Catalogue no. 82-003-X
ISSN 1209-1367

Health Reports

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Release date: January 15, 2020

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Changing trends in thyroid cancer incidence in Canada: A histologic examination, 1992 to 2016

by Larry F. Ellison and Tracey Bushnik

Abstract

Background: Age-standardized incidence rates (ASIRs) of thyroid cancer (TC) have increased in many parts of the world, primarily because of increased papillary TC detection. While rapid increases in TC incidence have also been reported in Canada, an analysis of incidence and survival by histologic subtype has been lacking. Moreover, recent data points in Canada suggest that the era of rapid annual increases may have ended.

Data and methods: Data are from the Canadian Cancer Registry, the Canadian Vital Statistics–Death Database and an analytic file linking the two. Annual percent changes (APCs) in incidence and mortality rates are estimated using Joinpoint regression. Net survival (NS) is derived using the Pohar Perme estimator.

Results: Among females, TC ASIRs decreased by 3.0% annually from 2012 to 2016, following years of rapid growth. Among males, a long period of rapid increase ended in 2012 with no subsequent decline. For both sexes the overall incidence trend was driven by changes over time in papillary TC and incidence trends in non-papillary TC varied significantly. From 1992 to 2016, TC mortality rates were stable among females and increased slightly among males (APC = 1.2). Five-year NS was higher among papillary cases (99%) than among non-papillary cases (80%) and among females (99%) than among males (94%). Overall, five-year NS increased by 2.1 percentage points from the period from 1992 to 1996 to the period from 2010 to 2014.

Interpretation: The results of this study confirm the central role of papillary TC cases in TC incidence and survival trends in Canada. Given recent changes in trend and TC management guidelines, projected increases in TC rates after 2016 could be re-examined.

Keywords: histology, incidence, mortality, net survival, registries, Joinpoint regression analysis, population-based study, survival analysis, thyroid neoplasms, trends

DOI: https://www.doi.org/10.25318/82-003-x202000100002-eng

In Canada, thyroid cancer (TC) was the fifth most frequently diagnosed cancer among females in 2016, behind breast, lung and bronchus, colorectal and uterine cancers.[1] Among males, it was the 13th most commonly diagnosed cancer. However, TC mortality is only a small fraction of incidence because of the generally excellent prognosis for this disease.[2] Until 2012, rapid increases in TC incidence in Canada had been observed and attributed to overdiagnosis of clinically unimportant lesions detected by modern imaging.[3] Both short- and long-term projections indicate continued increases in incidence.[4,5]

International studies have shown that TC incidence has increased in many parts of the world, primarily because of increased detection of papillary TC.[6-9] Papillary TC is the most common and least aggressive of all the TC histologies,[10] and the five-year survival rate exceeds 95% in much of Europe and North America.[8] However, less common histologies have less favourable prognoses and varying incidence and survival patterns.[8,10] Whether these international results pertain to Canada is uncertain, since an analysis of TC incidence and survival in Canada by histologic type has yet to be published.

After years of rapid increases, TC incidence trends have stabilized in the United States in recent years.[11] This is possibly a result of revised guidelines released by the American Thyroid Association that were designed to be more diagnostically conservative.[12-15] For example, the new guidelines call for less aggressive diagnostic management of small thyroid tumours because of concerns surrounding overtreatment of low-risk TC.[12,13] While similar changes to clinical practice guidelines were also recommended in Canada,[16] a full examination of potential changes in TC trends in Canada has yet to be undertaken.

The present study has two main purposes: first, to examine the extent to which increased detection of papillary TC affected previously reported increases in overall TC in Canada; and second, to use the most recently available data, until 2016, to determine whether the trend in TC incidence has changed. Using data from the Canadian Cancer Registry (CCR), this study examines TC incidence from 1992 to 2016. It presents sex-specific incidence estimates according to age, histology and province for the most recent five-year period (2012 to 2016), and examines changes in rates over the entire period. These findings are supplemented with similar information on TC mortality and five-year net survival (NS).

Methods

Data sources and definitions

Incidence

Cancer incidence data (1992 to 2016) are from the November 2018 CCR tabulation file released January 29, 2019. The CCR is a person-oriented, population-based database comprised of cases diagnosed among Canadian residents since 1992.[17] Each provincial and territorial cancer registry provides demographic and cancer-specific information to Statistics Canada in a standard format. Annual submissions by jurisdiction include additions and revisions to data submitted in previous years.

Cancer cases were defined based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[18] Cases were classified as TC if the topography (site) code was C73.9, excluding histology types 9050 to 9055, 9140

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and 9590 to 9992. Only malignant cases were considered. TC cases were divided into three main histologic types: papillary (8050, 8260, 8340 to 8344, 8350 and 8450 to 8460), non-papillary and unspecified (8000 to 8005 and 8010 to 8015). Non-papillary cases were further categorized into follicular (8290 and 8330 to 8335), medullary (8345 and 8510 to 8513), anaplastic (8020 to 8035) and other specified subtypes.[19] The International Agency for Research on Cancer multiple primary coding rules were used for this study.[20]

Mortality

Mortality data are from the June 28, 2018, release of the Canadian Vital Statistics–Death Database.[21] This database includes demographic and cause of death information for all deaths in Canada. TC deaths were identified using the World Health Organization's International Classification of Diseases, Tenth edition (ICD-10)[22] code C73 for deaths occurring from 2000 onward, and ICD-9[23] code 193 for deaths occurring from 1992 to 1999. Data were examined from 1992 to 2016 to coincide with the incidence data from the CCR.

Population

Population data were obtained from Canada's population estimates by age and sex released on January 25, 2019.[24]

Survival

An analytic file for survival was created by linking the November 2017 CCR tabulation file to mortality information until December 31, 2014.[25] This information was obtained from the Canadian Vital Statistics–Death Database and T1 personal master files (as reported on tax returns). Annual expected survival probabilities that are needed to calculate net survival (NS) were obtained from provincial and territorial life tables, available for three-year overlapping time periods. For example, expected survival data for 2014 were obtained from life tables for 2013 to 2015. More detail has been provided elsewhere.[2]

Statistical analysis

Incidence and mortality

Sex-specific TC incidence rates by age group, histologic type and province were calculated by dividing the number of new primary cases or deaths by the corresponding population counts. Age-standardized rates were calculated using the direct method, which involved weighting the age-specific rates according to the age distribution of the 2011 Canadian standard population.[26] Rates are expressed per 100,000 people. Incidence data from Quebec were entirely omitted because cases diagnosed in this province from 2011 onward had not yet been submitted to the CCR. Although mortality data were available for Quebec, they were also omitted for the sake of consistency.

Annual percent changes (APCs) in age-specific and age-standardized rates were estimated using Joinpoint regression software.[27,28] Default parameters were used with the exception that the minimum number of observations from a changepoint to either end of the data was set at four (i.e., 2012 to 2016 was the most recent time period for which an APC could be detected). Likewise, the minimum number of observations between two changepoints was also set at four. This is consistent with the approach that has historically been followed in the *Canadian Cancer Statistics* annual publication.[4] P-values associated with APCs correspond to two-sided tests of the null hypothesis that the underlying APC value is zero (i.e., stable) with a significance level of 0.05.

Net survival

Records from the analytic file for survival were excluded a priori if the diagnosis had been established through autopsy only or death certificate only, or if the year of birth or death was unknown (both circumstances are extremely rare). Survival analyses were then restricted to first primary TC cases[29,30] diagnosed from 1992 to 2014 among those aged 15 to 99. Finally, data from Quebec were excluded because cases diagnosed in this province from 2011 onward had not been submitted to the CCR.

Unstandardized (crude) survival analysis estimates were derived using an algorithm[31] that Ron Dewar of the Nova Scotia Cancer Care Program (Dewar R 2018, email communication, 19th April, 2018) has augmented to include the Pohar Perme estimator of NS.[32] The updated program uses the hazard transformation approach. Age-standardized NS estimates were calculated using the direct method and the Canadian cancer survival standard (CCSS) weights.[2] These weights—based on recent Canadian incidence data—were chosen to enhance the interpretability of the findings in the Canadian context. The CCSS weights for TC are as follows: 0.351 (ages 15 to 44), 0.256 (ages 45 to 54), 0.204 (ages 55 to 64), 0.127 (ages 65 to 74) and 0.062 (ages 75 to 99). Standard errors for age-standardized NS estimates were estimated by taking the square root of the sum of the squared, weighted, age-specific NS standard errors. Age-standardized NS estimates were additionally adjusted by sex and main histologic type (case-mix) to mitigate the effect on these estimates of differences in the distribution of TC cases over time by these variables. Similarly, sex-specific age-standardized estimates were separately adjusted for case-mix. Since no set of standard weights currently exists for such specialized adjustments, weights were developed using the same data source previously used to develop the age-standardized weights (Appendix Table A).[2]

NS estimates for 2010 to 2014 were predicted using the period method,[33] while estimates for 1992 to 1996 were calculated using the cohort method. The underlying methodology is essentially the same, except that the follow-up information used in the period method necessarily does not relate to a fixed cohort of people. Instead, period survival estimates are based on the assumption that people diagnosed in the period of interest will experience the most recently observed conditional probabilities of NS.

Estimates were suppressed if the corresponding standard error was greater than 0.10; caution was indicated if the standard error was greater than 0.05 but less than or equal to 0.10. Percentage point differences in survival over time were calculated before rounding to one decimal place.

Results

Thyroid cancer incidence

Incidence, 2012 to 2016

In total, almost 24,000 new primary TC cases were diagnosed in Canada from 2012 to 2016, corresponding to an age-standardized incidence rate (ASIR) of 17.4 per 100,000 (Table 1). Overall, females were diagnosed at a rate almost three times higher than males. Prior to age 35, the rate of TC diagnosis among females was about four times higher than among males. This ratio declined with age to about one and a half times higher among females aged 75 or older. Among males, diagnosis rates increased with age, peaking among those aged 65 to 74, at 18.9 per 100,000. Among females, diagnosis rates peaked earlier in life, among those aged 45 to 54, at 44.7 per 100,000.

During the period from 2012 to 2016, papillary TC cases comprised 93.1% of the TC cases where a main histologic type was specified, resulting in an ASIR that was 14 times higher for papillary TC (16.0 per 100,000) than for non-papillary cancer (1.2 per 100,000). The female-to-male ASIR ratio was almost twice as high for papillary TC than for non-papillary TC. The average age at anaplastic TC diagnosis was close to 20 years older than for other histologic subtypes (data not shown). Anaplastic TC was the least common subtype.

TC ASIRs were considerably higher in Ontario (23.1 per 100,000) and Newfoundland and Labrador (21.5 per 100,000) than elsewhere in the country—over two times higher than in Prince Edward Island, British Columbia,

Table 1
Sex-specific counts and age-standardized incidence rates (ASIRs) of new primary thyroid cancer cases, by age group, histologic type and province or territory, Canada excluding Quebec, 2012 to 2016

	Sex											
	Females				Males				Both			
	Number of cases	ASIR (per 100,000)	95% confidence interval		Number of cases	ASIR (per 100,000)	95% confidence interval		Number of cases	ASIR (per 100,000)	95% confidence interval	
			from	to			from	to			from	to
All	17,700	25.6	25.3	26.0	6,010	9.0	8.7	9.2	23,710	17.4	17.2	17.6
Age group												
24 or younger	665	3.4	3.2	3.7	180	0.9	0.7	1.0	845	2.1	2.0	2.2
25 to 34	2,150	22.8	21.9	23.8	540	5.7	5.2	6.2	2,685	14.2	13.7	14.7
35 to 44	3,715	40.3	39.0	41.6	985	11.0	10.3	11.7	4,705	25.9	25.1	26.6
45 to 54	4,550	44.7	43.4	46.0	1,375	13.5	12.8	14.3	5,925	29.1	28.4	29.9
55 to 64	3,480	38.4	37.1	39.7	1,365	15.4	14.6	16.3	4,845	27.1	26.3	27.8
65 to 74	2,105	34.9	33.4	36.4	1,060	18.9	17.8	20.1	3,165	27.2	26.2	28.1
75 to 84	850	24.2	22.6	25.9	435	15.2	13.8	16.7	1,280	20.1	19.0	21.3
85 or older	180	10.0	8.6	11.6	75	7.9	6.2	9.9	255	9.3	8.2	10.5
Histology												
Papillary	16,515	24.0	23.6	24.4	5,345	8.0	7.7	8.2	21,865	16.0	15.8	16.3
Non-papillary	1,030	1.5	1.4	1.6	585	0.9	0.8	1.0	1,620	1.2	1.1	1.2
Follicular	660	0.9	0.9	1.0	285	0.4	0.4	0.5	940	0.7	0.6	0.7
Medullary	185	0.3	0.2	0.3	155	0.2	0.2	0.3	335	0.2	0.2	0.3
Anaplastic	95	0.1	0.1	0.1	85	0.1	0.1	0.2	180	0.1	0.1	0.1
Other specified	95	0.1	0.1	0.2	65	0.1	0.1	0.1	160	0.1	0.1	0.1
Unspecified	155	0.2	0.2	0.2	75	0.1	0.1	0.2	230	0.2	0.1	0.2
Province or territory												
Nunavut	F	F	F	F	F	F	F	F	10	14.5	5.5	46.8
Northwest Territories	F	F	F	F	F	F	F	F	10	4.1	2.0	11.1
Yukon	F	F	F	F	F	F	F	F	10	5.5	2.6	12.2
British Columbia	1,610	13.1	12.4	13.7	610	5.1	4.7	5.5	2,220	9.1	8.7	9.5
Alberta	1,840	19.0	18.2	19.9	670	7.1	6.5	7.6	2,510	13.0	12.4	13.5
Saskatchewan	345	13.3	11.9	14.7	155	5.9	4.9	6.8	505	9.5	8.7	10.4
Manitoba	545	17.8	16.3	19.3	195	6.5	5.5	7.4	740	12.2	11.3	13.1
Ontario	11,940	34.3	33.7	35.0	3,840	11.5	11.2	11.9	15,780	23.1	22.8	23.5
New Brunswick	410	20.1	18.1	22.0	180	8.7	7.4	10.0	590	14.4	13.2	15.6
Nova Scotia	470	18.3	16.6	20.0	180	7.4	6.3	8.5	650	13.0	12.0	14.0
Prince Edward Island	35	9.4	6.6	13.1	20	6.1	3.8	9.4	60	7.7	5.7	9.7
Newfoundland and Labrador	480	32.6	29.6	35.5	150	10.2	8.5	11.8	625	21.5	19.8	23.2

F too unreliable to be published

Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All counts were randomly rounded to a base of five to protect confidentiality. Age-specific rates were based on rounded counts; ASIRs were not. ASIRs were calculated using weights from the 2011 Canadian standard population, see reference 26; age-specific rates were not age-standardized.

Source: Statistics Canada, Canadian Cancer Registry.

Saskatchewan, the Northwest Territories and Yukon. Overall, two-thirds of cases diagnosed from 2012 to 2016 originated from Ontario.

Trend change in 2012

Following periods of very rapid (APC = 11.4%, 1998 to 2003) to rapid (APC = 6.5%, 2003 to 2012) growth, the TC ASIR among females decreased by 3.0% annually from 2012 to 2016 (Table 2). Among males, ASIRs were relatively stable from 2012 to 2016 after a long period of rapid increase (APC = 6.5) dating back to at least 1992.

Differences in trends by histology

For both sexes, increases in papillary TC prior to 2012 were similar to, or exceeded, overall increases. This indicates that the rapidly rising trends in TC noted for these years were largely driven by increases in papillary TC (Figure 1, Table 2).

The decrease in TC ASIRs among females from 2012 to 2016 was also driven primarily by the papillary type, whose ASIR declined annually by 3.7% during this period (Figure 1, Table 2). Trends in non-papillary TC ASIRs varied by subtype (Table 2). From 1992 to 2016, annual increases were observed among cases classified as medullary (APC = 1.9%) and other specified (APC = 2.3%), while an annual decrease was detected among anaplastic cases (APC = -1.7%).

The stability in TC rates among males that began in 2012 also largely reflected the trend in papillary incidence (Figure 1, Table 2). Among non-papillary subtypes, only a 3.0% annual increase in the medullary TC ASIR was significant.

Trends variation by province

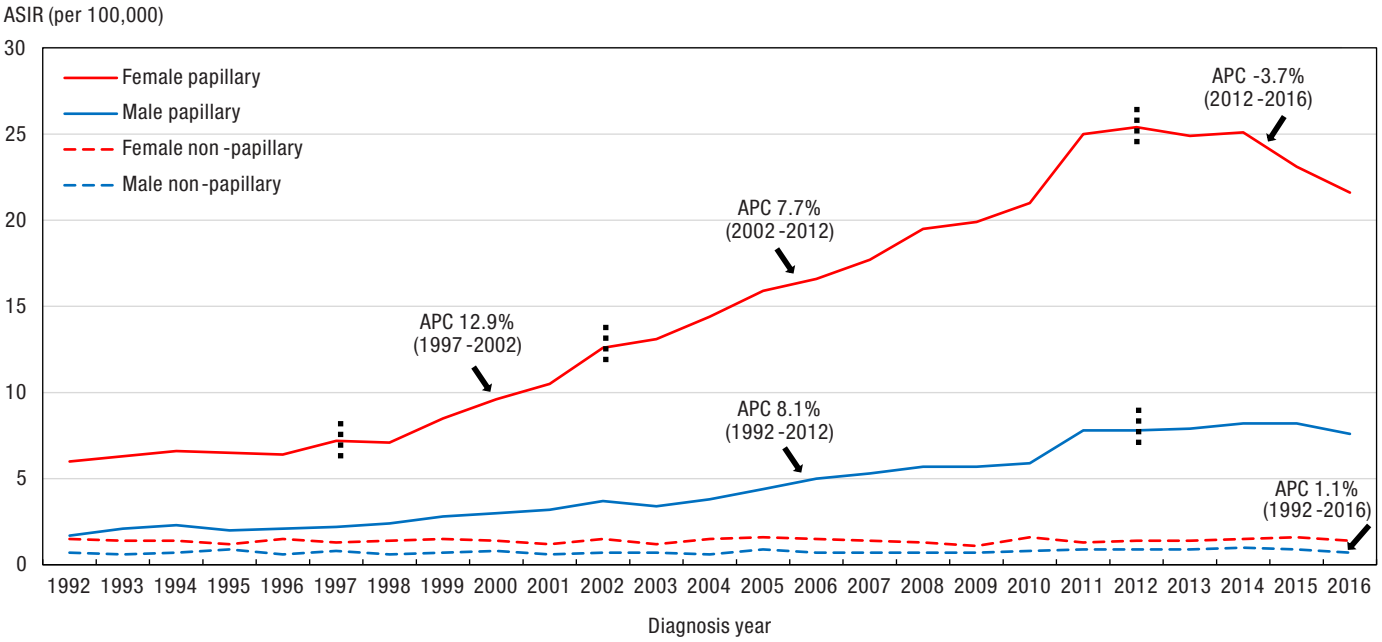
The overall decline in ASIRs from 2012 to 2016 among females was strongly influenced by trends in Ontario (APC = -3.1%, 2012 to 2016) and New Brunswick (APC = -10.2%, 2011 to 2016) (Table 2). In Alberta and Nova Scotia, no significant increases or decreases have been observed among females since the mid-2000s, while a long-term pattern of increase was noted in the remaining provinces, as well as among males for six of the provinces.

Differences in age-specific trends by sex

Among females, rates of TC diagnosis began to peak at ages 35 to 64 in the early 2000s. They continued to increase more rapidly over time compared with rates for females in the youngest and oldest age groups (Figure 2). For example, females aged 45 to 54 saw their rate increase from 25.6 per 100,000 in 2003 to 46.4 per 100,000 in 2012, compared with an increase from 17.3 per 100,000 to 24.7 per 100,000 among females aged 25 to 34. From 2012 to 2016, this pattern reversed and the largest decrease in rates was observed among females aged 55 to 64.

Rates of TC diagnosis among males younger than 85 steadily increased until 2012, rising more rapidly among those aged 35 to 74 and appearing to peak at ages 65 to 74 (Figure 2). From 2012 to 2016, no significant increase or decrease in age-specific rates was observed among males.

Figure 1
Sex-specific thyroid cancer annual age-standardized incidence rates (ASIRs), by histological type, Canada excluding Quebec, 1992 to 2016



Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. ASIRs were calculated using the 2011 Canadian standard population, see reference 26. Only annual percent change (APC) trends associated with a p-value ≤ 0.05 are marked on this figure.
Source: Statistics Canada, Canadian Cancer Registry.

Table 2
Sex-specific trends in thyroid cancer age-standardized incidence rates (ASIRs), by histologic type and province, Canada excluding Quebec, 1992 to 2016

	Trend analysis									
	Female					Male				
		Annual percent change in ASIR	95% confidence interval				Annual percent change in ASIR	95% confidence interval		
	Period		from	to	p-value	Period		from	to	p-value
All	1992 to 1998	2.5	-0.4	5.5	0.088	1992 to 2012	6.5	5.9	7.2	<0.001
	1998 to 2003	11.4	6.9	16.1	<0.001	2012 to 2016	1.2	-3.2	5.8	0.575
	2003 to 2012	6.1	5.0	7.2	<0.001	…	…	…	…	…
	2012 to 2016	-3.0	-5.5	-0.4	0.025	…	…	…	…	…
Histology										
Papillary	1992 to 1997	1.8	-2.4	6.1	0.379	1992 to 2012	8.1	7.4	8.9	<0.001
	1997 to 2002	12.9	7.7	18.4	<0.001	2012 to 2016	1.0	-3.6	5.9	0.649
	2002 to 2012	7.7	6.7	8.7	<0.001	…	…	…	…	…
	2012 to 2016	-3.7	-6.1	-1.2	0.007	…	…	…	…	…
Non-papillary	1992 to 2016	0.2	-0.4	0.7	0.575	1992 to 2016	1.1	0.4	1.9	0.005
Follicular	1992 to 2016	-0.2	-0.9	0.5	0.520	1992 to 2016	0.1	-0.9	1.1	0.830
Medullary	1992 to 2016	1.9	0.6	3.1	0.004	1992 to 2016	3.0	2.1	4.0	<0.001
Anaplastic	1992 to 2016	-1.7	-2.9	-0.5	0.007	1992 to 2016	1.3	-0.3	3.0	0.101
Other specified	1992 to 2016	2.3	0.7	3.9	0.006	1992 to 2016	1.5	-0.9	4.0	0.221
Unspecified	1992 to 2005	5.7	0.8	10.7	0.023	1992 to 2004	2.3	-2.2	7.0	0.307
	2005 to 2016	-17.2	-23.1	-10.9	<0.001	2004 to 2016	-8.3	-12.2	-4.2	<0.001
Province										
British Columbia	1992 to 2016	3.5	3.0	4.1	<0.001	1992 to 2016	3.5	2.8	4.1	<0.001
Alberta	1992 to 2005	7.1	5.2	9.1	<0.001	1992 to 2016	3.7	2.9	4.6	<0.001
	2005 to 2016	1.3	-0.3	2.8	0.100	…	…	…	…	…
Saskatchewan	1992 to 2016	3.6	2.6	4.6	<0.001	1992 to 2016	3.8	2.7	4.9	<0.001
Manitoba	1992 to 2016	4.6	3.5	5.7	<0.001	1992 to 2016	5.1	3.9	6.4	<0.001
Ontario	1992 to 1997	1.2	-3.5	6.1	0.612	1992 to 2016	6.7	6.0	7.4	<0.001
	1997 to 2002	13.9	7.9	20.2	<0.001	…	…	…	…	…
	2002 to 2012	6.8	5.7	7.9	<0.001	…	…	…	…	…
	2012 to 2016	-3.1	-5.9	-0.1	0.041	…	…	…	…	…
New Brunswick	1992 to 1998	-4.3	-12.5	4.7	0.311	1992 to 2008	10.7	6.9	14.5	<0.001
	1998 to 2005	18.3	10.2	27.0	<0.001	2008 to 2016	0.2	-5.7	6.5	0.937
	2005 to 2011	4.4	-1.9	11.2	0.162	…	…	…	…	…
	2011 to 2016	-10.2	-16.4	-3.7	0.005	…	…	…	…	…
Nova Scotia	1992 to 2001	0.6	-5.8	7.4	0.859	1992 to 2006	11.1	7.2	15.1	<0.001
	2001 to 2006	18.9	-0.5	41.9	0.056	2006 to 2016	3.2	-0.4	7.0	0.076
	2006 to 2016	1.4	-2.0	4.8	0.402	…	…	…	…	…
Prince Edward Island	..	..	..	..	..	..	..	..	..	..
Newfoundland and Labrador	1992 to 2016	8.4	6.7	10.1	<0.001	1992 to 2016	7.1	4.6	9.6	<0.001

.. not available for a specific reference period

… not applicable

Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. Trends associated with a p-value > 0.05 were considered stable. Otherwise, positive (increasing) or negative (decreasing) annual percent changes were considered as actual changes in the ASIR over time. Trends were not available for Prince Edward Island because there were no cases of thyroid cancer in one or more years during the reference period.

Source: Statistics Canada, Canadian Cancer Registry.

Thyroid cancer mortality and survival

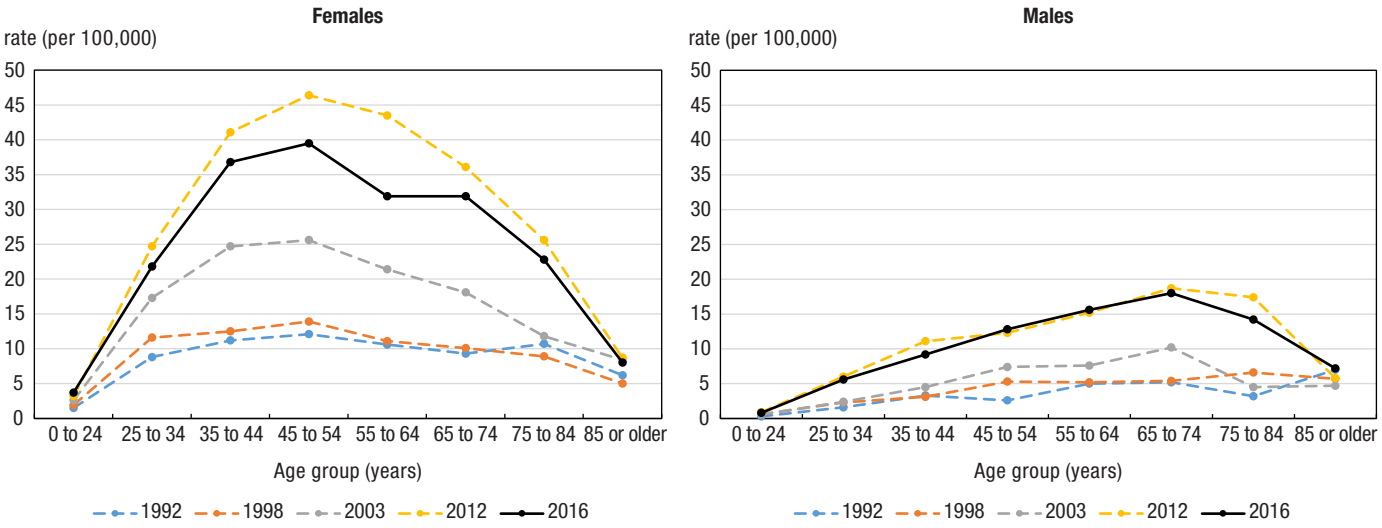
Variation in mortality rates

In total, about 850 deaths were attributed to TC in Canada from 2012 to 2016, corresponding to an age-standardized mortality rate (ASMR) of 0.60 per 100,000 (Table 3). There was a steady increase in mortality rates with increasing age. In contrast to the results for incidence, ASMRs were similar between the sexes and across the provinces. Overall mortality rates remained stable from 1992 to 2016, except that the rate increased slightly among males (APC = 1.2%) and among people aged 75 or older at diagnosis (APC = 0.9%).

Net survival

Five-year NS for TC was 98% during the period from 2010 to 2014 (Table 4). It declined moderately with advancing age to 85%, still favourable even among the most elderly (aged 75 to 99). Provincially, NS ranged from a low of 94% in Saskatchewan to a high of 98%

Figure 2
Age-specific thyroid cancer incidence rates, by sex and selected year of diagnosis, Canada excluding Quebec, 1992 to 2016



Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. Age-specific rates are based on counts that have been randomly rounded to a base of five to protect confidentiality. Selected years of diagnosis correspond to changepoints in trends of age-standardized incidence rates for either females or males (see Table 2).
Source: Statistics Canada, Canadian Cancer Registry.

Table 3
Thyroid cancer death counts, age-standardized mortality rates (ASMRs), and trends in ASMRs, by sex, age group and province, Canada excluding Quebec

	Mortality (2012 to 2016)				Trend analysis (1992 to 2016)				
			95% confidence interval				95% confidence interval		
	Number of deaths	ASMR (per 100,000)	from	to	Period	Annual percent change in ASMR	from	to	p-value
All	850	0.60	0.56	0.64	1992 to 2016	0.3	-0.4	1.0	0.417
Sex									
Female	455	0.58	0.52	0.63	1992 to 2016	-0.3	-1.1	0.6	0.487
Male	395	0.62	0.56	0.68	1992 to 2016	1.2	0.2	2.3	0.021
Age group									
44 and younger	25	0.03	0.02	0.05	..	..	..	..	..
45 to 54	55	0.27	0.20	0.35	1992 to 2016	-0.9	-3.0	1.2	0.388
55 to 64	130	0.73	0.61	0.86	1992 to 2016	-0.7	-2.1	0.8	0.357
65 to 74	220	1.89	1.65	2.16	1992 to 2016	0.2	-1.1	1.5	0.763
75 or older	415	4.56	4.13	5.02	1992 to 2016	0.9	0.1	1.7	0.033
Province									
British Columbia	145	0.55	0.46	0.63	1992 to 2016	-0.5	-1.7	0.8	0.451
Alberta	110	0.66	0.54	0.79	1992 to 2016	0.3	-1.5	2.2	0.709
Saskatchewan	35	0.56	0.38	0.79	1992 to 2016	-0.5	-3.0	2.1	0.702
Manitoba	50	0.75	0.55	1.00	1992 to 2016	0.5	-2.1	3.1	0.701
Ontario	415	0.58	0.52	0.64	1992 to 2016	0.2	-0.7	1.1	0.687
New Brunswick	25	0.57	0.37	0.85	..	..	..	..	..
Nova Scotia	40	0.73	0.52	1.01	1992 to 2016	2.0	-0.4	4.4	0.100
Prince Edward Island	5	0.58	0.19	1.48	..	..	..	..	..
Newfoundland and Labrador	25	0.81	0.52	1.22	1992 to 2016	2.6	-0.6	5.8	0.103

.. not available for a specific reference period

Notes: All counts were randomly rounded to a base of five to protect confidentiality. Age-specific rates were based on rounded counts; ASMRs were not. ASMRs were calculated using weights from the 2011 Canadian standard population, see reference 26; age-specific rates were not age-standardized. A positive annual percent change represents an increase in the ASMR, or age-specific mortality rate, over time, while a negative change represents a decrease. No changes in trend were detected in any of the analyses. Quebec is excluded for consistency with the incidence data.
Source: Statistics Canada, Canadian Vital Statistics–Death Database.

in Ontario, with the exception of the relatively lightly populated Prince Edward Island (90%). NS was higher among females (99%) than among males (94%), and consistently so within each age group and province.

Variation in net survival by histology

While a diagnosis of papillary TC was associated with very little to almost no

Table 4
Sex-specific, five-year predicted thyroid cancer net survival (NS) estimates, by age group, histologic subtype and province, Canada excluding Quebec, 2010 to 2014

	Sex								
	Females			Males			Both		
		95% confidence interval			95% confidence interval			95% confidence interval	
	NS (%)	from	to	NS (%)	from	to	NS (%)	from	to
All thyroid cancer	99	98	99	94	93	95	98	97	98
Age group									
15 to 44	100	99	100	99	98	99	100	99	100
45 to 54	100	99	100	96	94	97	99	98	99
55 to 64	99	98	99	93	91	95	97	96	98
65 to 74	97	95	98	90	86	93	95	93	96
75 to 99	88	82	91	80	71	87	85	81	89
Histology									
Papillary	100	F	100	97	96	98	99	99	100
Non-papillary	83	80	86	74	69	78	80	77	82
Follicular	94	91	96	93	86	97	94	91	96
Medullary	92	82	96	74[E]	62	83	83	76	88
Anaplastic	8	3	17	4	1	13	7	3	13
Other specified	68[E]	55	77	69[E]	54	81	68	58	76
Unspecified	61	52	68	41[E]	30	52	55	48	61
Province									
British Columbia	96	94	97	90	86	93	95	93	96
Alberta	98	97	99	93	89	96	97	96	98
Saskatchewan	98	91	100	84	72	91	94	90	97
Manitoba	97	93	99	93	84	97	96	93	98
Ontario	99	99	100	96	94	97	98	98	99
New Brunswick	99	92	100	89	81	94	97	93	98
Nova Scotia	96	92	98	95	84	99	96	92	98
Prince Edward Island	93	74	98	F	F	F	90[E]	74	96
Newfoundland and Labrador	99	83	100	90	79	96	97	92	99

[E] use with caution

F too unreliable to be published

Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. Net survival estimates were predicted using the period method. Caution is indicated when the standard error is > 0.05 and < 0.10; estimates associated with standard errors ≥ 0.10 were considered too unreliable to publish.

Sources: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2014) and life tables.

excess mortality (99% NS), the five-year NS among those diagnosed with a non-papillary TC was less favourable (80%). Among non-papillary cases, the subtype with the highest NS was follicular (94%), followed by medullary (83%), then anaplastic (7%). For each of the main diagnostic types, survival was higher among females than males once again. The excellent prognosis for papillary TC was consistently observed across all age groups (i.e., a minimum five-year NS of 99%). In contrast, the five-year NS for non-papillary TC steadily decreased with advancing age, from 98% (95% confidence interval (CI) = 95 to 99) among people aged 15 at 44 at diagnosis to 81% (95% CI = 76 to 86) among those aged 55 to 64 and to 51% (95% CI = 41 to 60) among those aged 75 to 99.

Net survival over time

In Canada, five-year age-standardized NS for TC increased from 93% during the period from 1992 to 1996 to 98% during the period from 2010 to 2014 (Table 5). However, the increase in NS was attenuated from 4.7 percentage points to 2.1 percentage points after considering sex-specific changes over time in the distribution of the main histologic types of TC (i.e., case-mix)—namely, the increased proportion of papillary cases. The case-mix adjustment also reduced apparent sex-specific increases in survival over time by about 2.5 percentage points. Increases in five-year age-standardized NS of 2.0 to 3.0 percentage points were observed among both those diagnosed with papillary TC and those diagnosed with non-papillary TC. The decrease in survival in the unspecified category is likely attributable, at least partially, to a notable decline in the proportion of such cases between the two time periods (data not shown).

What is already known on this subject?

- Age-standardized incidence rates (ASIRs) of thyroid cancer (TC) have increased in many parts of the world, primarily because of increased papillary TC detection.
- Until 2012, rapid increases in TC ASIRs in Canada had been observed and attributed to overdiagnosis of clinically unimportant lesions detected by modern imaging.
- The five-year survival prognosis for TC in Canada is generally excellent and results in mortality rates that are only a small fraction of corresponding incidence rates.

What does this study add?

- Papillary TC cases constitute 93% of TC cases diagnosed in Canada.
- In Canada, TC ASIRs declined for females and stabilized for males from 2012 to 2016.
- The shift in trend is primarily due to changes in papillary TC incidence that were not observed for non-papillary TC cases. The sex-specific age groups most affected by the shift were those that previously experienced the largest increases in TC rates.
- Overall, age-standardized mortality rates remained stable from 1992 to 2016, but increased slightly among males.
- The prognosis after a TC diagnosis in Canada is considerably influenced by the histology of the cancer—prognosis for papillary TC is excellent, but it is very poor for the anaplastic subtype.
- Five-year net survival for TC in Canada has increased slightly since the early 1990s.

Table 5
Standardized five-year thyroid cancer net survival (NS) estimates, by sex and histologic type, Canada excluding Quebec, 1992 to 1996 versus 2010 to 2014

	Age-standardized							Age-, sex- and case-mix-standardized						
	1992 to 1996			2010 to 2014				1992 to 1996			2010 to 2014			
		95% confidence interval			95% confidence interval		percentage point change		95% confidence interval			95% confidence interval		percentage point change
	NS (%)	from	to	NS (%)	from	to		NS (%)	from	to	NS (%)	from	to	
All thyroid cancer	93	92	94	98	97	98	4.7	96	95	97	98	98	99	2.1
Sex														
Male	89	87	91	95	94	96	5.7	92	89	94	95	94	96	3.3
Female	94	93	95	99	98	99	4.3	98	96	98	99	99	100	1.8
Histology														
Papillary	97	96	98	99	99	100	2.3	…	…	…	…	…	…	…
Non-papillary	84	81	86	86	85	88	2.9	…	…	…	…	…	…	…
Follicular	93	90	95	95	93	97	2.5	…	…	…	…	…	…	…
Medullary	88	80	93	84	78	89	-3.6	…	…	…	…	…	…	…
Anaplastic	..	..	..	..	..	..	..	…	…	…	…	…	…	…
Other specified	57	44	69	81	73	87	23.6	…	…	…	…	…	…	…
Unspecified	92	88	94	80	74	85	-11.9	…	…	…	…	…	…	…

.. not available for a specific reference period

… not applicable

Notes: Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. Net survival estimates were predicted using the period method. Age-standardized estimates were calculated using Canadian cancer survival standard weights, see reference 2. Age-standardized estimates for anaplastic thyroid cancer were not available because one or more age-specific estimates were undefined. The adjustment by sex applies only to all thyroid cancers combined.

Sources: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2014) and life tables.

Discussion

After a long period of rapid growth, TC incidence rates in Canada declined among females and stabilized among males from 2012 to 2016. These overall patterns primarily reflected a change in papillary TC incidence that was generally not shared by the other histologic types. This study also found that the overall prognosis for TC was excellent, having increased slightly since the early 1990s, but that NS was significantly different between papillary and non-papillary subtypes.

The significant change in TC incidence rates in Canada since 2012, chiefly in papillary TC, is a major finding of this study. From 2012 to 2016, papillary TC rates decreased by 3.7% per year among females and stabilized among males. Similar changes in trend occurred a few years earlier in the United States. The annual increase in SEER 9 delay-adjusted overall TC rates among females fell from 7.1% (1997 to 2009) to a stable trend (2009 to 2016), and among males from 5.5% (1997 to 2012) to a stable trend (2012 to 2016).[11] The change in trend in the United States coincided with the 2009 release of the revision to the American Thyroid Association guidelines, which called for less aggressive diagnostic management of small thyroid tumours because of concerns surrounding the overtreatment of low-risk TC.[12,13] In Canada, similar changes to clinical practice guidelines were recommended by the Canadian Society of Endocrinology and Metabolism.[16]

In light of the recent changes in TC incidence rates in Canada and the United States, it may be wise to re-examine the potential accuracy and therefore usefulness of corresponding short-term[4] and long-term[5,34] projected rates. For example, projected TC rates for 2016,[4] based on CCR incidence data until 2015, overestimated actual estimates by 26% for females and 19% for males. TC management guidelines have been modified recently to be even more diagnostically conservative.[14,15] This may further reduce the likelihood that the projected increases in TC rates after 2016[4] will be realized.

The rapid increase in TC rates seen until 2012 in Canada has also been observed in many other parts of the world.[6,8,35-37] Many researchers suggest that these years of increases largely reflect overdiagnosis,[3,6,7,9,35] that is, the diagnosis of thyroid tumours that would not result in symptoms or death if left untreated.[7] This overdiagnosis has been attributed to the introduction and increasing use of new screening and diagnostic techniques with the capacity to detect very small tumours. As has been reported elsewhere,[8,35,37-39] the increase in TC rates noted in the present study was mainly driven by increases in papillary TC. This type is often associated with a smaller tumour size and typically follows a more indolent course than many other cancers, with only a small proportion behaving aggressively.[35,40]

From 1992 to 2012, TC incidence rates in Canada progressively increased among middle-aged people, particularly females. Vaccarella et al.[6] reported similar changes in age-specific patterns in several different countries and used the findings to estimate the proportion of cases attributable to overdiagnosis for each one. Because the present study found a partial reversal of the age-specific increases among females and a stabilization among males since 2012, it appears that the recommendations of the American Thyroid Association and the Canadian Society of Endocrinology and Metabolism are being adopted. The large range in provincial ASIRs, with particularly high rates in Ontario and Newfoundland and Labrador, has been previously noted.[3] For Ontario, at least, these rates have mainly been ascribed to overdiagnosis.[3,39] Overdiagnosis also

provides a plausible explanation for the considerable divergence of both incidence and mortality trends observed by others[40] and reported in this study. It may also partially explain the simultaneous heterogeneity in provincial incidence rates and homogeneity of corresponding mortality rates. Topstad and Dickinson have argued that differences in risk factors or genetic mutations are unlikely explanations for provincial differences in incidence rates.[3]

However, it has been argued that a portion of increasing TC rates represents a true rise in the disease.[13,36,37,41,42] Some studies have found moderate increases in rates of larger-size and advanced-stage TC.[13,42-44] In addition, Lim et al.[13] reported increases in TC mortality rates for advanced-stage papillary TC. This seemed to be associated with increasing incidence of advanced-stage papillary TC.[13] While there were insufficient data to examine trends by tumour size and stage, the present study found that medullary TC incidence rates have increased over time and that the overall TC mortality rate has increased among males and remained stable among females. The lack of a decrease in mortality during an era with earlier diagnosis and better treatment has been proposed by some as evidence of a real increase in TC.[37,45] It has been hypothesized that population-level growth in the prevalence of a number of individual (e.g., obesity) and environmental (e.g., exposure to endocrine-disrupting chemicals) risk factors have contributed to this increase,[42] but strong evidence is generally lacking.[36,37,40]

This study found that the most recent sex-specific five-year TC survival estimates in Canada were closely aligned with what has been observed in the United States,[38] but were higher and had less of a spread across age groups than what was reported in the EUROCARE-5 study on cancer survival in Europe.[10] Given the consistently excellent prognosis for papillary TC across all age groups, these differences could potentially be explained by the considerably higher proportion of papillary TC cases in Canada (93%) compared with the proportion in the European study (71%). As in the United States and Europe,[10,11] survival in Canada was also higher among females than among males. Moreover, medullary TC was responsible for the largest absolute difference by histology in sex-specific survival (greater than 10 percentage points) in both the European and the present studies. None of the studies, however, considered stage at diagnosis. This may have confounded the relationship between sex and survival.[46,47]

Reported increases in TC survival over time in Europe and the United States have been attributed by some to dramatic increases in the relative proportion of papillary TC, including smaller-sized or earlier-stage tumours.[10,48] This attribution is partly based on the strong positive association reported between survival and incidence in Europe.[10] In the present study, the observed minor provincial variation in TC survival appeared to be somewhat positively correlated with TC incidence rates. Furthermore, the increase in TC survival over time in Canada was attenuated by controlling for the increase in the proportion of papillary TC. However, it was not possible to control for changes in size or stage of papillary TC over time. Therefore, some of the remaining increase in survival may be due to residual confounding that resulted from potential increases in the proportion of small, localized papillary TC tumours.

Strengths and limitations

The present study has a number of strengths, including the use of validated national cancer data to examine trends in histology-specific incidence and survival not previously reported in Canada. The use of CCSS weights[2] enhanced the interpretability of age-standardized survival estimates in the Canadian context. Alternative weights that are often used to facilitate international comparisons—based on the incidence data of European patients diagnosed from 1985 to 1989—place a greater emphasis on the survival of people diagnosed with TC at older ages.[49] This typically results in slightly lower age-standardized TC estimates than reported here (e.g., 96% five-year NS, versus 98% five-year NS in this present study).[2]

One limitation of this study was the absence of incidence data from the province of Quebec. While TC ASIRs have historically been lower in Quebec than in the rest of the country combined, its provincial rate of increase was such that its ASIR had reached the national average by 2010.[50] In addition, both national estimates of survival[51] and of mortality (data not shown) were each virtually the same for the most recent time periods available whether data from Quebec were included or not. A second constraint was that information on tumour size and stage for TC was very limited within the CCR. Third, the results were not adjusted for reporting delay to the registry,[52] which could result in an underestimation of counts and rates, particularly for the most recent data year. However, a comparison of TC incidence counts from the current CCR file (1992 to 2016) with counts from previous files covering cases until 2015 and 2014, respectively, found that any case reporting delay likely had a negligible effect on the reported incidence rate trends.

Conclusion

Following many years of increase, TC ASIRs declined overall among females and stabilized among males in Canada from 2012 to 2016. These diverse trends primarily result from changes in papillary TC incidence rates. TC survival in Canada is also considerably influenced by the histology of the cancer. Revisions to TC management guidelines, based on concerns surrounding overtreatment of low-risk TC, may have played a role in the recent shift in incidence trend. The extent to which this new trend will continue and how it may affect TC survival is not yet clear. A re-examination of projected TC incidence rates after 2016 and continued monitoring of histology-specific TC incidence and survival are recommended. ■

Appendix

Table A
Weights used in the case-mix standardization of net survival estimates for thyroid cancer

	Combined male and female		Sex-specific	
Histologic type	**Male**	**Female**	**Male**	**Female**
Papillary	0.213	0.710	0.886	0.935
Non-papillary	0.024	0.043	0.101	0.057
Unspecified	0.003	0.006	0.014	0.008

Note: Weights were based on the proportion of thyroid cancer cases diagnosed among those aged 15 to 99 years, in Canada (excluding Quebec), from 2010 to 2014.

Source: Statistics Canada's November 2017 Canadian Cancer Registry tabulation file (1992-to-2015), International Agency for Research on Cancer multiple primary rules version.

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