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Birthweight and risk of thyroid cancer and its histological types: A large cohort study

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ABSTRACT

Background: The aetiology of thyroid cancer is poorly understood, but it is possible that this malignancy has origins early in life. It is, however, currently unknown if birthweight, as an indicator of prenatal growth, is related to thyroid cancer risk.
Objective: To investigate if birthweight is associated with the later risk of thyroid cancer and its histological types.
Methods: 246,141 children (120,505 girls, 125,636 boys) from the Copenhagen School Health Records Register, born 1936–1989, were prospectively followed in the Danish Cancer Registry. Cox regressions were used to estimate hazards ratios (HR) and 95% confidence intervals (CI).
Results: During follow up, 241 individuals (172 women, 69 men) were diagnosed with thyroid cancer (162 papillary, 53 follicular). Birthweight was significantly and positively associated with risk of thyroid cancer overall (HR = 1.30 [95% CI: 1.03–1.64] per kilogram). There were no sex differences in the associations. Birthweight was positively and significantly associated with follicular thyroid cancer (HR = 1.74 [95% CI: 1.07–2.82] per kilogram), and although there was an indication of a positive association, it did not reach statistical significance for the more common papillary type (HR = 1.20 [95% CI: 0.90–1.59] per kilogram).
Conclusion: A heavier weight at birth is associated with an elevated risk of total and follicular thyroid cancer, which underscores that prenatal exposures may be important in thyroid cancer aetiology.

1. Introduction

Thyroid cancer is one of the less frequent cancers, nonetheless, it is the most common endocrine malignancy with more than 298,000 incident cases worldwide in 2012 [1]. During the last decades the incidence has steadily increased in numerous countries, including Denmark [2,3]. These increases are partly attributable to diagnostic changes and improvements, but potentially also caused by trends in certain lifestyle and environmental factors [4–6].

The aetiology of thyroid cancer is currently not fully understood and only a few risk factors have been established. The only modifiable risk factors are exposure to ionizing radiation and adult overweight and non-modifiable risk factors include age, gender, race/ethnicity, and genetics [7–9]. Emerging evidence suggests that hormonal and reproductive factors are important for thyroid cancer development, as the disease is most common among women, with the highest female-to-male ratio for incidence occurring at ages between menarche and menopause [7,10].

Thyroid cancers are generally diagnosed at younger ages compared with most other adult cancer forms. As most previous studies focused on risk factors acting in mid- and late-adulthood, they may not have evaluated the most relevant time window for thyroid carcinogenesis [7]. Previously we found, in agreement with the evidence on adult body size [9,11], that heavier children had an increased risk of thyroid cancer [12]. Evidence suggests that size at birth, as an indicator of prenatal growth, may also be related to the development of many forms of adult cancer [13–15]. Further, as the development of the thyroid gland begins very early in foetal life [16], it is plausible that size already at birth is relevant for thyroid cancer development. Nonetheless, the current evidence is scarce and inconclusive [17,18].

To examine the potential early origins of thyroid cancer, we prospectively investigated the associations between birthweight and the risk of adult thyroid cancer, including its histological types, using a large Danish cohort.

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2. Material and methods

2.1. Cohort

The Copenhagen School Health Records Register (CSHRR) is a unique Danish database including computerized school health records on 372,636 children, born 1930 through 1989 [19]. Virtually all children in both public and private schools in the Copenhagen municipality underwent mandatory health examinations. For children born 1936 onwards their birthweight, as reported by their parent (either from recall or birth records) at the first school health examination, was recorded on their health card. The correlations between parental reported birthweight registered in the CSHRR and medical birth records have been found to be high (above 0.93) [20], emphasising the validity of this information. Childhood weights and heights were measured by trained school physicians or nurses with high precision [19].

2.2. Linkages

Follow-up of children in the CSHRR was based on record linkages to national health registers using the unique government-issued identification number assigned to all Danish residents alive in 1968 or born thereafter [21]. These identification numbers were recorded on the health cards for children attending school in 1968 or later and retrieved for those leaving school prior to this time. Approximately 89% of the children in the cohort had an available identification number. Information on vital status was obtained from the Danish Civil Registration System [21].

Through linkages to the Danish Cancer Registry, which has almost complete coverage due to compulsory registration, and a very high validity as most tumours are morphologically verified, incident thyroid cancers were identified [22]. Due to a recoding project of the Danish Cancer Registry, International Classification of Disease (ICD) version 10 codes and ICD for Oncology version 3 (ICD-O-3) morphology codes were available for thyroid cancers diagnosed from 1968 onwards. In the current study, thyroid cancers diagnosed from 1968 to 2015 were included. Thyroid cancer was defined as malignant carcinoma of the thyroid gland and classified using the C73.9 disease code. Using ICD-O-3 morphology codes, thyroid cancers were sub-classified into the histological types of papillary (8050, 8260, 8340), follicular (8290, 8330, 8331), and other (8010, 8020, 8021, 8070, 8345, 8510). Individuals without morphology information were reclassified as non-cases and censored at the time of diagnosis (n = 6).

2.3. Study population

Individuals eligible for this study were born 1936–1989, had an available identification number and were alive and living in Denmark at the age of 15 years or older (Supplementary Fig. 1). Among these 290,946 individuals, we excluded individuals with a diagnosis of thyroid cancer before age 15 years (n = 2) or prior to 1968 (n = 1), with missing birthweight information (n = 39,960) and with birthweights outside of the reliable range of 2.0–5.5 kg (n = 4842) leaving a total of 246,141 individuals (120,505 women and 125,636 men) for analyses. From this group, 233,807 individuals (114,461 women and 119,346 men) had information available on body size at age 7 years.

Follow-up began at the age of 15 years or the age in 1968, whichever came later, and ended at the age of a diagnosis of thyroid cancer, emigration, death, loss to follow-up, or 31 December 2015, whichever occurred first.

2.4. Statistical analyses

Characteristics of the cohort are presented as means and standard deviations of birthweight across time and by sex. The associations between birthweight and risk of thyroid cancer, including its histological types, were investigated using Cox proportional hazard models and presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Age was used as the underlying time scale and analyses were stratified by birth cohort and sex (when applicable). The linearity of the associations was assessed using linear splines with 2 knots positioned at 3.25 and 3.75 kg using the likelihood ratio test. We did not detect non-linearity in any of the associations (all p-values ≥ 0.23), thus, associations are presented per kilogram of birthweight. Associations are also presented by birthweight categories (2.0–3.25, 3.26–3.75, 3.76–5.5 kg) for comparison with other studies examining birthweight associations. The assumption of proportional hazards in the associations were investigated by testing if these differed by categories of age at diagnosis using the likelihood ratio test. Potential interactions by sex and birth cohort, respectively, on the associations between birthweight and risk of thyroid cancer were similarly investigated using the likelihood ratio test. As birthweight and childhood body mass index (BMI) are correlated [23], in a subset of individuals with information on both birthweight and BMI at age 7 years, we examined the effect of adjusting the birthweight and thyroid cancer associations for childhood BMI. These analyses showed that the birthweight and thyroid cancer associations were essentially unchanged (results not shown).

Table 1
Birthweight characteristics by birth cohort and sex of individuals in the Copenhagen School Health Records Register born1936–1989.

	Women and men			Women			Men		
	n	Birthweight (kg)		n	Birthweight (kg)		n	Birthweight (kg)	
Year of birth		Mean	SD		Mean	SD		Mean	SD
Overall	246,141	3.37	0.54	120,505	3.31	0.52	125,636	3.43	0.55
1936-1939	21,200	3.43	0.57	10,081	3.37	0.56	11,119	3.48	0.57
1940-1944	39,649	3.40	0.55	19,466	3.33	0.53	20,183	3.46	0.56
1945-1949	41,504	3.39	0.55	20,467	3.32	0.53	21,037	3.45	0.56
1950-1954	30,012	3.35	0.55	14,815	3.29	0.53	15,197	3.41	0.55
1955-1959	24,330	3.33	0.54	11,891	3.27	0.52	12,439	3.39	0.55
1960-1964	19,610	3.35	0.53	9,655	3.28	0.51	9,955	3.41	0.55
1965-1969	17,720	3.36	0.52	8,763	3.29	0.51	8,957	3.42	0.53
1970-1974	14,770	3.36	0.52	7,245	3.29	0.50	7,525	3.42	0.53
1975-1979	12,459	3.36	0.52	6,069	3.30	0.49	6,390	3.41	0.53
1980-1984	11,142	3.35	0.52	5,304	3.28	0.49	5,838	3.41	0.53
1985-1989	13,745	3.40	0.52	6,749	3.34	0.50	6,996	3.46	0.53

SD = standard deviation; kg = kilogram.

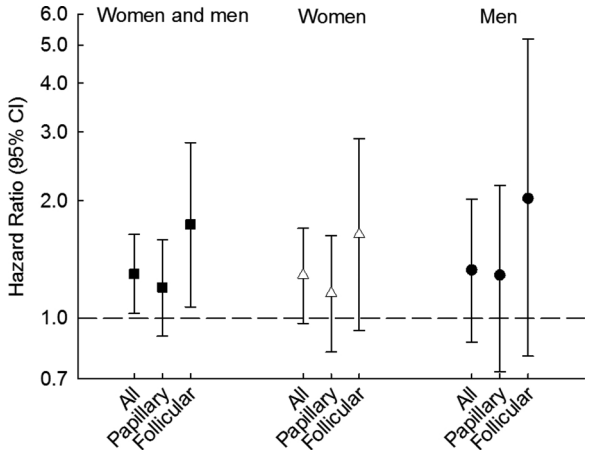

Fig. 1. Associations between birthweight (per kilogram) and thyroid cancer overall and by histological type for women and men combined and by sex[a].

3. Results

Among the 246,141 individuals (120,505 women and 125,636 men) included in the study, the mean birthweight varied little across time in women and men (Table 1). During 47 years and 9.1 million person-years of follow up, 241 individuals (172 women and 69 men) were diagnosed with thyroid cancer, of which 162 were papillary (117 women and 45 men), 53 follicular (40 women and 13 men) and the remaining 26 were other histological types. The median age at diagnosis with thyroid cancer overall was 48 years (range: 16–78 years) for both sexes combined, and 48 years (range: 16–78 years) for women and 48 years (range: 22–76 years) for men. For the papillary type, the median age at diagnosis was slightly lower, namely 46 years (range: 16–78 years), and slightly higher for the follicular type at 49 years (range: 27–69 years), for women and men combined.

Birthweight was significantly and positively associated with the risk of thyroid cancer overall, with a HR of 1.30 (95% CI: 1.03–1.64) per kilogram increase (Fig. 1, Supplementary Table 1). We similarly observed that birthweight was significantly and positively associated with the risk of follicular thyroid cancer, with a higher HR of 1.74 (95% CI: 1.07–2.82) per kilogram (Fig. 1, Supplementary Table 1). Nonetheless, the confidence intervals for the associations with overall thyroid cancer and the follicular type were overlapping. In contrast, although we found similar indications that birthweight and papillary thyroid cancer was positively associated, the association did not reach statistical significance (HR = 1.20 [95% CI: 0.90–1.59] per kilogram) (Fig. 1, Supplementary Table 1). We did not identify violations of the proportional hazards assumption (all p-values $\geq$ 0.20), sex interactions (all p-values $\geq$ 0.65) or birth cohort effects (all p-values $\geq$ 0.11) in any of the associations.

Although there were suggestions of positive associations between birthweight and thyroid cancer overall and its histological types for both women and men individually, none of these reached statistical significance (Fig. 1, Supplementary Table 1). When birthweight was modelled categorically, in comparison with children with an average size at birth, children in the highest birthweight category had an increased risk of follicular thyroid cancer and a borderline significantly increased risk of thyroid cancer overall in analyses combining women and men, whereas no significant associations were found for papillary thyroid cancer as well as in analyses for women and men separately (Table 2).

4. Discussion

In this large cohort study, birthweight was positively associated with the risk of thyroid cancer overall. When histological types were examined, we found that birthweight was positively associated with follicular thyroid cancer, despite a very low case number. In contrast we did not detect significant associations between birthweight and the most common histological type of papillary thyroid cancers.

Accumulating evidence during the last decades supports that early life factors, including size at birth as an indicator of foetal growth, are linked to the incidence and mortality of several cancers in adult life [13–15]. Owing to the rarity of thyroid neoplasms, often precluding investigations of histological types, and partly due to the scarcity of large cohort studies with prospective evaluations of exposures, much remains unknown about the associations between birthweight and thyroid cancer. In a study by Johnson et al. [17] the authors investigated associations between birthweight and childhood carcinomas ($\leq$14 years), including 159 thyroid cancers, and did not find that a high birthweight increased the risk of thyroid cancer (odds ratio [OR] = 1.02 [95% CI: 0.87–1.20] per 0.5 kg). The aetiology of childhood thyroid carcinomas is likely different from thyroid cancers occurring later in life making these findings less comparable with those of the present study, where the mean age at diagnosis was 49 years. A study by Crump et al. [18] found that size at birth of the offspring was positively related to risk of *maternal* thyroid cancer, however, these findings are not directly comparable with our study.

In another study using the CSHRR we previously found that a greater BMI during childhood ages was significantly and positively associated with risk of thyroid cancer overall and papillary but not follicular thyroid cancer [12]. Since a high birthweight is positively associated with childhood overweight among both boys and girls [23], we had hypothesized that birthweight and papillary thyroid cancer in particular would be positively associated. Somewhat surprisingly, we found that although there were indications that birthweight was positively associated with risk of papillary thyroid cancer, the association only reached statistical significance for the less common follicular thyroid cancer

A potential underlying mechanism that could explain the association observed between birthweight and risk of follicular thyroid cancer in our cohort study is fetal iodine deficiency. Iodine deficiency can lead to an increased risk of thyroid dysfunction in the mothers and offspring, which may, among other things, affect fetal growth [24]. In 1998, a national voluntary salt iodization program was introduced as the population of eastern Denmark, including Copenhagen, had been mildly iodine deficient while western Denmark was moderately iodine deficient. Following a mandatory fortification program initiated in 2000, the population iodine intake was found to be adequate in most groups [25]. Even in iodine sufficient populations, however, pregnant women remain vulnerable to iodine deficiency due to the high iodine requirements of the fetus. Iodine status has long been hypothesized to play a role in thyroid carcinogenesis, based on ecological studies showing higher follicular thyroid cancer incidence in areas of iodine deficiency and a higher ratio of papillary to follicular thyroid cancer incidence following regional iodine fortification programs [26–28]. Thus, it is plausible that iodine status is important in the link between birthweight and thyroid cancer risk, however, this and other mechanisms remain speculative and need to be elucidated further.

Among the major strengths of the present study are the available information on birthweight on a large unselected population of Copenhagen school children born before, during and after World War II. Another strength is that information on birthweight was available from parental recall of birthweight or birth records, with a short period of time of recall, which has a very high accuracy [20,29–31], as compared with studies asking individuals to recall their own birthweight several decades later. Additionally, record linkages via unique identification numbers to the high-quality national Danish Cancer Registry enabled almost complete follow-up for thyroid cancer incidence, starting from young ages, and included medically-verified histological types. This study might, however, be limited by a lack of information on gestational age and birth length as well as pregnancy characteristics

Table 2
Associations between categories of birthweight and thyroid cancer overall and by histological type for women and men combined and by sex[a].

		Women and men[b]					Women					Men				
Type	Categories	N	Cases	HR	95 % CI	p[c]	N	Cases	HR	95 % CI	p[c]	n	Cases	HR	95 % CI	p[c]
All	2-3.25 kg	106,069	97	0.92	0.68-1.23		58,021	75	0.96	0.68-1.35		48,145	22	0.82	0.47-1.45	
	3.26-3.75 kg	88,676	83	1.00 (ref.)			42,293	57	1.00 (ref.)			46,383	26	1.00 (ref.)		
	3.76-5.5 kg	51,299	61	1.38	0.99-1.92		20,191	40	1.47	0.98-2.21		31,108	21	1.20	0.68-2.14	
						0.87					0.81					0.23
Papillary	2-3.25 kg	106,166	97	0.90	0.63-1.27		58,021	75	1.02	0.68-1.54		48,145	22	0.63	0.31-1.26	
	3.26-3.75 kg	88,676	83	1.00 (ref.)			42,293	57	1.00 (ref.)			46,383	26	1.00 (ref.)		
	3.76-5.5 kg	51,299	61	1.12	0.74-1.71		20,191	40	1.25	0.74-2.09		31,108	21	0.90	0.44-1.85	
						0.95					0.71					0.72
Follicular	2-3.25 kg	106,166	97	1.04	0.53-2.04		58,021	75	0.98	0.46-2.07		48,145	22	1.31	0.29-5.86	
	3.26-3.75 kg	88,676	83	1.00 (ref.)			42,293	57	1.00 (ref.)			46,383	26	1.00 (ref.)		
	3.76-5.5 kg	51,299	61	2.26	1.14-4.48		20,191	40	2.07	0.93-4.61		31,108	21	2.91	0.73-11.65	
						0.88					0.90					0.51

CI = confidence interval; HR = hazard ratio; kg = kilogram.
[a] Cox proportional hazards regression models stratified by birth cohort.
[b] Additionally stratified by sex.
[c] Test for linearity using the likelihood ratio test for linear splines with 2 knots positioned at 3.25 and 3.75 kgs.

potentially related to foetal growth, such as maternal smoking, weight gain, vitamin supplementation and maternal iodine status during pregnancy. Nonetheless, as these behaviours and factors likely varied across the 54 years of birth included in our study and as we did not detect birth cohort effects, they are unlike to explain the entirety of the associations we observed. Even though birthweight information was available for a large population, the number of individuals registered with a diagnosis of thyroid cancer during follow-up was, unsurprisingly, relatively low, as thyroid cancer is a fairly uncommon cancer. Nonetheless, our study was sufficiently powered to investigate the associations under question. As individuals included in this study were largely Caucasians, our study findings are likely generalizable to many other populations of Western origin.

In conclusion, we found that weight at birth was positively and significantly associated with the risk of thyroid cancer overall and the histological type of follicular thyroid cancer, but only indications of a positive association with the most common histological type of papillary thyroid cancer. Although replication in other populations is needed and the direct clinical implications are limited, these findings aid in our understanding of thyroid carcinogenesis and point to a role of in utero exposures or shared genetic determinants of early life body size on thyroid cancer risk.

Author contributions

JA and JLB conceived and designed the study, JA analyzed the data, JA, CMK and JLB interpreted the data and drafted the manuscript and all authors read and approved the final version of the manuscript.

Statement of ethics

This study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for register-based studies.

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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.2019.07.003.

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