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Rare cancers in Canada, 2006–2016: A population-based surveillance report and comparison of different methods for classifying rare cancers

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ABSTRACT

Background: The cumulative burden from rare cancers has not been adequately explored in Canada. This analysis aims to characterize the occurrence of rare cancers among Canadians and estimate the probability of being diagnosed with a rare cancer among cancer patients with different demographic characteristics.

Methods: The Canadian Cancer Registry was used for this analysis. Cancer types were classified in three ways: using the SEER site recode scheme; by histology group; and by site/histology group. The age-standardized incidence rate (ASIR) and 95 % confidence intervals (CI) for each cancer type was estimated for diagnoses from 2006 to 2016. Two ASIR thresholds were used to classify cancers as rare:6/100,000/year and 15/100,000/year. Log-binomial regression was used to estimate the adjusted probability of having a rare cancer among those with cancer by age, sex and geographic region.

Results: Using the 6/100,000/year threshold, the incidence proportion (IP) of rare cancers ranged from 9.7 %(95 %CI:9.6,9.7 %)-17.0 %(95 %CI:16.9,17.0 %), and ranged from 19.2 %(95 %CI:19.1,19.3 %)-52.5 %(95 %CI:52.0,53.0 %) using the < 15/100,000/year threshold. The adjusted probability of being diagnosed with a rare cancer was highest among those aged ≤19 years. There was higher concordance in estimates of the burden of rare cancers across methods to classify cancer types when the lower incidence rate threshold was used to define rare cancers.

Interpretation: This analysis yielded evidence that rare cancers comprise a substantial proportion of annual cancer diagnoses among Canadians. Findings from this analysis point to using a lower incidence rate threshold, to generate estimates of the burden of rare cancers that are robust to different cancer classification schemes.

1. Introduction

There is a paucity of research on rare cancers in Canada. Research and surveillance efforts are largely directed to the most frequently diagnosed cancer types. The magnitude of the cancer burden that is ignored as a result of the tendency to focus on common cancers has not been adequately measured in Canada. Routine Canadian surveillance reports focus on reporting the frequencies of more common cancers individually and group many rare cancers into an “All Other Cancers” category. The use of an “All Other Cancers” category is not conducive to accurate estimation of the burden of rare cancers for two main reasons. First, while this classification can provide some information on the cumulative frequency of cancers that are not among the most commonly diagnosed, as inclusion in this category is not based on a predefined incident rate threshold, there remains uncertainty about whether the cumulative frequency of cancers in this group exclusively represents cancers that are rare [1]. Second, the absence of incident rates for individual rare cancers hinders our ability to estimate the associated burden or plan more efficient research and resource allocation. As a result, patients diagnosed with rare cancers are thought to have fewer treatment options and poor prognoses [2,3].

While there is no internationally agreed upon definition of a rare cancer, there are two currently in use: an incidence rate of < 6 cases/100,000/year as used by the RARECARE group in Europe (EU); and < 15 cases/100,000/year as used by the United States (US) National Cancer Institute (NCI) [4,5]. A definition for use in the Canadian context has not been developed. Additionally, routine surveillance reports in Canada follow the Surveillance Epidemiology and End Results (SEER) Program site recode scheme, which groups ICDO-3 site codes with some histology inclusion/exclusion criteria [6]. Therefore, while this scheme does incorporate some histology components, the classifications are largely based on the anatomical location of the

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tumour. Conversely, the clinical and research communities are moving further away from defining tumours exclusively by their site, with an increasing focus on histological and molecular features [7]. The growing divergence between the two approaches to classifying cancer types may mean that the surveillance data reported becomes less applicable in clinical and research settings and may not adequately support health services planning if health policy makers are making decisions based on disease distributions that do not reflect the disease types being managed by healthcare practitioners. Therefore, some consideration of what incidence thresholds and classification schemes make sense for surveillance and research on rare cancers in Canada and other geographic regions is needed, so that reports are relevant to clinical applications and appropriately reflect variation in frequencies.

The objective of this analysis is to characterize the occurrence of rare cancers in Canada using each of the current definitions, measure variation in estimates across methods of classifying cancer types, and to provide recommendations for which definition is most appropriate in the current Canadian context and going forward as additional changes to cancer classifications arise. Specifically, this analysis aims to:

1 Estimate the distribution of cancer diagnoses among Canadians from 2006 to 2016, using different methods of classifying cancer types;
2 Estimate the incidence proportion of rare cancers using two currently used definitions of rare cancer as a measure of the cumulative burden of rare cancers among Canadians;
3 Measure the level of agreement in labeling cancers as rare or not rare across different cancer classification schemes;
4 Estimate the probability of being diagnosed with a cancer that is rare among Canadian cancer patients with different demographic characteristics.

2. Methods

2.1. Data source

Data from the Canadian Cancer Registry (CCR) was used for this analysis. The CCR is an administrative dataset with data on cancer incidence from all 13 provinces and territories in Canada [8]. Data on the characteristics of the primary tumour diagnosis at the time of diagnosis are included in the CCR. Data submitted to the CCR by provinces is standardized and case ascertainment is considered complete, following legislation that mandates reporting of malignant tumour diagnoses in Canada [8]. Statistics Canada performs validation checks of the data submitted by the provinces/territories to identify errors in coding, including mismatches in tumour sites and histology codes [8]. Primary cancer diagnoses are coded using the ICD-O3 system. Data on relevant molecular markers are incomplete for most cancer types currently. Demographic characteristics of each patient include age at diagnosis, sex, and location of residence at the time of diagnosis. Method of diagnostic confirmation is included as a variable that represents the quality of the data on that diagnosis. The CCR datafile version 2016v1 was used for this analysis. This version is the most recent version available in the Research Data Centres and contains data on diagnoses occurring up to the year 2016 for 9 provinces and 3 territories and diagnoses occurring up to 2010 for Quebec [8].

2.2. Definition of a rare cancer

We labeled cancers as rare using each of the existing definitions (< 6 cases/100,000/year and < 15 cases/100,000/year) [5]. We then used these incidence rate thresholds to generate three categories of rareness: very rare (< 6/100,000/year); rare (≥ 6 & < 15/100,000/year) and not rare (≥ 15/100,000/year). Cancers were classified according to the adjusted incidence rates among the total population, other than for sex-specific sites.

2.3. Classification of cancer types

The ICD-O system developed by WHO/IARC classifies cancers based on site and histology [6]. The U.S Surveillance Epidemiology and End Results (SEER) program reports cancer frequencies based on this system, without aggregating cancer types based on other criteria [5,6]. We used this scheme to classify cancer types in three ways: using site and histology to define cancer groups based on the SEER site recode classification; using broad histology groups; and using a cross-tabulation of histology groups by site group (site/histology). The SEER site recode classification scheme is typically used in Canadian Cancer surveillance reports, although most categories are not reported individually [9]. Recent advances in our understanding of the genetic processes underlying tumorigenesis for different tumour types have highlighted molecular markers that can be used to differentiate between tumours and provide insights into tailored treatment strategies [10–12]. However, data on molecular features are incomplete or missing from the CCR. Therefore, we were unable to incorporate molecular features in our taxonomic classification schemes.

2.4. Statistical analysis

All analyses were conducted using STATA version 15. The incidence rate (IR) and 95 % confidence intervals (CI) for each cancer type was estimated for the period of 2006–2016. Estimates of the population size by year provided by Statistics Canada were used as person-time for all rate calculations [13]. Direct standardization was used to adjust for age and sex, using the 2011 Canadian census population as the standard. All adjusted IRs were rounded to 6 decimal places, and all counts were rounded to the nearest 5 in accordance with Statistics Canada's guidelines for releasing these data [8]. IRs and 95 %CIs are presented per 100,000 person-years and rounded to 2 decimal places. Cancer types were sorted by their annual frequency and stratified by categories of very rare, rare and not rare.

The distribution of cancer frequencies for the entire country was used to classify cancer types as "rare" or "not rare" according to each incidence rate threshold and using each cancer classification scheme. Log-binomial regression was used to estimate adjusted risk ratios (RR) and 95 %CIs as measures of the association between patient characteristics and being diagnosed with a rare cancer, among the Canadian cancer population. Patient characteristics included age, sex and province/territory of residence at the time of diagnosis. Additionally, a variable for whether the diagnosis was confirmed with histopathological examination was added to the model. Reference categories were those with the largest number of cancer patients, for optimal statistical power. Estimates from the regression models were used to generate predicted probabilities of having a rare cancer among those with cancer diagnoses that were confirmed histologically by age, sex and in different geographic regions in Canada. Percent agreement and 95 %CIs were estimated as measures of concordance on the number of cancer diagnoses that could be labeled rare between different cancer classification schemes using each incidence rate threshold.

3. Results

There were 1,703,880 incident primary cancer diagnoses in 12 Canadian provinces/territories from 2006 to 2016 and from Quebec from 2006 to 2010, with an annual average of 178,230. Age-adjusted IRs and 95 %CIs for each cancer type stratified by categories of very rare, rare and not rare are shown in Tables 1–3. Using the EU definition, the proportion of annual cancer diagnoses labeled as rare was: 17.0 % (95 %CI: 16.9 %, 17.0 %) using the SEER site recode scheme; 9.7 % (95 %CI: 9.6, 9.7 %) using histology group; and 16.1 % (95 %CI: 16.0, 16.1 %) using site/histology group. Using the U.S definition, the proportion of annual cases labeled as rare was: 34.4 % (95 %CI: 34.3 %, 34.5 %) using the SEER site recode scheme; 19.2 % (95 %CI: 19.1, 19.3 %) using

Table 1
Age-adjusted incidence rates by sex using SEER site recode classifications and grouped by rarity within site group, 2010-2016.

Site Group	Site	Incidence Rate (95 %CI)			Histologically Confirmed (%)
		Total Population[a]	Males[b]	Females[b]	
Oral Cavity and Pharynx	**Very Rare (< 6/100,000/year)**				
	Other Oral Cavity & Pharynx	0.33 (0.31, 0.34)	0.52 (0.48, 0.56)	0.17 (0.15, 0.19)	77.10
	Oropharynx	0.48 (0.45, 0.5)	0.78 (0.74, 0.83)	0.22 (0.2, 0.24)	81.90
	Hypopharynx	0.66 (0.63, 0.69)	1.2 (1.14, 1.25)	0.23 (0.2, 0.25)	86.64
	Floor of Mouth	0.68 (0.65, 0.7)	0.99 (0.94, 1.04)	0.42 (0.39, 0.45)	96.40
	Nasopharynx	0.76 (0.73, 0.79)	1.11 (1.05, 1.16)	0.46 (0.42, 0.49)	89.56
	Lip	0.99 (0.96, 1.02)	1.69 (1.63, 1.76)	0.47 (0.44, 0.5)	96.31
	Salivary Gland	1.32 (1.28, 1.36)	1.69 (1.62, 1.76)	1.11 (1.06, 1.16)	86.55
	Gum & Other Mouth	1.66 (1.61, 1.7)	2 (1.93, 2.08)	1.41 (1.35, 1.47)	94.95
	Tonsil	1.87 (1.83, 1.92)	3.11 (3.02, 3.2)	0.79 (0.75, 0.83)	92.30
	Tongue	3.28 (3.22, 3.35)	4.91 (4.79, 5.02)	1.92 (1.86, 1.99)	92.36
Digestive System	**Very Rare (< 6/100,000/year)**				
	Retroperitoneum	0.41 (0.39, 0.43)	0.46 (0.43, 0.49)	0.39 (0.36, 0.42)	88.56
	Peritoneum, Omentum & Mesentery	0.51 (0.48, 0.53)	0.22 (0.19, 0.24)	0.78 (0.74, 0.82)	69.37
	Other Digestive Organs	1.09 (1.06, 1.13)	1.21 (1.15, 1.27)	1.04 (0.99, 1.09)	60.86
	Appendix	1.13 (1.09, 1.17)	1.03 (0.98, 1.08)	1.26 (1.2, 1.31)	97.04
	Splenic Flexure	1.31 (1.27, 1.35)	1.64 (1.57, 1.7)	1.1 (1.05, 1.15)	94.77
	Gallbladder	1.36 (1.32, 1.4)	1.07 (1.02, 1.12)	1.68 (1.62, 1.74)	71.46
	Intrahepatatic Bile Duct	1.59 (1.54, 1.63)	1.78 (1.71, 1.85)	1.51 (1.45, 1.56)	53.64
	Anus, Anal Canal, & Anorectum	1.78 (1.74, 1.83)	1.47 (1.41, 1.54)	2.17 (2.1, 2.24)	95.57
	Heptatic Flexure	1.97 (1.92, 2.02)	2.36 (2.28, 2.44)	1.75 (1.69, 1.81)	94.68
	Descending Colon	2.21 (2.16, 2.26)	2.83 (2.74, 2.92)	1.81 (1.74, 1.87)	96.21
	Other Biliary	2.41 (2.35, 2.46)	3.06 (2.96, 3.15)	2.01 (1.95, 2.08)	63.57
	Small Intestine	2.47 (2.42, 2.53)	2.97 (2.88, 3.06)	2.18 (2.11, 2.25)	92.26
	Transverse Colon	3.37 (3.31, 3.43)	3.84 (3.74, 3.94)	3.13 (3.05, 3.21)	94.68
	Large Intestine, NOS[c]	3.4 (3.34, 3.46)	3.86 (3.76, 3.97)	3.16 (3.08, 3.24)	54.67
	Esophagus	5.36 (5.28, 5.44)	9.1 (8.95, 9.26)	2.43 (2.36, 2.51)	91.75
	Rectosigmoid Junction	5.53 (5.45, 5.61)	7.33 (7.19, 7.46)	4.26 (4.17, 4.36)	93.71
	Liver	5.62 (5.54, 5.7)	9.31 (9.16, 9.47)	2.63 (2.56, 2.71)	50.18
Digestive System Continued	**Rare (≥6/100,000/year & < 15/100,000/year)**				
	Ascending Colon	7.3 (7.2, 7.39)	7.94 (7.79, 8.08)	7.12 (7, 7.24)	96.04
	Stomach	9.41 (9.31, 9.52)	13.79 (13.6, 13.99)	6.27 (6.16, 6.39)	92.04
	Cecum	9.44 (9.34, 9.55)	10.16 (9.99, 10.33)	9.32 (9.18, 9.46)	95.03
	Sigmoid Colon	11.86 (11.75, 11.98)	15.67 (15.46, 15.87)	9.29 (9.15, 9.43)	95.77
	Pancreas	12.65 (12.53, 12.77)	14.62 (14.42, 14.82)	11.55 (11.39, 11.71)	49.55
	Not Rare (≥15/100,000/year)				
	Rectum	15.37 (15.24, 15.5)	21.45 (21.21, 21.69)	10.86 (10.71, 11.02)	96.05
Respiratory System	**Very Rare (< 6/100,000/year)**				
	Pleura	0.06 (0.06, 0.07)	0.1 (0.08, 0.11)	0.04 (0.03, 0.05)	61.90
	Trachea, Mediastinum & Other	0.23 (0.22, 0.25)	0.32 (0.29, 0.35)	0.16 (0.14, 0.18)	77.27
	Nose, Nasal Cavity & Middle Ear	0.74 (0.71, 0.77)	0.97 (0.92, 1.02)	0.58 (0.54, 0.61)	93.05
	Larynx	3.06 (3, 3.12)	5.68 (5.56, 5.8)	0.96 (0.92, 1.01)	93.05
	Not Rare (≥15/100,000/year)				
	Lung and Bronchus	69.29 (69.01, 69.58)	82.81 (82.34, 83.28)	62.71 (62.34, 63.08)	63.61
Bones and Joints	**Very Rare (< 6/100,000/year)**				
	Bones & Joints	1.02 (0.98, 1.05)	1.19 (1.13, 1.24)	0.89 (0.84, 0.93)	86.27
Soft Tissue including Heart	**Very Rare (< 6/100,000/year)**				
	Soft Tissue including Heart	3.46 (3.4, 3.53)	4.3 (4.2, 4.41)	2.9 (2.82, 2.98)	89.46
Skin Excluding Basal and Squamous Cell	**Very Rare (< 6/100,000/year)**				
	Other Non-Epithelial Skin	1.75 (1.7, 1.79)	2.29 (2.21, 2.37)	1.44 (1.38, 1.49)	97.74
	Not Rare (≥15/100,000/year)				
	Melanoma of the Skin	18.09 (17.94, 18.23)	21.64 (21.4, 21.88)	16.12 (15.93, 16.31)	97.87
Breast	**Not Rare (≥15/100,000/year)**				
	Breast	66.77 (66.49, 67.05)	1.25 (1.19, 1.3)	129.09 (128.54, 129.63)	97.10
Female Genital System	**Very Rare (< 6/100,000/year)**				
	Uterus, NOS[c]		–	0.75 (0.71, 0.79)	60.31
	Vagina		–	0.95 (0.9, 0.99)	91.74
	Other Female Genital Organs		–	1.4 (1.35, 1.46)	79.08
	Vulva		–	3.04 (2.96, 3.12)	96.52

(*continued on next page*)

Table 1 (*continued*)

Site Group	Site	Incidence Rate (95 %CI)			Histologically Confirmed (%)
		Total Population[a]	Males[b]	Females[b]	
Female Genital System Continued	**Rare (≥6/100,000/year & < 15/100,000/year)**				
	Cervix Uteri		–	8.1 (7.97, 8.24)	95.30
	Ovary		–	14.59 (14.41, 14.77)	79.39
	Not Rare (≥15/100,000/year)				
	Corpus Uteri		–	30.26 (30, 30.52)	98.21
Male Genital System	**Very Rare (< 6/100,000/year)**				
	Other Male Genital Organs		0.36 (0.33, 0.39)	–	95.24
	Penis		1.22 (1.16, 1.28)	–	96.87
	Testis		5.51 (5.4, 5.62)	–	97.96
	Not Rare (≥15/100,000/year)				
	Prostate		144.39 (143.77, 145)	–	93.74
Urinary System	**Very Rare (< 6/100,000/year)**				
	Ureter	0.53 (0.5, 0.55)	0.72 (0.67, 0.76)	0.4 (0.37, 0.43)	80.06
	Other Urinary Organs	1.06 (1.02, 1.1)	1.71 (1.64, 1.78)	0.61 (0.57, 0.64)	71.31
	Not Rare (≥15/100,000/year)				
	Kidney & Renal Pelvis	15.42 (15.28, 15.55)	21.22 (20.98, 21.45)	11.02 (10.86, 11.18)	84.95
	Urinary Bladder	23.8 (23.64, 23.97)	41.63 (41.29, 41.97)	10.95 (10.8, 11.11)	94.36
Eye & Orbit	**Very Rare (< 6/100,000/year)**				
	Eye & Orbit	0.98 (0.95, 1.01)	1.14 (1.09, 1.2)	0.89 (0.84, 0.93)	54.04
Brain and Other Central Nervous System	**Very Rare (< 6/100,000/year)**				
	Cranial Nerves, Other nervous System	0.43 (0.41, 0.45)	0.45 (0.41, 0.48)	0.42 (0.39, 0.45)	69.04
	Rare (≥6/100,000/year & < 15/100,000/year)				
	Brain	7.14 (7.05, 7.23)	8.7 (8.56, 8.85)	5.94 (5.83, 6.06)	82.05
Endocrine System	**Very Rare (< 6/100,000/year)**				
	Other Endocrine incl. Thymus	0.92 (0.89, 0.95)	1.02 (0.97, 1.07)	0.86 (0.81, 0.9)	81.52
	Not Rare (≥15/100,000/year)				
	Thyroid	15.44 (15.31, 15.58)	7.7 (7.56, 7.84)	23.21 (22.98, 23.44)	95.93
Lymphoma	**Very Rare (< 6/100,000/year)**				
	Hodgkin Lymphoma-Extranodal	0.04 (0.04, 0.05)	0.05 (0.04, 0.06)	0.04 (0.03, 0.05)	92.86
	Hodgkin Lymphoma-Nodal	2.67 (2.62, 2.73)	2.98 (2.9, 3.07)	2.34 (2.26, 2.41)	95.57
Lymphoma Continued	**Rare (≥6/100,000/year & < 15/100,000/year)**				
	Non-Hodgkin Lymphoma-Extranodal	7.03 (6.94, 7.12)	8.73 (8.57, 8.88)	5.96 (5.84, 6.07)	87.09
	Not Rare (≥15/100,000/year)				
	Non-Hodgkin Lymphoma-Nodal	15.27 (15.13, 15.4)	18.54 (18.32, 18.76)	13.13 (12.95, 13.3)	89.90
Myeloma	**Rare (≥6/100,000/year & < 15/100,000/year)**				
	Myeloma	7.12 (7.02, 7.21)	9.15 (9, 9.31)	5.84 (5.72, 5.95)	77.38
Leukemia	**Very Rare (< 6/100,000/year)**				
	Other Myeloid/Monocytic Leukemia	0.14 (0.13, 0.15)	0.18 (0.16, 0.2)	0.12 (0.1, 0.14)	64.13
	Acute Monocytic Leukemia	0.26 (0.24, 0.27)	0.32 (0.29, 0.35)	0.22 (0.19, 0.24)	94.08
	Other Acute Leukemia	0.36 (0.34, 0.38)	0.42 (0.39, 0.46)	0.33 (0.31, 0.36)	54.81
	Other Lymphocytic Leukemia	0.54 (0.51, 0.56)	0.87 (0.82, 0.91)	0.28 (0.25, 0.3)	77.40
	Aleukemic, subleukemic, NOS[c]	0.72 (0.69, 0.75)	0.86 (0.81, 0.91)	0.64 (0.6, 0.68)	51.69
	Acute Lymphocytic Leukemia	1.28 (1.24, 1.32)	1.44 (1.39, 1.5)	1.14 (1.09, 1.19)	88.33
	Chronic Myeloid Leukemia	1.82 (1.77, 1.86)	2.39 (2.31, 2.47)	1.43 (1.38, 1.49)	82.85
	Acute Myeloid Leukemia	3.65 (3.58, 3.71)	4.5 (4.39, 4.61)	3.13 (3.04, 3.21)	88.29
	Rare (≥6/100,000/year & < 15/100,000/year)				
	Chronic Lymphocytic Leukemia	6.65 (6.57, 6.74)	9.32 (9.16, 9.48)	4.8 (4.7, 4.91)	75.70
Mesothelioma	**Very Rare (< 6/100,000/year)**				
	Mesothelioma	1.58 (1.54, 1.62)	3 (2.9, 3.09)	0.56 (0.53, 0.6)	80.48
Kaposi Sarcoma	**Very Rare (< 6/100,000/year)**				
	Kaposi Sarcoma	0.22 (0.21, 0.24)	0.4 (0.37, 0.44)	0.07 (0.06, 0.08)	89.12
Miscellaneous	**Not Rare (≥15/100,000/year)**				
	Miscellaneous	19.93 (19.78, 20.08)	24.45 (24.19, 24.71)	17.51 (17.32, 17.71)	49.35

[a] Adjusted for age and sex.
[b] Adjusted for age.
[c] NOS = Not Otherwise Specified.

histology group; and 52.5 % (95 %CI: 52.0, 53 %) using site/histology group.

3.1. Agreement across cancer classification schemes

The concordance between cancer classification schemes in labeling a cancer case as rare or not rare is shown in Table 4. The level of agreement between cancer classification schemes depended on the incidence rate threshold used to label cancers as rare or not rare, with higher agreement using the EU definition. The average percent agreement between classification schemes using the EU and US definitions of rare were 84.8 % (95 %CI: 84.7, 84.8 %) and 71.2 % (95 %CI: 71.1, 71.3 %), respectively. The average difference in the estimated proportion of cancers that are rare across cancer classification schemes was 4.9 percentage-points using the EU definition and was 22.2 percentage-points using the US definition.

3.2. Age and sex

Age 60–69 years was used as the reference category in all regression models because the highest number of annual cancer diagnoses occurred among those in this age group. Using all cancer classification schemes and incidence rate thresholds, the risk of being diagnosed with a cancer that is rare was higher among all other age groups than among those aged 60–69 years (Supplementary tables 1–3). Pediatric/adolescent cancer patients were most likely to be diagnosed with a cancer that is rare (Fig. 1; Supplementary tables 1–3). Adjusted RRs comparing cancer patients 0–19 years to those aged 60–69 years ranged from 8.71 (95 %CI: 8.29, 9.15) to 54.87 (95 %CI: 51.03, 58.99) (Supplementary tables 1–3). The probability of being diagnosed with a cancer that is rare by age and sex using each cancer classification method and incidence rate threshold is shown in Fig. 1. This analysis yielded evidence of variation in the direction and magnitude of the effect of sex on risk of having a cancer that is rare across categories of age (Fig. 1; Supplementary tables 1–3). Males had a consistently higher probability of being diagnosed with a cancer that is rare until age 40–49 years using all cancer classification methods and definitions of rare (Fig. 1). The probability of being diagnosed with a cancer that is rare was higher among females relative to males after age 50–59 years using most classification methods and definitions of rare (Fig. 1).

3.3. Geographic region

The adjusted probabilities of being diagnosed with a rare cancer among those with a histologically confirmed cancer diagnosis from 2006 to 2016 across provinces/territories are shown in Fig. 2. The probability of having a cancer that is rare was highest among cancer patients residing in Nunavut followed by the other territories when the U.S definition of rare was used and cancers were classified using the SEER site recode scheme or by site/histology group (Fig. 2). However, the CIs around these estimates leave uncertainty about the magnitude of these effects. Conversely, when cancers were classified by histology group, the probability of being diagnosed with a cancer that is rare was lowest among residents of Nunavut (Fig. 2).

4. Discussion

Despite growing awareness of a gap in research and evidence for rare cancers, there have been limited advances in the Canadian context [2–5,14,15]. To our knowledge, this is the first comprehensive cancer surveillance report presenting the frequencies of all individual cancer types among Canadians. Additionally, to our knowledge, this is the first application of rare cancer definitions to Canadian cancer data, responding to the call by leading researchers in the field to address issues around classifying rare cancers for surveillance and research purposes [2,3,15]. This analysis highlights that rare cancers comprise a large proportion of the cancer burden in Canada, with up to 52.5 % (95 %CI: 52.0, 53 %) of annual cancer diagnoses being labeled as rare, depending on the incidence rate threshold and cancer classification method used. Therefore, continued focus on common cancers for surveillance and research purposes may neglect a substantial proportion of annual cancer diagnoses and exacerbate the public health burden of understudied cancers with relatively poor prognoses [2,3].

This analysis generated evidence that the probability of having a cancer that is rare is lower when cancers are defined by histology group relative to classification methods that incorporated site. These findings indicate that cancers are rare because of their anatomical location more often than because of their histology. However, tumours grouped this way are still at a higher level of aggregation than may be used in clinical or research settings. Of note, 2/7 common histology groups were epithelial tumours, not otherwise specified (NOS) and neoplasms NOS. These categories may be comprised of a heterogeneous group of tumours, potentially skewing the proportion of cancers labeled rare using histology to classify cancer types. However, the probability estimates were generated among those with histologically confirmed diagnoses, which largely excluded those with NOS diagnoses, as these groups had lower frequencies of histological confirmation (Table 2).

The variation in the probability of being diagnosed with a cancer that is rare across ages, sexes and geographic regions show subsets of the population that are most likely affected by the imbalance of research and surveillance efforts. Specifically, cancer patients of either sex aged 0–19 years were more likely to be diagnosed with a rare cancer than a common cancer. Similarly, males under the age of 40 years were more likely to be diagnosed with a rare versus common cancer (Fig. 1). There wasn't much variation in probability of being diagnosed with a cancer that is rare across geographic regions in Canada. However, this evidence suggested a higher probability among residents of Nunavut relative to other provinces/territories, when cancers were defined by SEER site recode and site group and histology group. Conversely, Nunavut residents had the lowest probability of being diagnosed with a rare histology. These findings highlight the need to better understand the risk of rare and understudied cancers among residents of remote regions where the logistical constraints around diagnosing and treating these cancers are magnified.

In addition to characterizing the frequency and distribution of rare cancers in Canada over a decade, this analysis has generated evidence that contributes to a broader understanding of the implications of different definitions of cancer types and thresholds for rare cancers. As taxonomic classifications of cancer change to incorporate molecular features, we may expect smaller disease categories. We were unable to assess the influence of molecular markers on the estimated burden of rare cancers in Canada for this analysis. However, we used a cross-tabulation of site and histology group to measure the impact of different definitions of rare on smaller disease categories, relative to classifications based on site or histology alone. This evidence suggests that using a lower incidence rate threshold to define rare cancers results in estimates of the burden of rare cancer that are less sensitive to the cancer classification methods chosen. This points to adopting a lower incidence threshold to allow more flexibility to use cancer classification methods that are most appropriate for different applications, while maintaining consistency in labelling cancers as rare or not. The degree to which the threshold of < 6 cases/100,000/year remains robust to classifying cancers using molecular markers will depend on the distribution of tumours with different molecular features in Canada. A lower threshold may need to be explored in the future as we learn more about important differences between tumours with different molecular characteristics.

Several groups worldwide have estimated that 1 in 4 individuals diagnosed with cancer will have a rare cancer in their respective geographic regions [4,5,14]. In a report by the RARECARE group in EU, the proportion of annual cancer diagnoses that are rare was 22 % [4]. Tamaki et al. (2014) applied the EU definition of a rare cancer to

Table 2
Age-adjusted incidence rates by sex using histology classification and grouped by rarity within histology group, 2006-2016.

Histology Groups	Incidence Rate (95 %CI)			Histologically Confirmed (%)
	Total Population[a]	Males[b]	Females[b]	
Very Rare (< 6 /100,000/year)				
Giant cell tumors	< 0.1	< 0.1	< 0.1	91.67
Myxomatous neoplasms	< 0.1	< 0.1	< 0.1	[c]
Mesonephromas	< 0.1	< 0.1	< 0.1	[c]
Lymphatic vessel tumors	< 0.1	< 0.1	< 0.1	[c]
Dontogenic tumors	< 0.1	< 0.1	< 0.1	90.00
Granular cell tumors/alveolar soft part	< 0.1	< 0.1	< 0.1	93.33
Special gonadal neoplasms	0.1 (0.1, 0.1)	< 0.1	0.2 (0.1, 0.2)	91.53
Paragangliomas and glomus tumors	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	84.44
Trophoblastic neoplasms	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	87.32
Meningiomas	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	73.75
Precursor cell lymphoblastic lymphoma	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0 (0, 0.1)	91.49
Basal cell neoplasms (other than skin)	0.2 (0.2, 0.2)	0.1 (0.1, 0.1)	0.3 (0.3, 0.4)	96.62
Fibroepithelial neoplasms	0.2 (0.2, 0.2)	< 0.1	0.5 (0.4, 0.5)	98.67
Synovial-like neoplasms	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	96.61
Miscellaneous bone tumors	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.2 (0.1, 0.2)	93.33
Miscellaneous tumors	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.1 (0.1, 0.2)	92.79
Nerve sheath tumors	0.2 (0.1, 0.2)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	93.27
Neoplasms of histiocytes/accessory lymphoid cells	0.2 (0.2, 0.2)	0.2 (0.2, 0.3)	0.2 (0.2, 0.2)	81.75
Thymic epithelial neoplasms	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	94.21
Mucoepidermoid neoplasms	0.4 (0.3, 0.4)	0.3 (0.3, 0.4)	0.4 (0.4, 0.4)	96.64
Neuroepithelialomatous neoplasms	0.4 (0.3, 0.4)	0.4 (0.3, 0.4)	0.3 (0.3, 0.4)	89.03
Immunoproliferative diseases	0.5 (0.4, 0.5)	0.6 (0.5, 0.6)	0.3 (0.3, 0.4)	72.33
Blood vessel tumors	0.6 (0.5, 0.6)	0.7 (0.7, 0.7)	0.4 (0.4, 0.5)	91.25
Adnexal and skin appendage neoplasms	0.7 (0.7, 0.8)	0.5 (0.5, 0.6)	0.9 (0.9, 1)	98.96
Osseous and chondromatous neoplasms	0.7 (0.6, 0.7)	0.7 (0.7, 0.8)	0.6 (0.5, 0.6)	94.91
Leukemia, NOS [d]	0.7 (0.7, 0.8)	0.7 (0.7, 0.7)	0.8 (0.7, 0.8)	40.50
Lipomatous neoplasms	0.9 (0.9, 1)	1.2 (1.1, 1.2)	0.7 (0.7, 0.7)	94.44
Other leukemia	0.9 (0.9, 1)	1.3 (1.2, 1.4)	0.6 (0.5, 0.6)	87.44
Soft tissue tumors and glomus sarcomas	1.1 (1.1, 1.1)	1.2 (1.1, 1.2)	1 (0.9, 1)	91.50
Fibromatous neoplasms	1.1 (1, 1.1)	1.2 (1.1, 1.2)	1 (0.9, 1)	98.13
Other hematologic disorders	1.1 (1.1, 1.1)	1.1 (1.1, 1.2)	1.1 (1, 1.1)	59.72
Myomatous neoplasms	1.2 (1.1, 1.2)	0.9 (0.9, 1)	1.4 (1.4, 1.5)	96.78
Mesothelial neoplasms	1.6 (1.5, 1.6)	2.6 (2.5, 2.7)	0.6 (0.6, 0.6)	80.48
Mature t- and nk-cell lymphoma	1.6 (1.6, 1.6)	1.9 (1.9, 2)	1.3 (1.2, 1.3)	94.20
Acinar cell neoplasms	1.7 (1.7, 1.8)	2.1 (2, 2.1)	1.4 (1.4, 1.5)	98.42
Complex epithelial neoplasms	1.8 (1.7, 1.8)	1.1 (1, 1.1)	2.5 (2.4, 2.5)	96.75
Complex mixed and stromal neoplasms	2.3 (2.3, 2.4)	1.3 (1.2, 1.3)	3.4 (3.3, 3.5)	95.70
Hodgkin lymphoma	2.7 (2.7, 2.8)	3 (2.9, 3.1)	2.4 (2.3, 2.5)	95.58
Germ cell neoplasms	3 (3, 3.1)	5.7 (5.6, 5.8)	0.4 (0.4, 0.4)	98.39
Chronic myeloproliferative disorders	4.1 (4, 4.1)	3.9 (3.8, 4)	4.2 (4.1, 4.3)	41.77
Malignant lymphomas, NOS[d] or diffuse	4.6 (4.6, 4.7)	5 (4.9, 5.1)	4.3 (4.2, 4.4)	67.90
Myelodysplastic syndrome	4.7 (4.6, 4.8)	5.5 (5.4, 5.7)	3.8 (3.8, 3.9)	54.56
Myeloid leukemia	5.3 (5.3, 5.4)	6 (5.8, 6.1)	4.7 (4.6, 4.8)	86.18
Rare (≥6/100,000/year & < 15/100,000/year)				
Gliomas	6.6 (6.5, 6.7)	7.7 (7.5, 7.8)	5.5 (5.4, 5.6)	88.24
Other	8 (7.9, 8.1)	9.1 (8.9, 9.2)	7 (6.8, 7.1)	78.31
Lymphoid leukemia	8.6 (8.5, 8.7)	10.5 (10.4, 10.7)	6.7 (6.6, 6.8)	74.63
Cystic, mucinous, and serous neoplasms	14.5 (14.4, 14.6)	8.1 (8, 8.3)	20.8 (20.5, 21)	96.17
Non-Hodgkin lymphoma	14.9 (14.8, 15.1)	16.4 (16.2, 16.6)	13.5 (13.3, 13.7)	96.96
Not Rare (≥15/100,000/year)				
Melanomas	19.2 (19, 19.3)	20.7 (20.5, 20.9)	17.7 (17.5, 17.9)	95.87
Transitional cell (papillary) carcinoma	24.3 (24.1, 24.4)	36.6 (36.3, 36.9)	12.2 (12, 12.3)	95.89
Epithelial neoplasms, NOS[d]	31.1 (30.9, 31.3)	32.5 (32.2, 32.7)	29.8 (29.5, 30.1)	59.12
Neoplasms, NOS[d]	32.3 (32.1, 32.5)	32.8 (32.5, 33.1)	31.9 (31.6, 32.1)	13.65
Squamous cell neoplasms (other than skin)	34.9 (34.7, 35.1)	41.2 (40.9, 41.5)	28.6 (28.3, 28.8)	90.12
Ductal and lobular neoplasms	62.7 (62.4, 63)	2.9 (2.8, 3.0)	121.5 (120.9, 122)	98.98
Adenocarcinomas	215 (214.5, 215.5)	269.5 (268.7, 270.3)	161.4 (160.8, 162)	92.21

[a] Adjusted for age and sex.
[b] Adjusted for age.
[c] Data suppressed due to Statistics Canada disclosure rules (< 5 cases in either the numerator or denominator).
[d] NOS = Not Otherwise Specified.

Japanese data and estimated that 15 % of annual cancer diagnoses can be labeled rare [14]. Both analyses conducted in EU and Japan yielded evidence of higher rates of rare cancers among younger age groups [14]. In their analysis of rare cancers occurring among U.S adults, Greenlee et al. (2010) estimated that 25 % of cancer diagnoses can be labeled rare, using the SEER site recode classification scheme and an incidence rate threshold of < 15 cases/100,000/year [5]. This estimate is lower than the comparable estimate from this analysis of 34.4 % (95 %CI: 34.3 %, 34.5 %). However, this discrepancy is likely because the pediatric and adolescent patient population was included in the present

Table 3
Age-adjusted incidence rates by sex using site/histology classifications and grouped by rarity within site group, 2006-2016.

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
	Very Rare (< 6/100,000/year)		
	Basal cell neoplasms (other than skin)	< 0.1	83.33
	Transitional cell (papillary) carcinomas	< 0.1	100
	Adnexal and skin appendage neoplasms	< 0.1	[b]
	Cystic, mucinous, and serous neoplasms	< 0.1	100
	Melanomas	< 0.1	100
	Soft tissue tumors and glomus sarcomas	< 0.1	100
	Fibromatous neoplasms	< 0.1	[b]
	Lipomatous neoplasms	< 0.1	[b]
	Myomatous neoplasms	< 0.1	100
	Synovial-like neoplasms	< 0.1	100
	Blood vessel tumors	< 0.1	100
Oral Cavity & Pharynx	Dontogenic tumors	< 0.1	100
	Miscellaneous tumors	< 0.1	98.63
	Ductal and lobular neoplasms	0.1 (0.1, 0.1)	[b]
	Complex epithelial neoplasms	0.1 (0, 0.1)	96.00
	Complex mixed and stromal neoplasms	0.1 (0.1, 0.1)	96.26
	Acinar cell neoplasms	0.2 (0.1, 0.2)	21.36
	Neoplasms, NOS[c]	0.3 (0.3, 0.3)	96.98
	Mucoepidermoid neoplasms	0.3 (0.3, 0.3)	93.38
	Adenocarcinomas	0.4 (0.4, 0.5)	82.74
	Epithelial neoplasms, NOS[c]	0.6 (0.6, 0.6)	83.33
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Squamous cell neoplasms (other than skin)	8.8 (8.7, 8.9)	94.60
	Very Rare (< 6/100,000/year)		
	Basal cell neoplasms (other than skin)	< 0.1	[b]
	Adnexal and skin appendage neoplasms	< 0.1	100
	Mucoepidermoid neoplasms	< 0.1	[b]
	Acinar cell neoplasms	< 0.1	88.00
	Paragangliomas and glomus tumors	< 0.1	[b]
	Fibromatous neoplasms	< 0.1	[b]
	Synovial-like neoplasms	< 0.1	100
Digestive System	Germ cell neoplasms	< 0.1	[b]
	Trophoblastic neoplasms	< 0.1	100
	Blood vessel tumors	< 0.1	84.21
	Osseous and chondromatous neoplasms	< 0.1	100
	Miscellaneous bone tumors	< 0.1	100
	Miscellaneous tumors	< 0.1	[b]
	Gliomas	< 0.1	100
	Neuroepithelialomatous neoplasms	< 0.1	94.12
	Nerve sheath tumors	< 0.1	[b]
	Transitional cell (papillary) carcinomas	0.1 (0.1, 0.1)	95.24
	Melanomas	0.1 (0.1, 0.1)	97.78
	Soft tissue tumors and glomus sarcomas	0.1 (0.1, 0.1)	87.72
	Myomatous neoplasms	0.1 (0.1, 0.1)	97.65
	Lipomatous neoplasms	0.2 (0.2, 0.2)	94.57
	Complex epithelial neoplasms	0.3 (0.3, 0.3)	94.71
	Complex mixed and stromal neoplasms	0.8 (0.7, 0.8)	91.52
Digestive System Continued	Ductal and lobular neoplasms	1.2 (1.2, 1.3)	93.23
	Epithelial neoplasms, NOS[c]	3.6 (3.6, 3.7)	47.61
	Squamous cell neoplasms (other than skin)	4.1 (4, 4.2)	95.26
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Cystic, mucinous, and serous neoplasms	7 (6.9, 7.1)	96.81
	Neoplasms, NOS[c]	8.9 (8.8, 9)	12.58
	Not Rare (≥15/100,000/year)		
	Adenocarcinomas	81.9 (81.6, 82.2)	91.00

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Table 3 (*continued*)

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
	Very Rare (< 6/100,000/year)		
	Soft tissue tumors and glomus sarcomas	0 (0, 0.1)	[b]
	Germ cell neoplasms	0 (0, 0.1)	90.48
	Basal cell neoplasms (other than skin)	< 0.1	100
	Transitional cell (papillary) carcinomas	< 0.1	96.15
	Adnexal and skin appendage neoplasms	< 0.1	71.43
	Mucoepidermoid neoplasms	< 0.1	[b]
	Ductal and lobular neoplasms	< 0.1	87.10
	Thymic epithelial neoplasms	< 0.1	95.00
	Fibromatous neoplasms	< 0.1	[b]
	Lipomatous neoplasms	< 0.1	95.24
	Myomatous neoplasms	< 0.1	[b]
	Complex mixed and stromal neoplasms	< 0.1	[b]
Respiratory System	Synovial-like neoplasms	< 0.1	90.00
	Trophoblastic neoplasms	< 0.1	[b]
	Blood vessel tumors	< 0.1	85.71
	Osseous and chondromatous neoplasms	< 0.1	100
	Miscellaneous bone tumors	< 0.1	[b]
	Miscellaneous tumors	< 0.1	[b]
	Nerve sheath tumors	< 0.1	100
	Melanomas	0.1 (0.1, 0.1)	98.00
	Neuroepithelialomatous neoplasms	0.1 (0.1, 0.1)	97.56
	Complex epithelial neoplasms	0.5 (0.5, 0.5)	94.08
	Cystic, mucinous, and serous neoplasms	0.6 (0.6, 0.7)	91.49
	Acinar cell neoplasms	1 (0.9, 1)	98.59
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Neoplasms, NOS[c]	10.1 (10, 10.2)	9.74
	Squamous cell neoplasms (other than skin)	14.7 (14.6, 14.8)	84.40
	Not Rare (≥15/100,000/year)		
Respiratory System Continued	Epithelial neoplasms, NOS[c]	21.5 (21.3, 21.6)	58.75
	Adenocarcinomas	24.5 (24.4, 24.7)	78.87
	Very Rare (< 6/100,000/year)		
	Squamous cell neoplasms (other than skin)	< 0.1	86.67
	Soft tissue tumors and glomus sarcomas	< 0.1	90.91
	Fibromatous neoplasms	< 0.1	[b]
	Myomatous neoplasms	< 0.1	[b]
	Germ cell neoplasms	< 0.1	100
	Blood vessel tumors	< 0.1	88.89
Bones & Joints	Giant cell tumors	< 0.1	83.33
	Dontogenic tumors	< 0.1	87.50
	Gliomas	< 0.1	100
	Nerve sheath tumors	< 0.1	100
	Neoplasms, NOS[c]	0.1 (0.1, 0.1)	23.88
	Miscellaneous bone tumors	0.1 (0.1, 0.1)	92.86
	Miscellaneous tumors	0.1 (0.1, 0.1)	92.98
	Osseous and chondromatous neoplasms	0.6 (0.5, 0.6)	94.61
	Very Rare (< 6/100,000/year)		
	Basal cell neoplasms (other than skin)	< 0.1	66.67
	Adenocarcinomas	< 0.1	79.17
	Adnexal and skin appendage neoplasms	< 0.1	100
	Cystic, mucinous, and serous neoplasms	< 0.1	66.67
	Paragangliomas and glomus tumors	< 0.1	[b]
	Myxomatous neoplasms	< 0.1	[b]
	Complex mixed and stromal neoplasms	< 0.1	92.59
	Germ cell neoplasms	< 0.1	100
	Lymphatic vessel tumors	< 0.1	[b]
	Giant cell tumors	< 0.1	100
	Miscellaneous bone tumors	< 0.1	95.83
Soft Tissue incl Heart	Miscellaneous tumors	< 0.1	93.33
	Gliomas	< 0.1	[b]
	Neuroepithelialomatous neoplasms	< 0.1	92.31
	Granular cell tumors/alveolar soft part sarcomas	< 0.1	[b]
	Epithelial neoplasms, NOS[c]	0.1 (0, 0.1)	80.00
	Squamous cell neoplasms (other than skin)	0.1 (0.1, 0.1)	90.20
	Synovial-like neoplasms	0.1 (0.1, 0.2)	95.88
	Blood vessel tumors	0.1 (0.1, 0.1)	89.61
	Osseous and chondromatous neoplasms	0.1 (0, 0.1)	100
	Nerve sheath tumors	0.1 (0.1, 0.1)	96.25
	Neoplasms, NOS[c]	0.2 (0.2, 0.3)	28.83
	Myomatous neoplasms	0.5 (0.5, 0.5)	96.19

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Table 3 (*continued*)

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
Soft Tissue incl Heart Continued	Fibromatous neoplasms	0.6 (0.5, 0.6)	98.09
	Soft tissue tumors and glomus sarcomas	0.7 (0.7, 0.7)	91.56
	Lipomatous neoplasms	0.7 (0.6, 0.7)	94.16
Skin excluding Basal and Squamous	**Very Rare (< 6/100,000/year)**		
	Ductal and lobular neoplasms	0 (0, 0.1)	[b]
	Transitional cell (papillary) carcinomas	< 0.1	[b]
	Mucoepidermoid neoplasms	< 0.1	[b]
	Cystic, mucinous, and serous neoplasms	< 0.1	96.67
	Complex epithelial neoplasms	< 0.1	[b]
	Lipomatous neoplasms	< 0.1	[b]
	Complex mixed and stromal neoplasms	< 0.1	[b]
	Lymphatic vessel tumors	< 0.1	100
	Nerve sheath tumors	< 0.1	100
	Soft tissue tumors and glomus sarcomas	0.1 (0.1, 0.1)	[b]
	Myomatous neoplasms	0.1 (0.1, 0.1)	98.04
	Blood vessel tumors	0.1 (0.1, 0.1)	[b]
	Fibromatous neoplasms	0.4 (0.4, 0.4)	98.15
	Adenocarcinomas	0.5 (0.5, 0.6)	96.09
	Adnexal and skin appendage neoplasms	0.5 (0.4, 0.5)	99.00
	Not Rare (≥15/100,000/year)		
	Melanomas	18.1 (17.9, 18.2)	97.87
Breast	**Very Rare (< 6/100,000/year)**		
	Basal cell neoplasms (other than skin)	< 0.1	100
	Transitional cell (papillary) carcinomas	< 0.1	[b]
	Acinar cell neoplasms	< 0.1	100
	Melanomas	< 0.1	100
	Soft tissue tumors and glomus sarcomas	< 0.1	[b]
	Fibromatous neoplasms	< 0.1	[b]
	Lipomatous neoplasms	< 0.1	100
	Myomatous neoplasms	< 0.1	100
	Complex mixed and stromal neoplasms	< 0.1	[b]
	Osseous and chondromatous neoplasms	< 0.1	100
	Blood vessel tumor	0 (0, 0.1)	[b]
	Squamous cell neoplasms (other than skin)	0.1 (0.1, 0.1)	96.63
	Adnexal and skin appendage neoplasms	0.2 (0.2, 0.3)	[b]
	Fibroepithelial neoplasms	0.2 (0.2, 0.2)	99.28
	Complex epithelial neoplasms	0.4 (0.4, 0.4)	99.64
	Epithelial neoplasms, NOS[c]	1.1 (1, 1.1)	85.78
	Cystic, mucinous, and serous neoplasms	1.1 (1.1, 1.2)	99.19
	Adenocarcinomas	1.2 (1.2, 1.2)	92.46
	Neoplasms, NOS[c]	1.4 (1.3, 1.4)	16.57
	Not Rare (≥15/100,000/year)		
	Ductal and lobular neoplasms	60.8 (60.6, 61.1	99.13

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Table 3 (*continued*)

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
	Very Rare (< 6/100,000/year)		
	Adnexal and skin appendage neoplasms	< 0.1	[b]
	Mucoepidermoid neoplasms	< 0.1	[b]
	Fibromatous neoplasms	< 0.1	100
	Lipomatous neoplasms	< 0.1	100
	Fibroepithelial neoplasms	< 0.1	[b]
	Mesonephromas	< 0.1	100
	Blood vessel tumors	< 0.1	100
	Miscellaneous bone tumors	< 0.1	100
	Miscellaneous tumors	< 0.1	100
	Gliomas	< 0.1	100
	Nerve sheath tumors	< 0.1	100
	Transitional cell (papillary) carcinomas	0.1 (0.0, 0.1)	[b]
	Special gonadal neoplasms	0.1 (0.1, 0.2)	90.20
	Soft tissue tumors and glomus sarcomas	0.1 (0.1, 0.2)	89.58
Female Genital System	Trophoblastic neoplasms	0.1 (0.1, 0.1)	76.92
	Basal cell neoplasms (other than skin)	0.2 (0.2, 0.2)	[b]
	Ductal and lobular neoplasms	0.2 (0.1, 0.2)	96.67
	Melanomas	0.2 (0.2, 0.2)	98.72
	Germ cell neoplasms	0.3 (0.3, 0.4)	98.15
	Myomatous neoplasms	0.6 (0.6, 0.7)	97.71
	Complex epithelial neoplasms	0.9 (0.8, 0.9)	98.96
	Epithelial neoplasms, NOS[c]	1.5 (1.5, 1.6)	69.69
	Complex mixed and stromal neoplasms	2.1 (2.1, 2.2)	98.66
	Neoplasms, NOS[c]	2.6 (2.5, 2.6)	15.08
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Squamous cell neoplasms (other than skin)	8.2 (8.1, 8.4)	97.62
	Cystic, mucinous, and serous neoplasms	10.2 (10.0, 10.3)	95.87
	Not Rare(≥15/100,000/year)		
	Adenocarcinomas	30.3 (30.0, 30.6)	96.41
	Very Rare (< 6/100,000/year)		
	Adnexal and skin appendage neoplasms	< 0.1	[b]
	Special gonadal neoplasms	< 0.1	[b]
	Melanomas	< 0.1	100
	Soft tissue tumors and glomus sarcomas	< 0.1	[b]
	Fibromatous neoplasms	< 0.1	100
Male Genital System	Complex mixed and stromal neoplasms	< 0.1	100
	Basal cell neoplasms (other than skin)	0.1 (0.0, 0.1)	[b]
	Transitional cell (papillary) carcinomas	0.1 (0.1, 0.1)	91.43
	Cystic, mucinous, and serous neoplasms	0.1 (0.1, 0.2)	[b]
	Complex epithelial neoplasms	0.1 (0.0, 0.1)	[b]
	Lipomatous neoplasms	0.1 (0.1, 0.1)	[b]
	Myomatous neoplasms	0.1 (0.1, 0.1)	[b]
	Trophoblastic neoplasms	0.1 (0.1, 0.1)	94.59
	Ductal and lobular neoplasms	0.5 (0.4, 0.5)	94.59
	Squamous cell neoplasms (other than skin)	1.2 (1.1, 1.3)	98.48
	Acinar cell neoplasms	1.2 (1.1, 1.2)	98.31
	Epithelial neoplasms, NOS[c]	1.9 (1.9, 2.0)	99.45
Male Genital System Continued	Germ cell neoplasms	5.4 (5.3, 5.5)	45.77
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Neoplasms, NOS[c]	7.7 (7.6, 7.9)	11.77
	Not Rare (≥15/100,000/year)		
	Adenocarcinomas	60.4 (60.2, 60.7)	98.32

(*continued on next page*)

Table 3 (*continued*)

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
	Very Rare (< 6/100,000/year)		
	Ductal and lobular neoplasms	< 0.1	[b]
	Acinar cell neoplasms	< 0.1	100
	Complex epithelial neoplasms	< 0.1	[b]
	Paragangliomas and glomus tumors	< 0.1	[b]
	Melanomas	< 0.1	100
	Soft tissue tumors and glomus sarcomas	< 0.1	87.50
	Fibromatous neoplasms	< 0.1	100
	Lipomatous neoplasms	< 0.1	[b]
	Myomatous neoplasms	< 0.1	[b]
	Synovial-like neoplasms	< 0.1	100
	Germ cell neoplasms	< 0.1	[b]
Urinary System	Blood vessel tumors	< 0.1	[b]
	Miscellaneous bone tumors	< 0.1	100
	Miscellaneous tumors	< 0.1	100
	Neuroepithelialomatous neoplasms	< 0.1	[b]
	Cystic, mucinous, and serous neoplasms	0.1 (0.1, 0.1)	97.67
	Complex mixed and stromal neoplasms	0.2 (0.2, 0.2)	95.80
	Squamous cell neoplasms (other than skin)	0.4 (0.4, 0.5)	93.97
	Epithelial neoplasms, NOS[c]	0.8 (0.7, 0.8)	71.06
	Neoplasms, NOS[c]	2 (1.9, 2)	22.32
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Adenocarcinomas	13.2 (13.1, 13.3)	90.17
	Not Rare (≥15/100,000/year)		
	Transitional cell (papillary) carcinomas	24.1 (23.9, 24.2)	95.93
	Very Rare (< 6/100,000/year)		
	Neoplasms, NOS[c]	< 0.1	18.18
	Epithelial neoplasms, NOS[c]	< 0.1	80.00
	Basal cell neoplasms (other than skin)	< 0.1	[b]
Eye & Orbit	Adenocarcinomas	< 0.1	83.33
	Adnexal and skin appendage neoplasms	< 0.1	[b]
	Mucoepidermoid neoplasms	< 0.1	100
	Lipomatous neoplasms	< 0.1	[b]
	Myomatous neoplasms	< 0.1	100
Eye & Orbit Continued	Squamous cell neoplasms (other than skin)	0.1 (0.1, 0.1)	95.08
	Neuroepithelialomatous neoplasms	0.1 (0.1, 0.1)	75.61
	Melanomas	0.7 (0.7, 0.8)	45.74
	Very Rare (< 6/100,000/year)		
	Epithelial neoplasms, NOS[c]	< 0.1	[b]
	Squamous cell neoplasms (other than skin)	< 0.1	[b]
	Adenocarcinomas	< 0.1	[b]
	Paragangliomas and glomus tumors	< 0.1	[b]
	Melanomas	< 0.1	85.71
	Soft tissue tumors and glomus sarcomas	< 0.1	100
	Fibromatous neoplasms	< 0.1	100
	Myomatous neoplasms	< 0.1	100
	Complex mixed and stromal neoplasms	< 0.1	100
Brain and Other CNS	Germ cell neoplasms	< 0.1	86.36
	Blood vessel tumors	< 0.1	92.86
	Osseous and chondromatous neoplasms	< 0.1	[b]
	Miscellaneous bone tumors	< 0.1	100
	Miscellaneous tumors	< 0.1	90.00
	Nerve sheath tumors	< 0.1	70.00
	Neuroepithelialomatous neoplasms	0.1 (0, 0.1)	91.18
	Meningiomas	0.1 (0.1, 0.1)	73.42
	Neoplasms, NOS[c]	0.7 (0.7, 0.7)	16.70
	Rare (≥6/100,000/year & < 15/100,000/year)		
	Gliomas	6.6 (6.5, 6.7)	88.21

(*continued on next page*)

Table 3 (*continued*)

Site group	Histology Group	Rate (95 %CI)[a]	Histologically Confirmed (%)
	Very Rare (< 6/100,000/year)		
	Paragangliomas and glomus tumors	0 (0, 0.1)	84.38
	Transitional cell (papillary) carcinomas	< 0.1	[b]
	Mucoepidermoid neoplasms	< 0.1	100
	Complex epithelial neoplasms	< 0.1	[b]
	Soft tissue tumors and glomus sarcomas	< 0.1	100
	Fibromatous neoplasms	< 0.1	100
	Myomatous neoplasms	< 0.1	100
	Complex mixed and stromal neoplasms	< 0.1	[b]
Endocrine System	Germ cell neoplasms	< 0.1	81.82
	Blood vessel tumors	< 0.1	[b]
	Miscellaneous tumors	< 0.1	100
	Gliomas	< 0.1	100
	Ductal and lobular neoplasms	0.1 (0.1, 0.2)	94.68
	Neuroepithelialomatous neoplasms	0.1 (0.1, 0.1)	87.50
	Neoplasms, NOS[c]	0.3 (0.3, 0.3)	36.41
	Epithelial neoplasms, NOS[c]	0.3 (0.3, 0.3)	73.37
	Thymic epithelial neoplasms	0.3 (0.3, 0.3)	94.15
	Squamous cell neoplasms (other than skin)	0.6 (0.6, 0.6)	90.55
Endocrine System Continued	**Rare (≥6/100,000/year & < 15/100,000/year)**		
	Adenocarcinomas	14.5 (14.4, 14.6)	97.06
	Very Rare (< 6/100,000/year)		
	Basal cell neoplasms (other than skin)	< 0.1	77.78
	Transitional cell (papillary) carcinomas	< 0.1	77.78
	Adnexal and skin appendage neoplasms	< 0.1	[b]
	Ductal and lobular neoplasms	< 0.1	75.00
	Complex epithelial neoplasms	< 0.1	86.36
	Paragangliomas and glomus tumors	< 0.1	75.00
	Melanomas	< 0.1	91.67
	Soft tissue tumors and glomus sarcomas	< 0.1	90.00
	Fibromatous neoplasms	< 0.1	100
	Lipomatous neoplasms	< 0.1	[b]
	Myomatous neoplasms	< 0.1	[b]
	Complex mixed and stromal neoplasms	< 0.1	77.78
	Synovial-like neoplasms	< 0.1	100
	Germ cell neoplasms	< 0.1	[b]
	Trophoblastic neoplasms	< 0.1	[b]
	Blood vessel tumors	< 0.1	90.91
Miscellaneous	Osseous and chondromatous neoplasms	< 0.1	[b]
	Miscellaneous bone tumors	< 0.1	[b]
	Miscellaneous tumors	< 0.1	[b]
	Gliomas	< 0.1	[b]
	Neuroepithelialomatous neoplasms	< 0.1	[b]
	Granular cell tumors/alveolar soft part sarcomas	< 0.1	[b]
	Other	0.1 (0.1, 0.1)	89.66
	Mucoepidermoid neoplasms	0.2 (0.2, 0.2)	[b]
	Neoplasms of histiocytes/accessory lymphoid cells	0.2 (0.2, 0.2)	81.75
	Immunoproliferative diseases	0.5 (0.4, 0.5)	72.33
	Squamous cell neoplasms (other than skin)	1 (1, 1.1)	74.74
	Other hematologic disorders	1.1 (1.1, 1.1)	59.72
	Adenocarcinomas	1.2 (1.2, 1.2)	69.62
	Epithelial neoplasms, NOS[c]	1.6 (1.6, 1.7)	55.81
	Neoplasms, NOS[c]	3.9 (3.8, 4)	17.51
	Chronic myeloproliferative disorders	4 (4, 4.1)	41.51
	Myelodysplastic syndrome	4.7 (4.6, 4.8)	54.56

[a] Adjusted for age.
[b] Data suppressed due to Statistics Canada disclosure rules (< 5 cases in either the numerator or denominator).
[c] NOS = Not Otherwise Specified.

Table 4
Concordance between cancer classification methods in labeling cancers as rare or not rare, 2006-2016.

Comparison	Percent Agreement [% (95 %CI)]	
	< 6/100,000	< 15/100,000
SEER Site Recode vs. Histology Group	82.9 (82.9, 83.0)	72.4 (72.3, 72.5)
SEER Site Recode vs. Site Group and Histology Group	79.5 (79.4, 79.6)	65.2 (65.1, 65.3)
Histology Group vs. Site Group and Histology Group	92.1 (92.0, 92.6)	76.0 (76.0, 76.1)

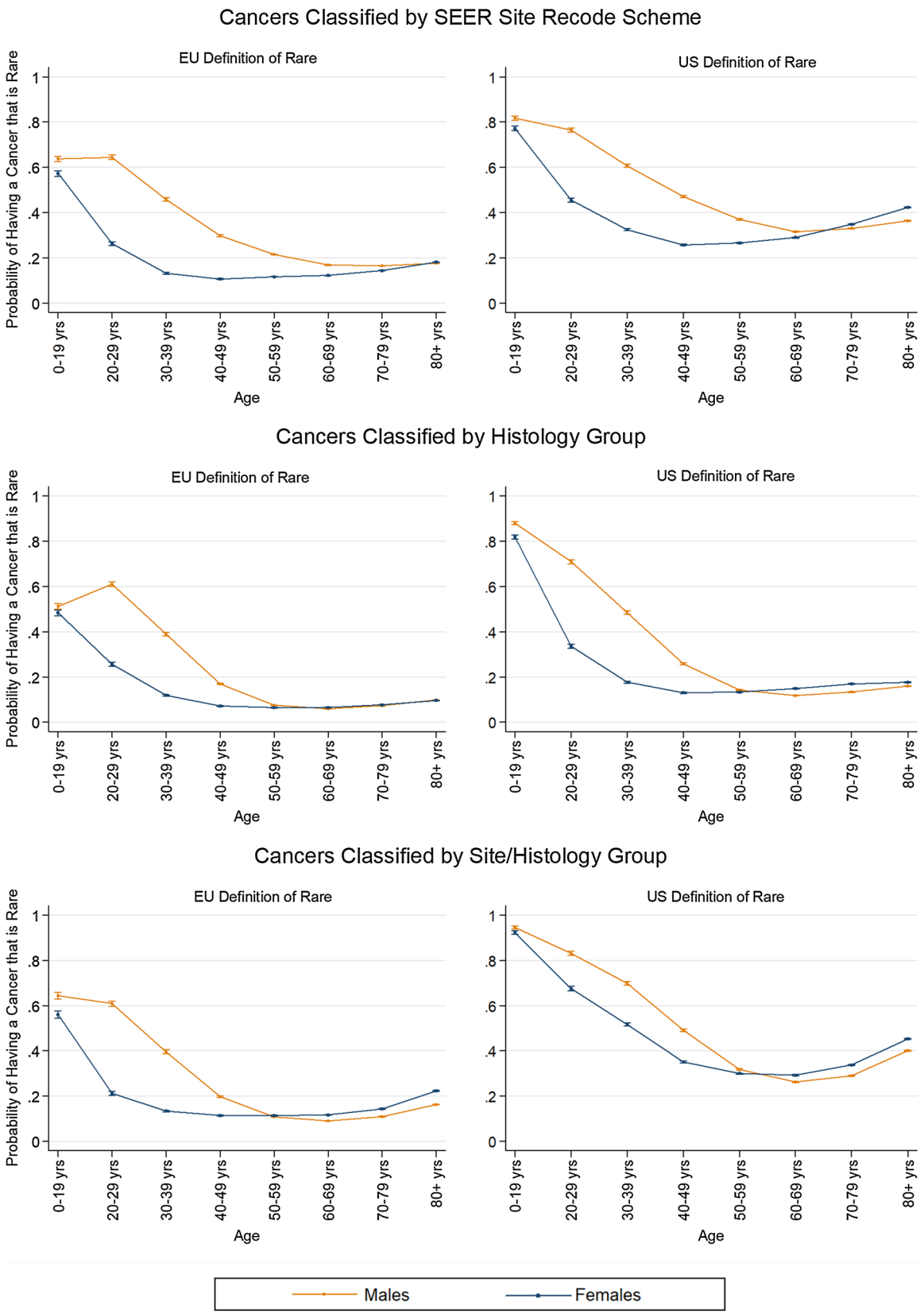

Fig. 1. The adjusted probability of being diagnosed with a rare cancer by age and sex among cancer patients with histologically confirmed cancer diagnoses from 2006-2016, adjusted for province.

analysis and not included in the analysis conducted by Greenlee et al. (2010) [5]. Greenlee et al. (2010) also reported an effect of sex and age on the rate of rare cancers in the U.S [5]. Their analysis yielded evidence of a higher rate of rare cancers among males relative to females under the age of 60, and a higher rate among females after the age of 60 [5]. While the overall proportion of cancers that can be

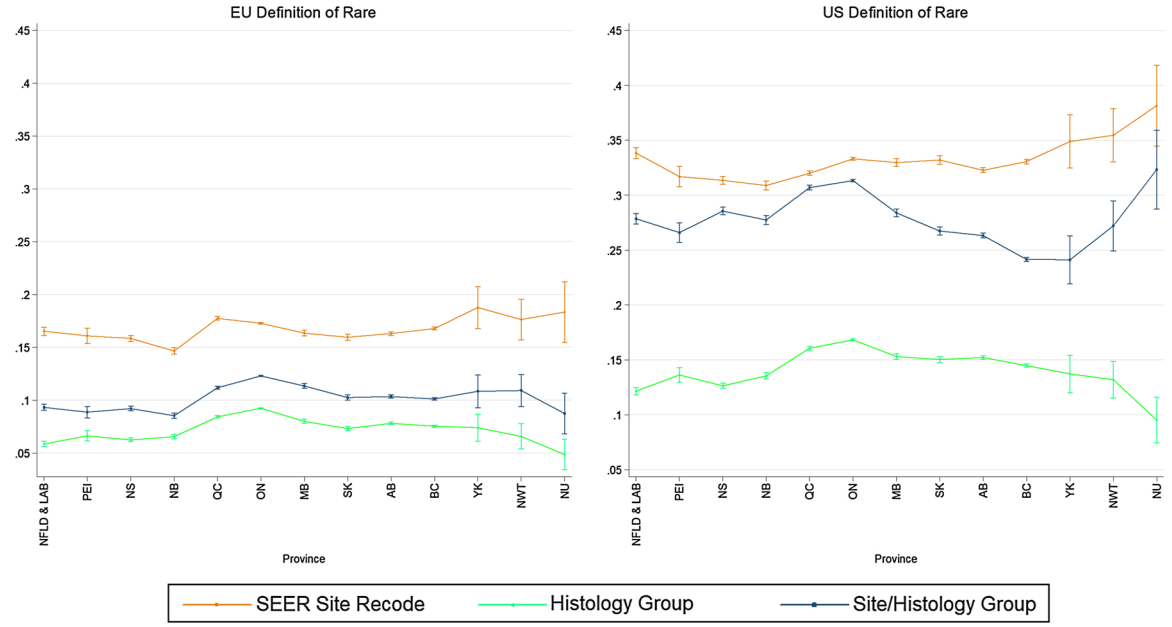

Fig. 2. The probability of being diagnosed with a rare cancer by province, among those with histologically confirmed cancer diagnoses from 2006-2016, adjusted for age and sex.

classified as rare in Canada is similar to estimates from other regions, the distribution of which cancers are rare may differ across populations.

4.1. Future directions

Findings from this analysis lay a foundation for more in-depth comparisons of rare versus common cancers. Future research should aim to measure the extent to which rare cancers are diagnosed at a later stage relative to common cancers, the relative survival among patients with rare versus common cancers, and the healthcare cost associated with diagnosing and managing these two groups of cancers.

4.2. Limitations

This analysis was limited by lack of data on patient characteristics other than age, sex and geographic location, and an absence of data on molecular markers. Therefore, we were unable to measure the effects of and adjust for other potentially relevant factors in these analyses. Additionally, data from Quebec was not available past 2010.

5. Conclusions

We present a comprehensive surveillance report on the frequency and distribution of rare cancers diagnosed among Canadians between 2006 and 2016. This evidence represents the first population-based estimates of rare cancer frequencies in Canada, and more detailed estimates of cancer frequencies than published in routine surveillance reports. More broadly, this analysis yielded evidence that lower incidence rate thresholds generate estimated frequencies of rare cancers that are more robust to different cancer classification methods. This finding supports adopting a lower incidence rate threshold, to maintain consistency in labeling cancers as rare or not, as cancer classification schemes change to incorporate molecular markers. As the distribution of tumours with different molecular features emerges, the incidence rate threshold used in Canada to define rare cancer may need to be revisited.

Authorship statement

EVW was responsible for designing the study, working on the analysis, interpreting the findings and writing the manuscript. EM worked on the analysis and reviewed the manuscript. FGD reviewed the interpretation of the findings and edited the manuscript. All co-authors have read and approved this manuscript and its submission to this journal.

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Declarations

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

E.V. Walker: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **E. Maplethorpe:** Formal analysis, Writing - original draft. **F.G. Davis:** Conceptualization, Writing - review & editing, Project administration, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2020.101721.

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