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Original article

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Association of hormonal and reproductive factors with differentiated thyroid cancer risk in women: a pooled prospective cohort analysis

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Abstract

Background: The incidence of differentiated thyroid cancer (DTC) is higher in women than in men but whether sex steroid hormones contribute to this difference remains unclear. Studies of reproductive and hormonal factors and thyroid cancer risk have provided inconsistent results.

Methods: Original data from 1 252 907 women in 16 cohorts in North America, Europe, Australia and Asia were combined to evaluate associations of DTC risk with reproductive and hormonal factors. Multivariable-adjusted Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CIs.

Results: During follow-up, 2142 women were diagnosed with DTC. Factors associated with higher risk of DTC included younger age at menarche (<10 vs 10–11 years; HR, 1.28; 95% CI, 1.00–1.64), younger (<40; HR, 1.31; 95% CI, 1.05–1.62) and older (≥55; HR, 1.33; 95% CI, 1.05–1.68) ages at menopause (vs 40–44 years), ever use of menopausal hormone therapy (HR, 1.16; 95% CI, 1.02–1.33) and previous hysterectomy (HR, 1.25; 95% CI, 1.13–1.39) or bilateral oophorectomy (HR, 1.14; 95% CI, 1.00–1.29). Factors associated with lower risk included longer-term use (≥5 vs <5 years) of oral contraceptives (HR, 0.86; 95% CI, 0.76–0.96) among those who ever used oral contraception and baseline postmenopausal status (HR, 0.82; 95% CI, 0.70–0.96). No associations were observed for parity, duration of menopausal hormone therapy use or lifetime number of reproductive years or ovulatory cycles.

Conclusions: Our study provides some evidence linking reproductive and hormonal factors with risk of DTC. Results should be interpreted cautiously considering the modest strength of the associations and potential for exposure misclassification and detection bias. Prospective studies of pre-diagnostic circulating sex steroid hormone measurements and DTC risk may provide additional insight.

Keywords: Thyroid cancer, parity, menarche, menopause, oral contraceptives, hysterectomy, hormone replacement therapy, oophorectomy.

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Key Messages

- Results suggest an association between reproductive and hormonal factors and risk for differentiated thyroid cancer (DTC) in females. Higher risks were observed for younger age at menarche, younger and older ages at menopause, ever use of oral contraceptives and menopausal hormone therapy, and previous hysterectomy or bilateral oophorectomy. Lower risks were observed for longer-term use (≥5 vs <5 years) of oral contraceptives and baseline post-menopausal status.
- Observed heterogeneity across cohorts for associations with hysterectomy and oophorectomy may reflect variability in the timing of these events in relation to other reproductive and hormonal exposures, as well as with thyroid cancer diagnosis.
- Large prospective studies with more detailed exposure information, information on other factors (e.g. breastfeeding), pre-diagnostic measures of sex steroid hormone concentrations and mode of DTC diagnosis, are needed.

Introduction

Thyroid cancer is the fifth most-commonly diagnosed cancer among women worldwide and the third most-commonly diagnosed cancer among reproductive age women.[1] Thyroid cancer disproportionately affects women and has an age-adjusted global incidence rate that is 3-fold higher than that of men.[1,2] Higher rates are most pronounced during women's reproductive years and are not explained by known or suspected thyroid cancer risk factors, including ionizing radiation or obesity.[1,3] Higher exposure to endogenous sex steroid hormones over the life course has been thought to at least partly contribute to the female predominance of this disease, with oestrogen playing a role in thyroid cancer growth and development.[4] Thyroid tumours commonly express oestrogen receptors and experimental studies have demonstrated a growth-promoting effect of oestrogen on benign and malignant thyroid cells.[5]

Reproductive and hormonal factors, such as parity and age at menarche and at menopause, and use of exogenous hormones, are considered proxies for lifetime exposure to sex steroid hormones, particularly oestrogens and progestogens, and have been associated with risk of other female-predominant or female-specific cancers.[6–8,9,10] Early thyroid cancer case–control studies suggested that some of these factors, including later menarche, menopause, age at first birth, current use of oral contraceptives (OC) and use of fertility treatments, may be associated with slightly higher risk of thyroid cancer.[10,11] However, findings from more recent case–control and prospective studies have been inconsistent.[9,12–14]

We conducted the first pooled analysis of prospective studies on reproductive and hormonal factors and risk of differentiated thyroid cancer (DTC, accounting for ∼95% of all thyroid cancers) as the first primary cancer[15] by combining individual-level data across 16 prospective cohorts in North America, Europe, Australia and Asia. We hypothesized that female reproductive characteristics representing higher circulating concentrations of sex steroid hormones, namely oestrogen, would be associated with an increased risk of DTC.

Methods

Study population

Cohorts participating in the National Cancer Institute's (NCI) Cohort Consortium were eligible for inclusion if the baseline year occurred on or after 1970 and the study ascertained data on parity, age at menarche, menopausal status, OC use, menopausal hormone therapy (MHT) use, previous hysterectomy and/or previous oophorectomy. Data on the female participants from 16 prospective cohort studies were available: National Institutes of Health American Association of Retired Persons Diet and Health (AARP); Breast Cancer Detection Demonstration Project (BCDDP); Cancer Prevention Study II (CPSII); California Teachers Study (CTS); European Prospective Investigation into Cancer and Nutrition (EPIC); Iowa Women's Health Study (IWHS); Melbourne Collaborative Cohort Study (MCCS); New York University Women's Health Study (NYUWHS); Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO); Sister Study (SISTER); Swedish Mammography Cohort (SMC); Shanghai Women's Health Study (SWHS); US Radiological Technologists Study (USRT); VITamins And Lifestyle Study (VITAL); Women's Health Study (WHS); and the Swedish Women's Lifestyle and Health Study (WLH). Design and recruitment details for each study have been previously published.[16–34]

From 1 321 371 eligible female study participants with accrued follow-up time, individuals were excluded if baseline age or age at end of follow-up were missing ($N = 2214$) or if diagnosed with any cancer other than non-melanoma skin cancer before completing the baseline questionnaire ($N = 66\,250$). The final analysis contained a pooled cohort of 1 252 907 women, including 2142 incident cases of DTC diagnosed during follow-up of the individual cohorts.

Case ascertainment

The follow-up date began when participants completed the baseline questionnaire and continued until occurrence of any first primary cancer other than non-melanoma skin cancer, loss to follow-up, death or the cohort-specific administrative end date. Information on cancer incidence was obtained via linkage to local, state or national cancer registries (AARP, CTS, IWHS, MCCS, SMC, VITAL and WLH), medical record confirmation of self-report (PLCO, SISTER, USRT and WHS) or a combination approach (BCDDP, CPSII, EPIC, NYUWHS and SWHS). Cases were those with a reported diagnosis of first primary DTC [International Classification of Disease for Oncology, 3rd Edition (ICD-O-3), topography code C73] with histologic types defined using ICD-O-3 morphology codes (papillary: 8050, 8260, 8340–8344, 8350, 8450–8460 and follicular: 8290, 8330–8335).[35] Population characteristics and case counts by study are available in Table 1.

Exposure assessment and data standardization

Cohort participants completed self-administered questionnaires at baseline that elicited information on general demographics (age, sex, race/ethnicity, education, marital status), lifestyle factors (cigarette smoking, alcohol intake, physical

Table 1. Baseline characteristics of participants in the pooled analysis, by cohort

Cohort	Cohort acronym	Geographic location	Participants	Cases	Calendar period of follow-up (range)	Years of follow-up, mean (SD)	Baseline age, mean (SD)	Parity (live births), mean (range)	Menarche age, mean (SD)	Ever oral contraceptive use	Ever menopausal hormone therapy use	Hyste rectomy	Oopho rectomy
NIH-AARP Diet & Health Study	AARP	USA	202 531	474	1995–2011	13.4 (4.2)	61.9 (5.4)	2.5 (0, 11)	12.0 (1.7)	39.2%	52.8%	40.7%	28.2%
Breast Cancer Detection Demonstration Project	BCDDP	USA	42 182	33	1987–1997	8.2 (1.7)	62.0 (8.2)	2.5 (0, 15)	12.8 (1.5)	30.6%	66.1%	43.3%	33.7%
Cancer Prevention Study II	CPSII	USA	82 604	125	1992–2009	12.8 (3.5)	62.1 (6.6)	2.9 (0, 9)	12.7 (1.5)	38.3%	56.4%	35.1%	24.9%
California Teachers Study	CTS	USA	105 667	265	1995–2010	12.8 (4.1)	52.3 (13.9)	1.7 (0, 13)	12.5 (1.5)	66.2%	NA	20.7%	14.7%
European Prospective Investigation into Cancer and Nutrition	EPIC	Europe (multiple sites)	345 158	474	1991–2010	11.0 (2.7)	50.9 (9.9)	1.9 (0, 17)	13.1 (1.5)	56.9%	24.2%	10.2%	6.1%
Iowa Women's Health Study	IWHS	USA	37 982	64	1986–2005	16.4 (5.5)	62.2 (4.2)	3.1 (0, 14)	12.9 (1.5)	18.9%	38.3%	32.4%	25.7%
Melbourne Collaborative Cohort Study	MCCS	Australia	22 354	30	1990–2009	15.2 (3.8)	54.8 (8.6)	2.4 (0, 16)	13.1 (1.6)	58.7%	24.7%	20.5%	8.8%
New York University Women's Health Study	NYU WHS	USA	13 358	46	1985–2007	18.7 (5.2)	50.6 (8.7)	1.5 (0, 12)	12.6 (1.5)	35.1%	NA	13.7%	12.4%
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Study	PLCO	USA	70 976	89	1993–2006	8.5 (2.6)	63.0 (5.4)	3.1 (0, 22)	13.2 (1.6)	54.2%	67.2%	35.4%	19.7%
Sister Study	SISTER	USA	47 805	118	2003–2012	8.3 (2.3)	55.4 (8.9)	2.0 (0, 12)	12.6 (1.5)	84.2%	44.4%	30.1%	23.4%
Swedish Mammography Cohort	SMC	Sweden	37 169	14	1998–2008	9.7 (2.2)	62.4 (9.3)	2.2 (0, 13)	13.2 (1.3)	56.7%	45.2%	1.5%	9.4%
Shanghai Women's Health Study	SWHS	China	74 933	143	1996–2009	10.8 (1.9)	52.6 (9.1)	1.8 (0, 10)	14.9 (1.7)	20.4%	NA	5.4%	4.2%
United States Radiological Technologists Study	USRT	USA	50 510	93	1994–2006	9.0 (1.5)	47.4 (8.4)	1.9 (0, 8)	12.5 (1.4)	75.0%	30.3%	22.9%	13.3%
VITamins and Lifestyle Study	VITAL	USA	33 730	74	2000–2009	7.4 (2.0)	61.0 (7.4)	2.3 (0, 5)	12.4 (1.9)	71.6%	59.0%	36.4%	21.4%
Women's Health Study	WHS	USA	39 779	96	1993–2010	14.7 (3.9)	54.7 (7.0)	2.5 (0, 6)	12.4 (1.5)	69.3%	49.9%	15.8%	20.1%
Swedish Women's Lifestyle and Health Study	WLH	Sweden	46 169	4	1991–2006	14.8 (1.8)	40.2 (5.8)	1.9 (0, 4)	13.0 (1.4)	82.9%	26.5%	10.9%	5.7%

AARP, American Association of Retired Persons; NIH, National Institutes of Health.

activity) and personal medical history. Reproductive and hormonal factor data were self-reported for all cohorts. Information on parity, menarche, oral contraceptive use, hysterectomy, oophorectomy and menopause was provided by all 16 cohorts, largely as these were considered potential covariates in an earlier pooled analysis.[34] For WHS, it was not possible to distinguish between participants who did not have a prior hysterectomy and those with unknown information; thus, WHS was dropped from models for hysterectomy. MHT use was provided by 13 studies (AARP, BCDDP, CPSII, EPIC, IWHS, MCCS, PLCO, SISTER, SMC, USRT, VITAL, WHS and WLH). Because the level of detail on exposure variables and covariates differed across the cohorts, we created harmonized variables for the aggregated cohort using standardized definitions and categories. More information on exposure assessment and data standardization is available in Table 1.

The number of reproductive years was estimated by subtracting age at menarche from age at menopause, restricting to post-menopausal women.[36] Because some questionnaires elicited age at menarche and age at menopause categorically, we used 1 minus the high end of the range for the lowest categories (e.g. 9 for ages <10 years), the midpoint for the middle categories (e.g. 10.5 for ages 10–11 years) and the bottom end of the range for the highest categories (e.g. 16 for ages ≥16 years) to calculate the number of reproductive years. Total number of lifetime ovulatory cycles was estimated by subtracting duration of OC use and 36 weeks for each live birth from the number of reproductive years, and assuming that these cycles averaged 28.1 days.[37,38] For these calculations, numerical values were reassigned for each category of OC use using the same method as for categorical designations of age at menarche and age at menopause. Negative values of reproductive years or ovulatory cycles were reassigned as 0 ($N = 301$). The total numbers of reproductive years and lifetime ovulatory cycles were divided into quartiles based on the distribution among women without DTC to create categories of reproductive years (0 to <31), (31 to <36), (36 to <39) and (≥39), and categories of ovulatory cycles (0 to <320), (320 to <402), (402 to <467) and (≥467).

Statistical analysis

Cox proportional-hazards models with attained age as the time metric and stratified by cohort were used to calculate hazard ratios (HRs) and 95% CIs for the association between hormonal and reproductive factors and DTC. We also separately evaluated associations by DTC subtype (e.g. papillary and follicular carcinoma). Models were adjusted for known and potential confounding factors including self-reported race (White, Black, Asian/Pacific Islander, other, missing), education (less than high school, high-school graduate, some college, college graduate, missing), baseline body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0, missing), smoking status (never, former, current, missing) and alcohol intake (0, <10 g/day, ≥10 g/day, missing). Missingness was handled through inclusion of a missing-indicator variable in the models.

Between-study heterogeneity was assessed using a random-effects meta-analysis to calculate the I^2 index,[39] with 0% indicating no heterogeneity and an I^2 of >50% representing substantial heterogeneity.[40] *P*-values for trend were obtained from the Wald test for categorical variables modelled continuously.

We conducted sensitivity analyses to identify whether certain reproductive factors were independently associated with thyroid cancer risk. One such analysis used a model mutually adjusted for oophorectomy and hysterectomy. Another model, restricted to post-menopausal women at baseline, mutually adjusted for oophorectomy, hysterectomy and ever use of MHT. All analyses were performed using SAS v9.4 (SAS Cary Institute Inc., Cary, NC).

Results

Over a mean 12.8 years of follow-up, 2142 first primary DTCs were identified among 1 252 907 individuals. The mean age at baseline was 54.8 years (range 40.2–63.0) and 86.6% of DTCs were diagnosed at age ≥50 years. Cohort characteristics are described in Table 1. The three largest studies were AARP, EPIC and CTS, with 474, 474 and 265 DTC cases, respectively. Together, AARP, EPIC and CTS accounted for 52% of participants and 57% of DTC cases.

Table 2 describes a univariate comparison of the number (%) of DTC cases and non-cases, as well as the total number of participants (%), according to baseline hormonal and reproductive factors. No major differences were observed by DTC case status apart from a slightly higher proportion of DTC cases than non-cases reporting a hysterectomy (28.6% vs 22.9%), ever use of MHT (58.4% vs 53.4%) and >5 years' duration of use of MHT (51.4% vs 47.5%).

Table 3 shows multivariable-adjusted HRs for reproductive and hormonal factors and DTC risk. Younger age at menarche (<10 vs 10–11 years) was associated with higher DTC risk (HR, 1.28; 95% CI, 1.00–1.64), as was baseline history of hysterectomy (HR, 1.25; 95% CI, 1.13–1.39) and bilateral oophorectomy (HR, 1.14; 95% CI, 1.00–1.29). Unilateral oophorectomy was not associated with DTC risk (HR, 1.06, 95% CI, 0.87–1.30). Among ever OC users, greater duration of use (≥5 vs <5 years) was associated with lower DTC risk (HR, 0.86; 95% CI, 0.76–0.96). Baseline post-menopausal status also was associated with lower DTC risk (HR, 0.82; 95% CI, 0.70–0.96). Younger (<40 vs 40–44 years; HR, 1.31; 95% CI, 1.05–1.62) and older (≥55 vs 40–44 years; HR, 1.33; 95% CI, 1.05–1.68) ages at menopause were associated with higher DTC risk. Among women who were post-menopausal at baseline, ever use of MHT was associated with higher DTC risk (HR, 1.16; 95% CI, 1.02–1.33). The other reproductive factors examined were not associated with DTC risk, including parity and, among post-menopausal women at baseline, duration of MHT use and estimated number of reproductive years or ovulatory cycles.

Heterogeneity across studies was observed for associations of hysterectomy ($I^2 = 27.4\%$, $P = 0.007$) and bilateral oophorectomy ($I^2 = 43.0\%$, $P = 0.04$) with DTC risk (Supplementary Figures, available as Supplementary data at *IJE* online). The positive associations for hysterectomy and DTC risk were observed in most of the larger studies, accounting for the overall positive pooled estimate. Associations for bilateral oophorectomy appeared less consistent across studies.

Tables 4 provides the HRs and 95% CIs by histologic type of DTC. Results were largely consistent for papillary and follicular thyroid cancer, with some exceptions. Namely, OC use, hysterectomy and bilateral oophorectomy were positively associated with risk of papillary, but not follicular, thyroid cancer.

Mutual adjustment of baseline oophorectomy and hysterectomy attenuated the point estimate for bilateral oophorectomy (HR, 0.97; 95% CI, 0.83–1.14) but did not change that for hysterectomy (HR, 1.25; 95% CI, 1.10–1.42). In a model

Table 2. Number (%) of cases with differentiated thyroid cancer and total number (%) of participants according to hormonal and reproductive factors

Factor	Cases	Non-cases	Total
Age at menarche (years)			
<10	78 (3.6%)	28 568 (2.3%)	28 646 (2.3%)
10–11	482 (22.5%)	248 509 (19.9%)	248 991 (19.9%)
12 to <14	1018 (47.6%)	593 384 (47.4%)	594 402 (47.4%)
14 to <16	412 (19.2%)	284 832 (22.8%)	285 244 (22.8%)
≥16	128 (6.0%)	73 558 (5.9%)	73 686 (5.9%)
Unknown	24 (1.1%)	21 914 (1.8%)	21 938 (1.8%)
Parity			
0	293 (13.7%)	177 022 (14.2%)	177 315 (14.2%)
1	339 (15.8%)	185 316 (14.8%)	185 655 (14.8%)
2	719 (33.6%)	397 673 (31.8%)	398 392 (31.8%)
3–4	598 (27.9%)	369 103 (29.5%)	369 701 (29.5%)
≥5	138 (6.4%)	85 674 (6.8%)	85 812 (6.8%)
Unknown	55 (2.6%)	35 977 (2.9%)	36 032 (2.9%)
Oral contraceptive use			
Never	927 (43.3%)	573 054 (45.8%)	573 981 (45.8%)
Ever	1177 (54.9%)	656 912 (52.5%)	658 089 (52.5%)
Unknown	38 (1.8%)	20 799 (1.7%)	20 837 (1.7%)
Duration of oral contraceptive use (years)			
<5	594 (50.5%)	321 575 (49.0%)	322 169 (49.0%)
≥5	528 (44.9%)	303 808 (46.2%)	304 336 (46.2%)
Unknown	55 (4.7%)	31 529 (4.8%)	31 584 (4.8%)
Hysterectomy			
No	1400 (68.4%)	875 355 (72.3%)	876 755 (72.3%)
Yes	586 (28.6%)	277 897 (22.9%)	278 483 (23.0%)
Unknown	60 (2.9%)	57 830 (4.8%)	57 890 (4.8%)
Oophorectomy			
No	1630 (76.1%)	951 748 (76.1%)	953 378 (76.1%)
Unilateral	102 (4.8%)	55 789 (4.5%)	55 891 (4.5%)
Bilateral	288 (13.4%)	138 658 (11.1%)	138 946 (11.1%)
Yes, number of ovaries removed unknown	9 (0.4%)	3266 (0.3%)	3275 (0.3%)
Unknown	113 (5.3%)	101 304 (8.1%)	101 417 (8.1%)
Menopausal status			
Pre-menopausal	589 (28.7%)	292 150 (25.8%)	292 739 (25.8%)
Post-menopausal	1276 (62.3%)	751 650 (66.3%)	752 926 (66.3%)
Unknown	184 (9.0%)	89 913 (7.9%)	90 097 (7.9%)
Age at menopause[a] (years)			
<40	178 (13.0%)	84 211 (10.3%)	84 389 (10.3%)
40–44	151 (11.1%)	97 437 (11.9%)	97 588 (11.9%)
45 to <50	329 (24.1%)	211 265 (25.7%)	211 594 (25.7%)
50 to <55	458 (33.6%)	288 490 (35.1%)	288 948 (35.1%)
≥55	137 (10.0%)	74 500 (9.1%)	74 637 (9.1%)
Unknown	111 (8.1%)	65 275 (7.9%)	65 386 (7.9%)
Menopausal hormone therapy use[a]			
Never	485 (40.6%)	325 609 (44.7%)	326 094 (44.7%)
Ever	698 (58.4%)	388 937 (53.4%)	389 635 (53.4%)
Unknown	13 (1.1%)	13 859 (1.9%)	13 872 (1.9%)
Duration of menopausal hormone therapy use[a] (years)			
≤5	275 (46.4%)	153 318 (46.9%)	153 593 (46.9%)
>5	305 (51.4%)	155 357 (47.5%)	155 662 (47.5%)
Unknown	13 (2.2%)	18 384 (5.6%)	18 397 (5.6%)
Reproductive years[a]			
Quartile 1 (0 to <31 years)	340 (27.3%)	186 826 (24.9%)	187 166 (24.9%)
Quartile 2 (31 to <36 years)	225 (18%)	153 327 (20.4%)	153 552 (20.4%)
Quartile 3 (36 to <39 years)	235 (18.8%)	156 426 (20.9%)	156 661 (20.9%)
Quartile 4 (≥39 years)	447 (35.8%)	253 332 (33.8%)	253 779 (33.8%)
Ovulatory cycles[a]			
Quartile 1 (0 to <320)	251 (26.3%)	133 228 (24.9%)	133 479 (24.9%)
Quartile 2 (320 to <402)	212 (22.2%)	131 338 (24.5%)	131 550 (24.5%)
Quartile 3 (402 to <467)	257 (26.9%)	134 841 (25.2%)	135 098 (25.2%)
Quartile 4 (≥467)	235 (24.6%)	136 285 (25.4%)	136 520 (25.4%)

[a] Restricted to post-menopausal women.

restricted to post-menopausal women at baseline, mutual adjustment of oophorectomy, hysterectomy and ever use of MHT attenuated the point estimate for bilateral oophorectomy (HR, 0.99; 95% CI, 0.83–1.17) and MHT (HR, 1.08; 95% CI, 0.95–1.23) but not hysterectomy (HR, 1.29; 95% CI, 1.11–1.49).

Table 3. Hazard ratios and 95% confidence intervals for differentiated thyroid cancer according to hormonal and reproductive factors

Factor	Cases	Person-years	HR[a] (95% CI)
Age at menarche (years)			
<10	78	327 175	1.28 (1.00–1.64)
10–11	482	2 976 607	1 (reference)
12 to <14	1018	6 916 907	0.99 (0.89–1.11)
14 to <16	412	3 244 178	0.92 (0.80–1.05)
≥16	128	816 317	1.09 (0.88–1.35)
Unknown	24	260 635	0.72 (0.48–1.09)
			P-trend = 0.06
Continuous (per year)			0.98 (0.96–1.01)
Parity			
0	293	2 073 725	0.89 (0.75–1.05)
1	339	2 103 623	1 (reference)
2	719	4 590 952	1.01 (0.88–1.17)
3–4	598	4 327 991	0.90 (0.77–1.04)
≥5	138	1 020 111	0.88 (0.71–1.08)
Unknown	55	425 418	0.85 (0.63–1.14)
			P-trend = 0.14
Continuous (per live birth)[b]			0.99 (0.96–1.02)
Oral contraceptive use			
Never	927	6 689 707	1 (reference)
Ever	1177	7 584 294	1.09 (0.99–1.20)
Unknown	38	267 818	0.97 (0.69–1.37)
Duration of oral contraceptive use (years)			
<5	594	3 787 714	1 (reference)
≥5	528	3 445 763	0.86 (0.76–0.96)
Unknown	55	350 818	1.24 (0.92–1.66)
Hysterectomy			
No	1400	10 013 122	1 (reference)
Yes	586	3 218 411	1.25 (1.13–1.39)
Unknown	60	724 542	0.66 (0.51–0.87)
Oophorectomy			
No	1630	11 018 045	1 (reference)
Unilateral	102	650 402	1.06 (0.87–1.30)
Bilateral	288	1 632 944	1.14 (1.00–1.29)
Yes, number of ovaries removed unknown	9	35 911	1.42 (0.72–2.78)
Unknown	113	1 204 518	0.71 (0.58–0.88)
Menopausal status			
Pre-menopausal	589	3 422 628	1 (reference)
Post-menopausal	1276	8 807 350	0.82 (0.70–0.96)
Unknown	184	1 054 167	1.04 (0.86–1.26)
Age at menopause[c] (years)			
<40	178	999 112	1.31 (1.05–1.62)
40–44	151	1 138 789	1 (reference)
45 to <50	329	2 437 133	1.06 (0.87–1.28)
50 to <55	458	3 318 156	1.10 (0.91–1.33)
≥55	137	803 705	1.33 (1.05–1.68)
Unknown	111	702 735	1.35 (1.04, 1.76)
			P-trend = 0.01
Continuous (per year)[c]			1.00 (0.99–1.01)
Menopausal hormone therapy use[c]			
Never	485	3 780 032	1 (reference)
Ever	698	4 356 044	1.16 (1.02–1.33)
Unknown	13	159 025	0.65 (0.37–1.17)
Duration of menopausal hormone therapy use[c] (years)			
≤5	275	1 664 767	1 (reference)
>5	305	1 710 651	0.98 (0.81–1.18)
Unknown	13	177 700	0.76 (0.43–1.37)
Reproductive years[c]			
Quartile 1 (0 to <31 years)	340	2 190 834	1 (reference)
Quartile 2 (31 to <36 years)	225	1 749 059	0.88 (0.74–1.05)
Quartile 3 (36 to <39 years)	235	1 796 601	0.92 (0.78–1.09)
Quartile 4 (≥39 years)	447	2 892 888	0.99 (0.85–1.14)
			P-trend = 0.42
Continuous (per year)			1.00 (0.99–1.01)

(continued)

Table 3. (continued)

Factor	Cases	Person-years	HR[a] (95% CI)
Ovulatory cycles[c]			
Quartile 1 (0 to <320)	251	1 553 939	1 (reference)
Quartile 2 (320 to <402)	212	1 551 509	0.86 (0.71–1.03)
Quartile 3 (402 to <467)	257	1 601 262	1.01 (0.85–1.21)
Quartile 4 (≥467)	235	1 607 859	0.88 (0.73–1.06)
			P-trend = 0.17
Continuous (per cycle)			1.00 (1.00–1.00)

HR, hazard ratio.
P-trend calculated using the Wald test for the exposure term modelled continuously using ordinal groups.
[a] Adjusted for attained age (used as time metric), race, education, body mass index, alcohol intake and smoking.
[b] Restricted to women with at least one live birth.
[c] Restricted to post-menopausal women.

Table 4. Hazard ratios and 95% confidence intervals for papillary and follicular thyroid cancer according to hormonal and reproductive factors

	Papillary thyroid cancer			Follicular thyroid cancer		
Factor	Cases	Person-years	HR[a] (95% CI)	Cases	Person-years	HR[a] (95% CI)
Age at menarche, years						
<10	66	327 175	1.23 (0.94–1.60)	12	327 175	1.68 (0.89–3.16)
10–11	424	2 976 607	1 (reference)	58	2 976 607	1 (reference)
12 to <14	900	6 916 907	0.99 (0.88–1.11)	118	6 916 907	1.00 (0.73–1.39)
14 to <16	352	3 244 178	0.88 (0.76–1.03)	60	3 244 178	1.15 (0.79–1.70)
≥16	114	816 317	1.06 (0.85–1.34)	14	816 317	1.24 (0.66–2.31)
Unknown	24	260 635	0.83 (0.55–1.26)	0	260 635	–
			P-trend = 0.15			*P*-trend = 0.60
Continuous (per year)			0.98 (0.95–1.01)			1.02 (0.95–1.11)
Parity						
0	259	2 073 725	0.86 (0.72–1.02)	34	2 073 725	1.19 (0.71–1.99)
1	309	2 103 623	1 (reference)	30	2 103 623	1 (reference)
2	628	4 590 952	0.98 (0.85–1.14)	91	4 590 952	1.30 (0.84–2.00)
3–4	518	4 327 991	0.88 (0.75–1.03)	80	4 327 991	1.07 (0.68–1.67)
≥5	118	1 020 111	0.87 (0.69–1.09)	20	1 020 111	0.97 (0.53–1.77)
Unknown	48	425 418	0.83 (0.61–1.14)	7	425 418	0.95 (0.40–2.25)
			P-trend = 0.19			*P*-trend = 0.70
Continuous (per live birth)[b]			1.00 (0.97–1.03)			0.96 (0.89–1.04)
Oral contraceptive use						
Never	794	6 689 707	1 (reference)	133	6 689 707	0.97 (0.74–1.28)
Ever	1052	7 584 294	1.11 (1.00–1.24)	125	7 584 294	0.60 (0.20–1.75)
Unknown	34	267 818	1.03 (0.72–1.48)	4	267 818	1.11 (0.54–2.28)
Duration of oral contraceptive use (years)						
<5	531	3 787 714	1 (reference)	63	3 787 714	1 (reference)
≥5	471	3 445 763	0.85 (0.75–0.97)	57	3 445 763	0.87 (0.60–1.25)
Unknown	50	350 818	1.33 (0.98–1.81)	5	350 818	0.67 (0.25–1.82)
Hysterectomy						
No	1229	10 013 122	1 (reference)	171	10 013 122	1 (reference)
Yes	515	3 218 411	1.28 (1.14–1.43)	71	3 218 411	1.07 (0.80–1.44)
Unknown	50	724 542	0.67 (0.50–0.90)	10	724 542	0.63 (0.32–1.24)
Oophorectomy						
No	1432	11 018 045	1 (reference)	198	11 018 045	1 (reference)
Unilateral	92	650 402	1.11 (0.90–1.38)	10	650 402	0.75 (0.40–1.42)
Bilateral	253	1 632 944	1.16 (1.01–1.33)	35	1 632 944	0.98 (0.68–1.43)
Yes, number of ovaries removed unknown	8	35 911	1.35 (0.66–2.76)	1	35 911	2.23 (0.29–17.32)
Unknown	95	1 204 518	0.74 (0.59–0.93)	18	1 204 518	0.57 (0.32–1.02)
Menopausal status						
Pre-menopausal	537	3 422 628	1 (reference)	52	3 422 628	1 (reference)
Post-menopausal	1106	8 807 350	0.82 (0.70–0.97)	170	8 807 350	0.81 (0.50–1.30)
Unknown	159	1 054 167	1.04 (0.85–1.27)	25	1 054 167	1.07 (0.63–1.82)
Age at menopause[c] (years)						
<40	158	999 112	1.29 (1.02–1.62)	20	999 112	1.47 (0.75–2.87)
40–44	136	1 138 789	1 (reference)	15	1 138 789	1 (reference)
45 to <50	284	2 437 133	1.00 (0.82–1.23)	45	2 437 133	1.54 (0.85–2.77)
50 to <55	395	3 318 156	1.04 (0.86–1.27)	63	3 318 156	1.62 (0.91–2.86)
≥55	113	803 705	1.19 (0.92–1.54)	24	803 705	2.63 (1.37–5.07)
Unknown	97	702 735	1.28 (0.97–1.69)	14	702 735	2.09 (0.97–4.52)
			P-trend = 0.05			*P*-trend = 0.08
Continuous (per year)[c]			1.00 (0.99–1.01)			1.02 (1.00–1.05)

(continued)

Table 4. (continued)

Factor	Papillary thyroid cancer			Follicular thyroid cancer		
	Cases	Person-years	HR[a] (95% CI)	Cases	Person-years	HR[a] (95% CI)
Menopausal hormone therapy use[c]						
Never	406	3 780 032	1 (reference)	79	3 780 032	1 (reference)
Ever	610	4 356 044	1.17 (1.03–1.34)	88	4 356 044	1.07 (0.78–1.47)
Unknown	13	159 025	0.81 (0.46–1.41)	0	159 025	0.00 (0.00–0.00)
Duration of menopausal hormone therapy use[c] (years)						
≤5	246	1 664 767	1 (reference)	29	1 664 767	1 (reference)
>5	264	1 710 651	0.93 (0.76–1.15)	41	1 710 651	1.33 (0.77–2.30)
Unknown	12	177 700	0.77 (0.42–1.42)	1	177 700	0.67 (0.09–5.10)
Reproductive years[c]						
Quartile 1 (0 to <31 years)	302	2 190 834	1 (reference)	38	2 190 834	1 (reference)
Quartile 2 (31 to <36 years)	194	1 749 059	0.85 (0.71–1.02)	31	1 749 059	1.15 (0.71–1.87)
Quartile 3 (36 to <39 years)	198	1 796 601	0.87 (0.72–1.04)	37	1 796 601	1.35 (0.85–2.15)
Quartile 4 (≥39 years)	386	2 892 888	0.95 (0.81–1.11)	61	2 892 888	1.30 (0.86–1.96)
			P-trend = 0.25			*P*-trend = 0.22
Continuous (per year)			1.00 (0.99–1.01)			1.02 (0.99–1.04)
Ovulatory cycles[c]						
Quartile 1 (0 to <320)	223	1 553 939	1 (reference)	28	1 553 939	1 (reference)
Quartile 2 (320 to <402)	187	1 551 509	0.85 (0.70–1.03)	25	1 551 509	0.92 (0.53–1.59)
Quartile 3 (402 to <467)	217	1 601 262	0.96 (0.80–1.16)	40	1 601 262	1.42 (0.87–2.33)
Quartile 4 (≥467)	195	1 607 859	0.82 (0.67–1.01)	40	1 607 859	1.37 (0.83–2.27)
			P-trend = 0.15			*P*-trend = 0.23
Continuous (per cycle)			1.00 (1.00–1.00)			1.00 (1.00–1.00)

HR, hazard ratio.
P-trend calculated using the Wald test for the exposure term modelled continuously using ordinal groups.
[a] Adjusted for attained age (used as time metric), race, education, body mass index, alcohol intake and smoking.
[b] Restricted to women with at least one live birth.
[c] Restricted to post-menopausal women.

Discussion

This is the first pooled analysis of prospective studies and one of the largest studies to date investigating DTC risk in relation to hormonal and reproductive factors. We found that DTC risk was associated with several reproductive and hormonal factors, which are thought to be reflective of exposure to oestrogens and progestogens over the life course, including younger age at menarche, both younger and older ages at menopause, hysterectomy, bilateral oophorectomy, and OC and MHT use, providing some evidence that lifetime exposure to sex steroid hormones is associated with risk of first primary DTC. However, in mutually adjusted models, the risk of DTC associated with hysterectomy remained elevated whereas that of bilateral oophorectomy and MHT were attenuated, which may indicate a role of factors other than sex steroid hormones (e.g. detection bias). Moreover, DTC risk declined, rather than increased, with greater duration of use of OCs. Other proxy measures of higher or prolonged sex steroid levels were not associated with DTC risk, including parity, duration of MHT use and estimated number of reproductive years and ovulatory cycles.

Because pregnancy is a time of increased exposure to oestrogens and progestogens, we hypothesized that a greater number of live births would be associated with higher DTC risk. We observed no association between parity and DTC risk overall, and the results were heterogeneous across studies. Although parity has been linked to other female or female-predominant cancers,[41] the underlying biological mechanisms are known or suspected to differ across these outcomes and may not be completely relevant for DTC. The inability of our study to detect an association between parity and DTC could be due a lack of information on pregnancy loss (miscarriages, abortions or stillbirths) and other relevant exposures, such as breastfeeding. The elevated risk of thyroid cancer observed in some studies immediately after pregnancy may reflect hormone-driven progression of pre-existing cancer or it may be due to greater medical surveillance during pregnancy, which increases the likelihood of thyroid cancer detection and diagnosis.[42–44] Studies evaluating these associations in more detail would be informative.

Results from this pooled analysis indicated that onset of menarche prior to age 10 years was associated with higher DTC risk. Early menarche is an indicator for greater lifetime number of ovulatory cycles and an elevated exposure to female sex steroid hormones at younger ages.[45] However, we found no association for estimated number of ovulatory cycles or reproductive years with DTC risk. The lower risk of DTC in the post-menopausal period is in agreement with previous studies,[42,46,47] although some studies found no association.[44,48–51] The lower DTC risk observed after menopause is consistent with the substantial reduction in circulating sex steroid hormones, although it could also reflect more frequent opportunities for incidental thyroid cancer detection during the reproductive years and perimenopausal period.

Determinants of age at menopause are important to consider as younger and older ages at menopause were both associated with higher risk of DTC. Consistently with previous studies,[50,52] we observed a higher DTC risk in women who had previously undergone a hysterectomy or bilateral oophorectomy. Most bilateral oophorectomies occur concurrently with hysterectomy and more than half of all hysterectomies are performed between the ages of 35 and 45 years.[53,54] Prior to 2002, >90% of women used MHT after bilateral oophorectomies likely, in part, because of data that demonstrated MHT use shortly after the time of surgery was effective in controlling symptoms, as well as reducing morbidity and mortality.[55,56] In this study, ever use of MHT, but not duration of use, was associated with higher DTC risk. A more

direct influence of MHT use on DTC risk could explain the discrepant findings for post-menopausal status, age at menopause and surgical procedures known to induce menopause. However, only hysterectomy remained associated with DTC risk in models mutually adjusted for hysterectomy, oophorectomy and MHT use. To some extent, the higher DTC risk associated with hysterectomy may reflect more frequent opportunities for incidental detection of thyroid cancer.[42] In a recent case–control study in Australia, 20% of the observed association between hysterectomy and thyroid cancer was mediated by frequency of healthcare utilization.[57]

Ever use of OCs was not associated with DTC in our study, consistently with several previous cohort studies on this topic.[42,44,46,48,49] Although we did not observe an association between DTC risk and ever use of OCs, our study indicated that longer duration of OC use was associated with lower first primary DTC risk among women who did use OCs. Past studies have reported both inverse associations[42,47] and no association[44,48–51] with duration of OC use. One possible explanation for these inconsistencies is that the formulations for OCs are variable and have changed over time. Similarly, lack of information on the formulation of MHT could account for some of the inconsistent findings in our study and previous studies. Most of the cohorts did not collect information on OC and MHT formulations, however.[34]

Women are more likely to develop thyroid disorders than men, which may be due in part to the effects of oestrogen on the hypothalamic–pituitary–thyroid (HPT) axis.[58] The resulting increase in thyroid stimulating hormone (TSH) related to an active HPT axis has long been hypothesized to increase thyroid cancer risk; however, recent prospective studies have demonstrated inverse, rather than positive, associations of TSH with thyroid cancer risk.[57,58] Oestrogen affects the thyroid directly by stimulating thyroid growth and secretion of thyroglobulin, which is a thyroid hormone precursor, and indirectly by increasing pituitary secretion of TSH.[57,58] Initial TSH increases among euthyroid women quickly return to normal whereas longer-term increases occur among women with hypothyroidism.[58] However, in this study, we were unable to assess differences in associations for women with, vs without, thyroid dysfunction.

This study has several strengths, including the prospective study design that limited the potential for differential recall and selection biases,[10,11] the large number of included studies from across the world, the ability to assess differences by histologic type and the ability to control for potential confounding factors, including socio-economic indicators, BMI, smoking and alcohol intake. Pooling of the data resulted in a relatively large number of cases, allowing more precise estimation of these associations than could have been achieved from any of these studies individually. Utilizing a standardized format for each exposure lowered the potential for bias due to methodological heterogeneity across studies.

Our study had other limitations not already mentioned above. Most cohort members were peri- or post-menopausal at study entry and were diagnosed with thyroid cancer at age $\geq$50 years. This precluded us from investigating risk factors for pre-menopausal thyroid cancer. Some participants, especially those enrolled at older ages, may have had difficulty recalling age at menarche and age at starting and stopping OC use. In addition to recall errors, which are likely to be non-differential in these studies and expected to bias associations towards the null, the factors examined in our study may be poor proxies of cumulative sex steroid hormone exposure or exposures occurring during potentially etiologically relevant time windows (e.g. puberty or pregnancy). We lacked detailed information on the timing of some of these exposures in relation to one another and to subsequent thyroid cancer diagnosis. Additionally, residual confounding for socioeconomic factors or healthy-user bias is also possible, especially in countries without universal healthcare, such as the USA. Confounding by iodine status may be possible as dietary iodine is often inadequate in pregnancy and residing in regions characterized by mild-to-moderate iodine deficiency can further increase the risk of developing severe iodine deficiency in pregnancy. Finally, we cannot rule out detection bias as a potential explanation for some of our findings, as some reproductive and hormonal factors may be associated with greater likelihood of incidental detection of thyroid cancer and we did not have information on the mode of thyroid cancer detection.

In conclusion, our study provides some evidence linking reproductive and hormonal factors with risk of DTC. Results should be interpreted cautiously considering the modest strength of the associations and potential for exposure misclassification and detection bias. Prospective studies of prediagnostic circulating sex steroid hormone measurements and DTC risk would overcome many of these limitations and may provide additional insight about a potential role of sex steroid hormones, including oestrogen, in the aetiology of DTC.

Disclaimer

The opinions, findings and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programmes. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Ethics approval

All studies received ethics and data-sharing approval from their local Institutional Review Board. Study participants provided informed consent, wherever applicable, and participated under ethically approved protocols. Data sets shared with the NCI were de-identified.

Data availability

The data underlying this pooled analysis were provided by cohorts participating in the NCI Cohort Consortium under a data-use agreement. Researchers interested in the individual-level data may submit an inquiry to the corresponding author and the principal investigators of the individual cohorts.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

T.J.O. and C.M.K. conceived of and designed the study. All authors (except T.J.O.) acquired the data. C.M.K. and T.J.O. performed the data analysis, created tables and compiled the results. T.O.G. produced the initial draft. All authors read and critically reviewed the manuscript for intellectual content. T.J.O. and C.M.K. revised the manuscript. C.M.K. supervised the work. All authors reviewed the manuscript and approved the final version.

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Conflict of interest

None declared.

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