Received Date : 29-Aug-2016
Revised Date : 04-Oct-2016
Accepted Date : 31-Oct-2016
Article type : 3 Original Article - Australia, Japan, SE Asia

Title

Higher thyrotropin concentration is associated with increased incidence of colorectal cancer in older men.

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Short title

Thyroid hormones and cancer outcomes

Keywords

Thyroid stimulating hormone, free thyroxine, cancer incidence, cancer death

Word count: 3 494 words

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Disclosures

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

Grants and funding

Hormone assays were funded by research grants from the Fremantle Hospital Medical Research Foundation, Fremantle Hospital, Western Australia, and the Ada Bartholomew Medical Research Trust, University of Western Australia. The Health In Men Study was funded by Project Grants 279408, 379600, 403963, 513823, 634492, 1045710 and 1060557 from the National Health and Medical Research Council of Australia. Yi X. Chan is supported by the Warren Jones/University of Western Australia Postgraduate Scholarship.

Acknowledgements

We thank the staff of Pathwest Laboratory Medicine, Fremantle, and the Royal Perth Hospitals, Perth, the ANZAC Research Institute, Sydney, the Data Linkage Unit, Health Department of Western Australia, for their assistance. We especially thank all the men and staff who participated in the Western Australian Abdominal Aortic Aneurysm Program and the Health In Men Study.

Abstract

Context

Thyroid hormones regulate cellular survival and metabolism; however their association with cancer incidence and death has not been well explored.

Objectives

Our aim was to examine the relationship between thyrotropin (TSH) and free thyroxine (FT4) with cancer incidence (all cancers, prostate, colorectal and lung cancer). Associations with cancer-related deaths were also explored.

Design and setting

A prospective cohort study involving community-dwelling men aged 70-89 years.

Main outcome measures

Thyroid hormones were measured in 3,836 men between 2001-2004. Competing risks analyses were used to perform longitudinal analyses with results expressed as sub-hazard ratios (SHR). Outcomes were ascertained through electronic linkage until 20th June 2013.

Results

Mean age was 77.0±3.6 years. 864 men developed cancers and 506 experienced cancer-related deaths. 340, 136, and 119 men developed prostate, colorectal and lung cancers respectively. After adjustments, there were no associations between TSH and incidence of all cancers, prostate, or lung cancer. Higher TSH was associated with increased colorectal cancer incidence (SHR=1.19, 95% CI 1.00-1.42; p=0.048 for every 1 SD increase in log TSH). This association was strengthened after excluding the first year of follow-up (SHR=1.23, 95% CI 1.02-1.48, p=0.028). FT4 was not associated with incidence of all cancers, prostate, colorectal or lung cancer. Thyroid hormones were not associated with cancer-related deaths.

Conclusion

In community-dwelling older men, FT4 was not associated with cancer incidence. Higher TSH is independently associated with increased incidence of colorectal cancer. Further investigation is warranted to determine if a causal relationship exists.

Introduction

The incidence of cancer increases with age and the risk of cancer is higher in men[1]. Mechanistic studies of human cancer cell lines suggest a role for thyroid hormones in tumour development[2-4]. These findings are supported by studies demonstrating non-genomic effects of the thyroid hormone receptor in activating pathways involved in cell growth and survival[5, 6]. Thyroid hormones can also induce proliferation and angiogenesis through direct activation of the integrin αvβ3 transmembrane receptor[7]. Conversely, inhibitory effects of thyroid hormone on cellular signalling pathways for colorectal cancer have also been demonstrated[8], and a previous study has implicated subclinical hypothyroidism as a potential risk factor for colorectal neoplasm[9]. Few prospective studies exploring the associations of thyroid hormones and cancer incidence have been performed, and these have reported conflicting results[10-14]. A prospective study of 19,710 women and 9,981 men found an increased risk of all cancers, lung and prostate cancer incidence with TSH levels of <0.5 mU/l[13]. However, a study of 18,156 patients with Graves' disease followed for 17 years reported a decreased risk of colon cancer[14]. Studies reporting associations of thyroid hormone and cancer mortality are contradictory[15-18].

The prevalence of thyroid dysfunction increases in the elderly, and mild thyroid dysfunction is more common than overt thyroid disease[19]. However, the clinical implications of subclinical thyroid disease are less well defined compared to overt thyroid disease[20]. Age is a

risk factor for both cancer development and thyroid dysfunction, therefore further clarification of the potential role of thyroid hormones in cancer development is required. In this study, we tested the hypothesis that thyroid hormones are independent predictors of cancer incidence and cancer-related mortality in a population of community-dwelling men aged ≥70 years. We explored associations of thyroid hormones with the incidence of all cancers, as well as the most common solid organ tumours in men- prostate, colorectal and lung cancer.

Methods

Study population

Methods for recruitment of participants has previously been described in depth[21]. Between 1996-1999, 19,352 men residing in Perth, Western Australia, were randomly selected from the electoral roll and invited to participate in a randomised controlled trial of screening for abdominal aortic aneurysm. 12,203 (63.1%) men attended a clinic visit and completed a health questionnaire and a physical examination. This baseline visit was termed wave 1 (W1) of data collection. Between 2001-2004, the surviving men (n=10,940) were invited to participate in a follow-up visit. 4249 of these men attended this visit and agreed to provide an early morning fasting blood sample. This follow-up visit was termed wave 2 (W2). The men who attended the W2 visit represented the inception cohort for this study. The men were almost entirely of Caucasian ethnicity. The Human Research Ethics Committee of the University of Western Australia approved the study protocol, and all men provided written informed consent to participate in the study.

Physical measurements and comorbidities

Men underwent physical examination including measurement of height (cm), weight (kg) and blood pressure at W1 and W2. Questionnaire and clinical data collected during W1 and W2 were used to identify lifestyle habits and comorbidities. Men provided information regarding smoking habits at both W1 and W2, and alcohol intake and physical activity at W1. Questionnaire data from W1 and W2, and biochemistry from W2 were used to identify men with diabetes mellitus. Diabetes mellitus was defined as men who had reported a previous diagnosis of diabetes, men who were on oral hypoglycaemic treatment (Anatomical Therapeutic Chemical or ATC code A10B) or insulin treatment (ATC code A10A), or men who had fasting or random glucose levels of ≥ 7.0 mmol/l or ≥11.1 mmol/l respectively.

Identification of men with existing thyroid disease

Questionnaire data was used to identify men who reported a history of thyroid disease, men who were on thyroxine replacement (ATC code H03A) or antithyroid medications (ATC codes H03B and H03C). As glucocorticoids and amiodarone can also modulate thyroid function, men who were on these medications were also identified (ATC code H02A for systemic glucocorticoids and C01BD01 for amiodarone). In addition to this, the Western Australian Data Linkage System (WADLS) was used to capture additional men who had a previous diagnosis of thyroid disorders[22]. This is a centralised system which links together records from the hospital morbidity data (including medical diagnoses from all admissions into private and public hospitals), death and cancer registries (established in 1981), and the Mental Health Information System in Western Australia. The following *International Classification of Diseases*, 10th revision (ICD-10) codes were used to identify men with thyroid disorders: iodine deficiency (E00, E01 and E02), established hypo- or hyperthyroidism (E03 and E05), thyroiditis (E06), non-toxic goitre (E04) and other specified

disorders of the thyroid gland (E07.8). The *International Classification of Diseases,* 9th revision (ICD-9) codes 240.x and 246.x were also used for this purpose.

Cancer diagnosis and ascertainment of outcome events

In Western Australia, notification of cancer diagnoses including *in situ* and invasive neoplasms, non-melanoma skin cancers (excluding primary skin basal cell carcinoma and squamous cell carcinoma), benign and malignant primary central nervous system tumours, ovarian neoplasms of borderline or uncertain malignant potential, neuroendocrine tumours and all lymphohaematopoietic neoplasms is mandatory[23, 24]. Prevalent cancers were identified through questionnaire data and through the WADLS using ICD-9 and ICD-10 codes. During the follow-up period, the WADLS was also used to identify men who developed incident cancer using ICD-10 codes. Cancer diagnoses were identified using ICD-10 codes C00-C97, and ICD-9 codes 140.x-209.x. Prostate cancer (ICD-10 code C61 and ICD-9 code 185), colorectal cancer (ICD-10 code C18-C21, ICD-9 code 153 and 154), and lung cancer (ICD-10 code C33 and C34, ICD-9 code 162) were also identified through this manner. We did not include benign neoplasms, *in situ* neoplasms, or neoplasms of unknown behaviour. Mortality data was obtained through the WADLS which contains data from the original death certificate, and the ICD-10 coded data. Cancer-related death was defined as deaths whereby the primary or contributing cause of death were malignant neoplasm (ICD-10 codes C00-C97). Deaths were categorised into cancer and non-cancer related deaths by Y.X.C., and reviewed by B.B.Y. Follow-up data was available until the 20th of June 2013.

Biochemical analysis

Bloods were sampled at W2 whereby aliquots of serum and plasma were immediately prepared and stored at -80°C until the time of assay as described previously[25]. Briefly, serum TSH and plasma free thyroxine (FT4) concentrations were measured using an Elecsys 2010

immunoanalyser (Roche Diagnostics Australia). Inter-assay imprecision values (coefficient of variation) were 4.5 and 4.2% at 0.4 and 5.0 mIU/l TSH and 4.0 and 5.2% at 14 and 37 pmol/l FT4. Reference intervals for these assays were 0.4-4.0 mIU/l for TSH and 10-23 pmol/l for FT4. Subclinical hypothyroidism was defined as a TSH of>4.0 mIU/l and a normal FT4 concentration. Conversely subclinical hyperthyroidism was defined as a TSH of <0.4 mIU/l with a normal FT4 concentration.

Statistical analysis

Statistical analysis was performed using Stata version 13.1 (StataCorp, College Station, TX, USA). Differences between groups were assessed using t-tests for continuous variables and Pearsons χ^2 test for categorical variables. These are reported as mean and standard deviation (SD) or percentages (%). Associations of hormonal parameters with cancer incidence and deaths were analysed using competing risks models as described by Fine and Gray[26]. We used this method because usual survival analysis does not take into account the chance of common competing events (such as death) occurring before the event of interest occurs, thus making it impossible for the event of interest to occur. Results are therefore reported as a sub-hazard ratio (SHR). To minimize the possibility of reverse causality, we excluded men who had previously been diagnosed with the outcome of interest. Lastly, cross-sectional analyses at baseline exploring associations of thyroid hormones with prevalent cancers, prostate, colorectal and lung cancers were also assessed using multiple logistic regression. Variables which were not normally distributed were log-transformed. These included TSH, fasting insulin levels and high sensitivity C-reactive protein (hsCRP) measurements. Results are reported for every 1 SD increase in log TSH and in FT4 levels. Analyses were also performed for hormone parameters categorised into quartiles. A 1 SD increase in log TSH above the mean TSH of 2.33 mIU/l equated to a 1.81 mIU/l increment in TSH. Adjustments were made

for risk factors which may plausibly affect these associations. Analyses were adjusted for age (model A1), then additional adjustments were made for body mass index (BMI), vigorous physical activity, smoking status and alcohol consumption (model A2). Further adjustments were made for diabetes, high density lipoprotein (HDL) and triglyceride (TG) levels (model A3), and lastly a history of prevalent cancers other than the cancer of interest were also added into models where this was relevant (model A4). Variables which did not satisfy the proportional hazards assumption were included in the models as time varying covariates. A p-value of <.05, or a 95% confidence interval that did not cross 1 was considered significant.

Results

Study population

Of the 4249 men, there were 324 men who had a history of thyroid disease, or were on thyroid/antithyroid, glucocorticoid or amiodarone treatment at baseline. A further 4 men had undiagnosed hyperthyroidism (TSH <0.4 mIU/l and FT4>23 pmol/l), and 9 men had undiagnosed hypothyroidism (TSH >4 mIU/l and FT4 <10 pmol/l). 75 men were excluded due to missing data, and 1 man subsequently withdrew consent. After exclusions, 3836 men were included in the analysis. In addition to this, 17 men were not included in the mortality analysis as their cause of death was uncertain.

Baseline characteristics

The mean age of the population was 77.0 ± 3.6 years, and men who developed cancers were slightly older than men who did not (77.2 vs 76.7 years, diff=0.6, 95% CI 0.27-0.83) (table 1). TSH levels were higher in men who developed colorectal cancer compared to men who did not, men who developed lung cancer had higher FT4 levels compared to men who did not. Men who developed incident cancer, colorectal and lung cancer were more likely to be

smokers. Men who developed lung cancer were also more likely to consume larger amounts of alcohol and men who developed prostate cancer were more physically active (table 1). In this cohort of men, TSH positively correlated with age, TG and log insulin levels, and negatively correlated with HDL (Table 2). There was a direct association between higher FT4 levels and increasing age and HDL levels, however there was an inverse association between FT4 and BMI, TG and log insulin levels. Smokers and ex-smokers had lower TSH and higher FT4 levels compared to non-smokers, and increased alcohol intake was associated lower FT4 levels compared to non-drinkers (table 2).

Thyroid hormones and cancer incidence

During a median follow-up period of 9.0 years, 864 men were diagnosed with cancer. Of these, 340, 136 and 119 men developed prostate, colorectal and lung cancer respectively. TSH was not associated with incidence of all cancers or prostate cancer (table 3). In the fully-adjusted analysis, higher log TSH was associated with an increased incidence of colorectal cancer (SHR 1.19, 95% CI 1.00-1.42, p=0.048). This remained significant after the first year of follow-up was excluded from the analysis (SHR 1.23, 95% CI 1.02, 1.48, p=0.028) (data not shown). This effect was attenuated when men with subclinical hyper- and hypothyroidism were excluded from the analysis (SHR 1.14, 95% CI 0.87, 1.49, p=0.339), and there was a non-significant increase in effect when men with subclinical hypothyroidism were compared to an euthyroid referent category (SHR 1.56, 95% CI 0.92, 2.63, p=0.096) (data not shown). There was also an inverse association between log TSH and lung cancer incidence in the univariate analysis (SHR 0.87, 95% CI 0.77-0.98, p=0.020), however this was not significant in the fully adjusted analysis (SHR 0.87, 95% CI 0.75-1.01, p=0.070).

In the univariate analysis, higher FT4 was associated with a higher incidence of lung cancer (SHR 1.21, 95% CI 1.04-1.41, p=0.014). This was not significant after adjustments were made (SHR 1.13, 95% CI 0.95-1.35, p=0.161) (table 3). There were no associations of FT4 with the incidence of all cancers, prostate or colorectal cancer (table 3). No significant associations were seen when hormone levels were assessed in quartiles (data not shown).

Thyroid hormones and cancer-related deaths

1434 men died during the follow-up period. Of these 506 deaths (35.25%) were cancer-related deaths. Neither log TSH or FT4 were associated with cancer-related deaths in the fully-adjusted analysis (table 4). Similar results were seen when hormones were assessed as quartiles (data not shown).

Thyroid hormones and prevalent cancer at baseline

There were 759 men who had prevalent cancers at baseline. Of these, 354, 118 and 21 men had prevalent prostate, colorectal and lung cancer respectively. After adjustments, TSH and FT4 were not associated with a previous diagnosis of any cancer, prostate, lung, or colorectal cancer (data not shown).

Discussion

In this cohort of community-dwelling men, higher log TSH was independently associated with increased incidence of colorectal cancer. Whilst there were apparent associations of higher FT4 and lower log TSH with incidence of lung cancer, this was not significant after adjusting for additional risk factors. There were no associations of thyroid hormones with incidence of all cancers or prostate cancer. Thyroid hormones were not associated with cancer-related deaths in this cohort of men.

Our results differ from findings of previous studies. Mondol et al. conducted a prospective case-control study involving 800 cases of prostate cancer and 401 controls from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)[11]. The ATBC population was derived from a randomised controlled trial of α-tocopherol and β-carotene supplements and cancer incidence in male smokers[11]. Men with a higher TSH and men who were hypothyroid had a lower risk of prostate cancer in the ATBC population[11]. Men with underlying thyroid disease were not excluded in the ATBC study, possibly accounting for differences seen in our results. Furthermore, all men on the ATBC study were smokers, limiting generalisability of these results to a community-dwelling population. A large prospective study of 29,691 men and women aged ≥20 years followed for 9 years showed an increased risk of all cancers, lung and prostate cancer with TSH levels of <0.5 mU/L after adjusting for age, sex and smoking status[13]. Associations with FT4 was not analysed in that study, and that study included a younger population compared to our study. A prospective study of 10,318 men and women reported direct associations of FT4 with all cancers, lung and breast cancer, and no association of thyroid hormones with a broader range of gastrointestinal cancers[27]. The differences in age may have accounted for a difference in associations seen, however further studies are required to assess if the associations of thyroid hormones and cancer risk are modulated by age.

There was a log-linear association of higher TSH with the incidence of colorectal cancer. Therefore, as TSH increases, larger increments are associated with a similar effect size compared to smaller increments at lower levels of TSH. In our cohort, a TSH of 4.19 mIU/l was associated with a 19% increase in risk of incident colorectal cancer compared to the mean TSH of 2.33 mIU/l, which is similar to a 19% increase in risk for a TSH of 18.02 mIU/l compared to 10 mIU/l. Our findings are in keeping with mechanistic studies demonstrating

inhibitory effects of thyroid hormones on the transcription of cyclin D1 in colon carcinoma cells[8]. This is an oncogenic cyclin which is positively regulated by the Wnt-signalling pathyway[8], and genetic alterations affecting this pathway have also been demonstrated in sporadic colorectal cancers[28]. Cancer stem cells (CSCs) represent a subset of cells in tumour mass that have tumourigenic potential in immunodeficient mice[29]. Studies have characterised a subset of colorectal cancer stem cells (CR-CSCs) with enhanced self-renewing capacity that exhibit high Wnt activity and increased expression of type 3 deiodinase (D3), an enzyme which inactivates thyroid hormones[30]. Treatment of CR-CSCs with triiodothyronine (T3) downregulated Wnt signalling and was associated with decreased engrafting capacity in immunodeficient mice[30]. Similarly, knockdown of D3 to increase intracellular T3 led to decreased *in vitro* clonogenicity and *in vivo* tumour growth[30]. It is therefore plausible that elevated TSH signifying lower exposure to T3 and thereby reduced tissue actions of thyroid hormones in CR-CSCs, could enhance the self-renewing and tumourigenic potential of these cells.

In our cohort, the lower confidence interval for the SHR of TSH and incident colorectal cancer was 1.00. The effect of this association was attenuated when men with subclinical thyroid disease were excluded from the analysis. Whilst there was a trend towards increased incidence of colorectal cancer in men with subclinical hypothyroidism, this did not reach statistical significance (p=0.096). The power to detect significant associations in these situations may be limited by a smaller number of outcomes or categorisation of variables. A link between hypothyroidism and colorectal neoplasm has also been reported in other observational studies. Cross-sectional studies have demonstrated an association of long-term thyroxine supplementation with a reduced relative risk of colorectal[31] and rectal cancer[32], and case-control studies have demonstrated an increased prevalence of subclinical

hypothyroidism in participants with colorectal neoplasm, and more advanced colonic lesions in participants with subclinical hypothyroidism[9]. A prospective study also found a lower incidence of colorectal cancer in patients with Graves Disease[14]. Given biologically plausible mechanisms for thyroid hormones in modulating colorectal development and increased prevalence of thyroid dysfunction in older populations, the signal for increased TSH and colorectal cancer incidence is concerning and warrants validation in other cohorts.

In the univariate analysis, there was an inverse association of TSH and incident lung cancer, and an association of higher FT4 with increased incidence of lung cancer. These results were not significant once adjustments were made for age, smoking, BMI and lifestyle factors. The incidence of cancer increases with age, and smoking is a known risk factor for lung cancer[1]. We have previously shown in this cohort a direct association of TSH and FT4 with age[25]. Smoking has been shown to be negatively associated with hypothyroidism and positively associated with hyperthyroidism[33]. This is supported by results from our cohort, which showed correlations between smoking with lower TSH and higher FT4 levels. Therefore, the apparent associations of thyroid function and lung cancer are possibly mediated through confounding factors such as age and smoking.

Studies of thyroid hormones and cancer-related mortality have shown conflicting results. Our results are in keeping with a study of 1587 older men followed for 8.3 years which found no association of TSH with all-cause or cancer-related mortality[16]. Similarly, a study of 3651 men and women reported no increase in cancer-related mortality when participants with hyper- or hypothyroidism were compared to an euthyroid reference group[15]. In a study of 21,246 South Korean men and women consisting of 335 cancer-related deaths, there were no associations of TSH and FT4, but an inverse association of free triiodothyronine (FT3) with

cancer-related deaths[17]. Similarly, a study of 115, 746 Taiwanese adults with 1532 cancer-related deaths found an association between subclinical hypothyroidism and cancer-related mortality[18]. That study consisted of a higher proportion of females in the group with subclinical hypothyroidism[18]. Differences in population characteristics such as age, gender and ethnicity may account for conflicting results observed amongst these populations. Furthermore, we did not measure FT3 levels, therefore associations of FT3 with cancer-related deaths may have been missed.

There are several limitations which we acknowledge in this observational study. Firstly, our study population was derived from an original cohort of 12, 203 men screened between 1996-1999, therefore there is potential for a 'healthy survivor' effect. Results from this study are likely to be more reflective of healthy community-dwelling men. The population consisted almost entirely of Caucasian men, therefore results may not apply to other ethnic populations. Thyroid hormones were measured on a single early morning samples, and serial thyroid hormone levels were not collected. Furthermore, FT3 was not measured in this cohort. Whilst men with underlying thyroid disease were excluded, baseline blood samples may have been affected by non-thyroidal illness. However, our cohort consisted of community-dwelling men who voluntarily attended for venesection, suggesting that intercurrent acute illness was unlikely. Cancer diagnosis was based on data linkage. This is likely adequate for lung and colorectal cancers as these cancers are unlikely to remain undiagnosed, however prostate cancers have a long latency period and some may have been missed. Strengths of our study include a large population-based cohort with a narrow age range and a long follow-up period. Analyses were performed using a competing risks approach, and we adjusted systematically for potential confounding factors. Outcomes were ascertained using the WADLS. Apart from

limitations of using this method for prostate cancer diagnosis, this allows near complete capture of lung and colorectal cancer, as well as cancer-related mortality.

In this study consisting of a large cohort of community-dwelling older men, log TSH and FT4 were not associated with the incidence of any cancer, prostate, or lung cancer. However, higher log TSH was independently associated with increased incidence of colorectal cancer. Further studies in other populations are required to validate this result, and to assess if a causal relationship exists between thyroid hormone exposure and colorectal cancer risk.

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	Entire sample	All cancers			Prostate cancer			Colorectal cancer			Lung cancer		
Variable	n=3836 mean ± SD	No n=2213 mean ± SD	Yes n=864 mean ± SD	P value	No n=3142 mean ± SD	Yes n=340 mean ± SD	P value	No n=3582 mean ± SD	Yes n=136 mean ± SD	P value	No n=3696 mean ± SD	Yes n=119 mean ± SD	P value
Age (y)	77.0 ± 3.6	76.7 ± 3.5	77.2 ± 3.6	<0.001	77.0 ± 3.6	76.8 ± 3.6	0.547	77.0 ± 3.6	77.8 ± 3.7	0.007	77.0 ± 3.6	77.5 ± 3.2	0.080
BMI (kg/m^2)	26.6 ± 3.6	26.5 ± 3.5	26.5 ± 3.6	0.929	26.5 ± 3.6	26.4 ± 3.5	0.544	26.5 ± 3.6	26.7 ± 3.6	0.605	26.6 ± 3.6	26.4 ± 3.7	0.626
Log TSH (mIU/l)	0.68 ± 0.6	0.67 ± 0.6	0.68 ± 0.6	0.381	0.68 ± 0.6	0.69 ± 0.6	0.932	0.68 ± 0.6	0.78 ± 0.5	0.048	0.68 ± 0.6	0.58 ± 0.5	0.071
FT4 (pmol/l)	16.0 ± 2.2	15.9 ± 2.2	15.9 ± 2.1	0.607	15.9 ± 2.2	16.0 ± 2.2	0.516	16.0 ± 2.2	15.8 ± 2.1	0.463	15.9 ± 2.2	16.4 ± 2.2	0.023
	n(%)				n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
Smoking				0.039			0.272			0.003			<0.001
Never	1293 (33.7)	787 (35.5)	265 (30.8)		1047 (33.3)	126 (37.1)		1229 (34.3)	35 (25.7)		1289 (34.9)	4 (3.4)	
Ex	2346 (61.2)	1306 (58.9)	549 (63.8)		1922 (61.2)	200 (58.8)		2162 (60.4)	100 (73.6)		2230 (60.4)	98 (82.4)	
Current	195 (5.1)	123 (5.6)	47 (5.46)		172 (5.5)	14 (4.1)		189 (5.3)	1 (0.74)		175 (4.8)	17 (14.3)	
Alcohol (drinks/week)				0.382			0.716			0.823			0.018
None	528 (14.5)	327 (15.5)	113 (13.7)		444 (14.8)	40 (12.5)		498 (14.6)	20 (15.5)		516 (14.7)	9 (7.8)	
<15	2433 (66.6)	1403 (66.5)	542 (65.9)		1987 (66.4)	218 (68.1)		2271 (66.6)	84 (65.1)		2349 (66.8)	74 (63.8)	
15-28	521 (14.3)	293 (13.9)	128 (15.6)		426 (14.2)	48 (15.0)		484 (12.2)	17 (13.2)		493 (14.0)	24 (20.7)	
>28	169 (4.6)	88 (4.2)	40 (4.9)		137 (4.6)	14 (4.6)		156 (4.6)	8 (6.2)		157 (4.5)	9 (7.8)	
Vigorous physical activity (mins/wk)				0.302			0.025			0.310			0.078
≥150	873 (22.8)	505 (22.8)	181 (21.1)		699 (22.3)	94 (27.7)		817 (22.8)	26 (19.1)		850 (23.0)	19 (16.1)	
<150	2959 (77.2)	1710 (77.2)	678 (78.9)		2439 (77.2)	246 (72.4)		2761 (77.2)	110 (80.9)		2843 (77.0)	99 (83.9)	
Diabetes mellitus	554 (14.4)	337 (15.2)	115 (13.3)	0.194	465 (14.8)	37 (10.9)	0.051	517 (14.4)	23 (16.9)	0.421	534 (14.5)	16 (13.5)	0.759

Table 1: baseline demographic and physical characteristics at W2 (2001-2004) of study participants for the entire cohort, and in men who developed incident cancer, prostate, colorectal and lung cancer.

Table 2: Associations of demographic, physical and biochemical measures of the population with TSH and FT4 levels.

	Log TSH (mU/L)		FT4 (pmol/L)	
	Est	P value	Est	P value
Age	0.032	<0.001	0.232	<0.001
BMI	0.016	0.094	-0.299	<0.001
Sysbp	0.010	0.300	0.027	0.464
Diabp	0.016	0.097	-0.073	0.043
Chol	-0.008	0.412	-0.005	0.890
HDL	-0.047	<0.001	0.139	<0.001
LDL	-0.006	0.548	0.015	0.674
TG	0.06	0.010	-0.211	<0.001
Glucose (fasting)	0.028	0.080	-0.011	0.852
Log insulin (fasting)	0.052	<0.001	-0.252	<0.001
Log hscrp	0.018	0.051	0.035	0.327
Smoking		<0.001		<0.001
Never smoked	1		1	
Ex-smoker	-0.023		0.202	
Current smoker	-0.228		0.756	
Alcohol (drinks/week)		0.173		0.014
non-drinker	1		1	
<15	-0.015		0.159	
15-28	-0.037		0.151	
>28	0.073		-0.374	
Vigorous physical activity (≥150 mins/week)	-0.007	0.776	-0.069	0.425
Diabetes mellitus	0.009	0.731	0.093	0.366

The table shows the estimated difference in mean log TSH and FT4 for every 1 standard deviation (SD) increase for continuous variables, and compared to a referent category, for categorical variables, with their corresponding p-values.

Table 3: Competing risks analysis for the association of log TSH and FT4 with incidence of all cancers, prostate, colorectal and lung cancers.

	Log TSH		FT4	
	SHR (95% CI)	P value	SHR (95% CI)	P value
All cancers				
Univariate	1.02 (0.95, 1.10)	0.534	1.02(0.95, 1.10)	0.536
A1	1.02 (0.95, 1.09)	0.604	1.01 (0.94, 1.08)	0.753
A2	1.00 (0.93, 1.07)	0.973	1.03 (0.96, 1.10)	0.441
A3	1.01 (0.94, 1.08)	0.888	1.03 (0.96, 1.11)	0.409
Prostate cancer				
Univariate	1.01 (0.90, 1.13)	0.920	1.04 (0.93,1.16)	0.482
A1	1.00 (0.88, 1.13)	0.976	1.05 (0.94, 1.17)	0.416
A2	1.00 (0.88, 1.14)	0.984	1.07 (0.96, 1.20)	0.203
A3	1.00 (0.90, 1.10)	0.933	1.08 (0.97, 1.21)	0.166
A4	1.00 (0.88, 1.14)	0.984	1.08 (0.97, 1.21)	0.166
Colorectal cancer				
Univariate	1.20 (1.01, 1.42)	0.038	0.94 (0.79, 1.11)	0.456
A1	1.18 (1.00, 1.40)	0.056	0.92 (0.77, 1.09)	0.375
A2	1.18 (0.99, 1.40)	0.064	0.95 (0.79, 1.14)	0.576
A3	1.19 (1.00, 1.41)	0.054	0.94 (0.78, 1.13)	0.525
A4	1.19 (1.00, 1.42)	0.048	0.94 (0.78, 1.13)	0.530
Lung cancer				
Univariate	0.87 (0.77, 0.98)	0.020	1.21 (1.04, 1.41)	0.014
A1	0.87 (0.78, 0.97)	0.060	1.20 (1.02, 1.40)	0.024
A2	0.87 (0.75, 1.01)	0.062	1.13 (0.95, 1.35)	0.157
A3	0.87 (0.75, 1.01)	0.072	1.14 (0.95, 1.36)	0.155
A4	0.87 (0.75, 1.01)	0.070	1.13 (0.95, 1.35)	0.161

Estimates represent subhazard ratios and 95% CIs for each SD increase in hormone level.
Adjustments were made for A1: age, A2: A1+BMI, physical activity, smoking and alcohol, A3: A2+ diabetes, HDL and TG, A4: A3+ history of prevalent cancer.

Table 4: Competing risks analysis for the association of log TSH and FT4 with cancer-related deaths.

	Log TSH		FT4	
	SHR (95% CI)	P value	SHR (95% CI)	P value
Cancer death				
Univariate	1.02 (0.93, 1.12)	0.682	1.01 (0.92, 1.10)	0.910
A1	1.01 (0.92, 1.10)	0.863	0.98 (0.90, 1.08)	0.719
A2	1.00 (0.91, 1.10)	0.994	0.97 (0.89, 1.06)	0.538
A3	1.00 (0.91, 1.10)	0.923	0.97 (0.89, 1.06)	0.498
A4	1.00 (0.90, 1.10)	0.986	0.97 (0.88, 1.06)	0.451

Estimates represent subhazard ratios and 95% CIs for each SD increase in hormone level.
Adjustments were made for A1: age, A2: A1+BMI, physical activity, smoking and alcohol, A3: A2+ diabetes, HDL and TG, A4: A3+ history of prevalent cancer.