RESEARCH

Thyroid dysfunction and cancer incidence: a systematic review and meta-analysis

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Abstract

In this study, we aimed to evaluate site-specific cancer risks associated with hyperthyroidism or hypothyroidism. We performed a systematic review of observational studies reporting associations between hyperthyroidism or hypothyroidism and subsequent site-specific cancer incidence, in MEDLINE and the COCHRANE library (inception-28/01/2019) (PROSPERO: CRD42019125094). We excluded studies with thyroid dysfunction evaluated as a cancer biomarker or after prior cancer diagnosis and those considering transient thyroid dysfunction during pregnancy or severe illnesses. Risk of bias was assessed using a modified Newcastle–Ottawa scale. Risk estimates were pooled using random-effects models when ≥ 5 studies reported data for a specific cancer site. Twenty studies were included, of which 15 contributed to the meta-analysis. Compared to euthyroidism, hyperthyroidism was associated with higher risks of thyroid (pooled risk ratio: 4.49, 95%CI: 2.84–7.12), breast (pooled risk ratio: 1.20, 95%CI: 1.04–1.38), and prostate (pooled risk ratio: 1.35, 95%CI: 1.05–1.74), but not respiratory tract (pooled risk ratio: 1.06, 95%CI: 0.80–1.42) cancers. Hypothyroidism was associated with a higher risk of thyroid cancer within the first 10 years of follow-up only (pooled risk ratio: 3.31, 95%CI: 1.20–9.13). There was no or limited evidence of thyroid dysfunction-related risks of other cancer sites. In conclusion, thyroid dysfunction was associated with increased risks of thyroid, breast, and prostate cancers. However, it remains unclear whether these findings represent causal relationships because information on treatments and potential confounders was frequently lacking.

Key Words

- ▶ hyperthyroidism
- ▶ hypothyroidism
- ▶ cancer
- ▶ incidence
- ▶ epidemiological studies
- ▶ meta-analysis

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Introduction

Thyroid dysfunction can present as decreased (hyperthyroidism) or elevated (hypothyroidism) thyroid-stimulating hormone (TSH) serum levels, leading to an increased or decreased production of thyroid hormones (triiodothyronine (T3) and/or thyroxine (T4)),

respectively. Autoimmune conditions, such as Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism), are the most common causes of thyroid dysfunction in iodine-replete areas. Thyroid dysfunction can occur in both sexes, but is particularly frequent

among women aged 40 years and older, with a prevalence of 5–15% in iodine-replete communities (Garmendia Madariaga *et al.* 2014, Journy *et al.* 2017).

Thyroid dysfunction may be involved in carcinogenesis. Thyroid hormones and TSH can directly enhance tumor proliferation through their cell surface receptors, estrogen pathways, increased angiogenesis, and gene expression regulation (Moeller & Führer 2013, Hercbergs *et al.* 2018). Moreover, thyroid dysfunction is associated with obesity (Laurberg *et al.* 2012), diabetes mellitus (Brandt *et al.* 2013), and vascular diseases (Brandt *et al.* 2013), which have been linked to an increased cancer risk or shared common risk factors. However, epidemiological evidence on the association between thyroid dysfunction and cancer risk has been contradictory. Several studies have reported increased risks of thyroid or breast cancer associated with hyperthyroidism and decreased or unchanged risks with hypothyroidism, compared to euthyroid individuals (Cristofanilli *et al.* 2005, Balasubramaniam *et al.* 2012, Søgaard *et al.* 2016, Kitahara *et al.* 2018). However, in some other large cohorts, there was no association between thyroid dysfunction and cancer risk (Metso *et al.* 2007, Hellevik *et al.* 2009). Four previous meta-analyses on breast cancer found no significantly increased or decreased risks with thyroid dysfunction, but highlighted the heterogeneity of results across studies published from 2002 to 2016 (Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017). A pooled analysis of case-control studies published in 1984–1997 showed an increased risk of thyroid cancer with self-reported hyperthyroidism, but not with hypothyroidism (Franceschi *et al.* 1999). Interpretation of these results is nevertheless hampered by several factors: lack of longitudinal studies, lack of data on thyroid dysfunction treatments, inclusion of prevalent cancer cases, and the possibility of reverse causality. Recently, two additional large studies have provided new evidence of an elevated risk of thyroid cancer in relation to thyroid dysfunction (Huang *et al.* 2017, Kitahara *et al.* 2018). Other studies reported associations with other cancer sites, such as prostate and lung (Mellemegaard *et al.* 1998, Hellevik *et al.* 2009), which have not yet been analyzed in a systematic review or meta-analysis.

In this systematic review and meta-analysis, we comprehensively summarized the published evidence up to 2019 on the associations of hyperthyroidism and hypothyroidism with site-specific cancer incidence. We also reported the current evidence on cancer risks associated with thyroid dysfunction treatments.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2009) (Supplementary Appendix 1, see section on [supplementary materials](#) given at the end of this article). Our protocol was registered in the PROSPERO International prospective register of systematic reviews database (CRD42019125094) prior to study.

Search strategy

We performed a systematic literature search in PubMed/MEDLINE and the Cochrane library from inception to January 28, 2019. We included case-control and cohort studies that reported a measure of association between thyroid dysfunction (overt and subclinical) or thyroid hormone levels compatible with thyroid dysfunction diagnosed before cancer diagnosis (Box 1) and subsequent site-specific cancer risk. Our search strategy included MeSH terms and key words in the titles and abstracts (Supplementary Appendix 2). We restricted the search to English, French and Vietnamese languages, and to studies in humans. Reference lists of eligible articles and previous systematic reviews (Franceschi *et al.* 1999, Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017) were hand searched to identify additional relevant studies.

Study selection

One investigator (T V T T) screened the title and abstract of all articles identified in the initial search and reviewed

Box 1. Definition of hyperthyroidism and hypothyroidism used in the search.

- Overt or subclinical hyperthyroidism and hypothyroidism, reported in medical or laboratory records, questionnaires, registry or medico-administrative databases, or measured in blood samples, prior to cancer diagnosis. People with Graves' disease, toxic nodular goiter, and thyrotoxicosis were considered as hyperthyroid and those with Hashimoto's disease as hypothyroid.
- Thyroid-stimulating hormone (TSH), free thyroxine (FT4) and/or free triiodothyronine (FT3) levels beyond reference levels in iodine-replete populations: TSH 0.4–4.0 mIU/L, FT4 9–25 pmol/L (0.7–1.9 ng/dL), and FT3 3.5–7.8 nmol/L (0.2–0.5 ng/dL). When possible, overt and subclinical thyroid dysfunction was differentiated, as defined in Supplementary Appendix 5.

the full text of potentially eligible articles. Our exclusion criteria were (1) hyperthyroidism and hypothyroidism not reported separately, (2) no information on specific cancer sites, (3) no reported measure of association between hyperthyroidism or hypothyroidism and cancer incidence, (4) thyroid dysfunction evaluated as a cancer biomarker (e.g. thyroid cancer), (5) thyroid dysfunction evaluated after cancer diagnosis or no/limited information on cancer history prior to thyroid dysfunction evaluation, (6) participants with a prior malignant condition or treated cancer, and (7) transient thyroid dysfunction during pregnancy or severe illnesses. Because thyroid dysfunction can also affect cancer survival (Sandhu *et al.* 2009, Minlikeeva *et al.* 2017), possibly through early or delayed cancer detection due to the management of thyroid function or associated comorbidities (e.g. diabetes, cardiovascular diseases) or differences in cancer treatment strategies due to the presence of comorbidities (Sarfati *et al.* 2016), it is difficult to disentangle the effects of thyroid dysfunction on cancer incidence and survival.

Consequently, we disregarded studies on cancer mortality, of which only two (Goldman *et al.* 1988, Journy *et al.* 2017) excluded individuals with prior cancer history at thyroid dysfunction assessment (exclusion criterion #5; Fig. 1, Supplementary Appendix 6).

Data extraction

Using pre-defined data extraction forms, two investigators (T V T T and N J) independently extracted the following information from the included studies: study setting and design, sample size, follow-up methods and duration, participant characteristics (age, sex, and menopausal status), thyroid dysfunction (definition, ascertainment methods, and treatments), cancer outcomes (definition and ascertainment methods), methods for statistical analysis (risk modelling and adjustment variables), and multivariable analysis results, including cases, controls number, and risk estimates. We retrieved data from the most informative studies in case of duplicate data sources.

Figure 1

PRISMA flow diagram outlining search strategy and the final included and excluded studies.

Previous reports of the study population were reviewed for additional information that was not available in the included article. Corresponding authors were contacted when necessary.

Quality assessment

Two investigators (T V T T and N J) independently assessed risk of bias of the included studies, in terms of participant selection, comparability of groups, and ascertainment of the outcome (in cohorts) or exposure (in case-control studies), using a modified Newcastle–Ottawa scale (NOS) (Wells 2001) (Supplementary Appendix 3). This scale contains a number of items (selection: $n=4$, comparability: $n=2$, outcome: $n=3$, and exposure: $n=5$), to which a point was awarded to modalities with the lowest risk of bias. To date, no consensus has been reached on the interpretation of assigned points to NOS items. Therefore, we arbitrarily considered ≥ 2 , ≥ 1 , ≥ 2 , and ≥ 3 points as ‘low-to-moderate’ risk of bias for selection, comparability, outcome, and exposure domains, respectively (Supplementary Appendix 4). In studies investigating several outcomes, the risk of bias could vary according to the cancer of interest. Inconsistent ratings between the two investigators were resolved by discussion.

Statistical analysis

For each study, we extracted risk estimates (relative risk, odds ratio, hazard ratio, or standardized incidence ratio) adjusted for the most covariables and 95% CIs from the original article. We pooled risk ratios when associations of hyperthyroidism or hypothyroidism and site-specific cancer incidence were reported in five studies or more. Estimates for respiratory tract cancers were combined with those for lung cancer only, which accounts for more than 90% of the former category (Forman *et al.* 2013). Pooled risk ratios were estimated using DerSimonian and Laird random-effect models (DerSimonian & Laird 1986). In sensitivity analyses, we compared our results with those using fixed-effect models. For studies which reported only sex-specific risk ratios, these risk estimates were pooled using a fixed-effect model in order to have a single risk ratio per study.

Heterogeneity across studies was evaluated using the Q-statistic with a conservative 10% P -value because it has low power (Petitti 2001) and the I^2 statistic (Higgins & Thompson 2002), which represents the proportion of total variance of a pooled risk ratio attributable to variability across studies. An I^2 value greater than

50% indicates a substantial heterogeneity level. To explore the heterogeneity sources, we conducted analyses stratified by thyroid dysfunction treatments: no treatment, radioactive iodine (RAI) only, thyroid hormone replacement therapy (THRT) only, mixed modalities, or unspecified treatments. No studies have investigated surgery and anti-thyroid drugs as a unique treatment of thyroid dysfunction. Except for the study of Goldman *et al.* (1988) which had some follow-up data, we analyzed only treatments ascertained at study inclusion due to the unavailability of follow-up data in all other cohort studies. Furthermore, we estimated pooled risk ratios stratified by sex (men or women), methods for thyroid dysfunction ascertainment (in-/out-patient hospital diagnoses, or others), study design (cohort or case-control), and geographic region (Asia, Australia, Europe, or North America). We also used the Q-statistic to test for subgroup differences – with P -values < 0.1 indicating evidence of heterogeneity. Other sensitivity analyses were restricted to studies with low-to-moderate risk of bias for each NOS domain or those with a minimum follow-up time of 1 year to minimize the probability of reverse causation (i.e. thyroid dysfunction due to cancer). We conducted an influence analysis by the leave-one-out method to assess whether the pooled risk estimates were driven by specific studies (Viechtbauer & Cheung 2010).

To further explore the possibility of reverse causation, we estimated pooled risk ratios as a function of time, since thyroid dysfunction diagnosis/detection in a meta-regression analysis (Thompson & Higgins 2002), among studies reporting risk ratios for at least two follow-up time categories. Only studies on thyroid cancer risk fulfilled this requirement. For each category, follow-up time was assigned as the midpoint between the upper and the lower bound. For open-ended upper categories, we applied the range of the previous category. We modeled the log (risk ratio) as a linear or non-linear function of follow-up time. Departure from linearity was assessed by testing the statistical significance of second and third degree polynomials terms and restricted cubic splines with four knots at 0.05, 0.35, 0.65, and 0.95 percentiles.

Publication bias was assessed by Egger tests and funnel plots (Egger *et al.* 1997). The analyses were performed in R version 3.5.3 (<https://www.R-project.org/>) using the ‘meta’ and ‘metafor’ packages.

Results

After screening the title and abstract of 3252 non-duplicated articles and reviewing the full text of

146 potentially eligible articles, we included 20 studies (12 cohort and 8 case-control studies) in the literature synthesis (Fig. 1). Of these, 15 studies contributed to the meta-analysis for thyroid ($n=8$), breast ($n=9$), prostate ($n=6$), and respiratory tract ($n=7$) cancers.

Study characteristics

Studies were conducted in Europe ($n=6$), the USA ($n=9$), Taiwan ($n=3$), Kuwait ($n=1$), and Australia ($n=1$). Thirteen studies were population-based (Mellemgaard *et al.* 1998, Memon *et al.* 2002, Welzel *et al.* 2007, Hellevik *et al.* 2009, Balasubramaniam *et al.* 2012, Chen *et al.* 2013a,b, Kang *et al.* 2013, Yeh *et al.* 2013, Chan *et al.* 2017, Huang *et al.* 2017, Petrick *et al.* 2017, Kitahara *et al.* 2018), of which five were nationwide (Mellemgaard *et al.* 1998, Chen *et al.* 2013a,b, Kitahara *et al.* 2018) or nationally representative (Yeh *et al.* 2013), where thyroid dysfunction was assessed through in- and/or out-patient hospital databases (Table 1). Three population-based studies had information on serum TSH and/or thyroid hormones concentrations (Hassan *et al.* 2009, Hellevik *et al.* 2009, Chan *et al.* 2017). Differences in study design resulted in widely variable sample size (ranging from 342 to 4.5 million) and mean/median follow-up time (ranging from 6 to 17 years on average; not reported for 13 studies). Fourteen studies included both females (proportion: 39% to 90%) and males. In cohort studies, the prevalence of hyperthyroidism and hypothyroidism ranged respectively from 0.3% to 2.5% and 0.6% to 7.8% across cohorts, respectively (mean age at thyroid dysfunction assessment: 40 to 62 years). Treatment modalities of thyroid dysfunction were: RAI only (Metso *et al.* 2007), THRT only (Cristofanilli *et al.* 2005), mixed modalities (Munoz *et al.* 1978, Goldman *et al.* 1988, Kang *et al.* 2013), no treatment (Hellevik *et al.* 2009, Yeh *et al.* 2013, Chan *et al.* 2017), or unspecified (Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Memon *et al.* 2002, Welzel *et al.* 2007, Hassan *et al.* 2009, Balasubramaniam *et al.* 2012, Mondul *et al.* 2012, Chen *et al.* 2013a,b, Huang *et al.* 2017, Petrick *et al.* 2017, Kitahara *et al.* 2018). Treatments were ascertained at study inclusion, since there was incomplete (Goldman *et al.* 1988) or no follow-up data in the original studies. Diabetes and overweight/obesity were the most commonly reported comorbidities, with a prevalence of 2–10% in cohorts and 10–46% in case-control studies. Overall, nine (45%) studies were considered as moderate-to-low risk of bias (Supplementary Appendix 4). Neither the funnel plots nor the Egger's test showed evidence of publication bias for any outcome (Supplementary Figs 1, 2, 3, 4, 5 and 6).

Thyroid cancer

Seven (Memon *et al.* 2002, Metso *et al.* 2007, Yeh *et al.* 2013, Balasubramaniam *et al.* 2012, Chen *et al.* 2013a, Huang *et al.* 2017, Kitahara *et al.* 2018) and five (Memon *et al.* 2002, Balasubramaniam *et al.* 2012, Chen *et al.* 2013b, Huang *et al.* 2017, Kitahara *et al.* 2018) studies reported risks associated with hyperthyroidism and hypothyroidism, respectively, with a total sample size of 12.9 million individuals. They consistently reported increased risks for both hyperthyroidism and hypothyroidism, reaching statistical significance in studies with the largest numbers of cases (Figs 2 and 3). Most studies regarding hyperthyroidism (Memon *et al.* 2002, Chen *et al.* 2013a, Yeh *et al.* 2013, Huang *et al.* 2017, Kitahara *et al.* 2018) and hypothyroidism (Memon *et al.* 2002, Chen *et al.* 2013b, Huang *et al.* 2017, Kitahara *et al.* 2018) had low-to-moderate risks of bias for the selection and outcome/exposure domains, but adjustment for potential confounding factors, particularly calendar year, BMI, diabetes, and reproductive factors, was lacking in some studies (Memon *et al.* 2002, Metso *et al.* 2007, Chen *et al.* 2013a,b). The pooled risk ratio was 4.49 (95%CI 2.83 to 7.12, 280 cases among the exposed) for hyperthyroidism and 3.31 (95%CI 1.20 to 9.13, 171 cases among the exposed) for hypothyroidism. However, there was a substantial evidence for heterogeneity in both analyses ($I^2>80\%$, $P<0.01$), due to different magnitudes of risk across studies. The log risk ratios of thyroid cancer linearly decreased with time since diagnosis/detection of hyperthyroidism (Balasubramaniam *et al.* 2012, Chen *et al.* 2013a, Yeh *et al.* 2013, Huang *et al.* 2017, Kitahara *et al.* 2018) and hypothyroidism (Balasubramaniam *et al.* 2012, Chen *et al.* 2013b, Huang *et al.* 2017, Kitahara *et al.* 2018) (Fig. 4). After 10 years of follow-up, the risk was no longer significantly increased in hypothyroid individuals (risk ratio=0.91, 95%CI 0.26 to 3.23, $I^2=87\%$, $P<0.0001$), but remained elevated in hyperthyroid individuals (risk ratio=2.50, 95%CI: 1.66 to 3.78, $I^2=47\%$, $P=0.02$). The detected outliers may indicate an under-estimation of the CI's upper bound, but the trend over time was consistent across studies.

There was a higher risk ratio for hyperthyroidism among untreated individuals (risk ratio=6.80, 95%CI 3.58 to 12.91) (Yeh *et al.* 2013) than among those treated with RAI only (risk ratio=1.80, 95%CI: 0.43 to 7.53) (Metso *et al.* 2007), though the difference among different treatment subgroups was not statistically significant ($p_{\text{heterogeneity}}=0.22$, Supplementary Fig. 8). However, very few studies enabled analyses stratified

Table 1 Characteristics of the 20 included studies.

Reference	Country	Study design	Methods of follow-up and cancer ascertainment	Follow-up time in years: mean/median (min-max) ^a	Size of study population	Age in years: mean/median (min-max)	% Post-menopausal Women	% Post-menopausal (women)	Definition	Method of ascertainment	Treatment(s) (%)	Statistical analysis	Covariates in multivariate analysis ^b
Munoz <i>et al.</i> (1978)	USA	Hospital-based cohort	Hospital medical records (2 centers)	13.8/NR (0.1-nr)	n = 342	NR	80.7	NR	Hypothyroidism: Graves' disease	Medical/laboratory reports	Desiccated thyroid, levothyroxine, radioactive iodine, Lugol's iodine, antithyroid drugs	SIR	Age, sex
Goldman <i>et al.</i> (1988)	USA	Single-institution, hospital-based cohort	Cooperative Thyroidosis Therapy Follow-up Study, hospital medical records, administrative databases (vital status), self-reported questionnaire	17/NR (1-33)	1762	47/NR (n=nr)	100.0	NR	Treated hyperthyroidism	Hospital medical records, self-reported questionnaire, physical exams	Radioactive iodine (n = 1406), surgery (n = 573), antithyroid drugs (n = 1089), combination of these treatments were possible	SMA, SIR	Mortality analysis: age, calendar time Incidence analysis: age, calendar time, race
Møllengaard <i>et al.</i> (1998)	Denmark	National cohort	National civil registration system, national cancer registry	NR/NR (1-15)	n = nr	NR/NR (0-100+) (64% > 50 years of age)	84.4	NR	Hyperthyroidism: thyrotoxicosis (ICD-8-CM code: 242)	National insurance database: in-patient claims	NR	SIR	Age, sex, calendar time
Mesa <i>et al.</i> (2007)	Finland	Hospital-based cohort	National population registry, national cancer registry	10/NR (0.1-39)	n = 5586	NR/62 (QR 50-75)	83.6	NR	Hyperthyroidism treated with RAI (Graves' disease: 57%, toxic multinodular goiter or adenoma, 43%)	Hospital medical records	Radioactive iodine (100%), mean cumulative dose = 305 MBq (range: 55-2664 MBq)	Mantel-Haenszel's incidence rate ratios	Age, sex
Hellevik <i>et al.</i> (2009)	Norway	Population-based cohort	National cancer registry	NR/9 (0-10)	26,691	NR/NR (20-nr)	66.4	NR	Hyperthyroidism: TSH < 0.50 mU/L; Hypothyroidism: TSH ≥ 3.6 mU/L No self-reported thyroid disease (types: nr)	Baseline blood test (DEFLIA from Wallac Oy ^c)	None at baseline	Cox proportional hazards regression model	Age, sex, smoking status
Balasubramanian <i>et al.</i> (2012)	USA	Population-based cohort	Inpatient discharge records of US Veterans Affairs medical system	All: 11.7/NR (1-27) Cases: 7.3/NR (n=nr)	4,501,578	NR/52.5 (18-100)	0.0	0.0	Hyperthyroidism: thyrotoxicosis (ICD-9-CM code: 242); Hypothyroidism: ICD-9-CM code: 244	Inpatient discharge records of US Veterans Affairs medical system	NR	Time-dependent Poisson regression model	Age, calendar time, race, follow-up time, number of hospitalizations
Yeh <i>et al.</i> (2013)	Taiwan	National-representative cohort	National insurance database (histological confirmation)	NR/NR (0.25-4)	n = 51,099	NR/NR (0-100+) (92% < 65 years old)	77.7	NR	Hyperthyroidism: ICD-9-CM code: 242	National insurance database: in- and out-patient claims	No radioactive iodine or thyroidectomy at baseline	Cox proportional hazards regression model	Age, sex, time, diabetes, hypertension, hyperlipidemia, gout, geographic region, income
Kang <i>et al.</i> (2013)	USA	Population-based cohort	Self-reported questionnaire, national death registry, US postal service	NR/6-8 (0-34)	EC analysis: n = 200,162 ^a OC analysis: n = 217,342 ^a	50/NR (25-100+)	100.0	NR	Hyperthyroidism/Graves' disease, Hypothyroidism	Baseline and follow-up self-reported questionnaires	Thyroid hormone replacement (levothyroxine), radioactive iodine, surgery, antithyroid drugs	Cox proportional hazards regression model	Shared covariates: age, time, cohort (NHS/NHSII, BMI, parity, oral contraceptive use history, age at menarche, age at menopause, use of estrogen only, postmenopausal hormone therapies, use of progesterone only, use of other postmenopausal hormone therapy, infertility, EC - and cigarette smoking, family history of uterine cancer, diabetes, age at the last birth OC: - and family history of breast or ovarian cancer, hysterectomy, tubal ligation
Chen <i>et al.</i> (2013b)	Taiwan	National cohort	National insurance database (histological confirmation)	NR/NR (0-14)	25,125	42/NR (20-100+)	77.3	NR	Hyperthyroidism: Graves' disease (ICD-9-CM code: 242.0)	National insurance database: ≥ 3 in- and out-patient claims	Thyroidectomy (0.14%)	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia
Chen <i>et al.</i> (2013b)	Taiwan	National cohort	National insurance database (histological confirmation)	NR/NR (0-13)	7605	40/NR (0-100+)	90.1	NR	Hypothyroidism: Hashimoto's thyroiditis (ICD-9-CM code: 245.2)	National insurance database: in- and out-patient claims	NR	Poisson regression model, Cox proportional hazards regression model	Age, sex, diabetes, hypertension, hyperlipidemia, heart disease
Chan <i>et al.</i> (2017)	Australia	Population-based cohort	Regional cancer and death registries	NR/NR (2-20)	3649	51/NR (25-84)	55.5	52.1	Subclinical hyperthyroidism: TSH < 0.1 mU/L and FT4 < 21 pmol/L Subclinical hypothyroidism: TSH > 4 mU/L and FT4 > 12.6 pmol/L	Baseline blood test (third generation assay)	No thyroid-related medications at baseline (thyroxine, levothyroxine, antithyroid medications, lithium, amiodarone, carbamazepine or phenytoin use)	Cox proportional hazards regression model	Age, sex, marital status, occupation, smoking, alcohol consumption, physical activities, BMI, diabetes, menopause, status, oral contraceptive use or HRT use

	Denmark	National cohort	National civil registration system, national cancer registry	NR/8 (1–36)	n = 8,258,807	NR/58 (0–100+)	84.0	NR	Hyperthyroidism: ICD-8-CM code: 242 or ICD-10-CM code: E05; Hypothyroidism: ICD-8-CM code: 244 or ICD-10-CM codes: E02, E03.2–E03.9, E89.0	National insurance database: in- and out-patient, emergency claims	NR	SIR	Age, sex, calendar time
Kitahara <i>et al.</i> (2018)													
Talarni <i>et al.</i> (1997)	Italy	Hospital-based case-control	Hospital records (histological confirmation) registry	NR/NR (0–nr)	n = 5157	NR/56 (20–74)	100.0	64.5	Hyperthyroidism, hypothyroidism	Structured interview (when the year after cancer diagnosis) to case/control status	NR	Logistic regression models	Age, study area, education, parity, BMI quintiles, menopausal status
Memon <i>et al.</i> (2002)	Kuwait	Population-based case-control	National cancer registry	NR/NR (3–nr)	n = 626	37/37 (6–69) ^f	76.0	NR	Hyperthyroidism, hypothyroidism	Interview (not blinded to case/control status)	NR	Conditional logistic regression model	Year of birth, sex, nationality, district of residence
Cristofanilli <i>et al.</i> (2005)	USA	Cancer screening center-based case-control	Hospital records (1 center)	NR/NR (0–nr)	n = 2224	51/NR (nr–nr)	100.0	63.7	Treated primary hypothyroidism	Self-reported questionnaire (blinded to case/control status)	Thyroid hormone replacement, e.g. Levothyroxine (100%)	Unconditional logistic regression model	Age, first degree family history of breast cancer, history of pregnancy, use of HRT, menopausal status
Weisel <i>et al.</i> (2007)	USA	Population-based case-control	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims; multi-regional cancer registry	NR/NR (3–nr) ^g	ICC analysis: n = 103,317 ICC analysis: n = 103,331	77/NR (68–100+) ^f	63.7	NR	Hyperthyroidism: thyrotoxicosis (ICD-9-CM codes: 242.0)	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims	NR	Logistic regression models	Age, sex, race, geographic region, low socioeconomic status-proxy
Hassan <i>et al.</i> (2009)	USA	Hospital-based case-control	Hospital records (1 center), pathology report	NR/NR (0–nr)	n = 1524	60/63/NR (nr–nr)	38.6	NR	Hyperthyroidism, hypothyroidism	Interview (not blinded to case/control status)	NR	Unconditional logistic regression model	Age, sex, race, educational level, smoking, alcohol consumption, family history of cancer, and HBV/HCV infection
Mondul <i>et al.</i> (2012)	Finland	Case-control (population-based primary prevention randomized controlled trial)	National cancer registry; national registry of death causes	NR/NR (3–20)	n = 1201	NR/NR (53–90)	0.0	0.0	Hyperthyroidism: TSH < 0.3 mU/L; Hypothyroidism: TSH > 3.0 mU/L and TT4 < 4.6 mg/dL	Baseline blood test (n = 2500 immunosay system ^h)	NR	Conditional logistic regression model	Age, time since exposure ascertainment, BMI, total cholesterol, alpha-tocopherol, beta-carotene, cigarettes smoked per day, years smoked, family history of prostate cancer, leisure time physical activity, education, marital status, urban residence, total intake of energy, dietary vitamin D, fruit, vegetables, red meat, alcohol, use of calcium supplements
Huang <i>et al.</i> (2017)	USA	Population-based case-control	U.S. Department of defense cancer registry (histological confirmation)	NR/NR (0.2–12)	n = 1482	NR/NR (21–100+) (30% > 40 years of age)	46.0	NR	Hyperthyroidism: TSH < 0.3 mU/L; Hypothyroidism: TSH > 4.2 mU/L	Blood tests (Roche Cobas E601 ^h) samples routinely collected and stored at the U.S. Department of Defense Serum Repository	NR	Conditional logistic regression model	Date of birth, sex, race/ethnicity, follow-up time, BMI, branch of military service
Petrick <i>et al.</i> (2017)	USA	Population-based case-control	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims; multi-regional cancer registry	NR/NR (3–nr) ^g	ICC analysis: n = 325,707 ECC analysis: n = 326,596	77/NR (68–100+) ^f	61.5	NR	Hyperthyroidism: thyrotoxicosis (ICD-9-CM codes: 242.40, 242.41, 242.48, 242.81, 242.90, 242.91)	National insurance database: ≥3-year in- and out-patient, skilled-nursing facility, hospice claims	NR	Logistic regression models	Age, sex, race, geographic region, low socioeconomic status-proxy

^aUntil otherwise specified, follow-up time was determined as following: for cohort studies, the time on study, considered from the date of the thyroid dysfunction evaluation to the date of cancer diagnosis or end of follow-up; for case-control studies, the period when participants were diagnosed with thyroid dysfunction in the past before cancer diagnosis; ^bfor main analysis; ^cTSH reference range in the analysis: Chan *et al.* (2017), 0.4–4.0 mU/L; Hellevik *et al.* (2009), 0.5–1.4 mU/L; Huang *et al.* (2017), 1.2–1.93 mU/L; Mondul *et al.* (2012), 0.3–3 mU/L; ^dDELIA hTSH Ultra: sensitivity, 0.03 mU/L; and total analytic variation, <5%; ^eNumber reported in the analysis was 177,848; ^fMean age weighted based on the available study data; ^gFollow-up time since thyroid dysfunction evaluation to cancer diagnosis was 0 year; ^hSensitivity, variation, and assay generation are not reported; ⁱNot used in the analyses; ^jamong exposed patients. EC: endometrial cancer; ECC: extrahepatic cholangiocarcinoma; HRT: hormone replacement therapy; ICC: intrahepatic cholangiocarcinoma; NR: not reported; OC: ovarian cancer; SIR: standardized incidence ratio; SMR: standardized mortality ratio.

Figure 2

Forest plots for hyperthyroidism and the risk of different cancer sites and individual study risk of bias: overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RAI: radioactive iodine; RR: risk ratio. *Case-control studies. Metso *et al.* (2007): results estimated based on a figure reporting the primary results of the article, exact results were not available. Mellemgaard *et al.* (1998): results for respiratory tract cancer pooled from separate risks for men and women reported with a fixed-effect model. Yeh *et al.* (2013) did not adjust for smoking but did adjust for all other important factors.

by treatment modalities for hyperthyroidism and none for hypothyroidism. Men with hyperthyroidism (risk ratio=5.12, 95%CI 3.03 to 8.67) or hypothyroidism (risk ratio=3.70, 95%CI 1.13 to 12.17) had higher risks than

women with the same condition (hyperthyroidism: risk ratio=3.87, 95%CI: 2.44 to 6.14; hypothyroidism: risk ratio=1.30, 95%CI: 0.91 to 1.87), but the difference between sexes was not statistically significant

Figure 3

Forest plots for hypothyroidism and the risk of different cancer sites and individual study risk of bias: overall risk ratios are displayed as diamonds. The size of each square is proportional to the weight of the study. CI: confidence interval; nr: not reported; PY: person-year; RR: risk ratio; THRT: thyroid hormone replacement therapy. *Case-control studies.

Figure 4
Effect of follow-up time on thyroid cancer risk of participants with thyroid dysfunction compared to euthyroid individuals. (A) For hyperthyroidism analysis. (B) For hypothyroidism analysis. Solid line: relative risk of thyroid cancer; dashed line: 95% confidence interval.

($p_{\text{heterogeneity hyperthyroidism}}=0.43$, $p_{\text{heterogeneity hypothyroidism}}=0.10$) (Supplementary Fig. 7). Moreover, for hypothyroidism, the subgroup analysis by sex was entirely driven by one study including only men that did not allow a comparison with women (Balasubramaniam *et al.* 2012).

Breast cancer

Risk of breast cancer associated with hyperthyroidism or hypothyroidism was investigated in seven (Goldman *et al.* 1988, Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013a, Chan *et al.* 2017) ($n=66,216$) and five (Talamini *et al.* 1997, Cristofanilli *et al.* 2005, Hellevik *et al.* 2009, Chen *et al.* 2013a, Chan *et al.* 2017) ($n=26,572$) studies, respectively. Most studies had low-to-moderate risk of bias in terms of participants' selection and exposure/outcome ascertainment. However, except in two studies (Cristofanilli *et al.* 2005, Chan *et al.* 2017), no adjustment

was made for potential confounders such as hormone replacement therapy/menopausal status, parity, or family history of breast cancer. Except one study reporting only one cancer case among the exposed (Chan *et al.* 2017), all other studies reported statistically significant (Metso *et al.* 2007, Chen *et al.* 2013a) or non-significant (Goldman *et al.* 1988, Talamini *et al.* 1997, Mellemgaard *et al.* 1998, Hellevik *et al.* 2009) increased risks with hyperthyroidism (Fig. 2). In contrast, most studies found decreased risks with hypothyroidism, though they were based on relatively small numbers of cases and mostly reported statistically non-significant associations (Fig. 3). This decrease was statistically significant in only one large study which considered adjustment for important potential confounders such as family history of breast cancer, hormone replacement therapy, and menopausal status (Cristofanilli *et al.* 2005).

The pooled risk ratio was 1.20 (95%CI: 1.04 to 1.38, 557 cases among the exposed) for hyperthyroidism, with weak evidence of heterogeneity ($I^2=27\%$, $P=0.22$), and 0.73 (95%CI 0.43 to 1.24, 144 cases among the exposed) for hypothyroidism, but with a substantial degree of heterogeneity ($I^2=77\%$, $P<0.01$). However, the only study reporting a positive association with hypothyroidism had no information on potential confounders (Chen *et al.* 2013b). Among the other studies, the risk estimates were relatively consistent, and the most influential study (Supplementary Fig. 18) accounted for important breast cancer risk factors (Cristofanilli *et al.* 2005).

The risk ratio associated with hyperthyroidism was higher among women treated with RAI only (risk ratio=1.54, 95%CI 1.08 to 2.19) (Metso *et al.* 2007) than in untreated women (risk ratio=0.82, 95%CI 0.24 to 2.81) (Hellevik *et al.* 2009, Chan *et al.* 2017). Nevertheless, the difference by different treatment subgroups was not statistically significant ($p_{\text{heterogeneity}}=0.54$, Supplementary Fig. 9). In contrast, breast cancer risk significantly decreased among women treated with THRT (risk ratio=0.44, 95%CI 0.32 to 0.60) (Cristofanilli *et al.* 2005), whereas no significant association with hypothyroidism was found among untreated women (risk ratio=0.82, 95%CI 0.56 to 1.21) (Hellevik *et al.* 2009, Chan *et al.* 2017) ($p_{\text{heterogeneity among treatment subgroups}}=0.03$, Supplementary Fig. 12).

Prostate cancer

Six (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Mondul *et al.* 2012, Chen *et al.* 2013a, Chan *et al.* 2017) ($n=14,891$) and four (Hellevik *et al.* 2009, Mondul *et al.* 2012, Chen *et al.* 2013b, Chan *et al.*

2017) ($n=41,272$) studies reported risks associated with hyperthyroidism and hypothyroidism, respectively. Risk of prostate cancer was significantly (Hellevik *et al.* 2009) or non-significantly (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013a, Chan *et al.* 2017) increased with hyperthyroidism in five cohorts (Fig. 2). In contrast, except in one study reporting only one cancer case in the exposed (Chen *et al.* 2013b), the risk decreased with hypothyroidism in the three other studies (Hellevik *et al.* 2009, Mondul *et al.* 2012, Chan *et al.* 2017), one of which reached statistical significance (risk ratio=0.48, 95%CI 0.28 to 0.81) (Supplementary Table 2).

The pooled risk ratio for hyperthyroidism was 1.35 (95%CI 1.05 to 1.74, 92 cases among the exposed), with no evidence of heterogeneity ($I^2=0\%$, $P=0.60$), based on studies with low risk of bias for participants' selection and exposure/outcome ascertainment. However, this risk estimate was mostly unadjusted for important potential confounders, such as family history of cancer, ethnicity, and BMI (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013a, Chan *et al.* 2017). Furthermore, the risk ratio varied across subgroups. In particular, it was higher in untreated men (risk ratio=1.94, 95%CI 1.13 to 3.34) (Hellevik *et al.* 2009, Chan *et al.* 2017) than in those treated by RAI (risk ratio=1.50, 95%CI 0.79 to 2.85) (Metso *et al.* 2007), even though the difference among different treatment subgroups was not significant ($P_{\text{heterogeneity}}=0.27$, Supplementary Table 10). Given the limited number of studies, we combined the published risk estimates for hypothyroidism with a random-effect model, for exploratory purposes, and found a pooled risk ratio of 0.70 (95%CI 0.45 to 1.07, 46 cases among the exposed) with a low level of heterogeneity ($I^2=23\%$, $P=0.3$).

Respiratory tract cancer

A total of 121,616 individuals were included in seven cohorts on hyperthyroidism (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013a, Yeh *et al.* 2013, Chan *et al.* 2017). Two studies indicated a significantly increased risk (Mellemgaard *et al.* 1998, Hellevik *et al.* 2009), while the five others did not show any association based on the few cases (Fig. 2). The pooled risk ratio was 1.06 (95%CI 0.80 to 1.42, 262 cases among the exposed), with weak evidence of heterogeneity ($I^2=39\%$, $P=0.13$). Heterogeneity was possibly explained by a study reporting a 2-fold higher risk among hyperthyroid individuals (Hellevik *et al.* 2009), while the others found no association or a marginally increased risk (Supplementary Fig. 16). All but two (Goldman *et al.*

1988, Metso *et al.* 2007) studies had moderate-to-low risk of bias in terms of participants' selection and outcome ascertainment, but most studies lacked data on potential confounding factors such as smoking history and family history of cancer (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013a, Yeh *et al.* 2013). The pooled risk ratio restricted to the two studies providing estimates adjusted for important confounding factors, including smoking, was 2.13 (95%CI 1.17 to 3.90, 12 cases among the exposed) (Hellevik *et al.* 2009, Chan *et al.* 2017) (Supplementary Table 6). The results did not statistically differ between the three studies reporting risks restricted to lung cancer and the four studies investigating all respiratory tract cancers combined ($P=0.81$, Supplementary Table 6). However, they varied according to hyperthyroidism treatment modalities, with a pooled risk ratio of 1.42 (95%CI 0.70 to 2.88) among untreated individuals (Hellevik *et al.* 2009, Yeh *et al.* 2013, Chan *et al.* 2017) and 0.85 (95%CI 0.48 to 1.52) among individuals treated with RAI (Metso *et al.* 2007), but the difference by different treatment subgroups was not significant ($P_{\text{heterogeneity}}=0.47$, Supplementary Fig. 11). Of three studies investigating the association between hypothyroidism and respiratory tract cancer risk, one study reported a non-significantly decreased risk of 0.87 (95%CI 0.43 to 1.74) (Hellevik *et al.* 2009) and two others reported no cancer case in the exposed group (Chen *et al.* 2013, Chan *et al.* 2017).

Other outcomes

Risk estimates from individual studies on other cancer sites are reported in Supplementary Tables 1 and 2. Two large case-control studies reported significantly increased risks of extra- and/or intra-hepatic cholangiocarcinoma with hyperthyroidism, based on a total of 162 cases among the exposed (Welzel *et al.* 2007, Petrick *et al.* 2017). Two other studies reported non-significantly elevated liver cancer risks in hyperthyroid individuals, based on only 13 and 8 cases respectively (Hassan *et al.* 2009, Chen *et al.* 2013a). The estimated liver cancer risks with hypothyroidism were inconsistent across studies (Hassan *et al.* 2009, Chen *et al.* 2013b). We also identified three studies investigating brain cancer risk, which suggested an increased risk (varying from 1.3 to 2.3) with hyperthyroidism (Goldman *et al.* 1988, Mellemgaard *et al.* 1998, Metso *et al.* 2007) based on a few cases. No study provided results on the hypothyroidism-brain cancer risk association. Renal cancer risk also appeared elevated among hyperthyroid individuals (Mellemgaard *et al.* 1998, Metso *et al.* 2007, Chen *et al.* 2013a), with significantly

increased risks in two studies (risk ratio=2.32, 95%CI: 1.06 to 5.01, 20 cases among the exposed (Metso *et al.* 2007); risk ratio=1.3, 95%CI: 1.0 to 1.8, 44 cases among the exposed (Mellemegaard *et al.* 1998)). Last, two studies reported a non-significantly decreased risk ratio (varying from 0.8 to 0.9) of skin cancer associated with hyperthyroidism (Mellemegaard *et al.* 1998, Metso *et al.* 2007). Very little data were available for other outcomes.

Other sensitivity and subgroup analyses

No substantial difference in the estimated risk ratios was observed between random- and fixed-effect models (Supplementary Tables 3, 4, 5 and 6). For all outcomes and exposure groups, cohorts yielded higher risk ratios than case-control studies. The pooled risk ratios for breast and thyroid cancers were also higher in studies where thyroid dysfunction was assessed through hospital or health insurance databases compared to studies using blood measurements or self-reported data. Subsequently, studies conducted in Europe reported the smallest risk estimates for all outcomes, while those conducted in Asia yielded the highest risk estimates. However, pooled risk ratios did not statistically differ among regions, with the exception of breast cancer after hypothyroidism. Other sensitivity-, subgroup-, and influence analyses did not substantially modify the results (Supplementary Figs 13, 14, 15, 17 and Supplementary Tables 3, 4, 5, 6).

Discussion

This systematic review uncovered several studies evaluating the relationship between thyroid dysfunction, mostly as overt disorder, and cancer risk by tumor site, including thyroid, breast, prostate, respiratory tract, liver, brain, kidney, and skin cancers. Our meta-analysis of 15 cohort and case-control studies showed that hyperthyroidism was associated with 20%, 35%, and 4.5-fold higher risks of breast, prostate, and thyroid cancer, respectively, compared to euthyroidism. We found no clear evidence of an association between hyperthyroidism and other site-specific cancer risks, based on very few studies. Hypothyroidism was significantly associated with a 3-fold higher risk of thyroid cancer, which was limited to the first 10 years after diagnosis of hypothyroidism. Hypothyroidism was not significantly associated with risk of other cancer sites, including breast and prostate cancers.

While previous reviews focused on thyroid and breast cancers (Sarlis *et al.* 2002, Angelousi *et al.* 2012, Hardefeldt *et al.* 2012, Fang *et al.* 2017), the present

review is the first one to report associations between hyperthyroidism and hypothyroidism and risk of a wide range of cancer types and pooled risk estimates for prostate and respiratory tract cancers. Our findings are partly consistent with previous meta-analyses. A previous meta-analysis of 12 case-control studies published through 1997 reported an increased thyroid cancer risk associated with self-reported hyperthyroidism (diagnosed at least one year prior to cancer diagnosis) in both women (risk ratio=1.4, 95%CI: 1.0 to 2.1) and men (risk ratio=3.1, 95%CI: 1.0 to 9.8), but not with hypothyroidism (Franceschi *et al.* 1999). This study found weaker associations for both types of thyroid dysfunction compared to ours. This might be explained by differing practices in the management of hyperthyroidism according to age and country. Treatment of hyperthyroidism, especially when using radioactive iodine, often results in hypothyroidism. This may thus lead to somewhat confounded risk associations with hypothyroidism in the most recent studies, due to a higher proportion of hypothyroid individuals who were previously treated for hyperthyroidism than in the past studies. Moreover, most recent studies may benefit from a better thyroid dysfunction diagnosis and/or enhanced cancer surveillance strategies in the most recent years. Indeed, there is now evidence that increased TSH levels is a marker of thyroid cancer among patients with nodules, with a dose-response relationship (McLeod *et al.* 2012, Hu *et al.* 2016). Our results are compatible with recent findings of an inverse association between prediagnosis TSH levels and thyroid cancer risk in a healthy population (Rinaldi *et al.* 2014) and common genetic variants for low TSH levels and thyroid cancer (Gudmundsson *et al.* 2012).

Unlike previous meta-analyses (Hardefeldt *et al.* 2012, Fang *et al.* 2017), we found a significantly increased risk of breast cancer with hyperthyroidism after inclusion of a recent, large longitudinal study (Chen *et al.* 2013a) and exclusion of studies with prevalent cancers where thyroid dysfunction might result from cancer symptoms or treatment toxicities. Our findings are compatible with two recent large cohort studies reporting an elevated breast cancer risk in relation to increasing T4 and T3 levels within normal ranges (Tosovic *et al.* 2010, 2012). They are also consistent with previous meta-analyses which reported no association between hypothyroidism and breast cancer risk (Angelousi *et al.* 2012).

High heterogeneity across individual studies was observed for thyroid and breast cancers, but not for other cancer sites. Risk estimates widely varied across studies in terms of magnitude of thyroid cancer risk with hyperthyroidism (risk ratios ranging from 1.7 to 10.4)

or hypothyroidism (risk ratios ranging from 1.8 to 11.8), and in terms of direction of the association between hypothyroidism and breast cancer. The different ascertainment methods of thyroid dysfunction across studies is probably one factor explaining this heterogeneity, since higher risks were estimated in studies based on hospital or health insurance data compared to population-based studies using blood measurements or self-reported data. The different risk estimates between hospital- and population-based studies may also reflect different severity degrees of thyroid dysfunction or comorbidities – but data were lacking to investigate this hypothesis. Differences in potential confounding factors, for example, calendar year, family cancer history, or menopausal status, can also account for some heterogeneity, but these data were lacking in many studies (Talamini *et al.* 1997, Memon *et al.* 2002, Metso *et al.* 2007, Hellevik *et al.* 2009, Chen *et al.* 2013a,b), particularly in those based on health insurance databases.

Biological mechanisms underlying associations between thyroid dysfunction and cancer are not well known, but a number of hypotheses have been suggested in *in vitro* and *in vivo* studies. TSH has been found to stimulate follicular thyroid cell growth and differentiation (Hard 1998). T3 and T4 can be anti-apoptotic and have a proliferative effect on thyroid, breast, and prostate cancer cell lines by regulating gene expression (TGF- α , B-cell translocation gene 2) (Tsui *et al.* 2008, Pinto *et al.* 2011), causing phosphorylation by MAPK pathways, binding in the integrin $\alpha v \beta 3$ (Moeller & Führer 2013, Hercborgs *et al.* 2018), and stimulating estrogen-like effects (Dinda *et al.* 2002). Moreover, excessive or insufficient iodine intake, which plays a key role in thyroid hormone production, could also be a risk factor of breast and thyroid cancers (Dong *et al.* 2018). Current experimental evidence thus support epidemiological findings on a positive association between hyperthyroidism and cancer risk.

Nonetheless, the interpretation of those findings as a causal relationship between hyperthyroidism and cancer incidence is not straightforward. Indeed, thyroid dysfunction can be subsequent to cancer or cancer treatments. Our study minimized the possibility of reverse causation by excluding prevalent or previous cancer cases at the time of thyroid dysfunction diagnosis/detection. However, the decreased pooled risk ratios of thyroid cancer with time since thyroid dysfunction diagnosis/detection (Fig. 4) are suggestive of a surveillance bias (e.g. incidental cancer cases detected by thyroidectomy for hyperthyroidism treatment) in the first years of follow-up. Nevertheless, while thyroid cancer risk was

no longer increased in hypothyroid individuals after 10 years of follow-up, it remained significantly increased in hyperthyroid individuals with a risk ratio of 2.50 (95%CI: 1.66 to 3.78) compared to euthyroid individuals. Unfortunately, few studies have reported data on tumor histology (Huang *et al.* 2017, Kitahara *et al.* 2018), size (Cristofanilli *et al.* 2005, Huang *et al.* 2017) and stage at diagnosis (Cristofanilli *et al.* 2005, Kitahara *et al.* 2018), which could strengthen the assessment of a potential surveillance bias. Though risk factors (e.g. iodine intake, radiation exposure) and age at diagnosis differ according to thyroid cancer histology (Aschebrook-Kilfoy *et al.* 2013, Liu *et al.* 2017), Kitahara *et al.* (2018) found very similar thyroid dysfunction-related risks for papillary and follicular thyroid cancers. The authors nevertheless reported a higher hyperthyroidism-related risk for localized thyroid cancer than regional/distant thyroid cancer as compared to the general population, which suggests that a certain proportion of, but not all, the increased risk related to hyperthyroidism may be due to a surveillance bias. This study also showed a non-significantly increased risk of localized thyroid cancer with hypothyroidism, but no association for regional/distant cancer (based on very few cancer cases), which is also indicative of a surveillance bias. Similarly, Cristofanilli *et al.* (2005) found that, among women diagnosed with breast cancer, hypothyroid women were more frequently diagnosed with an early-stage or small-size (≤ 2 cm) tumor than euthyroid women. Current evidence thus suggest that part of the thyroid dysfunction-related excess risks may be associated with non-clinically relevant thyroid and breast cancers, but this should be confirmed (Staniforth *et al.* 2016, Lim *et al.* 2017). The remaining elevated risk, 10 years after thyroid dysfunction diagnosis/detection, may also reflect the effect of underlying autoimmune diseases, which are associated with increased risk of thyroid and breast cancer (Shu *et al.* 2010, Resende de Paiva *et al.* 2017).

The estimated cancer risks could have also been mediated or modified by thyroid dysfunction treatments. Indeed, our results show differences in risk estimates by treatment modalities (Supplementary Figs 8, 9, 10, 11 and 12), for example, hypothyroid women treated with THRT had a reduced risk of breast cancer, whereas no significant association was found among untreated hypothyroid women. However, very few studies contributed to the analyses stratified by treatments, and treatment-specific risk estimates were available only for RAI and THRT, which was insufficient for the interpretation of the role of thyroid dysfunction treatments in the relationship between thyroid dysfunction and cancer risk.

Moreover, as the populations may differ in many other aspects than treatments, it remains very difficult to disentangle whether those differences reflect the impact of the treatment itself, its impact on thyroid dysfunction, or different severities of thyroid dysfunction and associated comorbidities.

The present study has several strengths. We conducted an extensive and systematic literature search on the association between both hyper- and hypothyroidism and cancer risk, with no restriction to cancer type. This enabled us to report results on cancer sites that have not been considered in previous meta-analyses (e.g. prostate and respiratory tract cancer) and investigate the possible role of thyroid hormones for hormone-dependent (e.g. thyroid, breast, and prostate cancers) and non-hormone-dependent cancers (e.g. respiratory tract cancer). Unlike previous meta-analyses, we applied no restriction on the method for thyroid dysfunction ascertainment to retrieve a maximal number of relevant publications. However, we excluded studies with cancer history prior to thyroid dysfunction diagnosis/detection to minimize the possibility of reverse causation. Subgroup and sensitivity analyses were conducted to explore potential factors that could explain heterogeneity of results

There are also several limitations to our study. Firstly, data on treatments and important potential confounding factors (e.g. family history of cancer, BMI, and reproductive factors) were lacking in most studies, which prevented us from investigating their impact on the risk estimates. In addition, even though information was available on time since thyroid dysfunction diagnosis/detection, no data were available on the duration of overt dysfunctional state and status after thyroid dysfunction treatment (e.g. euthyroidism or hypothyroidism after treatment for hyperthyroidism). Secondly, high levels of heterogeneity were found for thyroid cancer after hypo- or hyperthyroidism and breast cancer after hypothyroidism. Outliers were also observed in the analysis of follow-up time. This questions the robustness of the pooled risk estimates. Last, different measures of association (relative risk, odds ratio, hazard ratio, and standardized incidence ratio) were pooled together, which involves the following assumptions: rare outcome (for odds ratio and hazard ratio), no association between the exposure and censoring status (for hazard ratio), and the use of data from the general population as a comparison group (for standardized incidence ratio) (Goldman *et al.* 1988, Mellemegaard *et al.* 1998, Kitahara *et al.* 2018), which were nevertheless verified for most studies.

In conclusion, current evidence from epidemiological studies showed that hyperthyroidism is associated with

increased risks of thyroid, breast, and prostate cancers, compared to euthyroidism. Hypothyroidism is associated with an increased risk of thyroid cancer within the first 10 years of follow-up. However, it remains unclear whether these findings represent causal relationships because information on important potential confounders, thyroid dysfunction treatments, associated comorbidities, underlying disease, cancer stage at diagnosis, and histology was lacking in most studies. Further prospective studies should investigate possible confounding or mediating effects of treatments, comorbidities, and major cancer risk factors on the associations between thyroid dysfunction and cancer risk.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/ERC-19-0417>.

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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Ethics approval and consent to participate

This systematic review and meta-analysis only used published data, with no access to individual data. No ethical approval or participants' consent to participate was thus required for this study.

Data availability

All data reported in this manuscript can be found in the original articles mentioned in the list of references.

Author contribution statement

T T V T and N J designed the study protocol, performed the literature search, extracted data from the original articles and assessed risk of biases of the included studies, and drafted the first version of the manuscript. T T V T conducted the statistical analyses. C M K, F D, and M C B R contributed to the interpretation of the results and the drafting of the paper. All co-authors approved the publication of the manuscript in its final version.

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