RESEARCH

Pulmonary and overall healthcare utilization after childhood and young adult thyroid cancer

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Abstract

Differentiated thyroid carcinoma (DTC) in children, adolescents, and young adults is associated with excellent prognosis. However, little is known about the long-term utilization of healthcare resources among survivors. The objective of this study was to compare the utilization of healthcare resources among DTC survivors to the general population, with a focus on pulmonary-related resource utilization. Population-based linked data were used to retrospectively ascertain DTC patients from the Ontario Cancer Registry, age <30 years at diagnosis between 1992 and 2011. DTC cases were individually matched 1:10 to the general population on age, sex, diagnosis year, and rural status. Billing records for all-cause hospitalizations, emergency department visits, pulmonary subspecialist visits, and chest imaging were compared using incidence rate ratios (IRR). A total of 2456 individuals with DTC were identified, with women representing the majority (82.8%) of cases. Compared to controls, hospitalization and emergency department visit IRRs were 2.56 (95% CI, 2.49–2.63) and 2.22 (95% CI, 2.18–2.26), respectively. An excess of pulmonary diagnostic imaging was observed for chest radiography (IRR, 2.7; 95% CI, 2.6–2.8) and pulmonary CT's (IRR, 17.5; 95% CI, 15.8–19.3). Patients who underwent radioactive iodine therapy had a higher incidence of pulmonary-related healthcare utilization than those who did not. The highest healthcare utilization for all modalities was observed in the 30 to 90 days after DTC diagnosis with a steady decline further from diagnosis; however, elevated utilization was observed throughout the observation period. Health services utilization is high for primary DTC survivors, irrespective of the time since diagnosis. Radioactive iodine therapy is associated with higher rates of utilization. These findings have ramifications for treatment, surveillance and for policy formulation.

Key Words

- thyroid carcinoma
- health services utilization
- medical imaging
- cancer survivors
- pediatric
- adolescent and young adult

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy, and the most frequently diagnosed malignancy among adolescents and young adults (Araque *et al.* 2017), with a significant female

predominance (Massimino *et al.* 2018). The incidence of DTC in North America is rising (Vergamini *et al.* 2014, Pole *et al.* 2017), although the prognosis is highly favorable, with 5-, 15- and 30-year disease-specific survival

of nearly 100% among those 0–20 years at diagnosis (Golpanian *et al.* 2016). As a consequence, there is a large, and growing ‘at-risk’ population of adolescent and young adult survivors treated for DTC, with potential medical sequelae of their disease or treatment-related adverse effects (Araque *et al.* 2017).

Treatment of DTC is primarily surgical. Historically, a focus on attaining a disease-free state prompted widespread utilization of adjuvant radioactive iodine (RAI) therapy. In 2015, clinical practice guidelines for treatment of children with DTC prompted a transition to more selective utilization of RAI for those with intermediate to high risk of persistent or recurrent disease (Francis *et al.* 2015). RAI is generally recognized to be safe, although recent evidence suggests potential for clinical sequelae with prolonged latency, including salivary gland dysfunction, second primary malignancies and pulmonary fibrosis, particularly among those with diffuse pulmonary metastases (Marti *et al.* 2015, Zhang *et al.* 2016, Albano *et al.* 2017). Life-long follow-up for recurrent disease is advocated (Francis *et al.* 2015), although the optimal frequency and modality of surveillance has not been clearly defined.

Pulmonary metastases are common among young patients, with an estimated prevalence of 20–27% (Bal *et al.* 2004, Golpanian *et al.* 2016, Lazar *et al.* 2016, Livhits *et al.* 2016, Alzahrani *et al.* 2019), in contrast to 5% of adults with DTC (Chopra *et al.* 2015, Lim *et al.* 2017). Even in the face of distally metastatic disease, mortality remains low in young patients (Pawelczak *et al.* 2010); however, only a minority of patients clear their disease completely (Durante *et al.* 2006, Song *et al.* 2015, Alzahrani *et al.* 2019). The long-term health consequences of distally metastatic disease among survivors, and impacts on healthcare utilization, have not been well defined.

The province of Ontario, Canada is a single-payer healthcare system. All encounters with the healthcare system are billed centrally, allowing the entire population to be captured using linked administrative healthcare databases. We sought to determine whether children, adolescents and young adult (CAYA) survivors of DTC, age 0–29 years at diagnosis, were accessing the healthcare system more frequently than the general population. Using provincial administrative databases, we identified CAYA diagnosed with DTC and assessed how frequently they were accessing the healthcare system. Given the relatively high rate of pulmonary metastases within the CAYA population, we elected to focus on pulmonary-related utilization. We then compared this with a matched sample of the general population with no medical history of cancer.

Materials and methods

Data sources, study population and cohort creation

A population-based retrospective matched cohort study was performed using the Ontario Cancer Data Linkage (‘cd-link’) project, an initiative which has been previously described (Earle 2014). In brief, a unique encrypted health insurance number was used to deterministically link administrative healthcare databases at ICES for every individual eligible for health insurance coverage in the province of Ontario, Canada. The Ontario Cancer Registry (OCR), a population-based provincial cancer registry of all incident cancer diagnoses, was used to identify thyroid carcinoma cases. Hospitalization data were obtained from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), which contains information from the discharge abstracts of all Ontario hospital admissions starting in 1988. Beginning in 2002, emergency department (ED) visits for all hospital- and community-based ambulatory care were identified from CIHI using the National Ambulatory Care Reporting System (NACRS) database. The Ontario Health Insurance Plan (OHIP) database contains all fee-for-service physician billing records and was used to identify interactions with the healthcare system (including ED visits prior to 2002) classified according to billing codes established by the provincial health ministry (Ontario Ministry of Health and Long Term Care 2015).

Establishment of this cohort was previously described (Pole *et al.* 2017). Briefly, thyroid carcinoma diagnoses were identified using International Classification of Disease, 9th edition (ICD-9) code 193 for malignant neoplasm of the thyroid gland. Primary thyroid cancer cases were identified in CAYA subjects aged <30 years with a diagnosis in the OCR between January 1, 1992 and December 31, 2011. To ensure the highest level of diagnostic certainty, only individuals whose cancer case status was ascertained by the Regional Cancer Centre Registration or by a confirmed pathology report were included. Individuals with a previous cancer prior to the incident thyroid carcinoma ($n=44$) were excluded. Medullary thyroid carcinoma cases ($n=47$) were identified using ICD-O histology codes (World Health Organization 2013): 8510, 8511, 8246, and 8345 and excluded from the cohort due to the association of this cancer subtype’s association with hereditary cancer syndromes which could confound future healthcare utilization (Kloos *et al.* 2009).

DTC cases were followed from the diagnosis date (index date) of their thyroid carcinoma and censored at

the earlier of a secondary malignant neoplasm, death, or date of last contact with the healthcare system. A reference population with no previous medical history of cancer was identified using a random sample of the Ontario population during this study period. Cases were individually matched 1:10 to controls on age, sex, rural status, and diagnosis index year using an exact greedy match (Bergstralh *et al.* 1996). Controls were followed from the same index date as their matched case and were censored at a cancer diagnosis or death or end of study follow-up. All matched controls were censored when a case was censored. Ethics approval was obtained from The Hospital for Sick Children, Toronto, Ontario, Canada.

Pulmonary healthcare utilization and other covariates

Administrative databases (CIHI-DAD, OHIP and NACRS) were used to identify pulmonary-related health service utilization (HSU) beginning 30 days after the diagnosis date (index date) until December 31, 2011. A start date of 30 days after the thyroid cancer diagnosis was chosen to capture utilization subsequent to early clinical therapies, as the majority of definitive surgeries would have been completed by this time. Chest radiography (CXR) and computerized tomography (CT) were identified using hospital and out-patient procedure billing codes. The Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the Canadian Classification of Health Interventions coding structure were used to identify CXR and CT utilization (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article) (Statistics Canada 1986, Canadian Institute for Health Information 2012b). Pulmonary function tests (PFTs) were captured from the OHIP database for the most common test types: simple spirometry, flow-volume loop, plethysmography, carbon monoxide diffusing capacity, and oxygen saturation (Gershon *et al.* 2012). A full list of the pulmonary-related utilization procedure codes used are supplied in Supplementary Table 1. DTC patients that underwent RAI therapy after the diagnosis date of DTC (index date) were identified using the OHIP billing code X326. Imaging procedure codes for pulmonary-related HSU were captured across the CIHI-DAD, NACRS, and OHIP databases and were de-duplicated using the billing date associated with the imaging study. This de-duplication procedure was performed: (i) to prevent overestimating utilization; and (ii) under the assumption that survivors would infrequently undergo multiple pulmonary-related imaging studies late into survivorship on the same day.

Incident hospital admissions and ED visits for all causes were captured during the observation period. The primary diagnostic code associated with each hospitalization and/or ED visit was obtained using ICD-9-CM and ICD-10-CA codes (US Department of Health and Human Services 1988, Canadian Institute for Health Information 2012a). Diagnostic codes were converted between ICD-9 and ICD-10 using a conversion file maintained by ICES. Fee-for-service billing records were analyzed from OHIP to identify the responsible physicians' area of specialty. This is a list of specialties or disciplines recognized by the Royal College of Physicians and Surgeons of Canada relevant to services covered under the Ministry of Health and Long-Term Care. Physician subspecialty was categorized as general practitioner, respiratory diseases specialist, otolaryngologist, or endocrinologist based on the physicians' declared specialty associated with the billing record (Ontario Ministry of Health and Long Term Care 2015).

Sociodemographic characteristics of the population were determined from administrative records. Age, sex, and index year were captured at the index date of cohort entry. Area based neighborhood income quintiles were determined by linking Canadian Census data at the index date using the residential postal code, using methods that have been described previously (Pole *et al.* 2017). Urban and rural status were also determined based on residential postal code at index date.

Sensitivity analysis was performed *ad hoc* to determine HSU for other anatomical sites throughout the study period. Abdominal and pelvic CT exams were selected as a 'negative tracer' (Supplementary Fig. 1), as the abdomen and pelvic regions are unlikely to be involved in the direct context of either primary thyroid carcinoma or with its associated therapies. In this context the 'negative tracer' is unlikely to be impacted by the underlying diagnosis or intervention (i.e. DTC treatment in this study), and thus remains constant over the period of investigation. It therefore serves as a control to demonstrate a true excess of utilization in the measure of interest and temporal trends, rather than a generalized increase in utilization of the healthcare system or of specific diagnostic modalities.

Statistical analysis

Frequencies and proportions were calculated to describe population characteristics and were stratified by sex. Non-parametric and χ^2 tests were used to compare differences in the distributions of baseline characteristics among cases

and controls. Incidence rates for HSU were calculated overall, and for the following time periods after diagnosis (index date): 30 to <90 days, 90 to <180 days, 180 days to <1 year, 1 to <2 years, 2 to <3 years, 3 to <5 years, 5 to <10 years, 10 to <15 years, and 15 to 21 years. These groupings were chosen to capture any changes in utilization rates during active treatment for thyroid cancer immediately after diagnosis and long into the survivorship period. Rates were calculated as events per 1000 person-years of observation and incidence rate ratios (IRRs) were calculated comparing DTC cases with controls. Confidence intervals (95% CI) for the IRR were calculated using the Poisson distribution approximation. Where appropriate, analyses were stratified by the inclusion of RAI therapy as part of the treatment protocol to determine differences in HSU among DTC patients. Reported *P* values represent two-sided tests with values <0.05 considered statistically significant. Statistical analyses were performed in SAS version 9.4 (SAS Institute) at the Pediatric Oncology Group of Ontario.

Results

A total of 2456 CAYA patients were diagnosed with DTC during the study period and matched to 24,560 population controls. Both cases and controls had a median and interquartile range (IQR) follow-up time of 7.4 years (IQR, 3.8–12.2). Characteristics of the cohort stratified by sex are presented in Table 1. Overall, 2034 (82.8%) of diagnoses were identified in women. AYAs aged 20–29 years represented most incident thyroid cancer patients in this cohort ($n=2031$; 82.7%). Approximately 8% of DTC patients were individuals living in a rural area. No difference in mortality was observed for DTC patients ($n=9$, 0.4%) when compared to controls ($n=115$, 0.5%).

Slightly more than half ($n=1390$, 56.6%) of the DTC patients underwent RAI therapy. Among DTC patients there was no impact of sex on rates of RAI therapy, CXR, chest CT, PFTs, or respiratory disease subspecialty billing (all $P>0.05$).

Hospitalizations, emergency department visits and diagnoses associated with hospital visits

All-cause hospitalization and ED visit incidence (beginning 30 days after the index date) are illustrated in Fig. 1. Overall, the IRR of all-cause hospitalizations for DTC patients was 2.56 times larger relative to the general population (95% CI, 2.49–2.63). Similarly, ED visits had an

IRR 2.22 (95% CI, 2.18–2.26) times larger than population controls. The highest incidence in hospitalizations and ED visits were seen in the time-period closest to the index date and found to decrease over time (Fig. 1A). There was a late increase in hospitalizations and ED visits in the 15- to 21-year period after primary treatment relative to the immediately preceding time periods (Fig. 1A). When stratified by RAI therapy, individuals who underwent RAI were associated with higher IRRs of hospitalizations and ED visits than those who did not undergo RAI (Fig. 1B). The overall IRR for individual in-patient hospitalization of patients who underwent RAI therapy was 2.93 (95% CI, 2.84–3.03) versus 2.10 (95% CI, 2.01–2.19) for those who did not receive RAI. Similarly, total ED visits were higher in the RAI group (IRR, 2.50; 95% CI, 2.30–2.41) than those who did not receive RAI (IRR, 2.03; 95% CI, 1.96–2.09). Absolute incidence rates for hospitalizations and ED visits stratified by time period are presented in Supplementary Table 2.

The primary indications for hospitalization in DTC patients were identified as ‘neoplasm’ (35.2%) related to the primary DTC, pregnancy and childbirth (18.6%), health services for medical procedures and aftercare (14.5%), digestive system diseases (6.7%), and genitourinary diseases (5.4%). Hospitalizations for unaffected controls followed a similar pattern; pregnancy and childbirth (51.3%), genitourinary diseases (11.0%), digestive system diseases (10.3%), and symptoms and ill-defined conditions (3.3%). When stratified by time since index, pregnancy and childbirth, genitourinary diseases, and digestive system diseases were frequently among the top four diagnostic reasons of hospitalization for both DTC cases and controls two years post index date (Supplementary Table 3).

Incidence and incidence rate ratio of pulmonary-related health services utilization

There was a significant excess of individuals with DTC accessing pulmonary-related health services beginning 30 days after the index date when compared with the general population. Specifically, there was increased use of CXR (57.5 vs 28.5%), chest CT (21.6 vs 1.7%), PFT (15.7 vs 10.5%), and consultation with a respiratory disease specialist (6.7 vs 3.0%) when compared to controls (all $P<0.001$).

Time-period-specific and overall incidence rates and IRRs for pulmonary-related HSU are presented in Fig. 2 and Table 2. Overall, the IRR of CXR was 2.7 (95% CI, 2.6–2.8), while the incidence rates for chest

Table 1 Population characteristics and outcomes of thyroid cases and population controls after 30 days from index date.

Characteristics	Cases					Population controls					P-value ^a
	Female		Male		Total	Female		Male		Total	
	No.	(%)	No.	(%)	No.	No.	(%)	No.	(%)	No.	
Total cases (n)	2034	100	422	100	2456	20,340	100	4220	100	24,560	100
Age at diagnosis (years)											
0–12	31	1.5	13	3.1	44	310	1.5	130	3.1	440	1.8
13–16	106	5.2	18	4.3	124	1060	5.2	180	4.3	1240	5.1
17–19	206	10.1	51	12.1	257	2060	10.1	510	12.1	2570	10.5
20–22	317	15.6	54	12.8	371	3170	15.6	540	12.8	3710	15.1
23–25	425	20.9	77	18.3	502	4250	20.9	770	18.3	5020	20.4
26–27	433	21.3	85	20.1	518	4330	21.3	850	20.1	5180	21.1
28–29	516	25.4	124	29.4	640	5160	25.4	1240	29.4	6400	26.1
Diagnosis year											
1992–2001	770	37.9	177	41.9	947	7700	37.9	1770	41.9	9470	38.6
2002–2006	644	31.7	119	28.2	763	6440	31.7	1190	28.2	7630	31.1
2007–2011	620	30.5	126	29.9	746	6200	30.5	1260	29.9	7460	30.4
Income quintile ^b											
1 (lowest)	433	21.3	82	19.4	515	4608	22.7	935	22.2	5543	22.6
2	389	19.1	75	17.8	464	4227	20.8	891	21.1	5118	20.8
3	440	21.6	78	18.5	518	3984	19.6	774	18.3	4758	19.4
4	412	20.3	83	19.7	495	3761	18.5	803	19.0	4564	18.6
5 (highest)	352	17.3	99	23.5	451	3657	18.0	764	18.1	4421	18.0
Rural ^c											
No	1869	91.9	389	92.2	2258	18690	91.9	3890	92.2	22580	91.9
Yes	162	8.0	29	6.9	191	1620	8.0	290	6.9	1910	7.8
Radioactive iodine treatment	1135	55.8	255	60.4	1390	N/A ^d		N/A		N/A	
Pulmonary utilization											
Chest X-ray	1154	56.7	257	60.9	1411	5791	28.5	1197	28.4	6988	28.5
Chest CT	426	20.9	105	24.9	531	334	1.6	71	1.7	405	1.7
Pulmonary function tests	326	16.0	59	14.0	385	2181	10.7	386	9.2	2567	10.5
Pulmonologist visit	136	6.7	29	6.9	165	595	2.9	139	3.3	734	3.0
Vital status											
Alive	–	–	–	–	2447	20255	99.6	4190	99.3	24445	99.5
Deceased	–	–	–	–	9	85	0.4	30	0.7	115	0.5
Follow-up time (years), median (IQR)	7.4 (3.8, 12.2)		7.5 (3.9, 12.8)		7.4 (3.8, 12.2)	7.4 (3.8, 12.2)		7.4 (3.9, 12.7)		7.4 (3.8, 12.2)	0.82

^aP value represents statistical significance test between 'Total' groups; ^bIncome quintile data missing for 13 (0.53%) cases and 156 (0.65%) controls; ^cRural status missing for 7 (0.29%) cases and 70 (0.29%) controls; ^dN/A, not applicable; –, cell suppressed due to small sample size restrictions; IQR, interquartile range.

Figure 1

All-cause hospitalization and emergency department visits for primary differentiated thyroid carcinoma patients. (A) Overall and (B) stratified by radioactive iodine therapy. d, days; y, years; RAI, radioactive iodine therapy. A full colour version of this figure is available at <https://doi.org/10.1530/ERC-19-0463>.

CT for DTC patients and controls were 51.7 and 3.0 per 1000 person-years, respectively, representing an IRR of 17.5 (95% CI, 15.8–19.3). PFT had IRR 1.8 (95% CI, 1.7–1.9) for DTC cases compared to controls (Table 2). Rates of CXR and chest CT were highest in the 30- to 90-day time-period following the index date and decreased over time (Fig. 2A). An increase in IRR was observed in the 15- to 21-year time-period for all HSU when compared to the preceding 10 to 15-year time period. Patients who underwent RAI treatment accessed pulmonary-related health resources more often than those who did not (Fig. 2B). Absolute incidence rates for pulmonary-related HSU are presented in Supplementary Table 4.

To ensure that any observed changes in pulmonary-related HSU did not reflect an artifact of the administrative data, a 'negative tracer' analysis examining the utilization of a diagnostic modality unlikely to be associated with DTC or its treatment, abdominal/pelvic CT, was undertaken to compare to chest imaging (Supplementary Fig. 1).

Outpatient physician visits

The distribution of IRRs for physician billing records varied between subspecialty disciplines (Fig. 3). Not surprisingly,

visits to Endocrinologists and Otolaryngologists demonstrated the highest relative incidence among disciplines for DTC patients compared to controls with an overall IRR of 43.48 (95% CI, 40.34–46.87) and 10.89 (95% CI, 10.57–11.22), respectively. Overall, the IRR of respiratory disease specialist billings was 2.25 (95% CI, 2.06–2.44). There was a relative excess of visits to pulmonologists among DTC patients versus controls in all periods of observation except during the 2 to 3 years (IRR, 1.16; 95% CI, 0.82–1.65) and 3 to 5 years (IRR, 1.12; 95% CI, 0.87–1.46) after the index date. A relative increase in visits to pulmonologists was observed beginning five years after diagnosis and thereafter. Figure 3 illustrates a rise in the IRRs of all subspecialty billings in the 15- to 21-year time period, concordant with the increases seen with diagnostic imaging of the chest and PFTs. The absolute incidence rates for outpatient physician visits is presented in Supplementary Table 5.

Discussion

In this population-based retrospective study, we describe increased rates of all-cause hospital admissions, ED visits, outpatient physician (generalist and specialist)

Figure 2

Incidence rate ratio of pulmonary specific healthcare services utilization for primary differentiated thyroid cancer patients. (A) Overall and (B) stratified by radioactive iodine therapy. d, days; y, years; RAI, radioactive iodine therapy. A full colour version of this figure is available at <https://doi.org/10.1530/ERC-19-0463>.

visits, and pulmonary-related diagnostic testing, among DTC patients during the first 21 years of survivorship compared to matched population controls. Given the generally favorable prognosis of CAYA DTC, these results were somewhat unanticipated. Temporal trends in the incidence rate utilization of healthcare services were noted over the entire follow-up period, with the largest IRR in the period immediately following the diagnosis of DTC, decaying as time from treatment elapsed. These findings are not unexpected, as the most intense interaction with the health system would be expected in close temporal proximity to initial treatment of DTC with tapering utilization thereafter. We did, however, observe a sustained excess utilization of all modalities of health service late into survivorship, long after a period wherein such utilization would be anticipated as part of routine surveillance. In contrast, usage of abdominal/pelvic CT demonstrated no clear trend over time, rather IRR fluctuated between two and four over the entire duration of follow-up (Supplementary Fig. 1).

Survivors of CAYA DTC demonstrated an overall IRR of CXR and pulmonary CT utilization of 2.7 (95% CI, 2.6–2.8) and 17.5 (95% CI, 15.8–19.3) times greater, respectively, than matched population controls who did not experience cancer. Heightened utilization of diagnostic medical imaging seen in our study align

with other studies in young adults which have defined patterns of diagnostic imaging in long-term survivors of AYA cancer (Daly *et al.* 2015). A recent study by Daly and colleagues (Daly *et al.* 2015) report the diagnostic imaging rates in long-term survivors of thyroid carcinoma were 1.32 (95% CI, 1.26–1.38) and 1.93 (95% CI, 1.73–2.16) times higher for CXR and chest CT, respectively, among AYAs aged 20–44 years compared to cancer-free controls after 5–15 years post diagnosis. While our study focused exclusively on pulmonary-related diagnostic imaging in CAYAs (aged 29 and younger), both studies demonstrate that individuals who experience thyroid cancer early in life interact with the healthcare system more frequently than the general population, which persists long into survivorship.

Importantly, while these data identify increased utilization of the healthcare system by DTC survivors, they do not specifically identify increased morbidity. In considering diagnostic testing (i.e. imaging, PFTs), we cannot exclude a high rate of testing that is not justified by underlying disease. Further exploration of this may identify an opportunity for significant cost-savings by reduction of unnecessary testing through clinician and patient education. Alternatively, it may identify a reservoir of pulmonary disease that has thus far gone undescribed. Of late, the principal of ‘Choosing Wisely’

Table 2 Utilization of pulmonary-related diagnostics.

Time period	Cases				Population controls				Incidence rate ratio (IRR)			
	No.	Person-time (years)	CT		Rate	Person-time (years)	CT		Rate	X-ray	Rate	PFT
			Rate	Rate			Rate	Rate				
30 days to <90 days	2456	403	126.5	701.9	64.5	24,560	1.0	69.5	30.8	127.5 (46.1–352.8)	10.1 (8.6–11.9)	2.1 (1.4–3.2)
90 days to <180 days	2451	603	119.5	312.0	39.8	24,508	1.7	72.9	33.7	72.0 (37.2–139.5)	4.3 (3.6–5.1)	1.2 (0.8–1.8)
180 days to <1 year	2442	1234	81.0	241.4	53.5	24,414	2.1	72.9	27.0	38.4 (25.0–59.2)	3.3 (2.9–3.8)	2.0 (1.5–2.6)
1 to <2 years	2421	2330	67.8	218.1	46.4	24,194	2.4	70.4	27.1	27.7 (20.5–37.5)	3.1 (2.8–3.4)	1.7 (1.4–2.1)
2 to <3 years	2217	2110	48.8	174.9	46.4	22,142	2.7	69.9	26.3	18.4 (13.3–25.4)	2.5 (2.2–2.8)	1.8 (1.4–2.2)
3 to <5 years	2004	3610	52.1	186.4	43.5	20,003	3.4	73.3	29.0	15.2 (12.1–19.1)	2.5 (2.3–2.8)	1.5 (1.3–1.8)
5 to <10 years	1630	6175	41.0	169.9	46.2	16,248	2.9	77.4	27.5	14.1 (11.6–17.0)	2.2 (2.1–2.3)	1.7 (1.5–1.9)
10 to <15 years	880	3027	37.0	167.5	50.9	8738	4.1	79.6	25.0	8.9 (6.9–11.6)	2.1 (1.9–2.3)	2.0 (1.7–2.4)
15 to 21 years	378	923	20.6	147.3	55.3	3736	2.5	37.4	10.6	8.2 (4.4–15.0)	3.9 (3.2–4.8)	5.2 (3.7–7.3)
Overall	2456	20,414	51.7	196.5	47.5	24,560	3.0	73.1	26.7	17.5 (15.8–19.3)	2.7 (2.6–2.8)	1.8 (1.7–1.9)

IRR, incidence rate ratio; PFT, pulmonary function tests; Rate, per 1000 person-years.

Figure 3

Fee-for-service physician billing for primary differentiated thyroid cancer patients. d, days; y, years. A full colour version of this figure is available at <https://doi.org/10.1530/ERC-19-0463>.

has challenged conventional medical practice, advocating clinicians to perform only necessary diagnostics in an effort to reduce healthcare overuse (Cassel & Guest 2012, Coon *et al.* 2019, Morgan *et al.* 2019). Paradigm shifts eliminating CT scans in other favorable-outcome pediatric cancer surveillance programs have demonstrated that survival is not compromised, while affording a reduction in radiation exposure and associated healthcare costs (Mullen *et al.* 2018); such efforts may therefore apply to the DTC population as well.

While a true excess of medical complexity is likely among survivors, other explanations for increased access to the healthcare system also likely contribute to the observed excess. First, lifelong surveillance for tumor recurrence is advocated, generating an obligate, albeit small, increase in HSU. In addition, most survivors in this cohort underwent total thyroidectomy and require routine monitoring of thyroid replacement in the context of visit to primary-care physician or specialists. Additionally, we speculate that there is likely a referral bias where primary care providers' identification of patients as cancer survivors may prompt a lower threshold to investigate or refer medical complaints that may not have been otherwise referred, absent a cancer history.

One must also consider survivors' perceptions of medical vulnerability and its contribution to increased HSU (Morley & Goldfarb 2015, Goldfarb & Casillas 2016). Evron and colleagues recently demonstrated

differences in rates of physician visits, ultrasounds and RAI scans among DTC survivors based on an individuals' propensity to 'minimize' vs 'maximize' health risk in the post-operative phase (Evron *et al.* 2019). AYAs experience more fear of recurrence than adult survivors of cancer in general, with up to 85% of AYA survivors expressing recurrence fear (Yang *et al.* 2019). Cancer-related worry has also been described among AYA survivors of DTC (Bresner *et al.* 2015). This cancer-related worry and fear of cancer recurrence translates into increased healthcare utilization in survivors (Lebel *et al.* 2013). Indeed, health-seeking behaviors among DTC survivors may contribute to the excess utilization observed in the current study (Evron *et al.* 2019).

Substantial differences in HSU were observed between RAI and non-RAI treated patients in the early time periods after diagnosis. While previous studies of RAI therapy support an increased rate of HSU early in treatment (Haymart *et al.* 2011), it does not fully explain the heightened utilization we observed in individuals who did not undergo RAI therapy, nor can it explain the sustained excess utilization 5+ years into survivorship.

Patients in this cohort who underwent RAI therapy had increased rates of pulmonary imaging and a higher incidence of hospitalizations and ED visits. A proportion of this group will have had distal (primarily pulmonary) metastatic disease, which would justify ongoing thoracic imaging. However, the 56.6% of patients who underwent RAI in this cohort far exceeds the estimated 7.6–27% (Hogan *et al.* 2009, Golpanian *et al.* 2016) with pulmonary metastases. Thus, by inference, a majority of patients treated with RAI had M0 disease.

RAI therapy is associated with an increased risk of secondary malignancy, including that of the hematopoietic system, gastrointestinal tract and salivary glands (Sawka *et al.* 2009). In this cohort, we previously reported a total of 17 patients with secondary malignancies (Pole *et al.* 2017). This low incidence is therefore unlikely to have contributed substantially to healthcare utilization in the current analysis. Pulmonary fibrosis may develop as a consequence of RAI treatment of patients with diffuse iodine-avid pulmonary metastases, particularly after multiple courses and/or high cumulative exposure (Albano *et al.* 2017). Changes in PFTs have been associated with RAI therapy and pulmonary metastases of DTC (Jang *et al.* 2015). Thus, a causal link between increased pulmonary diagnostic testing and respiratory disease is plausible, albeit not demonstrated in the current study.

A common observation in this DTC survivor cohort was a decaying rate of HSU as time from diagnosis

elapsed, with a noticeable upward inflection in usage of all modalities of in the period 15–21 years post diagnosis. Negative-tracer results from abdominal CT scans did not mimic this trend (Supplementary Fig. 1). Pregnancy and childbirth, genitourinary diseases, and digestive system diseases were identified as main reasons for hospital admission, and there were no differences in the diagnostic reasons in later years of our study between DTC patients and population controls (Supplementary Table 3). Late into survivorship, DTC patients were hospitalized at a higher rate than matched population controls, although indications for admission are comparable (Fig. 2 and Supplementary Table 3). While we report IRRs for HSU relative to matched controls, absolute incidence rates for all HSU and pulmonary-related utilization presented in Supplementary Tables 2, 4 and 5 illustrate that the incidence of HSU for controls was consistent throughout the study period, whereas among DTC cases it remained higher.

This study benefits from the use of a provincially mandated cancer registry, permitting population capture of thyroid carcinomas diagnosed between 1992 and 2011. We were also able to capture all healthcare system interactions of individuals in our cohort using physician billing records and administrative databases in our single-payer healthcare system. This allowed the comprehensive monitoring of HSU among affected patients from the time of diagnosis date until the end of study.

While this matched cohort study design robustly controls for baseline confounding by normalizing against a control population, several limitations must be considered when interpreting the results of this study. First, the use of population-based administrative databases allowed the assessment of a large CAYA DTC cohort longitudinally at the expense of detailed individual-level data. Second, the clinical care of DTC evolved over the 21-year period of study with varying approaches to treatment and post-treatment surveillance. Third, this population-level data set does not capture *individual* cancer staging, precluding an association between stage and utilization, nor can these data associate individual therapeutic exposures such as RAI (or administered activity) with subsequent health or HSU outcomes. Finally, response to therapy and/or relapses in disease could not be determined and limited our ability to control for advanced disease, which may have confounded healthcare utilization analysis.

Together, these observations identify that survivors of CAYA DTC interact more frequently with the healthcare system than matched population controls. This is true of ED visits, hospital admissions and outpatient

physician visits. Survivors also undergo more frequent thoracic imaging, suggesting the possibility of excess pulmonary risk, although this is speculative at this point. Not surprisingly, access to the healthcare system is greatest immediately after diagnosis and decays over time, yet utilization never returns to levels observed in population controls. Cross-sectional and/or prospective longitudinal studies of survivors and their medical needs will ultimately be required to provide a better resolution of this question; however, this study raises the possibility of excess morbidity among survivors of CAYA DTC.

We cannot explain the late inflection in usage, however, rigorous re-examination of the primary data and comparison to other modes of healthcare utilization suggest it to be a genuine signal. Future research should explore the long-term adverse events of DTC therapy in children and AYAs, 15+ years into survivorship, which could further identify late sequelae and healthcare system use. Furthermore, studies should explore the economic impact of DTC survivorship on the healthcare system, and identify opportunities for optimization of resource utilization.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/ERC-19-0463>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

G D, J D W, and J D P conceived and designed the study. G D and A M Z procured the study data set and performed the data analysis. J D P and J D W supervised data analyses. G D wrote the first draft of the manuscript and all authors contributed to subsequent drafts and approved the manuscript before submission for publication. All authors had full access to the study data and vouch for the integrity and accuracy of the analysis. J D W and J D P: Co-senior authors.

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