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Thyroid cancers potentially preventable by reducing overweight and obesity in Australia: a pooled cohort study

Running title: Preventable thyroid cancer burden in Australia

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KEYWORDS

Thyroid cancer, risk factors, body fatness, population attributable fraction, prevention, pooled cohort study

ABBREVIATIONS

AIHW	The Australian Institute of Health and Welfare
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
ICD-O	International Classification of Diseases for Oncology
PAF	Population attributable fraction

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ABSTRACT

Thyroid cancer incidence and the prevalence of overweight and obesity are increasing, but the future thyroid cancer burden attributable to contemporary levels of overweight and obesity has not been evaluated before. We quantified this burden in Australia, and assessed whether the overweight/obesity-attributable burden differed by sex or other population subgroupings. We estimated the strength of the associations of overweight and obesity with thyroid cancer with adjusted proportional hazards models using pooled data from seven Australian cohorts (N=367,058) with 431 thyroid cancer cases ascertained from linked national cancer registry data during a maximum 22-year follow-up. We combined these estimates with nationally representative 2017-2018 estimates of overweight and obesity prevalence to estimate Population Attributable Fractions (PAFs) of future thyroid cancers attributable to overweight and obesity, accounting for competing risk of death, and compared PAFs for population subgroups. Contemporary levels of overweight and obesity explain 18.6% (95%CI=5.2%-30.2%), and obesity alone 13.7% (95%CI=5.2%-21.4%), of the future thyroid cancer burden. The obesity-attributable thyroid cancer burden is 21.4% (95%CI=2.8%-36.5%) for men and 10.1% (95%CI=0.8%-18.6%) for women. Were the currently obese overweight instead, 9.9% (95%CI=1.0%-18.1%) of thyroid cancers could be avoided. The relative overweight/obesity-attributable burden is higher for those consuming on average more than two alcoholic drinks per day (63.4%) and for those who are not married/co-habiting (33.2%). In conclusion, avoiding excess weight, especially obesity, should be a priority for thyroid cancer prevention. Further studies, with findings stratified by tumour size, may reveal the potential role of overdiagnosis in our results.

KEYWORDS Thyroid cancer, risk factors, body fatness, population attributable fraction, prevention, pooled cohort study

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INTRODUCTION

Thyroid cancer incidence, especially papillary thyroid carcinoma, is increasing at a rate faster than any other cancer in Australia[1] and worldwide.[2,3] Between 1982 and 2019 in Australia, the age-standardised thyroid cancer incidence rate increased by almost 400% from 2.7 to 13 per 100,000 persons.[1] Thyroid cancer is currently the tenth most common cancer in Australia, with incidence rates in women 2-3 times those in men.[1,4] The increase in thyroid cancer is in large part due to new diagnostic techniques, such as neck ultrasonography, which enable the detection of smaller thyroid tumours.[1,3-6] This has been argued to have led to overdiagnosis of thyroid cancer, especially as thyroid cancer mortality has remained relatively stable.[5,6] Overdiagnosis has been found to be more common in women than in men, proportionate to the difference in thyroid cancer incidence.[6] However, overdiagnosis may not fully explain the thyroid cancer trends as the incidence of larger and advanced thyroid cancers has also been reported to have increased.[7] Moreover, the adverse physical and mental effects of non-fatal thyroid cancer can be considerable and significantly affect quality of life.[8] This emphasises the importance of thyroid cancer prevention by addressing the rising prevalence of causal risk factors, overweight (body mass index (BMI) 25.0-29.9 kg/m^2) and obesity (BMI $\geq$ 30.0 kg/m^2) in particular.[4,5,9-13] In Australia, prevalence of overweight/obesity increased from 50% in 2001 to 67% in 2017-2018, mirrored by an increase in obesity (from 16% in 2001 to 31% in 2017-2018).[14,15]

The burden of thyroid cancer attributable to overweight and obesity can be quantified using the population attributable fraction (PAF), which accounts for both the risk and prevalence of exposure to determine the fraction of cancer that would not occur in its absence.[16] Several studies have estimated the thyroid cancer burden attributable to overweight/obesity.[12,17-20] However, these estimates are based on past overweight and obesity prevalences, and therefore likely underestimate the currently preventable thyroid cancer burden. Moreover,

high body fatness has been more strongly associated with thyroid cancer risk in men than women,[21] but no study to our knowledge has statistically compared the overweight/obesity-attributable thyroid cancer burden by sex, or other socio-demographic factors and other exposures. Such evidence can be used to inform targeted prevention.

We assessed the future thyroid cancer burden in Australia attributable to current levels of overweight and obesity, based on large pooled Australian cohort data and representative contemporaneous national exposure prevalence data,[22] and compared the preventable burden by sex and other population subgroups.

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METHODS

Cohort data

We pooled individual-level data from the Australian cancer-PAF cohort consortium,[22] which comprises seven well-established Australian prospective cohort studies (N =369,515). We excluded 2,457 men and women who enrolled in more than one cohort and 1,885 who did not consent to record linkage. After further excluding 583 with a history of thyroid cancer, our final study sample comprised 364,590 men and women (**Table 1**).

Prevalence data

We obtained the risk factor exposure prevalence estimates from the 2017-2018 Australian National Health Survey (NHS)[15] (**Table 1, Supplementary Table 1**).

Data collection and harmonisation

We examined modifiable behavioural exposures with sufficient or limited evidence of a causal association with thyroid cancer,[4,9,23] if they were measured in our cohort and prevalence data were available. Body fatness (approximated by BMI) was the only exposure fullfilling these criteria. BMI (kg/m^2) was calculated from measured weight and height in the NHS and in four cohort studies, and from self-reported weight and height in three cohort studies (**Supplementary Table 1**).

We further harmonised other behavioural exposures (smoking, alcohol consumption, fruit and vegetable consumption, physical activity) as well as country of birth, marital status, educational attainment, socio-economic status and residential location (rurality) across the cohort studies and external prevalence data for use in subgroup analyses (**Supplementary Table 1**).

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Data linkage and ascertainment of outcomes

The AIHW linked the pooled cohort to the Australian Cancer Database and National Death Index using probabilistic matching.[24] These records were available until 31st December 2012, providing a maximum of 8-22 years follow-up (**Table 1**).

We classified primary invasive thyroid cancers according to the International Classification of Diseases for Oncology (ICD-O-3; C73). We further classified thyroid cancers by histological subtype to papillary (morpohology 8050, 8260, 8340-8344, 8350, 8450-8460), follicular (8290, 8330-8335), medullary (8345, 8510-8513) and anaplastic (8020-8035) carcinomas.[25]

Statistical methods

Follow-up time accrued from baseline to the date of cancer diagnosis, death or end of follow-up, whichever occurred first. In primary analyses, we used the maximum 22 years follow-up. In secondary analyses, we restricted follow-up to 10 and 15 years to evaluate the impact of follow-up time and potential changes over time in baseline exposures, and to generate more comparable estimates across the cohorts. We estimated the strength of exposure-cancer and exposure-death associations using a parametric piecewise constant exponential hazards model, and expressed them as hazard ratios (HR) and their 95% confidence intervals (CI). We evaluated and tested heterogeneity between the cohort-specific HRs using the asymptotic DerSimonian and Laird Q statistic and a complementary I^2 statistic.

We modelled BMI adjusting for age, sex and study. We tested non-linearity in the BMI-cancer association using a restricted cubic spline model with three knots (minimum AIC). We combined the strength of association estimates with the corresponding exposure prevalence estimates from the NHS, and estimated PAFs and their 95% CIs.[16,26] PAF estimates the expected excess cancer incidence during the follow-up time due to certain risk factors, and

thus the future burden of thyroid cancer that could be avoided if the current exposure distribution could be modified. Our PAF method accounts for potential competing risk of death, which can bias PAF estimates,[16] and allows a flexible choice of the risk and reference level for the hypothetical exposure modification (**Supplementary Materials and Methods**).[26] We evaluated scenarios in which the exposure was either completely removed or reduced, i.e., scenarios in which those overweight or obese instead had BMI < 25 kg/m^2 or in which those obese were overweight.

We tested for potential differences in the distribution of the overweight/obesity-attributable thyroid cancer burden by sex, other socio-demographic factors and other exposures by including an interaction term between BMI and the potential effect modifying factor in the model and calculating the 95% CI for the difference in PAF estimates between the categories of the effect modifying factor (**Supplementary Materials and Methods**).[26] If this CI did not include zero, the PAF estimates were deemed to differ.

We conducted sensitivity analysis excluding the first year of follow-up, to assess the potential effect of reverse causality.

We estimated the number of thyroid cases over the next 10 years that could be attributed to the current exposure level by multiplying the PAF estimates (for the 10-year follow-up) by the projected numbers of thyroid cases (2021-2030), as provided by the AIHW using their standard methodology.[27]

We performed all analyses using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and our publicly available PAF program.[26]

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RESULTS

We followed-up individuals for 2,849,471 person-years, or a mean of 8 years (range 0-22 years), and observed 431 incident thyroid cases (93 in men and 338 in women) and 32,029 deaths (**Table 1**).

Thyroid cancer risk factors

We found no significant heterogeneity between the cohort-specific HRs for thyroid cancer in relation to risk factors (**Supplementary Table 2**). We found no evidence of non-linearity in the BMI-cancer association (p for non-linearity = 0.43).

Women had twice the risk of thyroid cancer (HR 2.18, 95% CI: 1.71-2.77) compared with men after adjustment for age and BMI (**Supplementary Table 2**).

During the maximum 22 years follow-up, a 5-unit increase in BMI increased the thyroid cancer risk by 19% (HR 1.19, 95% CI: 1.09-1.30 per 5 kg/m^2 increase), 32% (HR 1.32, 95% CI: 1.06-1.65) in men and 17% (HR 1.17, 95% CI: 1.06-1.29) in women (**Table 2**). Compared with BMI < 25 kg/m^2, obesity increased the overall thyroid cancer risk by 46% (HR 1.46, 95% CI: 1.14-1.87), whereas overweight did not (HR 1.09, 95% CI: 0.86-1.37). Obese men were at a 2-fold (HR 2.07, 95% CI: 1.14-3.78) and obese women a 1.4-fold (HR 1.37, 95% CI: 1.04-1.81) increased risk of thyroid cancer compared with those with BMI < 25 kg/m^2 (**Table 2**). Overweight men had a suggestively higher thyroid cancer risk (HR 1.66, 95% CI: 0.97-4.26), whereas the thyroid cancer risk in overweight women did not differ from that for those with BMI < 25 kg/m^2. In analyses where follow-up was restricted to 10 and 15 years, the association between overweight and thyroid cancer in men was stronger (HR 2.24, 95% CI: 1.18-4.26 and HR 1.78, 95% CI: 1.01-3.15, respectively), as was the association between obesity and thyroid cancer (HR 2.97, 95% CI: 1.49-5.92 and HR 2.34, 95% CI: 1.25-

4.36, respectively; **Supplementary Tables 3 and 4**). Overweight/obesity was more strongly associated with thyroid cancer risk for men compared with women in 10 years follow-up (p for interaction = 0.03) but not for longer follow-up periods.

Excluding the first year of follow-up attenuated the associations between BMI and thyroid cancer but did not affect the significance of the findings (HR 1.33, 95% CI: 1.02-1.74 for the association of obesity with thyroid cancer in 22 years follow-up).

Risk factor exposure prevalence

In Australia, 67% of adults, 75% of men and 60% of women, are overweight/obese. The corresponding figures are 36%, 42% and 30% respectively for overweight and 31%, 33% and 30% respectively for obese (NHS 2017-2018; **Table 2**).

Thyroid cancer burden

Overall burden

Current levels of overweight/obesity contribute 18.6% (95% CI: 5.2%-30.2%) of the future thyroid cancer burden in Australia, with obesity explaining 13.7% (95% CI: 5.2%-21.4%), based on the maximum 22 years follow-up (**Table 2**). The respective PAFs for 10 years follow-up (21.3%, 95% CI: 6.6%-33.8% and 16.0%, 95% CI: 6.5%-24.5%; **Supplementary Table 3**) correspond to 9,800 overweight/obesity-attributable and 7,300 obesity-attributable thyroid cancers over the next 10 years. If all those currently obese were instead only overweight, 9.9% (95% CI: 1.0%-18.1%) of the thyroid cancer burden could be prevented in the next 22 years.

Burden by population subgroups

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The overweight/obesity-attributable future thyroid cancer burden is suggestively higher for men compared with women (p-difference = 0.06), with 38.5% (95% CI: 4.8%-60.3%) of thyroid cancers in Australian men attributable to overweight/obesity versus 9.5% (95% CI: -4.5%-21.7%) for women during the maximum 22-year follow-up (**Table 2**). The obesity-attributable thyroid cancer burden is 21.4% (95% CI = 2.8%-36.5%) for men and 10.1% (95% CI = 0.8%-18.6%) for women. During the shorter 10- and 15-year follow-up periods the overweight/obesity-attributable future burden is higher for men than women (53.8% compared with 6.3%, p-difference = 0.002 and 43.2% compared with 10.3%, p-difference = 0.03, respectively; **Supplementary Tables 3 and 4**). The overweight-attributable thyroid cancer burden is also higher for men than women in 10-and 15-year follow-ups (24.1% compared with -3.3%, p-difference = 0.004 and 18.5% compared with -0.8%, p-difference = 0.04, respectively), and the obesity-attributable future thyroid cancer burden in a 10-year follow-up (29.7% compared with 9.7%, p-difference = 0.046).

The relative future thyroid cancer burden attributable to overweight/obesity is higher for those consuming on average more than two standard drinks of alcohol per day compared with those consuming less (63.4% compared with 11.1%, p-difference = 0.01) and those not married/co-habiting compared with those who are married/co-habiting (33.2% compared with 5.0%, p-difference = 0.02), with these differences driven by differences in the thyroid cancer risk in relation to overweight/obesity (**Table 3**). Difference in future thyroid cancer burden by marital/co-habiting status was also present in the 10- and 15-year follow-up periods, while the difference in thyroid cancer burden by alcohol consumption was present in the 15-year follow-up (data not shown).

Burden by histological subtype

The findings for papillary carcinomas, constituting the majority (78%, n = 323) of thyroid cancers, were similar to the overall findings although slightly attenuated (**Supplementary**

Table 5). The obesity-attributable future burden of papillary carcinomas is 11.0% (95% CI: 1.1%-20.0%) compared with 13.7% (95% CI: 5.2%-21.4%) for all thyroid cancers during the 22-year follow-up. The overweight/obesity-related risk and burden of other histological subtypes could not be reliably evaluated due to the small numbers of cases.

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DISCUSSION

Our findings show that one in five future thyroid cancers in Australia is potentially attributable to current levels of overweight and obesity.

Previously, 2%-16% of thyroid cancers have been attributed to overweight and obesity.[12,18,19] However, these estimates are based on past prevalences of overweight and obesity. As the worldwide prevalence of overweight and obesity has increased,[11] they underestimate the currently preventable overweight/obesity-attributable thyroid cancer burden, which we estimate to be 19% for Australia. We are the first to provide an estimate of the thyroid cancer burden attributable to obesity alone (14%). With obesity explaining 75% of the overweight/obesity-attributable thyroid cancer burden and the prevalence of obesity doubling in Australia during the last two decades (16% in men and 17% in women in 2001 compared with 33% and 30% in 2017-2018),[14,15] targeting obesity for the prevention of thyroid cancer appears especially important. We showed that 10% of thyroid cancers could be prevented if all those currently obese were instead overweight.

This study is the first to assess the difference in the thyroid cancer burden attributable to overweight and obesity by sex. We found a suggestively higher overweight/obesity-attributable burden in men compared with women (39% compared with 10%) during the maximum 22-year follow-up, with the sex difference in the burden being stronger during the shorter 10- and 15-year follow-ups. Both the overweight- and obesity-attributable burdens are higher for men compared with women in the 10-year follow-up. These differences were due to both higher overweight- and obesity-related risks and prevalences for men compared with women. Our findings align with the literature which has reported BMI to be positively associated with thyroid cancer in men and women but more strongly associated in men than

women.[21] Some studies have reported PAF point estimates by sex, but they did not present confidence intervals for the point estimates or compare them statistically.[17,19,20]

We also identified significant differences in the overweight/obesity-attributable thyroid cancer burden by alcohol consumption and marital/co-habiting status, with those consuming more than two alcoholic drinks per day and those not married/co-habiting experiencing a significantly higher overweight/obesity-related burden compared with their counterparts. If confirmed, our subgroup findings may inform targeted, in addition to population-wide, strategies to reducing overweight and obesity, and consequently thyroid cancer burden.

Strengths and limitations

Our study was based on large harmonised individual-level Australian cohort data and representative contemporaneous exposure prevalence data.[22] Applying our advanced PAF method to these data allowed us to assess the future thyroid cancer burden attributable to current levels of overweight and obesity, accounting for potential competing risk of death and the length of follow-up, and to evaluate differences in the preventable burden between population subgroups.[16,22,26]

Although BMI was measured in four cohort studies and self-reported in three, we did not observe any between-cohort heterogeneity. We were unable to evaluate or adjust for exposure to ionizing radiation and iodine deficiency, established risk factors for thyroid cancer,[4,23,28] as they were not measured in our cohort and there is no available prevalence data. As overweight and obese individuals are often exposed to higher doses of medical ionizing radiation and may be more likely to have iodine deficiency,[29] part of the impact of overweight/obesity on thyroid cancer burden may be via these exposures. We also cannot exclude the possibility of residual confounding of the observed associations by unknown causal factors. Furthermore, changes in baseline BMI during follow-up may have

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underestimated the associations of overweight/obesity with thyroid cancer.[30,31] This is supported by the stronger associations between overweight/obesity and thyroid cancer we observed the shorter the follow-up. However, longer follow-up allows for a longer latency period between exposure and cancer diagnosis. Although weight change is typically gradual and baseline BMI can be considered a proxy for recent past BMI, not accounting for any lag between baseline BMI and thyroid cancer in our main analyses may have overestimated the associations of overweight/obesity with thyroid cancer. Excluding the first year of follow-up in sensitivity analyses attenuated the associations between overweight/obesity and thyroid cancer but did not change the significance of the findings or indicate reverse causality. We could not reliably evaluate the impact of a longer than a one-year lag on the association between overweight/obesity and thyroid cancer because of the drop in statistical power.

We presented PAF estimates for the future thyroid cancer burden avoidable by changes in the prevalence of overweight and obesity. Our PAF method also allows for evaluation of continuous exposures.[16,26] However, due to ethical restrictions on the use of the NHS exposure prevalence data, we could not compute PAF for the shift in the continuous BMI distribution. For the same reason, we were unable to incorporate the uncertainty in the exposure prevalence estimates in our PAF estimates.[22] Despite the large cohort, statistical power for our subgroup analyses may have been inadequate. Finally, PAF estimation assumes an immediate risk reduction to the level of those unexposed following the hypothetical exposure modification, although in reality there is a lag. The lag can be taken into account in the PAF estimation and interpretation,[32] however reliable evidence on the lag in risk reduction following reduction in weight is currently lacking.

We were unable to reliably estimate the association of overweight and obesity with thyroid cancer subtypes other than papillary thyroid cancer. However, consistent associations of body fatness with all subtypes except for medullary carcinoma have been reported.[21] Finally,

neither tumour size nor cancer stage were available, preventing stratified analyses. Much stronger associations between thyroid cancer and overweight (HR 4.31; 95% CI, 1.26-14.7 in men, and HR 1.65; 95% CI, 0.44-6.18 in women) and obesity (HR 7.62; 95% CI, 2.11-27.5 in men, and HR 3.58; 95% CI, 1.02-12.5 in women) than observed in this study have been found for large (>4 cm) tumours.[12] The association of obesity with thyroid cancer in men is also reportedly stronger for regional and distant cancers compared with localized cancers.[12]

The stronger association of overweight and obesity with larger tumours and more advanced cancer suggests that prevention of overweight and obesity is more likely to reduce the incidence of thyroid cancers with poor survival outcomes that require more aggressive clinical management, rather than low risk thyroid cancers that are more likely to be incidentally detected due to improved diagnostics.[12,33] The lack of association of overweight and obesity with smaller tumours,[12] on the other hand, may explain the lack of significant association of overweight and the weaker association of obesity with thyroid cancer in women, whose thyroid cancer is reportedly more likely to be overdiagnosed, possibly due to their greater health-seeking behaviour and exposure to health care.[6] Analyses of the overweight/obesity-attributable thyroid cancer burden, stratified by tumour size and cancer stage and optimally adjusted for health care exposure, are needed to clarify the impact of thyroid cancer overdiagnosis on our results, especially the overweight/obesity-attributable thyroid cancer burden in women.

Conclusions

Current levels of overweight and obesity in Australia appear responsible for every fifth future thyroid cancer, and two fifths of thyroid cancers in men. Obesity is responsible for the majority of this burden. These findings add evidence to the urgent need to halt and reverse the current global trend in weight gain, especially obesity and especially in men. Public health policies, practices and incentives that promote and support exercise and healthy

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choices when eating and drinking, together with policies that address the social, economic and environmental determinants of health, may be of value for the prevention of thyroid and multiple other cancers.

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CONFLICT OF INTEREST

Professor Karen Canfell is co-PI of an investigator-initiated trial of cervical screening, Compass, run by the VCS Foundation, which is a government-funded not-for-profit charity; the VCS Foundation has received equipment and a funding contribution from Roche Molecular Diagnostics. She is also co-PI on a major investigator-initiated implementation program Elimination of Cervical Cancer in the Western Pacific (ECCWP) which will receive support from the Minderoo Foundation, the Frazer Family Foundation and equipment donations from Cepheid Inc. Neither KC nor her institution on her behalf receive direct funding from industry for any project. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Australian Institute of Health and Welfare (AIHW) Ethics Committee approved the study (EC2013/4/62). This study is a data linkage study where data linkage was carried out by external authorities and all data was de-identified.

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As the incidence of thyroid cancer has increased, questions have arisen regarding possible associations with increasing incidence of overweight and obesity. Here, the authors projected the future burden of thyroid cancer in Australia with regard to incidence of overweight and obesity. Analyses show that current levels of overweight and obesity in Australia explain about 19 percent of future thyroid cancers, with 14 percent of cancers attributed to obesity alone. Moreover, if currently obese individuals were instead overweight, nearly 10 percent of thyroid cancers could be avoided. The findings suggest that many thyroid cancers could be prevented through improved weight management.

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Table 1. Characteristics of the individual and pooled cohort and external data sources

Characteristic	Cohort data								Prevalence data
	MCCS	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**CHAMP**	**45&Up**	**Pooled**	**NHS**
Baseline year(s)	1990-1994	1992-1993	1996	1999-2000	1999-2003	2005-2007	2006-2009	1990-2009	2017-2018
State/Territory	VIC	NSW	All	All	SA	NSW	NSW	All	All
Population (n)	41,496	3,653	38,355	11,185	4,036	1,625	264,240	364,590	16,370
Follow-up time in years, mean (range)	18 (0-22)	16 (0-21)	15 (0-17)	12 (0-14)	11 (0-13)	6 (0-8)	5 (0-8)	8 (0-22)	-
Incident thyroid cancers (n)[1]	76	4	86	17	6	0	242	431[3]	-
Deaths (n)[1]	7,341	1,656	6,449	1,189	354	455	14,585	32,029	-
Age in years at baseline, mean (range)	55 (27-76)	66 (45-97)	45[2] (18-75)	51 (25-95)	50 (18-90)	77 (70-97)	62 (45->100)	59 (18->100)	47 (18-99)
Women (%)	59	57	100	55	52	0	53	59	51

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); CHAMP (Concord Health and Ageing in Men Project); MCCS (Melbourne Collaborative Cohort Study); NHS (National Health Survey); NSW (New South Wales); NWAHS (North West Adelaide Health Study); SA (South Australia); VIC (Victoria)

[1] During the maximum 22-year follow-up.

[2] The ALSWH recruited three cohorts aged 18-23, 45-50 and 70-75 so the age distribution is not continuous.

[3] Distribution by histological subtype: n = 323 papillary, n = 71 follicular, n = 16 medullary, n = 9 anaplastic, and n = 12 other carcinomas.

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Table 2. BMI frequencies, population exposure prevalences, hazard ratios and fractions of thyroid cancers avoidable by change in BMI; 22-year follow-up

	Cohort n/N (%)[1]			Population prevalence[2]			HR (95% CI)[3]		
Body mass index (BMI)	**All**	**Men**	**Women**	**All**	**Men**	**Women**	**All**	**Men**	**Women**
Per 5 kg/m^2							**1.19 (1.09, 1.30)**	**1.32 (1.06, 1.65)**	**1.17 (1.06, 1.29)**
1. <25.0 kg/m^2	161/136,934 (40%)	18/44,086 (31%)	143/92,848 (47%)	33%	26%	40%	1	1	1
2. 25.0-29.9 kg/m^2	139/131,644 (39%)	48/68,130 (48%)	91/63,514 (32%)	36%	42%	30%	1.09 (0.86, 1.37)	1.66 (0.97, 4.26)	0.98 (0.75, 1.28)
3. ≥30.0 kg/m^2	109/72,363 (21%)	26/30,310 (21%)	83/42,053 (21%)	31%	33%	30%	**1.46 (1.14, 1.87)**	**2.07 (1.14, 3.78)**	**1.37 (1.04, 1.81)**
PAF% (2-3 → 1)[4]							**18.6 (5.2, 30.2)**	**38.5 (4.8, 60.3)**	9.5 (-4.5, 21.7)
PAF% (2 → 1)[4]							4.9 (-2.5, 11.8)	17.1 (-1.5, 32.2)	-0.6 (-7.8, 6.2)
PAF% (3 → 1)[4]							**13.7 (5.2, 21.4)**	**21.4 (2.8, 36.5)**	**10.1 (0.8, 18.6)**
PAF% (3 → 2)[4]							**9.9 (1.0, 18.1)**	8.2 (-11.6, 24.5)	**10.8 (0.9, 19.7)**

BMI (Body mass index); CI (Confidence interval); HR (Hazard ratio); PAF (Population attributable fraction)
* HR/PAF for men differs from HR/PAF for women.
Statistically significant values ($p<0.05$) are shown in bold.
[1] Number of cancer cases / total N (%) per risk factor category.
[2] Population exposure prevalence from the National Health Survey 2017-2018.
[3] Adjusted for age, sex, and study. Sex-specific results are based on a model including sex interaction.
[4] PAF% and 95% confidence interval for modification of risk factor exposure level → target reference level. Overall PAF% results are based on the model including sex interaction.
Note: some prevalences do not add up to 100% because of rounding.

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Table 3. Exposure prevalences, hazard ratios and fractions of thyroid cancer attributable to overweight and obesity by potential effect modifying factors; 22-year follow-up

Effect modifier	BMI categories							
	1. BMI < 25.0 kg/m^2		2. BMI 25.0-29.9 kg/m^2		3. BMI ≥ 30.0 kg/m^2			
	PR[1]	HR	PR[1]	HR (95% CI)[2]	PR[1]	HR (95% CI)[2]	PAF% (2-3 → 1)[3]	PAF% (3 → 1)[3]
Smoking								
Never regular smoker	67%	1	59%	1.10 (0.82, 1.47)	52%	**1.46 (1.06, 2.00)**	13.4 (-2.5, 26.8)	**10.7 (1.0, 19.5)**
Former regular smoker	19%	1	28%	1.07 (0.69, 1.66)	34%	1.41 (0.89, 2.24)	15.5 (-14.6, 37.7)	13.4 (-6.2, 29.4)
Current regular smoker	14%	1	13%	1.09 (0.52, 2.26)	14%	1.69 (0.80, 3.79)	20.2 (-25.5, 49.2)	17.9 (-12.4, 39.9)
P-value[4]				0.85_{1v2}; 0.95_{1v3}; 0.96_{2v3}		0.83_{1v2}; 0.70_{1v3}; 0.63_{2v3}	0.89_{1v2}; 0.73_{1v3}; 0.84_{2v3}	0.79_{1v2}; 0.61_{1v3}; 0.78_{2v3}
Alcohol consumption								
≤ 2 drinks/day	88%	1	81%	1.02 (0.80, 1.31)	89%	**1.38 (1.07, 1.78)**	11.1 (-2.5, 22.9)	**10.4 (1.7, 18.3)**
> 2 drinks/day	12%	1	19%	2.93 (0.95, 9.00)	11%	**4.04 (1.21, 13.4)**	**63.4 (3.9, 86.1)**	**35.1 (1.7, 57.2)**
P-value[4]				0.07		0.08	**0.01**	0.09
Fruit consumption								
< 2 serves/day	48%	1	47%	1.16 (0.72, 1.88)*	51%	**1.71 (1.05, 2.79)***	22.1 (-5.9, 42.7)	**18.0 (0.2, 32.5)**
≥ 2 serves/day	52%	1	53%	0.95 (0.70, 1.30)	49%	1.22 (0.87, 1.71)	4.7 (-13.9, 20.3)	6.2 (-5.0, 16.1)
P-value[4]				0.41		0.17	0.24	0.23
Vegetable consumption								
< 5 serves/day	91%	1	91%	1.00 (0.72, 1.39)	90%	1.36 (0.96, 1.92)	10.0 (-9.4, 25.9)	9.9 (-2.1, 20.5)
≥ 5 serves/day	9%	1	9%	1.08 (0.70, 1.66)	10%	1.39 (0.88, 2.19)	12.9 (-13.4, 33.1)	10.6 (-5.6, 24.2)
P-value[4]				0.73		0.93	0.84	0.94
Physical activity[5]								
< 150 min/week	71%	1	73%	0.86 (0.55, 1.34)	83%	0.97 (0.61, 1.53)	-6.1 (-35.8, 17.1)	-1.3 (-18.9, 13.8)
≥ 150 min/week	29%	1	27%	1.32 (0.85, 2.05)	17%	**1.95 (1.23, 3.10)***	**23.5 (1.1, 40.8)**	**14.9 (3.1, 25.2)**
P-value[4]				0.06		**0.003**	0.08	0.11
Age group (years at baseline)								
< 65 years	35%	1	35%	1.03 (0.78, 1.35)	30%	**1.37 (1.03, 1.83)**	10.4 (-4.9, 23.5)	**9.7 (0.2, 18.2)**
≥ 65 years	24%	1	38%	1.28 (0.83, 1.99)	37%	**1.79 (1.11, 2.91)**	28.4 (0.5, 48.4)	**21.1 (2.3, 36.2)**
P-value[5]				0.33		0.27	0.20	0.24
Country of birth								
Australia	31%	1	35%	1.09 (0.83, 1.42)	34%	**1.47 (1.11, 1.95)**	15.6 (0.2, 28.7)	**13.2 (2.9, 22.5)**
Other	36%	1	38%	1.05 (0.65, 1.69)	26%	1.39 (0.83, 2.33)	10.3 (-17.8, 31.7)	8.8 (-6.5, 21.8)

P-value[4]				0.89		0.70	0.71	0.61
Marital status								
Not married	38%	1	33%	1.46 (0.95, 2.24)	29%	**2.23 (1.44, 3.46)***	**33.2 (12.2, 49.2)***	**23.9 (9.4, 36.1)***
Married/de facto	30%	1	38%	0.93 (0.71, 1.23)	33%	1.24 (0.92, 1.66)	5.0 (-12.4, 19.6)	7.1 (-3.5, 16.7)
P-value[4]				**0.04**		**0.01**	**0.02**	**0.048**
Educational attainment								
Low	32%	1	34%	1.06 (0.77, 1.48)	35%	**1.48 (1.06, 2.08)**	15.6 (-3.7, 31.3)	**13.9 (1.3, 24.8)**
Intermediate	29%	1	36%	1.11 (0.71, 1.73)	36%	1.53 (0.94, 2.47)	18.1 (-9.9, 38.9)	15.2 (-3.8, 30.7)
High	40%	1	38%	1.02 (0.63, 1.66)	22%	1.10 (0.59, 2.04)	2.9 (-25.1, 24.6)	2.2 (-12.7, 15.2)
P-value[4]				0.81_{1v2}; 0.84_{1v3}; 0.71_{2v3}		0.89_{1v2}; 0.08_{1v3}; 0.18_{2v3}	0.87_{1v2}; 0.41_{1v3}; 0.38_{2v3}	0.90_{1v2}; 0.21_{1v3}; 0.25_{2v3}
Residential location								
Major city	35%	1	36%	1.04 (0.73, 1.49)	29%	**1.48 (1.01, 2.16)**	13.0 (-7.1, 29.3)	11.7 (-0.9, 22.8)
Regional or remote	28%	1	35%	1.21 (0.83, 1.75)	38%	**1.72 (1.17, 2.51)**	**25.0 (3.3, 41.9)**	**19.9 (5.0, 32.5)**
P-value[4]				0.43		0.44	0.36	0.37
Socio-economic status (SES)								
SES quintile 1 (low)	28%	1	34%	0.95 (0.56, 1.61)	38%	1.28 (0.75, 2.21)	8.5 (-27.6, 34.3)	9.9 (-14.0, 28.8)
SES quintile 2	31%	1	34%	0.87 (0.45, 1.68)	35%	1.92 (1.06, 3.51)	21.6 (-16.4, 47.2)	24.9 (-0.6, 44.0)
SES quintile 3	34%	1	36%	**1.99 (1.12, 3.54)**	30%	**2.19 (1.17, 4.08)**	**40.8 (10.2, 60.9)**	**21.1 (2.4, 36.2)**
SES quintile 4	34%	1	37%	1.03 (0.59, 1.79)	29%	1.19 (0.63, 2.22)	5.8 (-29.5, 31.5)	4.9 (-15.3, 21.7)
SES quintile 5 (high)	37%	1	38%	0.91 (0.50, 1.64)	25%	1.44 (0.74, 2.81)	6.8 (-27.8, 32.0)	9.8 (-11.3, 26.9)
				0.74_{1v2}; **0.01_{1v3}**; 0.78_{1v4}; 0.87_{1v5}; **0.005_{2v3}**; 0.55_{2v4}; 0.88_{2v5}; **0.02_{3v4}**; **0.01_{3v5}**;		0.18_{1v2}; 0.09_{1v3}; 0.79_{1v4}; 0.73_{1v5}; 0.72_{2v3}; 0.11_{2v4}; 0.33_{2v5}; 0.06_{3v4}; 0.26_{3v5};	0.55_{1v2}; 0.10_{1v3}; 0.90_{1v4}; 0.94_{1v5}; 0.34_{2v3}; 0.47_{2v4}; 0.49_{2v5}; 0.08_{3v4}; 0.08_{3v5};	0.33_{1v2}; 0.42_{1v3}; 0.73_{1v4}; 1.00_{1v5}; 0.78_{2v3}; 0.17_{2v4}; 0.31_{2v5}; 0.20_{3v4}; 0.38_{3v5};
P-value[4]				0.66_{4v5}		0.57_{4v5}	0.96_{4v5}	0.72_{4v5}

BMI (Body mass index); CI (Confidence interval); HR (Hazard ratio); PAF (Population attributable fraction); PR (Prevalence); SES (Socio-economic status)

* HR/PAF for this subgroup differs from HR/PAF for other subgroup(s).

Statistically significant values ($p<0.05$) are shown in bold.

[1] Population exposure prevalence from the National Health Survey 2017-2018.

[2] Adjusted for age, sex, and study.

[3] PAF% and 95% confidence interval for modification of risk factor exposure level → target reference level.

[4] P-value for difference between HR/PAF estimates.

[5] ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity or a combination of the two.

Note: some prevalences do not add up to 100% because of rounding.

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