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Opposing effects of thyroid hormones on cancer risk: a population-based study

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Abstract

Objective: The association between dysregulated thyroid hormone function and cancer risk is inconclusive, especially among different age groups and uncommon malignancies. We sought to determine the relation of TSH and free T4 levels with overall cancer risk as well as risk of specific cancer types.

Design and methods: Data on thyroid hormone profile was collected from 375 635 Israeli patients with no prior history of cancer. Cancer cases were identified via the Israel National Cancer Registry. Cox proportional hazards model was used to assess hazard ratios for overall cancer as well as 20 cancer subgroups.

Results: In this study, 23 808 cases of cancer were detected over median follow up of 10.9 years. Among patients younger than 50 at inclusion, TSH in the hyperthyroid range, elevated free T4 and subclinical hyperthyroidism were associated with increased cancer risk (HR: 1.3, 1.28 and 1.31, respectively). In contrast, patients 50 or older with clinical hyperthyroidism were at lower cancer risk (HR: 0.64). Elevated TSH was associated with decreased risk of prostate cancer (HR: 0.67). Log-TSH elevation was associated with decreased risk of thyroid cancer (HR: 0.82) and increased risk of melanoma (HR: 1.11) and uterine cancer (HR: 1.27). Elevated free T4 was associated with increased lung cancer risk (HR: 1.54), while free T4 levels above the normal range and clinical hyperthyroidism were related to lower colorectal cancer risk (HR: 0.59 and 0.08, respectively).

Conclusions: Thyroid hormones display opposing effects on cancer risk, based on patient age and cancer type.

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Introduction

Thyroid hormones are essential for normal growth and development. Disorders of thyroid function are common, affecting an estimated 5% of the general population (1) and are known to be positively correlated with patient age (2). Cancer is a leading cause of death worldwide and active research is conducted for the identification of novel cancer risk factors.

Preclinical research has demonstrated an effect of thyroid hormones on cancer growth. Thyroid hormones were shown to induce *in vitro* proliferation in multiple cancer cell types (3, 4, 5, 6, 7) as well as promote *in vivo* tumor growth (8, 9, 10) and angiogenesis (8, 10, 11, 12). Data from population-based research support an association between dysregulation of thyroid hormone function and cancer risk (13, 14, 15). However, the nature of this relationship remains inconclusive and ill-defined. While hyperthyroidism may be related to increased risk of several common malignancies, such as lung, breast

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and prostate cancer (13, 14, 15, 16, 17), it may also offer a protective effect for others (18, 19). Most population studies relied on measurements of thyroid-stimulating hormone (TSH), the chief regulator of thyroid hormone synthesis, and did not determine the effect of thyroxine (T4), the main hormone produced by the thyroid. Research mainly focused on the most common malignancies and studies were underpowered to assess the association for uncommon cancer types. Moreover, most population studies focused on middle-aged to elderly patients and did not perform a risk analysis for younger patients. As the relative incidence of specific malignancies may vary with age, an analysis of cancer risk in young as well as older patient groups is mandated. Finally, no previous study conducted an adjustment of the statistical analysis for multiple comparisons.

We performed a large exploratory population-based study to determine the relation between TSH and Free T4 (FT4) levels and risk of cancer in different age groups and for multiple cancer types, including assessment of the risk of uncommon malignancies.

Methods

Study population

A population-based historical cohort study was performed, including individuals medically insured by Clalit Health Services (CHS), the largest health maintenance organization in Israel, providing healthcare for 4.6 million residents. CHS has a comprehensive integrated electronic medical database, encompassing all medical information regarding primary care and specialist clinic visits, pharmacy purchasing, laboratory tests and hospital admissions. Diagnoses are captured in the registry by means of diagnosis-specific codes, in accordance with the International Classification of Diseases, Ninth Revision (ICD-9). The current study was conducted in the Sharon-Shomron district of Israel, which accounts for 14.7% of all patients insured by CHS. Adult patients (>18 years) who had a blood test for TSH levels between January 2000 and December 2016 were included. TSH tests are routinely conducted in Israel and one test or more was performed for 68.9% of the district population insured by CHS during the study period. Patients were included at the date of the first TSH test and followed until a diagnosis of cancer, death or the end of follow up (December 31, 2016). We excluded patients who prior to study inclusion were diagnosed with cancer, had a diagnosis of thyroid function disorder (hypothyroidism or hyperthyroidism, per ICD-9 code) or were treated with thyroid hormone altering medication (levothyroxine, liothyronine, propilthiouracil or methimazole), as well as patients with missing gender data. Based on these criteria, 34 734 patients were excluded (Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

Data collection

All patients had blood tests collected for TSH. For FT4, tests available on the date of inclusion were also collected. Data on covariates were collected at baseline and included age, gender, ethnicity (Jewish or non-Jewish), socioeconomic status (low, medium or high income), BMI, smoking status, comorbidities (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, chronic lung disease, chronic liver disease) and thyroid function disorder (hyperthyroidism or hypothyroidism). Data on thyroid hormone altering medication use was collected throughout the study period. Socioeconomic status was defined based on patient's neighborhood of residence. Comorbidities were defined based on ICD-9 codes. Thyroid hormone altering treatment was defined as at least one prescription issued of medication affecting the thyroid hormone axis. Relevant ICD-9 codes are detailed in Supplementary Table 1.

Laboratory measurements

Serum TSH and FT4 levels were measured at the CHS central hormone laboratory using a commercial RIA kit (RIA-gnost® hTSH and free T4, Schering-Cis Bio International, Gif-sur-Yvette, France) with lower limits of detection of 0.01 mIU/L and 0.06 ng/dL, respectively. The normal range was 0.55–4.78 mIU/L for TSH and 0.78–1.55 ng/dL for FT4.

Cancer diagnosis

Data on cancer cases were obtained from the Israel National Cancer Registry (INCR), a pathology-based registry covering the entire Israeli population. Reporting to the INCR has been mandatory since 1982. Data are collected on all malignant neoplasms except basal and squamous cell carcinomas of the skin. Cancer site and morphology are coded according to the codes of the International Classification of Diseases for Oncology, Third Edition (ICD–O-3). Linking patients to the cancer registry

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database was conducted using the unique nine-digit national identification number and was authenticated by first and last name, date of birth and gender. Cancer occurrence was defined as any malignancy (invasive or *in situ*) diagnosed during the study period. Cancer cases were divided into 20 cancer subgroups, defined according to ICD-O-3 topography codes. Cancer site classification is detailed in Supplementary Table 2.

Statistical analysis

Missing data was imputed using the Markov Chain Monte Carlo method to create five imputed datasets that were pooled for analysis. Missingness was <10% for all covariates, except for BMI which was <15%. Multivariable Cox proportional hazard models were constructed to assess the association between thyroid hormones and the risk of cancer. Hazard ratios (HRs) with their 95% CI were determined. Log-log survival curves established that the proportional hazards assumption was met. All models were adjusted for age, gender, smoking status, socioeconomic state, ethnicity, BMI and comorbidities. Analyses were performed separately for TSH and FT4. Risk was determined for both continuous and categorical representations of hormone levels. Due to the skewed distribution of TSH levels, log-transformed data was used for the continuous analysis. For categorical analysis, TSH and FT4 were respectively divided into five groups: three categories within the normal range, one below the normal range and one above the normal range. The largest population group served as reference: the lowest tertile within the normal range for TSH and the middle tertile for FT4. Trends were determined using Spearman correlation between five equally sized TSH and free T4 groups and the multivariate-adjusted HRs, with the lowest level serving as reference. In addition, five thyroid function groups were defined based on both TSH and FT4 levels: Euthyroidism (FT4 and TSH within the normal range), clinical hypothyroidism (FT4 below normal range and TSH above the normal range), subclinical hyperthyroidism (FT4 within normal range and TSH above the normal range), clinical hyperthyroidism (FT4 above normal range and TSH below the normal range) and subclinical hypothyroidism (FT4 within normal range and TSH below the normal range), with the euthyroid groups serving as reference.

Analysis was conducted for overall cancer as well as the 20 predefined cancer subgroups. To allow risk assessment for multiple malignancies while minimizing the risk of false-positivity, a stepwise analysis was performed. The omnibus test of model coefficients (based on Chi-square test) was first conducted to determine the significance for inclusion of the respective thyroid hormone variables (TSH, FT4 or thyroid function groups) in the cancer risk model. Benjamini-Hochberg (BH) correction for the resulting *P*-values was then performed to control the false discovery rate (FDR). BH correction, introduced in 1995, allows for effective control of type I errors in multiple testing scenarios (20). Adjusted hazard ratios based on the Cox model were determined only for cancer groups significant at $P < 0.1$ following FDR correction. Significance was set at $P < 0.05$ for the final analysis. Two subgroup analyses were conducted, one based on gender and another based on patient age at inclusion. As previous studies tended to include middle-aged and older patients (13, 14), we defined two age groups above and below 50 years at inclusion in order to separately assess the risk for young and older adults. Finally, four sensitivity analyses were conducted: excluding the first 2 years of follow up in order to eliminate reverse causality, excluding patients treated with thyroid hormone altering medications during the study period, excluding patients with thyroid cancer and excluding patients with missing data.

All statistical analyses were performed using the SPSS software (version 25, SPSS Inc, Chicago, Ill), except for FDR correction which was performed using R (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the CHS ethics committee in accordance with the Declaration of Helsinki.

Results

The study population consisted of 375 635 patients who underwent a thyroid hormone test during the study period. All included patients underwent TSH testing, and 110 607 patients (29.4%) had FT4 levels. At inclusion, the majority of patients (91.7%) had TSH values within the normal reference range. A higher proportion of patients were women (54.9%), especially at TSH levels above and below the normal reference range, reflecting increased incidence of thyroid disorders in this gender group. Median age at inclusion was 43 (interquartile range, 30–58). Sixty-one percent (229 830 patients) were younger than 50 at inclusion. The most common comorbidities were dyslipidemia (43%), hypertension (25.5%), diabetes mellitus (16.1%) and ischemic heart disease (11.7%) (Table 1). Compared with persons with a TSH level in the normal range, patients in the higher and lower TSH categories

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Table 1 Baseline characteristics of study participants. Data are presented as *n* (%) or as median (IQR).

Variables	Values
n	375 635
TSH, mIU/L	1.90 (1.32–2.72)
Age, years	43 (30–58)
Follow up years	10.9 (6.7–13.6)
BMI, kg/m^2	26.7 (23.5–30.7)
Women	206 081 (54.9%)
Dyslipidemia	160 563 (42.7%)
Hypertension	95 865 (25.5%)
Diabetes mellitus	60 535 (16.1%)
Ischemic heart disease	43 907 (11.7%)
Congestive heart failure	13 073 (3.5%)
Chronic lung disease	11 689 (3.1%)
Cerebrovascular disease	10 458 (2.8%)
Chronic renal failure	10 358 (2.8%)
Chronic liver disease	1019 (0.3%)
Smoking	105 592 (28.1%)
Ethnicity	
Jewish	287 713 (76.7%)
Non-Jewish	87 172 (23.3%)
Socioeconomic status	
Low income	110 392 (32.3%)
Middle income	130 922 (38.4%)
High income	100 143 (29.3%)
Thyroid medication	
Antithyroid treatment	1780 (0.5%)
Thyroid replacement	21 231 (5.6%)

IQR, interquartile range; TSH, thyroid stimulating hormone.

had higher rates of comorbidities (Supplementary Table 3). For 17 776 patients with available data of 3–12 months following the initial test, who did not receive thyroid altering medication, a significant consistency existed for thyroid function group (Spearmen's r, 0.67; $P < 0.0001$). Over a median follow up of 10.9 years, 23 808 cases of cancer were detected throughout 3 687 710 person-years of follow up, affecting 6.3% of the study population. Site-specific cancer cases by age groups and TSH strata are detailed in Supplementary Table 4.

The association of TSH levels with cancer risk is dependent on age and tumor type

The first aim of this study was to identify associations between TSH levels and cancer risk. There was no significant association between log-TSH levels and overall risk of cancer (Table 2). A significant interaction exists between TSH and age in the cancer risk model ($P < 0.001$). Patients younger than 50 at inclusion (Table 3 and Supplementary Table 5) with TSH in the hyperthyroid range (<0.55 mIU/L) were at increased overall risk of cancer, compared with the reference group (adjusted HR: 1.3; 95% CI: 1.12–1.51). Following FDR correction, inclusion of TSH levels in the cancer risk model was significant for prostate cancer, thyroid cancer, melanoma and uterine cancer (Supplementary Table 6) and hazard ratios were determined for these cancer subtypes (Table 2). Patients with TSH in the hypothyroid range (>4.78 mIU/L) were at significantly lower risk of prostate cancer (adjusted HR: 0.67; 95% CI: 0.54 to 0.85). The risk of thyroid cancer decreased with increasing log-TSH levels (adjusted HR: 0.82; 95% CI: 0.75 to 0.9 per unit log-TSH increase) and doubled in patients with TSH in the hyperthyroid range (adjusted HR: 2.01, 95% CI: 1.74 to 2.32). However, a significant trend for thyroid cancer risk was not demonstrated ($P = 0.5$). Log-TSH increase was associated with increased risk of melanoma (adjusted HR:, 1.11; 95% CI: 1.02 to 1.20, P for trend = 0.04) and uterine cancer (adjusted HR: 1.27; 95% CI: 1.13 to 1.41, P for trend < 0.0001). For both malignancies, this effect was mainly driven by increased risk within the normal TSH range. Sensitivity analyses corroborated our findings (Supplementary Table 7). Specifically, results remained significant following exclusion of first 2 years of follow up, suggesting the demonstrated relations were not related to reverse causality. Notably, prostate cancer was the only malignancy for which the association was lost following the exclusion of thyroid altering medication use during the study period.

Free T4 differentially affects cancer risk based on age and malignancy type

We next sought to examine the association between FT4 and cancer risk. Following FDR correction, inclusion of FT4 levels in the cancer risk model was significant for overall cancer as well as for lung cancer and colorectal cancer (Supplementary Table 6). Hazard ratios were determined for overall cancer and both cancer subtypes (Table 4). Overall risk of cancer was slightly higher for patients with FT4 in the upper tertile of the normal range (adjusted HR: 1.1; 95% CI: 1.03–1.17). A significant interaction was demonstrated between FT4 and age in the cancer risk model ($P = 0.003$). In patients younger than 50, elevated FT4 was associated with an increased overall cancer risk (adjusted HR: 1.28; 95% CI: 1.1–1.49 per unit FT4 increase), while patients 50 or older (Table 3) with hyperthyroxinemia (FT4 > 1.55 ng/dL) were at lower cancer risk (adjusted HR: 0.87; 95% CI: 0.76–0.99). Elevated FT4 was associated with increased lung cancer risk (adjusted HR:, 1.54; 95% CI: 1.1–2.03, P for trend = 0.04), an effect driven mainly by increased risk within the normal FT4 range. Patients with hyperthyroxinemia had significantly

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Table 2 Hazard ratios for overall and site-specific cancers by TSH strata. HRs are adjusted for age, gender, smoking status, socioeconomic state, ethnicity, BMI and comorbidities (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, chronic lung disease, chronic liver disease).

Malignancy/TSH strata (mIU/L)	**Events** (*n*)	**Participants** (*n*)	**HR** (95% CI)	***P*-value**
Any cancer[a]	23 808	375 635	1.00 (0.98–1.02)[†]	0.95
<0.55	893	11 338	0.99 (0.98–1.06)	0.79
0.55–1.96	11 623	186 116	Reference	Reference
1.96–3.37	7657	123 474	1.04 (1.01–1.07)	0.02
3.37–4.78	2243	34 860	1.02 (0.98–1.07)	0.28
>4.78	1392	19 847	0.97 (0.91–1.02)	0.23
Prostate cancer[ʃb]	2406	169 554	0.96 (0.91–1.02)[†]	0.25
<0.55	77	4189	0.90 (0.71–1.13)	0.35
0.55–1.96	1320	90 860	Reference	Reference
1.96–3.37	767	54 838	1.03 (0.94–1.12)	0.56
3.37–4.78	165	13 267	0.87 (0.75–1.01)	0.09
>4.78	77	6400	0.67 (0.54–0.85)	0.001
Thyroid cancer[ʃc]	866	375 635	0.82 (0.75–0.90)[†]	<0.0001
<0.55	55	11 338	2.01 (1.74–2.32)	<0.0001
0.55–1.96	422	186 116	Reference	Reference
1.96–3.37	243	123 474	0.83 (0.71–0.97)	0.02
3.37–4.78	96	34 860	1.10 (0.88–1.37)	0.40
>4.78	50	19 847	0.95 (0.70–1.29)	0.75
Melanoma[ʃd]	1189	375 635	1.11 (1.02–1.20)[†]	0.02
<0.55	31	11 338	0.89 (0.74–1.08)	0.55
0.55–1.96	523	186 116	Reference	Reference
1.96–3.37	430	123 474	1.25 (1.10–1.43)	0.001
3.37–4.78	138	34 860	1.39 (1.16–1.67)	0.001
>4.78	67	19 847	1.09 (0.84–1.40)	0.53
Uterine cancer[ʃe]	617	206 081	1.27 (1.13–1.41)[†]	<0.0001
<0.55	14	7149	0.66 (0.39–1.14)	0.13
0.55–1.96	238	95 256	Reference	Reference
1.96–3.37	232	68 636	1.36 (1.13–1.63)	0.001
3.37–4.78	84	21 593	1.49 (1.16–1.91)	0.001
>4.78	49	13 447	1.25 (0.92–1.70)	0.15

[ʃ]Significant in FDR-adjusted model (Supplementary Table 5); [†]HR per unit log-TSH increase; *P* for trend: [a]0.75; [b]0.87; [c]0.5; [d]0.04; [e]<0.0001.
HR, hazard ratio; TSH, thyroid stimulating hormone.

lower risk of colorectal cancer (adjusted HR: 0.59; 95% CI: 0.41–0.85). Subgroups analysis suggested this effect was most prominent in women and patients 50 and older (Supplementary Table 8). The associations for lung cancer and colorectal cancer remained significant following exclusion of first 2 years of follow up (Supplementary Table 9).

Hyperthyroidism is associated with reduced overall and colorectal cancer risk

Lastly, we assessed the correlation between thyroid function status and cancer risk. Following FDR correction, inclusion of thyroid function groups in the cancer risk model was significant for colorectal cancer and hematological malignancies (Supplementary Table 6). Hazard ratios were determined for overall cancer risk and both cancer subtypes (Table 5). Analysis indicated a reduction in the overall risk of cancer among patients with clinical hyperthyroidism (adjusted HR: 0.68; 95% CI: 0.52–0.89). There was a significant interaction between thyroid function and age in the overall cancer risk model (P = 0.001), yet not for specific cancer types. Patients younger than 50 with subclinical hyperthyroidism (Table 3 and Supplementary Table 10) had higher overall risk of cancer (adjusted HR: 1.31; 95% CI: 1.06–1.61), while patients aged 50 or older with clinical hyperthyroidism had lower cancer risk (adjusted HR: 0.64; 95% CI: 0.47–0.87). Clinical hyperthyroidism was associated with lower risk of colorectal cancer (adjusted HR: 0.08; 95% CI: 0.01–0.60). No association was demonstrated between thyroid function and risk of hematological malignancies in the final analysis. Results were similar following exclusion of first 2 years of follow-up, thyroid altering medication use during the study period (Supplementary Table 11) and thyroid cancer patients (Supplementary Table 12).

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Table 3 Hazard ratios for overall cancer by thyroid hormone function and patient age at inclusion.

	Age < 50			Age ≥ 50		
	Events/participants	HR (95% CI)	*P*-value	Events/participants	HR (95% CI)	*P*-value
TSH[a,c], mIU/L	5209/229 830	0.97 (0.93–1.01)[†]	0.10	18 599/145 805	1.01 (0.99–1.03)[†]	0.27
<0.55	184/5828	1.30 (1.12–1.51)	0.001	709/5510	0.98 (0.91–1.06)	0.59
0.55–1.96	2587/114 648	Reference	Reference	9036/71 468	Reference	Reference
1.96–3.37	1741/77 547	1.06 (0.99–1.12)	0.08	5916/45 927	1.04 (1.01–1.08)	0.02
3.37–4.78	435/21 133	0.99 (0.89–1.09)	0.81	1808/13 727	1.07 (1.01–1.12)	0.01
>4.78	262/10 674	1.06 (0.93–1.20)	0.37	1130/9173	0.98 (0.96–1.01)	0.62
Free T4[b,d], ng/dL	1443/65 376	1.28 (1.10–1.49)[‡]	0.004	5275/45 231	1.07 (0.96–1.2)[‡]	0.22
<0.78	31/1292	0.79 (0.55–1.13)	0.20	128/1190	0.88 (0.74–1.05)	0.20
0.78–1.04	470/20 971	0.99 (0.88–1.11)	0.87	1470/13 232	0.96 (0.90–1.03)	0.27
1.04–1.3	651/32 819	Reference	Reference	2332/20 113	Reference	Reference
1.3–1.55	243/8700	1.30 (1.12–1.50)	0.001	1106/8505	1.08 (1.00–1.16)	0.04
>1.55	48/1594	1.27 (0.94–1.70)	0.11	239/2191	0.87 (0.76–0.99)	0.04
Thyroid function						
Hyperthyroidism	11/339	1.13 (0.62–2.03)	0.69	42/501	0.64 (0.47–0.87)	0.004
SC hyperthyroidism	95/3113	1.31 (1.06–1.61)	0.01	380/2859	1.08 (0.97–1.20)	0.15
Euthyroidism	1094/51623	Reference	Reference	3786/32 867	Reference	Reference
SC hypothyroidism	175/7754	1.01 (0.93–1.10)	0.86	742/6124	1.04 (0.96–1.12)	0.38
Hypothyroidism	13/605	0.63 (0.36–1.08)	0.09	86/750	0.96 (0.78–1.19)	0.71

[†]HR per unit log-TSH increase; [‡]HR per unit free T4 increase; *P* for trend, age < 50: [a]0.62; [b]0.19; age ≥ 50: [c]0.10; [d]0.04.
HR, hazard ratio; SC, subclinical; T4, thyroxine; TSH, thyroid stimulating hormone.

Discussion

In this exploratory population-based study, we have demonstrated associations between thyroid hormone levels and cancer risk that are tumor-specific and age-dependent. These associations were driven by alterations in thyroid hormone levels not only above and below the reference range but also within the normal range.

The relation between thyroid hormones and cancer risk has been examined in several population studies (13, 14, 15). However, these studies included relatively small patient cohorts, limiting the analysis to common cancer types, and did not present stratification by age. Our large study was sufficiently powered for assessment of risk for multiple cancer subtypes. As cancer is an age-related disease, we also performed separate analyses for different age groups. The use of FDR correction for multiple comparisons decreased the likelihood of false-positivity and validated the demonstrated relations. Furthermore, adjustment for multiple clinical parameters and utilization of several sensitivity analyses decreased the likelihood of bias. Finally, analysis of the full spectrum of TSH and FT4, for both continuous and categorical ranges, allowed determination of hormone effects above, below and within the normal range. Collectively, the design of our study enabled us to identify novel associations for both common and uncommon malignancies and to determine differing effects of thyroid hormones on cancer risk based on age. Specifically, our analysis suggests that hyperthyroid function is associated with increased cancer risk in younger patients but may have a protective effect in older patients. As the tumor promoting effect of thyroid hormones appears to be site-specific, these results may signify the differing incidence of dominant cancer types in different age groups. In particular, a relatively high incidence of thyroid cancer in the younger patient group and a high incidence of colorectal cancer in the older age group (21). The demonstrated interaction between age and thyroid hormones for overall cancer risk, yet not for the risk of any specific malignancy, supports this hypothesis.

In our study, hyperthyroid TSH levels were associated with increased risk of thyroid cancer and elevated FT4 with increased lung cancer risk. Correspondingly, hypothyroid TSH levels were related to decreased risk of prostate cancer. Associations remained significant for 2 years and more prior to cancer diagnosis, further supporting a causal relation. For lung cancer, a positive trend was demonstrated, suggesting a dose-dependent effect of FT4. As the degree of TSH change relative to free T4 varies

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Table 4 Hazard ratios for overall and site-specific cancers by free T4 (FT4) strata. HRs are adjusted for age, gender, smoking status, socioeconomic state, ethnicity, BMI, and comorbidities (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, chronic lung disease, chronic liver disease).

Malignancy/FT4 strata (ng/dL)	**Events** (*n*)	**Participants** (*n*)	**HR** (95% CI)	***P*-value**
Any cancer[ʃa]	6718	110 607	1.05 (0.95–1.15)[‡]	0.38
<0.78	159	2482	0.90 (0.76–1.05)	0.19
0.78–1.04	1940	34 203	1.00 (0.94–1.06)	1.00
1.04–1.3	2983	52 932	Reference	Reference
1.3–1.55	1349	17 205	1.10 (1.03–1.17)	0.005
>1.55	287	3785	0.89 (0.78–1.00)	0.05
Lung cancer[ʃb]	583	110 607	1.54 (1.16–2.03)[‡]	0.002
<0.78	20	2482	1.38 (0.87–2.18)	0.17
0.78–1.04	136	34 203	0.87 (0.71–1.07)	0.19
1.04–1.3	252	52 932	Reference	Reference
1.3–1.55	142	17 205	1.29 (1.04–1.58)	0.02
>1.55	33	3785	1.20 (0.83–1.73)	0.33
Colorectal cancer[ʃc]	890	110 607	0.82 (0.62–1.09)[‡]	0.17
<0.78	18	2482	0.67 (0.42–1.07)	1.00
0.78–1.04	247	34 203	0.87 (0.76–1.01)	0.09
1.04–1.3	433	52 932	Reference	Reference
1.3–1.55	161	17 205	0.85 (0.71–1.02)	0.07
>1.55	31	3785	0.59 (0.41–0.85)	0.004

[ʃ]Significant in FDR-adjusted model (Supplementary Table 5); [‡]HR per unit free T4 increase; *P* for trend: [a]0.28; [b]0.04; [c]0.87.
HR, hazard ratio; T4, thyroxine.

significantly among individuals (22), a corresponding association for TSH may not be demonstrated. Our results are in accordance with previous research on lung (13, 14), thyroid (23, 24) and prostate cancer (13, 15, 25). To the best of our knowledge, this is the first population study to suggest a relation between hyperthyroidism, based on TSH blood levels and thyroid cancer risk. However, as hyperthyroid patients are more likely to undergo thyroid imaging, diagnostic work-up bias cannot be ruled out. The growth promoting effects of thyroid hormones in cancer were demonstrated in large body of preclinical research. T4 was shown to stimulate lung (6, 7, 8, 26),

Table 5 Hazard ratios for overall and site-specific cancers by thyroid function groups. HRs are adjusted for age, gender, smoking status, socioeconomic state, ethnicity, BMI, and comorbidities (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic renal failure, chronic lung disease, chronic liver disease).

Malignancy/thyroid function group	**Events** (*n*)	**Participants** (*n*)	**HR** (95% CI)	***P*-value**
Any cancer[ʃ]				
Hyperthyroidism	53	840	0.68 (0.52–0.89)	0.005
SC hyperthyroidism	475	5972	1.09 (0.99–1.20)	0.06
Euthyroidism	4880	84 490	Reference	Reference
SC hypothyroidism	917	13 878	1.01 (0.94–1.09)	0.72
Hypothyroidism	99	1355	0.93 (0.76–1.13)	0.45
Colorectal cancer[ʃ]				
Hyperthyroidism	1	840	0.08 (0.01–0.60)	0.01
SC hyperthyroidism	57	5972	0.93 (0.71–1.22)	0.58
Euthyroidism	648	84 490	Reference	Reference
SC hypothyroidism	136	13 878	1.10 (0.92–1.33)	0.30
Hypothyroidism	13	1355	0.88 (0.51–1.52)	0.64
Hematological malignancy[ʃ]				
Hyperthyroidism	1	840	0.14 (0.02–1.02)	0.05
SC hyperthyroidism	46	5972	1.20 (0.88–1.63)	0.25
Euthyroidism	430	84 490	Reference	Reference
SC hypothyroidism	93	13 878	1.20 (0.96–1.51)	0.11
Hypothyroidism	7	1355	0.76 (0.36–1.61)	0.48

[ʃ]Significant in FDR-adjusted model (Supplementary Table 5).
HR, hazard ratio; SC, subclinical.

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thyroid (27) and prostate (28) cancer growth, while a hypothyroid environment slowed tumor growth (29, 30, 31). One of the main mechanisms mediating these effects is thyroid hormone binding to the plasma membrane integrin αvβ3, leading to cancer cell proliferation and tumor angiogenesis (32).

Our study has also demonstrated an inverse relation between thyroid function and the risk of specific malignancies. Hyperthyroid patients were at significantly lower risk of colorectal cancer. This finding is in accordance with previous works on thyroid function and colorectal cancer risk (18, 33, 34), as well as with studies demonstrating a protective effect of levothyroxine treatment on colorectal cancer risk (35, 36, 37). However, our study is the first to demonstrate the effect of hyperthyroid function on colorectal cancer risk irrespective of thyroid altering medication use. We further identified that TSH in the hypothyroid range was associated with increased risk of uterine cancer and melanoma. Notably, as these associations remained significant for 2 years and more prior to cancer diagnosis, they cannot be attributed to thyroid hormone dysfunction secondary to the malignancy, such as the sick euthyroid syndrome. These results are novel, with only a single study suggesting that hypothyroidism is related to poor uterine cancer outcomes (38). The biological basis for these effects is not well-defined. Treatment of colorectal cancer cells with thyroid hormones induces differentiation and leads to reduced proliferation (39, 40). Both endometrial tissue (41) and melanocytes (42) express the TSH receptor and a direct growth-promoting effect of TSH may be involved in the pathogenesis of uterine cancer and melanoma.

For several malignancies, including lung cancer, uterine cancer and melanoma, risk appeared to be driven by changes within the reference range. These results are in-line with a growing body of research suggesting changes of thyroid hormones within the normal range are associated with adverse clinical outcomes, including fractures (43, 44), cardiovascular outcomes (45, 46) and adverse lipid profile (47). Our findings suggest that for at-risk patients, there may be benefit to maintain TSH and free T4 levels with a narrow range.

This study has several limitations that need to be considered. Our analysis was based on thyroid hormone measurements at a specific time point, and we could not determine the effect of changes in thyroid hormone levels over time. Moreover, specifically for breast cancer, we were unable to adjust for important risk factors, including menopausal status and female hormone use. This may explain why our analysis did not demonstrate an association between thyroid hormones and breast cancer risk, which was noted in previous population-based studies (14, 16, 17, 48). We also could not adjust for radioiodine therapy use, which could affect thyroid cancer risk (49) and were unable to differentiate between primary and secondary thyroid disorders. Finally, our historical cohort study consisted of patients who had underwent thyroid hormone tests and may be potentially biased toward cases with thyroid dysfunction. However, as TSH tests are routinely conducted in Israel and the majority of our patients had thyroid hormone values within the normal range, our finding may be representative of the general population.

To conclude, this study demonstrates opposing effects of thyroid hormones on cancer risk, based on patient age and specific cancer types. These findings mandate further studies and suggest a rationale for future inclusion of thyroid hormone profile in cancer risk assessment of individual patients.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-20-1123.

Declaration of interest

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

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Author contribution statement

E K designed the study and collected, analyzed, and interpreted the data. B S provided the information on cancer diagnoses. D M S and D Y assisted with statistical analysis. S G assisted in data collection. O F assisted in database establishment. A H, P J D and M E assisted in interpretation of the clinical data. O A F designed the study and analyzed and interpreted the data. E K and O A F wrote the manuscript. All authors read and approved the manuscript.

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