PAPER

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Risk of Advanced Papillary Thyroid Cancer in Obese Patients

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Objective: To determine whether increasing body mass index (BMI) is associated with more aggressive disease and adverse surgical outcomes in patients with papillary thyroid cancer (PTC).

Design: Retrospective review of a prospective database.

Setting: Single academic tertiary care center.

Patients: A total of 443 patients older than 18 years who underwent total thyroidectomy for PTC from January 1, 2004, through March 31, 2011, were included in the analysis. Patients were organized into 4 BMI (calculated as weight in kilograms divided by height in meters squared) groups: normal (18.5-24.9), overweight (25-29.9), obese (30-39.9), and morbidly obese (≥40).

Main Outcome Measures: Disease stage at presentation, histologic subtype, duration of anesthetic induction and extubation, duration of surgery, surgical complications, length of hospital stay, and American Society of Anesthesiologists (ASA) class.

Results: Ages ranged from 18 to 89 years. Greater BMI was associated with more advanced disease stage at presentation ($P<.001$) and more aggressive PTC histopathologic subtype ($P=.03$). Morbidly obese patients presented more frequently with stage III or IV disease (odds ratio, 3.67; $P<.001$). Greater BMI was also associated with longer duration of anesthetic induction ($P<.001$), increased length of stay ($P<.001$), and higher ASA class ($P<.001$). Duration of surgery was not associated with BMI. There was a trend toward larger tumors with increasing BMI ($P=.06$). Obese BMI was associated with more preoperative vocal cord paralysis due to local invasion (odds ratio, 9.21; $P=.001$).

Conclusions: Obese patients present with more advanced stage and more aggressive forms of PTC. This finding suggests that obese patients should be screened for thyroid cancer.

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THE INCREASING PREVALENCE of obesity in the United States has been a concerning issue in recent decades. Interest is increasing in understanding the debilitating effects and disease risks associated with increased body fat percentage. Elevated body mass index (BMI) is associated with a number of medical comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, and cancer.[1]

See Invited Critique at end of article

The incidence and prevalence of thyroid cancer are also on the rise in the United States.[2,3] Most of this increase is due to papillary thyroid cancer (PTC).[2] It is still debatable whether the cause of this increase is a result of enhanced risk of the development of cancer or an increase in detection capabilities in light of the new and more sensitive technology.[4] Regardless, thyroid cancer remains the most common endocrine cancer and is responsible for more deaths every year than all other endocrine malignant tumors combined.[4]

Obesity is now recognized as a risk factor for a variety of cancers in patient populations around the world. Body mass index has been associated with esophageal adenocarcinoma, colon cancer, endometrial cancer, and renal cancer.[5] In addition, some studies[5-10] have linked a higher BMI to an increased incidence of thyroid cancer in the United States, Korea, Norway, and French Polynesia.

Furthermore, increased BMI has also been linked to a more severe presentation and a higher risk of death from other types of cancers. Presentation of more advanced

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stages of breast cancer has been attributed to certain racial groups, explained by obesity differences among the groups, as well as other factors.[11] In patients with prostate cancer, higher-grade cancers and a higher risk of recurrence after treatment have also been associated with obesity.[12] Excess body weight has been shown to be associated with a higher mortality risk from all cancers combined.[13]

An association between higher BMI and more aggressive or later-stage cancer has never been shown with PTC. We conducted this study to address the association of increasing BMI with PTC stage at presentation, the presence of aggressive malignant features, and adverse surgical outcomes.

METHODS

We reviewed the medical records of all patients older than 18 years who underwent total thyroidectomy as an initial procedure for PTC or its variants from January 1, 2004, through March 31, 2011, at a single tertiary referral center. These patients were identified using the UCLA Cancer Registry and UCLA Financial Services databases. We excluded patients who had missing data, underwent less than a total thyroidectomy as the initial procedure, underwent concomitant parathyroid disease or parathyroid operations, and/or had other types of thyroid cancer. Patients with missing data were evenly spread throughout BMI groups.

International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes were used to identify all patients with PTC, as well as their subtype and variants. For inpatient cases only (n=363), the *ICD-9-CM* codes were also used to define surgical complications, according to coding previously applied in other studies and adding codes that are specific to thyroid surgery.[14] A complete list of *ICD-9* coding for diagnosis complications is given in **Table 1**. The number of complications were tallied to create summary scores. For some analyses, complications were dichotomized into absent (0) or present (1) categories. Medical complications and comorbidities were grossly undercoded and therefore not used in this study. Of note, our surgeons do not routinely perform preoperative and/or postoperative laryngoscopy. American Society of Anesthesiologists (ASA) class was taken from anesthesia records. Staging was performed by applying American Joint Committee on Cancer (AJCC) criteria. This information was supplied by the UCLA Cancer Registry.

We set power at 80% with a 2-sided α of .05 to estimate the sample size needed for a logistic regression, with an expected odds ratio (OR) range of 1.52 to 2.23.[5] The effect size was based on the expected association between BMI and thyroid cancer. With these parameters, a minimum sample size of 196 patients would be required. With the same power and 2-sided α values, we also calculated that a sample size of 434 patients would be needed to detect a 3% complication rate if 5 or fewer predictors were used in multivariable analyses. Power analyses were calculated using GPower 3.1.0 software (Franz Faul, Universitat Kiel).[15]

Body mass index was calculated as weight in kilograms divided by height in meters squared. Patients were organized into 4 BMI groups: normal (18.5-24.9), overweight (25-29.9), obese (30-39.9), and morbidly obese ($\geq$40). Histopathologic subtype was separated into 4 groups: papillary, papillary with follicular variant, papillary microcarcinoma, or other (hyalinizing, tall cell, or sclerosing). Surgical time was defined as the time from incision to closure. Anesthesia induction time was defined as anesthesia start time to surgical incision time.

Univariate analyses, including χ^2 test or 1-way analysis of variance, were conducted to study differences in BMI by demographic or clinical factors. Multivariable regression analyses were applied to control for the influence of cofactors that affect outcomes, such as surgical time or length of hospital stay. Body mass index was the main predictor in all analyses. The main outcome measures studied were disease stage at presentation, histologic subtype, duration of anesthetic induction and extubation, duration of surgery, surgical complications, length of stay, and ASA class. All analyses were conducted using Stata/SE v.11 statistical software (StataCorp). The research protocol was approved by the UCLA institutional review board.

RESULTS

Of 551 patients, 443 patients were included in the final analysis. **Table 2** lists the demographic information. Mean age was 48.2 years (range, 18-93 years). Normal-weight patients were slightly younger than patients in the other BMI categories ($P<.001$). Although women represent most cases overall, men were more overweight and obese than females in this cohort ($P<.001$). African Americans were more obese and morbidly obese than other races ($P<.001$). A higher frequency of ASA class 3 was represented in the obese and morbidly obese categories ($P<.001$).

Greater BMI was associated with more advanced disease stage at presentation ($P=.04$) (**Table 3**). Specifically, the obese and morbidly obese categories presented more as stage III or IV disease. No difference was found in overall subtype of papillary cancer histologic subtype among BMI groups as defined in the "Methods" section. However, in a subgroup analysis, a significant increase was found in the percentage of the more aggressive subtype of tall cell variant of PTC in the obese and morbidly obese categories compared with the normal weight and overweight categories ($P=.03$). No association was found between those with tall cell variant and age in this cohort ($P=.62$). A trend was also seen toward greater tumor size in patients with increasing BMI.

Patients did not demonstrate any association between total surgical complication rates and BMI groups (**Table 4**). However, those in the obese BMI group had significantly more recurrent laryngeal nerve dysfunction (10 [12.2%]) than those in the normal weight (2 [2.0%]) and overweight (3 [2.6%]) categories (χ^2 test $P=.001$). Most of this dysfunction was due to presentation with preoperative vocal cord dysfunction with more advanced local disease. Obese BMI (n=9) was associated with more preoperative vocal cord paralysis due to local invasion (OR, 9.2; 95% CI, 1.9-43.9; $P=.001$) when compared with normal-weight individuals (n=2). These preoperative paralyses were not included in the number of surgical complications in Table 4. No difference was found among the BMI groups in complications related to wound infection, bleeding (n=5), hypocalcemia (n=16), respiratory issues, and/or reintubation rates. However, the number of patients was underpowered to detect a less than 3% complication rate.

Increasing BMI was a significant predictor of longer length of stay on univariate and multivariable analyses (Table 4, $P=.004$). On multivariable analysis, controlling for surgeon and ASA class, only the obese BMI class was associated with increased length of stay ($P=.001$).

Table 1. *ICD-9-CM* Index Codes for Surgical Complications

Complication	Code Type	Code No.	Description
Hemorrhagic complications	*ICD-9D*	998.1	Hemorrhage, hematoma, or seroma complicating a procedure
	ICD-9D	998.11	Hemorrhage complicating a procedure
	ICD-9D	998.12	Hematoma complicating a procedure
	ICD-9D	998.13	Seroma complicating a procedure
	ICD-9D	998.2	Unintentional puncture or laceration during a procedure
	ICD-9D	E870.0	Surgical operation
	ICD-9P	6.01	Aspiration of thyroid field
	ICD-9P	6.02	Reopening of wound of thyroid field
	ICD-9P	39.98	Control of hemorrhage, not otherwise specified
	ICD-9P	99.04	Transfusion of packed cells
Respiratory complications	*ICD-9D*	465	Acute upper respiratory tract infections of multiple or unspecified sites
	ICD-9D	465.9	Acute upper respiratory tract infections of multiple or unspecified sites—unspecified site
	ICD-9D	482	Other bacterial pneumonia
	ICD-9D	482.0	Pneumonia due to *Klebsiella pneumoniae*
	ICD-9D	482.1	Pneumonia due to *Pseudomonas*
	ICD-9D	482.2	Pneumonia due to *Haemophilus influenzae*
	ICD-9D	482.41	Methicillin-susceptible pneumonia due to *Staphylococcus aureus*
	ICD-9D	482.82	Pneumonia due to other specified bacteria—*Escherichia coli*
	ICD-9D	482.83	Pneumonia due to other specified bacteria—other gram-negative bacteria
	ICD-9D	486	Pneumonia, organism unspecified
	ICD-9D	511.9	Pleurisy—unspecified pleural effusion
	ICD-9D	518	Other diseases of lung
	ICD-9D	518.0	Pulmonary collapse
	ICD-9D	518.4	Acute edema of lung, unspecified
	ICD-9D	518.5	Pulmonary insufficiency after trauma and surgery
	ICD-9D	518.81	Acute respiratory failure
	ICD-9D	518.82	Other pulmonary insufficiency, not elsewhere classified
	ICD-9D	518.84	Acute and chronic respiratory failure
	ICD-9D	799.1	Other ill-defined and unknown causes of morbidity and mortality—respiratory arrest
	ICD-9D	997.3	Complications affecting specified body systems, not elsewhere classified—respiratory complications
Neurologic complications and issues related to recurrent laryngeal nerve dysfunction	*ICD-9D*	478.3	Paralysis of vocal cords or larynx
	ICD-9D	478.31	Paralysis of vocal cords or larynx—unilateral, partial
	ICD-9D	478.32	Paralysis of vocal cords or larynx—unilateral, complete
	ICD-9D	478.33	Paralysis of vocal cords or larynx—bilateral, partial
	ICD-9D	478.34	Paralysis of vocal cords or larynx—bilateral, complete
	ICD-9D	784.49	Voice disturbance—other (change in voice, dysphonia, hoarseness, hypernasality, hyponasality)
Wound-related complications	*ICD-9D*	682.1	Other cellulitis and abscess—neck
	ICD-9D	998.3	Disruption of wound
	ICD-9D	998.31	Disruption of internal operation (surgical) wound
	ICD-9D	998.32	Disruption of external operation (surgical) wound
	ICD-9D	998.5	Postoperative infection
	ICD-9D	998.51	Infected postoperative seroma
	ICD-9D	998.59	Other postoperative infection
	ICD-9D	998.83	Nonhealing surgical wound
	ICD-9P	86.04	Other incision with drainage of skin and subcutaneous tissue
	ICD-9P	86.22	Excisional debridement of wound, infection, or burn
Hypocalcemia	*ICD-9D*	252.1	Hypoparathyroidism—tetany
	ICD-9D	275.4	Disorders of calcium metabolism
	ICD-9D	275.41	Hypocalcemia
	ICD-9D	781.7	Tetany (carpopedal spasm)
Complications from reintubation	*ICD-9P*	31.1	Temporary tracheostomy
	ICD-9P	31.21	Permanent tracheostomy—mediastinal tracheostomy
	ICD-9P	31.29	Permanent tracheostomy—other permanent tracheostomy
	ICD-9P	96.04	Insertion of endotracheal tube
	ICD-9P	96.70	Invasive mechanical ventilation, not otherwise specified
	ICD-9P	96.71	Continuous invasive mechanical ventilation for <96 consecutive hours
	ICD-9P	96.72	Continuous invasive mechanical ventilation for ≥96 consecutive hours
Cerebrovascular accidents	*ICD-9D*	997.0	Complications affecting specified body systems, not elsewhere classified—nervous system complications
	ICD-9D	997.01	Central nervous system complication (anoxic brain damage; cerebral hypoxia)
	ICD-9D	997.02	Iatrogenic cerebrovascular infarction or hemorrhage
	ICD-9D	997.09	Other nervous system complications

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-9D*, diagnosis code; *ICD-9P*, procedure code.

In univariate analysis, morbidly obese patients had a significantly longer anesthesia induction time (mean, 43.1 minutes; $P < .001$) compared with other groups. A trend was also seen toward longer extubation times with increasing BMI. In both univariate and multivariable analyses (controlling for surgeon and AJCC stage), a trend was seen toward longer total surgical times associated with increasing BMI (Table 4).

In the entire cohort, higher BMI was a significant predictor of presenting with either stage III or IV dis-

Table 2. Demographics and Clinical Characteristics of 443 Patients[a]

Predictor	Normal (BMI, 18.5-24.9) (n = 175)	Overweight (BMI, 25-29.9) (n = 141)	Obese (BMI, 30-39.9) (n = 99)	Morbidly Obese (BMI, ≥40) (n = 28)	*P* Value
Age, mean (SD), y[b]	44.9 (15.4)	51.5 (15.2)	50.3 (12.9)	48.3 (10.4)	<.001[c]
Sex[d]					
Male (n = 120)	30 (25.0)	52 (43.3)	32 (26.7)	6 (5.0)	.001[c]
Female (n = 323)	145 (44.9)	89 (27.6)	67 (20.7)	22 (6.8)	
Race[d]					
White (n = 320)	117 (36.6)	103 (32.2)	77 (24.0)	23 (7.2)	<.001[c]
African American (n = 18)	0	7 (38.9)	8 (44.4)	3 (16.7)	
Asian/Pacific Islander (n = 76)	45 (59.2)	19 (25.0)	10 (13.2)	2 (2.6)	
Other/undetermined (n = 29)	13 (44.8)	12 (41.4)	4 (13.8)	0	
ASA class[d]					
1 (n = 33)	21 (63.6)	9 (27.3)	3 (9.1)	0	<.001[c]
2 (n = 310)	139 (44.8)	97 (31.3)	61 (19.7)	13 (4.2)	
3 (n = 95)	13 (13.7)	33 (34.7)	34 (35.8)	15 (15.8)	
4 (n = 1)	0	0	1 (100.0)	0	
Admission type					
Inpatient (n = 363)	148 (40.7)	113 (31.1)	82 (22.6)	20 (5.5)	.35
Ambulatory (<23 h) (n = 80)	27 (33.8)	28 (35)	17 (21.3)	8 (10)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Data are presented as number (row percentage) of patients unless otherwise indicated.
[b] One-way analysis of variance.
[c] Statistically significant.
[d] χ^2 Test.

Table 3. Association of BMI With Disease Stage and Histologic Subtype[a]

Predictor	Normal (BMI, 18.5-24.9) (n = 175)	Overweight (BMI, 25-29.9) (n = 141)	Obese (BMI, 30-39.9) (n = 99)	Morbidly Obese (BMI, ≥40) (n = 28)	*P* Value
AJCC stage[b]					
1	144 (82.3)	99 (70.2)	69 (69.7)	18 (64.3)	.04[c]
2	8 (4.5)	10 (7.1)	6 (6.1)	0	
3	15 (8.6)	15 (10.6)	9 (9.1)	6 (21.4)	
4	8 (4.6)	17 (12.1)	15 (15.2)	4 (14.3)	
Papillary subtype cancer histologic subtype[b]					
Papillary	92 (52.6)	73 (51.8)	46 (46.5)	11 (39.3)	.16
Papillary with follicular variant	43 (24.5)	44 (31.2)	24 (24.2)	6 (21.4)	
Papillary microcarcinoma	32 (4.6)	21 (14.9)	20 (20.2)	9 (32.1)	
Other	8 (18.3)	3 (2.1)	9 (9.1)	2 (7.1)	
Tumor size, mean (SD), cm[d]	1.53 (1.1)	1.71 (1.5)	2.03 (1.99)	2.12 (2.90)	.06
Tall cell variant PTC[a]					
Absent	173 (98.9)	138 (97.9)	92 (92.9)	26 (92.9)	.03[c]
Present	2 (1.1)	3 (2.1)	7 (7.1)	2 (7.1)	

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PTC, papillary thyroid cancer.
[a] Data are presented as number (column percentage) of patients unless otherwise indicated.
[b] χ^2 Test.
[c] Statistically significant.
[d] One-way analysis of variance.

ease compared with normal weight (**Table 5**) (overweight: OR, 1.94; 95% CI, 1.07-3.50; obese: OR, 2.11; 95% CI, 1.20-3.99; and morbidly obese: OR, 3.67; 95% CI, 1.51-8.93). When excluding microcarcinomas, this association was strengthened in all 3 BMI groups, noted especially in the morbidly obese group's OR of 5.22 (95% CI, 1.90-14.39). Likewise, when excluding tall cell variants from the group, the morbidly obese group remained significantly associated with later-stage disease (OR, 2.90; 95% CI, 1.13-7.43). When analyzing only the microcarcinoma group, no significant association was found between BMI and late-stage presentation.

When analyzing only those older than 45 years (n=256), the morbidly obese group remained significantly associated with later-stage disease (OR, 3.66; 95% CI, 1.24-10.24). When analyzing only those younger than 45 years (n=187) in their presentation of either stage I or II disease, no patients presented with stage II disease. In addition, in this younger cohort, significantly more

Table 4. Univariate Analyses

Predictor	Mean (SD)				*P* Value
	Normal (BMI, 18.5-24.9)	Overweight (BMI, 25-29.9)	Obese (BMI, 30-39.9)	Morbidly Obese (BMI, ≥40)	
No. of surgical complications[a]					
0	141	104	75	19	.62
≥1	7	9	7	1	
Anesthesia induction time, min[b]	34.0 (16.6)	33.8 (17.8)	41.4 (21.0)	43.1 (21.3)	<.001[c]
Extubation time, min[b]	11.7 (7.4)	13.5 (12.4)	15.6 (16.4)	13.1 (8.0)	.06
Surgical time, min[b]	148 (64)	156 (77)	171 (92)	171 (93)	.10
Length of stay, d[b]	1.8 (1.1)	2.3 (1.9)	2.7 (1.9)	2.4 (1.9)	<.001[c]

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] χ^2 Test.
[b] One-way analysis of variance.
[c] Statistically significant.

Table 5. Multivariable Analyses

Predictor	Odds Ratio (95% CI)			
	Normal (BMI, 18.5-24.9)	Overweight (BMI, 25-29.9)	Obese (BMI, 30-39.9)	Morbidly Obese (BMI ≥40)
Presenting with AJCC stage III or IV (whole cohort)[a]	1 [Reference]	1.94 (1.07-3.50)[b]	2.11 (1.20-3.99)[b]	3.67 (1.51-8.93)[c]
Presenting with AJCC stage III or IV (for those ≥45 years old only, n = 256)[a]	1 [Reference]	1.32 (0.70-2.52)	1.57 (0.78-3.18)	3.66 (1.24-10.24)[b]
Presenting with AJCC stage III or IV (excluding tall cell variant, n = 429)[a]	1 [Reference]	1.81 (0.997-3.29)	1.70 (0.87-3.31)	2.90 (1.13-7.43)[b]
Presenting with AJCC stage III or IV (excluding microcarcinomas, n = 361)[a]	1 [Reference]	2.02 (1.09-3.75)[b]	2.24 (1.14-4.41)[b]	5.22 (1.90-14.39)[b]
Presenting with AJCC stage III or IV (for men only, n = 120)[a]	1 [Reference]	2.89 (0.86-9.65)	3.40 (0.94-12.2)	6.35 (0.94-44.1)
Presenting with AJCC stage III or IV (for women only, n = 323)[a]	1 [Reference]	1.45 (0.70-3.00)	1.59 (0.74-3.46)	3.09 (1.11-8.57)[b]

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Logistic regression.
[b] $P < .05$.
[c] $P < .01$.

patients had lymph node involvement than in the older cohort (19.8% vs 9.7%, $P = .003$). However, in the younger cohort, no significant association was found between BMI and lymph node status or T3/T4 status.

When analyzing only women, the morbidly obese group remained significantly associated with later-stage disease (OR, 3.09; 95% CI, 1.11-8.57). A similar trend was also seen in men (morbidly obese: OR, 6.5; $P = .06$); however, the group was underpowered to detect a difference (n = 120).

COMMENT

Our study shows that those patients with increasing BMI have a progressively increasing risk in presenting with late-stage PTC (Table 5). This finding is especially seen in the obese and morbidly obese populations.

It has been shown that thyroid cancer has an increased incidence in the obese population.[8,9,16] Our study is novel in that it assesses the risk of presenting with both aggressive and disseminated disease. In addition, this study was performed in a multiethnic population with a large sample size. Paes et al[17] performed a study in a predominately white population to assess the relationship between obesity and thyroid cancer pathologic subtype and stage. Their study was unable to show any significant trends or associations. However, this study, we believe, was most likely underpowered (n = 250).

We believe that the cause of this increase in aggressive PTC behavior in the overweight and obese population could be multifactorial. It may be explained by both delayed detection and a possible biological or physiologic cause, as has been postulated in other cancers. As noted in the introduction, increased BMI has been linked to a more severe presentation and a higher risk of death from other types of cancers. Presentation of more advanced stages of breast cancer has been partially explained by obesity differences among the groups, as well as other factors.[11] Higher-grade prostate cancer and a higher risk of recurrence in these patients after treatment have also been associated with obesity.[12] It has also been shown that excess body weight is associated with a higher mortality risk from all cancers combined.[13]

To investigate the possible biological causes of more aggressive PTC tumor types in the obese population, we measured the prevalence of PTC tumors with more aggressive tall cell variant within the 4 groups. We found that the obese and morbidly obese groups presented with a higher prevalence of PTC tall cell variant (Table 3), suggesting that these groups have a higher risk of more aggressive tumor types. This association was seen regardless of age. Other studies[8,17]

have suggested there was no difference in histologic PTC subtype associated with obesity. However, one of these studies[8] did not assess specifically the tall cell variant. The other study[17] was also likely underpowered to detect a difference. In addition, we showed that obese patients were more likely to present with preoperative vocal cord paralysis due to locally advanced disease. One limitation to this finding, however, is that our surgeons do not routinely perform preoperative and/or postoperative laryngoscopy. Thus, the denominator for the number of postoperative vocal cord paralyses is not truly known.

Other groups have also noted an increase in certain obesity biomarkers that are linked with cancer. For example, leptin, an adipocyte-derived cytokine, has been shown to be involved in cancer development and progression.[16] Hedayati et al[18] recently found that there are higher leptin levels in patients with PTC compared with healthy individuals. Cheng et al[16] also demonstrated that PTCs expressing leptin receptors and/or leptin have a higher incidence of lymph node metastasis.

Another plausible biological link between obesity and thyroid cancer may be through diabetes. It is well known that obesity is linked to diabetes. Recently, a study[19] of 500 000 patients from the National Institute of Health–AARP Diet and Heath study showed an increased risk of PTC in women with diabetes (hazard ratio of 1.25). Because medical comorbidities, especially the prevalence of diabetes, were undercoded in our cohort, we could not assess this relationship.

Exclusion of microcarcinomas from our analysis led to an accentuated association between advanced stage and obesity. This association is likely attributable to the omission of a subset of patients with stage I disease who were overrepresented among the obese patients. Excluding tall cell variants from our analysis revealed a persistent increased risk in the morbidly obese category but eliminated the risk in the other categories. This finding suggests that factors other than cancer subtype may also explain the link between obesity and presenting with later-stage thyroid cancer.

One factor to consider in this population, other than a potential physiologic link between obesity and disease aggressiveness, is a delay in diagnosis, which may arise from difficulty in detecting thyroid nodules when examining the obese neck. To investigate this in the obese population, we measured the primary tumor size among the groups (Table 3). Although there was a trend toward greater tumor size with increasing BMI, the variance was too great and no statistical difference was observed.

Studies[8,10] have shown an increase in the incidence of thyroid cancer in obese women. Our study also showed that morbidly obese women have a significantly higher presentation of late-stage disease compared with normal-weight individuals. This finding was not corroborated in men, although this group was likely underpowered to detect a difference (n = 120).

The rarity of adverse events after total thyroidectomy for cancer limited our ability to assess the full range of potential complications with adequate statistical power. However, we found a significant increase in preoperative recurrent laryngeal nerve dysfunction associated with obesity. This finding was mostly due to more locally aggressive and invasive disease. A recent National Surgical Quality Improvement study[20] of 26 000 patients undergoing thyroidectomy also suggested an increase in morbidity due to obesity.

We found that increasing BMI was a significant predictor of increased length of stay and anesthesia induction times. This finding suggests that obese patients consume additional hospital resources during thyroid cancer treatment.

Given our findings, we believe that obese patients are at a higher risk of developing aggressive thyroid cancers and thus should be screened for thyroid cancer by sonography, which has been shown to be more sensitive in detecting thyroid cancer than physical examination alone.[21] Patients more likely to benefit from screening are those who are overweight, obese, or morbidly obese and those older than 45 years, who, by AJCC stage definition, have a higher risk of stage III or IV disease. Our recommendation mirrors a similar proposal for breast cancer screening, where studies[22] have suggested that a more vigilant mammogram screening regimen should be instituted for obese patients.

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REFERENCES

1. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. *Int J Obes (Lond).* 2005;29(3):334-339.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA.* 2006;295(18):2164-2167.
3. Yu GP, Li JC, Branovan D, McCormick S, Schantz SP. Thyroid cancer incidence and survival in the National Cancer Institute surveillance, epidemiology, and end results race/ethnicity groups. *Thyroid.* 2010;20(5):465-473.
4. Wartofsky L. Increasing world incidence of thyroid cancer: increased detection or higher radiation exposure? *Hormones (Athens).* 2010;9(2):103-108.
5. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol.* 2005;23(21):4742-4754.
6. Engeland A, Tretli S, Akslen LA, Bjørge T. Body size and thyroid cancer in two million Norwegian men and women. *Br J Cancer.* 2006;95(3):366-370.
7. Brindel P, Doyon F, Rachédi F, et al. Anthropometric factors in differentiated thy-

roid cancer in French Polynesia: a case-control study. *Cancer Causes Control*. 2009;20(5):581-590.
8. Kitahara CM, Platz EA, Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev*. 2011;20(3):464-472.
9. Meinhold CL, Ron E, Schonfeld SJ, et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol*. 2010;171(2):242-252.
10. Ron E, Kleinerman RA, Boice JD Jr, LiVolsi VA, Flannery JT, Fraumeni JF Jr. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst*. 1987;79(1):1-12.
11. Hahn KM, Bondy ML, Selvan M, et al. Factors associated with advanced disease stage at diagnosis in a population-based study of patients with newly diagnosed breast cancer. *Am J Epidemiol*. 2007;166(9):1035-1044.
12. Amling CL, Riffenburgh RH, Sun L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol*. 2004;22(3):439-445.
13. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638.
14. Stavrakis AI, Ituarte PH, Ko CY, Yeh MW. Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. *Surgery*. 2007;142(6):887-899.
15. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149-1160.
16. Cheng SP, Yin PH, Hsu YC, et al. Leptin enhances migration of human papillary thyroid cancer cells through the PI3K/AKT and MEK/ERK signaling pathways. *Oncol Rep*. 2011;26(5):1265-1271.
17. Paes JE, Hua K, Nagy R, Kloos RT, Jarjoura D, Ringel MD. The relationship between body mass index and thyroid cancer pathology features and outcomes: a clinicopathological cohort study. *J Clin Endocrinol Metab*. 2010;95(9):4244-4250.
18. Hedayati M, Yaghmaei P, Pooyamanesh Z, Zarif Yeganeh M, Hoghooghi Rad L. Leptin: a correlated peptide to papillary thyroid carcinoma? *J Thyroid Res*. 2011;2011:832163. doi: 10.4061/2011/832163.
19. Aschebrook-Kilfoy B, Sabra MM, Brenner A, et al. Diabetes and thyroid cancer risk in the National Institutes of Health–AARP Diet and Health Study. *Thyroid*. 2011;21(9):957-963.
20. Buerba R, Roman SA, Sosa JA. Thyroidectomy and parathyroidectomy in patients with high body mass index are safe overall: analysis of 26,864 patients. *Surgery*. 2011;150(5):950-958.
21. Marqusee E, Benson CB, Frates MC, et al. Usefulness of ultrasonography in the management of nodular thyroid disease. *Ann Intern Med*. 2000;133(9):696-700.
22. Schur EA, Elmore JG, Tracy O, Wernli KJ, Sickles E, Haneuse S. The impact of obesity on follow-up after an abnormal screening mammogram. *Cancer Epidemiol Biomarkers Prev*. 2012;21(2):327-336.

INVITED CRITIQUE

ONLINE FIRST

Thyroid Cancer Operations for Obese Patients

The Bad News and the Good News

Harari and colleagues[1] from UCLA (University of California, Los Angeles) showed us one more reason to be concerned about the current obesity epidemic—obese patients have more advanced thyroid cancer. The incidence of thyroid cancer has increased in the United States during the past several decades. The reason for this increase is partially earlier diagnosis and partially some as-yet-unidentified environmental risks (radiation perhaps?). This parallel increase in the rates of obesity and thyroid cancer is intriguing, but without a much larger population study, we cannot determine whether obesity causes thyroid cancer. However, the authors found that higher body mass index is associated with a later stage of thyroid cancer.

Why would obesity be associated with more advanced stage of cancer? One obvious answer would be an overall delay in the diagnosis of thyroid cancer because of obesity, which can cause a more difficult physical examination and/or less appropriate medical care. This delay would then select the more advanced cancer to present in the more obese patients. The concern of delay in diagnosis is what leads the authors to conclude with a recommendation to routinely screen obese patients for thyroid cancer. However, this hypothesis of delay in the diagnosis in obese patients is contradicted by the findings of a higher proportion of obese patients having micropapillary cancer (20%-30% instead of 5% having tumors smaller than 1 cm). Thus, delay in diagnosis is likely not the answer, or at least not the only answer.

An alternative explanation is that the biology of obesity somehow increases the risk and severity of cancer, such as in patients with breast cancer. There is recent literature implicating the role of leptin and insulinlike growth factor in the obesity-cancer relationship.[2] One may speculate that the risk of higher-stage thyroid cancer in obese patients is related to an increase in insulin or insulinlike growth factor in obesity.

Obese patients also pose technical and clinical challenges to the surgeons. Some findings in this study are not surprising, including the longer anesthesia and operation time needed for obese patients. What is somewhat surprising is the lack of increase in surgical complications in obese patients. The higher rate of recurrent laryngeal nerve palsy (12%) in obese patients is explained by the invasion of recurrent laryngeal nerve by advanced cancer before the operation. There is no increase in the obese patients for other complications, such as deep venous thrombosis, pneumonia, respiratory distress, and urinary tract infection, as one would have expected. The overall low complication rates of thyroidectomy may have prevented the detection of a small difference (a type II error). It is also possible that the use of *International Classification of Diseases, Ninth Revision* codes to define complications instead of full medical record