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History of thyroid disease and survival of ovarian cancer patients: results from the Ovarian Cancer Association Consortium, a brief report

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Background: Findings from *in vitro* studies suggest that increased exposure to thyroid hormones can influence progression of ovarian tumours. However, epidemiologic evidence on this topic is limited.

Methods: We pooled data from 11 studies from the Ovarian Cancer Association Consortium. Using multivariate Cox proportional hazards models, we estimated associations between hyper- and hypothyroidism and medications prescribed for these conditions with 5-year all-cause survival among women diagnosed with invasive ovarian cancer.

Results: Overall, there was a nonsignificant association with history of hyperthyroidism ($n = 160$ cases) and mortality (HR = 1.22; 95% CI = 0.97–1.53). Furthermore, diagnosis of hyperthyroidism within the 5 years before ovarian cancer diagnosis was associated with an increased risk of death (HR = 1.94; 95% CI = 1.19–3.18). A more modest association was observed with history of hypothyroidism ($n = 624$ cases) and mortality (HR = 1.16; 95% CI = 1.03–1.31). Neither duration of hypothyroidism nor use of thyroid medications was associated with survival.

Conclusions: In this large study of women with ovarian cancer, we found that recent history of hyperthyroidism and overall history of hypothyroidism were associated with worse 5-year survival.

Ovarian cancer is the most deadly gynaecological cancer with 5-year survival rate of ~46% (Siegel *et al*, 2017). Some previous epidemiologic studies have shown that hormonal factors, including hormone therapy (HT) and cortisol, can impact mortality (Rodriguez *et al*, 1995; Mascarenhas *et al*, 2006; Schrepf *et al*, 2015).

In addition to HT and cortisol, there is recent evidence that exposure to thyroid hormones may also play a role in ovarian

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cancer progression. An *in vitro* study has demonstrated that 3,5,3′-triiodo-L-thyronine (T_3) and L-thyroxine (T_4) hormones at physiological levels are able to initiate proliferation and improve survival of ovarian cancer cells, whereas exposure to these hormones at concentrations below normal serum levels may result in slower growth of ovarian cancer cells (Shinderman-Maman *et al*, 2015). The results of the only epidemiologic study that assessed the association between thyroid disease and ovarian cancer mortality were suggestive of a possible link between hyperthyroidism and mortality among these patients (Journy *et al*, 2017). However, the study was based on a very small number of cases.

We evaluated associations between history of hyper- and hypothyroidism and all-cause mortality using a large international study of women diagnosed with ovarian cancer.

MATERIALS AND METHODS

We pooled data on history of hyper- and hypothyroidism from the studies participating in the Ovarian Cancer Association Consortium (OCAC). Of all the studies in OCAC, 11 included data on history of hyperthyroidism and 10 on hypothyroidism. All participants provided informed consent; and study protocols were approved by the institutional review boards or ethics committees for each study site. Characteristics of the studies included in this pooled analysis are presented in Table 1. Although most of the data were based on self-report, three studies (HJO, HOP, and LAX) included data collected from medical records. Almost all the studies, except for JPN, provided information on the age at diagnosis with either of these diseases, and four studies (HJO, LAX, NEC, and NJO) also collected information on use of medications prescribed for these conditions including radioactive iodine, antithyroid agents, and thyroid hormones.

Our final study population included patients diagnosed with epithelial invasive ovarian, peritoneal, or fallopian tube cancers. Among these women, 5198 had information on history of hyperthyroidism and 5662 had information on history of hypothyroid disease (yes/no). Hyperthyroidism was defined as any hyperthyroid disease, including Grave's disease, and hypothyroidism as any hypothyroid disease, including Hashimoto's disease.

An additional exposure of interest was time since being diagnosed with these thyroid conditions before the date of diagnosis of ovarian cancer. This was calculated by subtracting age at the time of being diagnosed with either hyper- or hypothyroid disease from the age of diagnosis with ovarian cancer. We then dichotomised this variable using the 5 years as the cutpoint. Another exposure of interest was the use of medications prescribed for hyper- or hypothyroid disease, dichotomised as yes/no. The outcome of interest was overall survival (OS) after ovarian cancer diagnosis censored at 5 years of follow-up defined as the time period between the date of diagnosis and the date of death, date of last contact, or 5 years after the date of diagnosis, whichever occurred first. Additional outcome of interest was survival censored at 10 years of follow-up.

We used age-, stage-, and site-adjusted Cox proportional hazards models to estimate associations between each of these exposures and all-cause mortality by calculating hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). We also adjusted the models for each of the descriptive and disease characteristics indicated in Table 2. However, because such adjustment did not change the age-, stage-, and site-adjusted associations by $>10\%$, none of these covariates were included in the final models.

We assessed statistical heterogeneity between study-specific HRs using I^2 statistics and Cochran's Q-statistics (Higgins *et al*, 2003). No heterogeneity was observed, and therefore we estimated and reported pooled HRs and 95% CIs.

Furthermore, we examined whether associations differed between strata of histotype (serous *vs* non-serous), BMI ($18.5\,kg\,m^{-2} < BMI < 25.0\,kg\,m^{-2}$ *vs* BMI $\geqslant 25.0\,kg\,m^{-2}$), age at diagnosis ($<65$ *vs* $\geqslant 65$ years), and stage of disease (local/regional *vs* distant). Presence of multiplicative interaction was examined by including cross-product terms between the exposures of interest and potential effect modifiers (histotype, BMI, age at diagnosis, and stage of disease) and utilising likelihood ratio tests to assess significance of these terms. We additionally accounted for left truncation in all the models to take into consideration time between the date of ovarian cancer diagnosis and date of the interview and the inability to enroll women who had died before the recruitment date.

Finally, we conducted additional analyses after excluding patients who reported history of both hyper- and hypothyroid disease ($n=23$). For medication use, we also conducted separate analyses limited to patients with a corresponding thyroid disease.

All statistical tests used in the analyses were two sided; P-values of <0.05 were considered significant.

RESULTS

Descriptive and clinical characteristics of the participants according to thyroid disease status are presented in Table 2. Participants diagnosed with hyperthyroidism or hypothyroidism were more likely to be older and postmenopausal. Those with history of hypothyroidism were also more likely to be white, obese, more educated, and have a history of hysterectomy, and less likely to breastfeed. Median follow-up times from ovarian cancer diagnosis for patients with neither hypo- nor hyperthyroid disease, patients with hyperthyroidism, and patients with hypothyroidism were 1791, 1574, and 1459 days, respectively.

We observed a positive association between history of hyperthyroidism and overall mortality censored at 5 years of follow-up in the overall sample of patients diagnosed with ovarian cancer, although this association was not statistically significant (HR = 1.22; 95% CI = 0.97–1.53; Table 3). In strata defined by time since diagnosis, only hyperthyroid disease diagnosed within 5 years of ovarian cancer diagnosis was associated with increased mortality (HR = 1.94; 95% CI = 1.19–3.18). History of hypothyroidism was associated with a slight increased risk of death (HR = 1.16; 95% CI = 1.03–1.32). No association was observed between time since diagnosis of hypothyroidism and mortality. For 10-year survival, HRs were slightly attenuated and, for hypothyroidism and duration of hyperthyroidism of 5 years or less before ovarian cancer diagnosis, were no longer statistically significant.

Ever use of anti-hyper- or anti-hypothyroid medications was also not associated with mortality (HR = 0.69; 95% CI = 0.17–2.80 and HR = 1.04; 95% CI = 0.77–1.40, respectively). The associations were not modified by histotype, BMI, age at diagnosis of ovarian cancer, or stage of disease. For medications, conducting analysis among individuals with a corresponding thyroid disease did not considerably influence the observed associations. Accounting for left truncation did not considerably change the HRs observed in the main analysis.

DISCUSSION

In this large study, we found that recent history of hyperthyroidism and overall history of hypothyroidism were associated with increased 5-year all-cause mortality among ovarian cancer patients.

Table 1. Characteristics of studies included in the analysis: Ovarian Cancer Association Consortium[a]

Study acronym	Study name	Study location, time of enrolment	Data collection method	Median time of follow-up, days (range of follow-up)	Determination of history of hyper/ hypothyroidism	Patients with hyperthyroid disease, *N* (%)	Patients with hypothyroid disease, *N* (%)
AUS (Merritt *et al*, 2008)	Australian Ovarian Cancer Study	Australia, Jan 2002 to Jun 2006	Self-completed questionnaire	1705 (19-3672)	Q: Ever having disease requiring regular medical care	10 (0.9)	27 (2.3)
DOV (Rossing *et al*, 2007; Bodelon *et al*, 2012)	Disease of the Ovary and their Evaluation Study	USA: Washington, 2002–2005 (DOV) 2006–2009 (DVE)	In-person interview	1398 (243–3192)	Q: Disease diagnosed by physician or health care professional before being diagnosed with ovarian cancer	13 (2.6)	100 (16.7)
GER (Royar *et al*, 2001)	German Ovarian Cancer Study	Germany, 1993–1996	Self-administered questionnaire	1464 (18–6060)	Q: Ever having disease diagnosed by physician	10 (4.4)	7 (3.1)
HAW (Goodman *et al*, 2008; Lurie *et al*, 2008)	Hawaii Ovarian Cancer Study	USA: Hawaii, 1993–2008	In-person interview	2750 (143–7662)	Q: Disease diagnosed by physician before being diagnosed with ovarian cancer	22 (4.6)	25 (5.2)
HJO (Song *et al*, 2009)	Hannover-Jena Ovarian Cancer Study	Germany 2007–2011	MRR	707 (9–8722)	MRR: reporting of disease	7 (5.4)	29 (19.1)
HOP (Lo-Ciganic *et al*, 2012)	Hormones and Ovarian Cancer Prediction Study	USA: Pennsylvania, Ohio, and New York, 2003–2009	In-person interview and MRR	1821 (40–3982)	Q: Disease diagnosed by physician or health care professional before being diagnosed with ovarian cancer; MRR: reporting of disease	25 (4.2)	109 (16.1)
JPN (Hamajima *et al*, 2001)	Hospital-based Research Program at Aichi Cancer Center	Japan, 2001–2005	In-person interview	1069 (43–3396)	Q: Ever having disease	2 (3.1)	0
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	USA: California, 1989 to present	MRR	1498 (13–8239)	MRR: reporting of disease	3 (1.1)	56 (17.3)
NCO (Schildkraut *et al*, 2008, 2010)	North Carolina Ovarian Cancer Study	USA: North Carolina, 1999–2008	Self-completed questionnaire	1836 (93–5730)	Q: Disease diagnosed by physician before being diagnosed with ovarian cancer	32 (3.9)	133 (14.3)
NEC (Terry *et al*, 2005; Merritt *et al*, 2013)	New England Case-Control Study of Ovarian Cancer	USA: New Hampshire and Massachusetts, 1992–2003	In-person interview	2904 (70–7709)	Q: Ever having disease before being diagnosed with ovarian cancer	25 (3.3)	97 (11.6)
NJO (Bandera *et al*, 2011; Chandran *et al*, 2011; Gifkins *et al*, 2012)	New Jersey Ovarian Cancer Study	USA: New Jersey, 2002–2008	Phone interview	2375 (165–4085)	Q: Disease diagnosed by health care professional before being diagnosed with ovarian cancer	11 (5.4)	41 (17.7)

Abbreviations: MRR = medical record review; Q = question.
[a]JPN did not provide information on the age at being diagnosed with hyper- or hypothyroid disease; LAX did not provide information on the age at being diagnosed with hyperthyroidism; AUS patients were not specifically asked about thyroid disease, and thyroid disease history was determined from the answers to the open-ended question on having other diseases; HJO, LAX, NEC and NJO collected information on anti-hyper- and anti-hypothyroid medication intake.

This increased mortality associated with hyperthyroidism may be explained by the biological activity of thyroid hormones. One of these hormones, T_3, has been shown to promote expression of genes associated with inflammation including cyclooxygenase-2 and matrix metalloproteinase-9 (Rae *et al*, 2007), both of which can play a role in tumour invasion or angiogenesis (Lee *et al*, 2006; Hu *et al*, 2012). In one preclinical study, both T_3 and T_4 inhibited transcription of genes involved in tumour suppression, GDF-15 and IGFBP-6, and cell cycle, p21 and p16 (Shinderman-Maman *et al*, 2015), thereby influencing proliferation and survival of ovarian cancer cells. A recent increase in exposure to these hormones may result in increased proliferation and invasiveness of ovarian tumours and, consequently, impact survival of ovarian cancer patients, possibly explaining the association observed in our study.

Out of the four studies conducted to examine the link between thyroid disease and ovarian cancer (Ness *et al*, 2000; Brinton *et al*, 2007; Kang *et al*, 2013), only one was conducted to assess the association with survival (Journy *et al*, 2017). Similarly to us, the authors of the survival study concluded that there was a suggestion of the association between hyperthyroidism and mortality among ovarian cancer patients (Journy *et al*, 2017). However, our study was considerably larger; we were also able to control for important prognostic factors.

We found that overall history of hypothyroidism was also associated with a slightly increased mortality. This finding is different from what we had expected based on the *in vitro* finding that thyroid hormones below biologically normal levels slow growth of ovarian cancer cells (Shinderman-Maman *et al*, 2015). There are several possible explanations for our observation. One treatment for hyperthyroidism is radioiodine therapy; this treatment can result in transient or permanent hypothyroidism in patients (Burch and Cooper, 2015). The observed decreased 5-year survival that we found associated with hypothyroidism could be the result of previous hyperthyroidism. In our study population, however, exclusion of 23 patients with history of both hyper- and hypothyroidism from the analysis did not change the observed estimates.

Another possible explanation is that external thyroid hormones prescribed for hypothyroidism might be in excess of what is physiologically required or that treatment regimens do not replicate normal secretion patterns. This excessive exposure to

Table 2. Demographic and disease characteristics of ovarian cancer patients, Ovarian Cancer Association Consortium[a]

Characteristics	No history of either hyper- or hypothyroidism, $N=5038$	History of hyperthyroidism, $N=160$	P-value[b]	History of hypothyroidism, $N=624$	P-value[b]
Age at diagnosis with ovarian cancer, mean (s.d.)	56.8 (11.4)	61.6 (9.1)	<0.001	60.1 (9.7)	<0.001
Race, *N* (%)					
White	4260 (85.2)	131 (81.9)	0.24	580 (93.5)	<0.001
Non-white	737 (14.8)	29 (18.1)		40 (6.5)	
BMI, kg m^{-2}					
18.5–24.9	2058 (44.6)	72 (48.6)	0.58	204 (35.2)	<0.001
25 to ⩽30	1353 (29.3)	42 (28.4)		168 (29.0)	
⩾30	1202 (26.1)	34 (23.0)		207 (35.8)	
Education, *N* (%)					
High school or less	2078 (42.8)	73 (48.3)	0.18	194 (32.6)	<0.001
More than high school	2773 (57.2)	78 (51.6)		401 (67.4)	
Family history of breast or ovarian cancer, *N* (%)					
No	1180 (23.4)	37 (23.1)	0.58	140 (22.4)	0.27
Yes	1008 (20.0)	27 (16.9)		142 (22.8)	
Unknown/missing	2850 (56.6)	96 (60.0)		342 (54.8)	
Menopausal status, *N* (%)					
Premenopausal	1480 (30.1)	25 (16.0)	<0.001	122 (20.2)	<0.001
Postmenopausal	3438 (69.9)	131 (84.0)		483 (79.8)	
Ever breastfed, *N* (%)					
Never pregnant	933 (19.8)	29 (19.2)	0.39	100 (17.9)	0.03
Pregnant but not breastfed	1719 (36.5)	63 (41.7)		236 (42.3)	
Breastfed	2063 (43.7)	59 (39.1)		222 (39.8)	
Hysterectomy, *N* (%)					
No	3903 (82.0)	112 (77.8)	0.20	403 (71.7)	<0.001
Yes	858 (18.0)	32 (22.2)		159 (28.3)	
Pregnancy ever, *N* (%)					
No	933 (18.9)	29 (18.5)	0.88	100 (16.8)	0.19
Yes	3993 (81.1)	128 (81.5)		497 (83.2)	
Oral contraceptive use ever, *N* (%)					
No	1951 (41.5)	75 (48.4)	0.09	210 (38.6)	0.19
Yes	2746 (58.5)	80 (51.6)		334 (61.4)	
Tubal ligation, *N* (%)					
No	3931 (81.3)	120 (77.9)	0.29	476 (80.3)	0.55
Yes	905 (18.7)	34 (22.1)		117 (19.7)	
Stage, *N* (%)					
Localised	819 (16.3)	23 (14.4)	0.18	91 (14.6)	0.10
Regional	904 (17.9)	38 (23.7)		99 (15.9)	
Distant	3229 (64.1)	94 (59.7)		417 (66.8)	
Unknown	86 (1.7)	5 (3.2)		17 (2.7)	
Grade, *N* (%)					
Well differentiated	535 (10.6)	13 (8.1)	0.19	56 (9.0)	0.25
Moderately differentiated	1086 (21.6)	28 (17.5)		133 (21.3)	
Poorly differentiated	2765 (54.8)	89 (55.6)		339 (54.3)	
Undifferentiated	301 (6.0)	14 (8.8)		50 (8.0)	
Unknown	351 (7.0)	16 (10.0)		46 (7.4)	
Histology, *N* (%)					
Serous	3004 (59.6)	72 (45.0)	0.24	395 (63.3)	0.08
Non-serous	2034 (40.4)	88 (55.0)		229 (36.7)	

Abbreviation: BMI = body mass index.
[a]Numbers may not add up because of missing observations.
[b]*P*-value for χ^2 test for categorical variables and *t*-test for age at diagnosis variable; tests used to compare diseased and non-diseased patients.

thyroid hormone, therefore, can result in activation of the biological processes described above. We did not observe any association between intake of thyroid hormones and survival. However, it could be that duration and timing of thyroid hormone intake are more important than the overall exposure to thyroid hormones. Data on timing of thyroid hormone replacement were not available to us; therefore, we were not able to explore these associations further.

In interpreting of this study, understanding of the strengths and weaknesses is critical. Important strengths include a large study size allowing us to examine main effects as well as associations within strata of potential effect modifiers. Because ovarian cancer is relatively rare, pooled data such as these are critical for a more detailed examination of factors related to survival. Limitations of the study include reliance on self-report of hyper- and hypothyroidism rather than medical reports or even actual measurement of

Table 3. Association between history of hyperthyroidism and hypothyroidism and 5-year overall survival following a diagnosis of invasive ovarian cancer, Ovarian Cancer Association Consortium

	Dead	Alive	HR (95% CI)[a]	*P*-value
No history of hyper-or hypothyroidism	2206	2832	1.00 (Ref)	
History of hyperthyroidism	80	80	1.22 (0.97–1.53)	0.08
Duration of hyperthyroidism				
⩽5 Years	16	12	1.94 (1.19–3.18)	0.01
>5 Years	56	62	1.07 (0.82–1.40)	0.61
P for trend			0.32	
History of hypothyroidism	315	309	1.16 (1.03–1.31)	0.01
Duration of hypothyroidism				
⩽5 Years	65	59	1.21 (0.95–1.56)	0.13
>5 Years	189	196	1.12 (0.96–1.30)	0.12
P for trend			0.08	
Use of hyperthyroid medications				
No	360	306	1.00 (Ref)	
Yes	6	5	0.69 (0.17–2.80)	0.61
Use of hypothyroid medications				
No	351	306	1.00 (Ref)	
Yes	108	71	1.04 (0.77–1.40)	0.79

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.
[a]Adjusted for age at diagnosis (continuous), stage of disease (local, regional, distant), and study site.

T_3 and T_4 hormones. Moreover, there is a possibility that our finding can be explained by chance only or by the presence of residual confounding because of our inability to control for treatment after ovarian cancer diagnosis. Finally, the outcome of interest was all-cause mortality instead of ovarian cancer-specific mortality. However, as shown in other OCAC survival studies, among these patients, most deaths are likely to be attributable to ovarian cancer (Cannioto *et al*, 2016; Minlikeeva *et al*, 2017).

Nonetheless, our findings potentially could have important clinical implications in relation to prognosis of ovarian cancer among women diagnosed with hyper- or hypothyroid diseases if validated in other studies. Clinicians may need to be aware of the fact that ovarian cancer patients with history of thyroid disease, particularly hyperthyroidism, can experience worse prognosis compared with patients without such history. It could also be important to monitor and correct thyroid hormones levels at the time of diagnosis with ovarian cancer.

Future studies need to confirm whether history of thyroid disease influences survival outcomes among ovarian cancer patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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