancer). Yet, there is increasing

Table 4
Summary of the number of cases and proportion of cancers attributable to infections in Canada in 2015

Infection, cancer(s)	Total			Men			Women		
	Obs cases[a]	AC[b]	% Attributable[c]	Obs cases	AC	% Attributable	Obs cases	AC	% Attributable
Hepatitis B and C virus									
Hepatocellular carcinoma	1750	480	27.4	1345	400	29.7	405	80	19.8
Hepatitis C virus									
Non-Hodgkin lymphoma	8290	29	0.4	4620	19	0.4	3670	10	0.3
Helicobacter pylori									
Stomach, MALT lymphoma	560	322	57.5	265	151	57.0	295	171	58.0
Stomach, non-cardia	2515	1730	68.8	1445	993	68.7	1070	737	68.9
Epstein-Barr virus									
Burkitt lymphoma	85	30	35.3	65	23	35.4	20	7	35.0
ENKTL – nasal type	25	25	100.0	15	15	100.0	10	10	100.0
Hodgkin lymphoma	940	336	35.8	525	226	43.0	415	110	26.6
Nasopharynx	270	187	69.4	195	135	69.4	75	52	69.4
Human papillomavirus, high-risk types									
Anus	640	589	92.0	225	197	87.6	415	392	94.5
Cervix	1375	1375	100.0	…	…	…	1375	1375	100.0
Penis	205	81	39.3	205	81	39.3	…	…	…
Vagina	180	130	72.2	…	…	…	180	130	72.2
Vulva	635	301	47.4	…	…	…	635	301	47.4
Human papillomavirus, type 16									
Oropharynx[h]	1800	1083	60.2	1380	830	60.2	420	253	60.2
Oral cavity	1560	127	8.2	940	77	8.2	620	51	8.2
Larynx	1115	142	12.7	925	118	12.7	190	24	12.7
Human herpesvirus, type 8									
Kaposi sarcoma	90	90	100.0	70	70	100.0	20	20	100.0
Primary effusion lymphoma	10	10	100.0	10	10	100.0	…	…	100.0
Human T-cell lymphotropic virus, type 1									
Adult T-cell leukemia and lymphoma	30	30	100.0	15	15	100.0	15	15	100.0
All associated cancers[d]	22,075	7097	32.2	12,245	3360	27.4	98,30	3738	38.0
All cancers[g]	189,530	7097	3.7	96,070	3360	3.5	93,460	3738	4.0

Abbreviations: Obs = observed, AC = attributable cases, MALT = mucosa-associated lymphoid tissue, ENKTL = extranodal natural killer T-cell lymphoma.

[a] Cancer incidence data for the year 2015 from the Canadian Cancer Registry. Quebec's cancer incidence was estimated. Hepatocellular carcinoma incidence was estimated by applying the proportion 0.797 to liver cancer incidence.

[b] Number of cancer cases at individual cancer sites that can be attributed to infection.

[c] Proportion attributable was calculated by dividing the number of cases attributable to infection by the number of the associated cancer cases. It differs from PAR which for some cancers varied by age and/or sex.

[d] All associated cancers includes all cancers known to be associated with infections listed in the table.

[g] All cancers includes all incident cancer cases in Canada among those 18 and older in 2015.

[h] Includes the base of the tongue and tonsils.

evidence that other infection cancer associations including EBV in gastric carcinoma, HBV in non-Hodgkin lymphoma and HCV in cholangiocarcinoma, among others, may also cause cancer. If these associations were included, the impact of infections on cancer incidence would have been higher than what we reported here.

4.1. Hepatitis B and C viruses, and H. pylori

The combined impact of the hepatitis viruses resulted in 27.4% of hepatocellular carcinoma incidence being attributable to HBV/HCV. Since HBV can be avoided with vaccination that began in Canada in the early 1980s, and because HCV can be prevented through a variety of behavioral interventions and treated with direct-acting antivirals, the future burden of hepatocellular carcinoma has the potential to decrease by reducing the prevalence of these viruses.

Globally, *H. pylori* was responsible for 89% of non-cardia gastric cancers (Plummer et al., 2015). We calculated that 68.8% of incident non-cardia gastric cancers in Canada were due to this infection. We estimated PARs based on elimination of the infection. This information is helpful for understanding the impact of infections on cancer incidence; however, in practice, elimination may not be entirely feasible. For example, *H. pylori* can be treated with quadruple antibiotic therapy, but challenges in the scalability of screening for the infection and concerns over antibiotic resistance limit the prospect of eliminating the infection at the population level (Bourke et al., 2005; Hunt et al., 2004; Fallone et al., 2016).

4.2. EBV, HHV-8 and HTLV-1

Although EBV is the infection with the highest prevalence with > 90% of adults infected (de-The et al., 1975), it was responsible for only 8.1% of the infection-caused cancers in Canada in 2015. In a similar vein, some infections with PARs of 100% were responsible for a small number of cancers (e.g. HHV-8 and HTLV-1) because of the rarity of cancers they cause.

4.3. Human papillomavirus

We found that 54% of the infection-associated cancers were due to HPV. This percentage is higher than the reported 29.5% global contribution of HPV to infection-associated cancers (Plummer et al., 2016). In particular our estimates for HPV16's role in head and neck cancers were higher than global estimates. Meta-analyses have reported higher HPV prevalence in oropharyngeal cancers in North American populations compared to other continents (Ndiaye et al., 2014; Mehanna et al., 2013). Our estimate of 60.2% with E6/E7 detection, albeit numerically similar to that of Ndiaye et al. (60.4%) (Ndiaye et al., 2014), is actually higher than the latter because it represents detection of HPV16, whereas the 60.4% estimate in that study is for all HPV types combined. The oropharynx had the third highest number of attributable cases. Since 1997, oropharyngeal and oral cancer incidence has increased in Canada, especially among men, this is in part due to HPV's role in head and neck cancers (Canadian Cancer Society's Advisory Committee on

Cancer Statistics, 2015). The Canadian Cancer Society estimated that in 2012, cervical and oropharyngeal cancers each accounted for 35% of the HPV-associated cancer burden. We too, found that approximately one-third of the HPV associated cancer burden was due to cervical (35.9%) and oropharyngeal (28.3%) cancers. Since we examined the contribution of HPV16, any of the three available HPV vaccines provide coverage against this HPV type. Although a smaller proportion of oral cavity and laryngeal cancers are attributable to HPV16 (8.2% and 12.7%, respectively), they added 269 cases to the infection-associated cancer burden. School-based HPV immunization programs began in Canada in 2007. More recently, these programs have been extended to boys (Shapiro et al., 2017). We found that one-third (34.0%) of HPV associated cancers were diagnosed among men, which further emphasizes the importance of vaccinating boys.

4.4. Limitations

The main limitation of our study was the lack of Canadian-specific infection data and the subsequent reliance on data collected in the United States and for *H. pylori* data collected from European populations. We have assumed that the exposure prevalence and strength of the relationship between the infection and cancer as observed in American and European populations were comparable to what would have been observed in Canada. For example, we reweighted the age, sex and race/ethnicity distribution from a population-based survey of *H. pylori* prevalence in the United States (NHANES) to match that of the Canadian population in the closest available year. Reweighting assumed that differences in the prevalence of *H. pylori* between the two countries were due to age, sex, and race/ethnicity – but these variables do not likely fully account for the potential differences between Canada and the United States. For some infection cancer site pairs, irrespective of including data collected outside of Canada and performing more targeted literature searches, the data remained sparse. This situation was particularly true for: *H. pylori* and gastric mucosa-associated lymphoid tissue lymphoma, EBV and Burkitt lymphoma, and HPV and vaginal cancer. This result was anticipated since the cancer sites with sparser evidence were also the rarer cancers.

Focusing exclusively on Canada allowed us to obtain much of the rare and subsite cancer incidence data we required for accurate estimates of the number of attributable cases. However, we estimated rather than directly obtained hepatocellular carcinoma and Quebec's cancer incidence. For cancer sites with fewer than 500 cases in Canada in 2015, the five-year incidence rates were averaged but this averaging relies on assumptions that the average of the last five years of available cancer incidence for Quebec (2006–2010) is representative of the 2015 cancer incidence, and that the trend has remained stable.

Since we used existing data, our findings inherited the methodologic flaws of included studies and population-based surveys. This concern was at least partially mitigated by including only those studies that met stringent inclusion criteria aimed at enhancing the validity of our estimates. We attempted to correct for measurement error; however, some error may remain. Additionally, our correction for error in assessing the association between *H. pylori* and non-cardia gastric cancer did not account for confounders. Although the included studies were matched case-control studies, unmatched confounders have not been adjusted for.

By not conducting a separate analysis for HIV, we potentially underestimated the impact of infections on cancer incidence. The proportion of cancer attributable to EBV has the potential to increase since non-Hodgkin lymphomas among HIV positive populations were not included in this analysis.

5. Conclusion

We estimated that 3.7% of cancers diagnosed among Canadians aged 18 and older in 2015 were attributable to seven carcinogenic infections. This percentage translated into 7097 cancers, where ~6400 could potentially be prevented with currently available vaccines or treatments. HPV was responsible for more cancers than other infections, comprising more than half of the infection-associated cancer burden. The presence of three vaccines that confer 95% efficacy against the HPV types responsible for cancer incidence is encouraging (Kash et al., 2015). Although Canada has a lower infection-associated cancer burden relative to many other countries (Plummer et al., 2016), infection-associated cancers continue to impact cancer incidence and increasing vaccine hesitancy has the potential to limit the progress that could be made in reducing the HPV and HBV associated cancer burden.

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Competing interests

None.

Disclosure

E.L.F. has served as occasional consultant to companies involved with HPV diagnostics and vaccination (Merck, GSK, Roche, and BD). His institution has received grants from Merck and Roche to supplement investigator-initiated studies that he leads at McGill University.

E.L.F. is Editor-in-Chief at Preventive Medicine and K.D.V. is an Assistant Editor at Preventive Medicine. The process of soliciting the special issue, sending out manuscripts for review, the peer-review process and editorial decision making was conducted entirely outside of the Preventive Medicine online system (for which E.L.F. and K.D.V. have access to through their regular Preventive Medicine duties).

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Appendix A. Supplementary data

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