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Trends in thyroid cancer: Retrospective analysis of incidence and survival in Denmark 1980–2014

Christian Mirian[a,*], Christian Grønhøj[a], David Hebbelstrup Jensen[a], Kathrine Kronberg Jakobsen[a], Kirstine Karnov[a], Jakob Schmidt Jensen[a], Christoffer Holst Hahn[a], Tina Agander Klitmøller[b], Jens Bentzen[c], Christian von Buchwald[a]

[a] Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark
[b] Department of Pathology, Head and Neck Cancer, Rigshospitalet, University of Copenhagen, Denmark
[c] Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark

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ABSTRACT

Background: Thyroid cancer incidence has been reported to be increasing since the 1970 s. The aim of this study was to investigate the change in incidence and survival from 1980 to 2014 in Denmark.
Methods: We identified patients registered with thyroid cancer in the period 1980–2014. We evaluated the age-adjusted incidence rate (AAIR) and the average annual percentage change (AAPC), constructed age–period–cohort models (APCs), and evaluated relative survival (RS).
Results: We included 5139 patients. The AAIR was 1.6 cases per 100,000 in 1980 and 4.5 cases in 2014 with an AAPC of 3.4%. The AAIR for papillary carcinomas (n = 2864) quintupled in the study period, and accounts for most of the observed increase in incidence with an AAPC of 4.9%. Follicular carcinomas (n = 920) nearly tripled in AAIR and had the second greatest increase in AAPC. Papillary carcinomas had the best prognosis with 1-year and 5-year RSs of 95% and 91%, followed by the follicular carcinomas with 1-year and 5-year RSs of 90% and 80%, respectively. Anaplastic carcinomas (n = 320) had the worst prognosis with 1-year and 5-year RSs of 18% and 12%. We found a significant age effect in the APC model for the incidence of thyroid cancer but no significant cohort or period effects.
Conclusion: The incidence of thyroid cancer is rising. This is primarily attributable to an increase in papillary carcinomas. The relative survival has improved significantly in Denmark since 1980. The cause of the increasing incidence remains to be established, but enhanced diagnostic scrutiny and increased iodine intake may be influential.

1. Introduction

Thyroid cancer is the most common endocrine malignancy in the Western world [1]. Its incidence has been increasing for nearly 3 decades in most developed countries, while the total mortality has decreased [2].

Thyroid cancer often manifests as a palpable nodule which is a frequent clinical presentation; it has a prevalence of 4–7% among the Western adult population. Roughly 5% of palpable thyroid tumors are malignant, and are nearly three times more frequent in women than in men [3].

The WHO categorizes thyroid cancer into nine subtypes based on histology. The differentiated thyroid cancers comprise the vast majority of histological types and are associated with an excellent prognosis; in contrast, the anaplastic carcinoma has a poor prognosis [5].

The increase in thyroid cancer is almost exclusively attributable to an increase in papillary carcinomas. The advancements in diagnostic methods, with the implementation of advanced imaging modalities (e.g. ultrasound and PET-CT) in the past decades, have led to the recognition of papillary microcarcinomas (< 1 cm). This is the group of carcinomas that has predominantly increased, and the diagnosis usually occurs incidentally [2,6].

The overall survival rate of thyroid cancer has improved in parallel with the increasing incidence [2]. The introduction of iodine therapy is among the improved treatment modalities for differentiated thyroid cancer [7]. In Denmark, thyroid cancer is treated at highly specialized university centers based on a multidisciplinary collaboration between head and neck surgeons, oncologists, pathologists, nuclear physicians,

* Corresponding author at: Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.
E-mail address: christian.mirian.larsen@regionh.dk (C. Mirian).

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Table 1
Univariate and multivariate Cox regression analyses of overall survival for patients with thyroid cancer in Denmark 1980–2014.

			Univariate		Multivariate	
	Cases	Events	HR (95%CI)	p	HR (95%CI)	p
Total	5139	1919				
Male	1455	651	Ref		Ref	
Female	3684	1288	0.86 (0.78; 0.94)	0.001	0.91 (0.82; 1.00)	0.055
Papillary carcinomas	2854	649	Ref		Ref	
Follicular carcinomas	920	401	1.47 (1.30; 1.67)	< 0.0001	1.51 (1.33; 1.71)	< 0.0001
Low diff. carcinomas	14	2	0.53 (0.13; 2.13)	0.37	0.63 (0.16; 2.51)	0.51
Anaplastic carcinomas	341	316	6.22 (5.43; 7.13)	< 0.0001	6.16 (5.30; 7.18)	< 0.0001
Medullary carcinomas	352	181	2.02 (1.71; 2.39)	< 0.0001	1.93 (1.64; 2.29)	< 0.0001
Non-epithelial tumors	45	37	3.50 (2.51; 4.89)	< 0.0001	3.80 (2.69; 5.36)	< 0.0001
Secondary tumors	571	331	1.74 (1.52; 1.99)	< 0.0001	1.76 (1.53; 2.02)	< 0.0001
Unclassified tumors	42	22	1.08 (0.71; 1.67)	< 0.0001	0.99 (0.64; 1.52)	0.95
Age 00–09	8	0	Inf	Inf	Inf	Inf
Age 10–19	101	1	Ref		Ref	
Age 20–29	394	65	0.66 (0.40; 1.08)	0.09	0.69 (0.42; 1.14)	0.15
Age 30–39	798	123	0.44 (0.27; 0.70)	< 0.001	0.47 (0.29; 0.76)	0.001
Age 40–49	970	199	0.43 (0.27; 0.70)	< 0.001	0.46 (0.29; 0.73)	< 0.001
Age 50–59	864	295	0.57 (0.36; 0.89)	0.01	0.59 (0.37; 0.94)	0.02
Age 60–69	844	426	0.68 (0.43; 1.07)	0.09	0.58 (0.37; 0.91)	0.02
Age 70–79	733	496	0.72 (0.46; 1.14)	0.16	0.49 (0.31; 0.78)	0.002
Age 80–89	376	271	0.57 (0.36; 0.91)	0.01	0.38 (0.24; 0.60)	< 0.0001
Age 90–99	51	43	0.60 (0.35; 1.02)	0.06	0.36 (0.21; 0.62)	< 0.0001
Years 1980–1984	531	363	Ref		Ref	
Years 1985–1989	489	299	0.79 (0.68; 0.92)	0.002	0.78 (0.66; 0.90)	0.001
Years 1990–1994	532	276	0.68 (0.58; 0.80)	< 0.0001	0.74 (0.63; 0.87)	< 0.001
Years 1995–1999	640	288	0.64 (0.55; 0.75)	< 0.0001	0.70 (0.60; 0.82)	< 0.0001
Years 2000–2004	750	272	0.51 (0.44; 0.60)	< 0.0001	0.60 (0.51; 0.70)	< 0.0001
Years 2005–2009	861	230	0.42 (0.35; 0.49)	< 0.0001	0.47 (0.40; 0.56)	< 0.0001
Years 2010–2014	1336	211	0.30 (0.25; 0.36)	< 0.0001	0.34 (0.29; 0.40)	< 0.0001

HR, hazard ratio; 95%CI, 95% confidence interval; Ref, reference; Inf, infinite.

endocrinologists, physicians, and radiologists. In Denmark, surgery is the primary choice of treatment for the various types of thyroid cancer; low-risk patients undergo hemithyroidectomy, whereas high-risk patients undergo total thyroidectomy and neck dissection (most often followed by treatment with radioactive iodine) [8].

This study presents trends in thyroid cancer based on age-adjusted incidence rates, age–period–cohort effects, and survival in a national setting covering more than three decades.

2. Materials and methods

All Danish citizens are issued with a unique personal identification (CPR) [9] which enables accurate individual linkage of data between registries. We included patients registered in the Danish Cancer Registry (DCR) diagnosed with a thyroid cancer between 1980 and 2014. The DCR was established in 1943 to ensure nationwide registration of all cancers. It has been mandatory to report to the DCR since 1987. Information on age at diagnosis, date of diagnosis, cancer location, and histology was derived from the DCR. Vital status (e.g. date of death or date of emigration) was obtained through linkage with the CPR.

Patients were categorized into nine histological groups defined by the WHO in 2018 [10] (Supplementary Table S1). This histological classification is adopted by the Danish National Guidelines and reflects the clinical approach to thyroid cancer nationwide. The study was approved by The Danish Data Protection Agency.

2.1. Statistical analyses

Statistical analyses were performed with R-Studio v. 1.0.136.

Age-specific population counts were derived from the National Statistical Database [9]. We calculated age-adjusted incidence rates (AAIRs) per 100,000 inhabitants using the direct method with R statistics and the package EpiTools using the WHO World Standard Population as reference [11]. We used Joinpoint Trend Analysis Soft v. 4.2.0.2 to analyze the average annual percentage change (AAPC). We assumed the growth to be logarithmic. The joinpoint regression analysis estimates possible joinpoints (significant change in trend, i.e. 'trend breaks') with either a straight line or a segmented line if there were trend breaks. We allowed a maximum of five joinpoints in the analysis of AAPCs from 1980 to 2014.

Relative survival is defined as the all-cause observed survival in the cancer population under study divided by the expected survival of a comparable group in the general population. The relative survival is then calculated as the observed survival rate to the expected survival rate in Denmark matched by age, sex, and calendar year. Relative survival is therefore a measure for the excess survival associated with a diagnosis of cancer. Patients who were alive at the last date of follow-up were censored at this date. The date for last follow-up was 1st December 2016. Patients who emigrated during time of follow-up were censored. We tested the proportional hazards assumption of the relative survival models by Brownian Bridge statistics.

We also evaluated the effect of age, calendar period, and birth cohort on incidence using an age–period–cohort model. The study populations were categorized into 10-year age groups and 5-year calendar-period groups according to their age and date of diagnosis, respectively. We defined the reference year to be 1900 for the cohort effects. The reference year for period effects was 1982.5.

We restricted the analyses to patients between 30 and 84 years of age, because the numbers of cases before the age of 30 and after the age of 84 were too small and could potentially produce statistical instability.

3. Results

We identified 5139 patients registered with thyroid cancer between 1980 and 2014 in the DCR. The mean age at diagnosis was 54 years, with a female-to-male ratio of 2.5:1 (females 72%, n = 3684). Papillary thyroid carcinoma was the most frequent histology (56%, n = 2864)