The Impact of Socioeconomic Status on the Use of Adjuvant Radioactive Iodine for Papillary Thyroid Cancer

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Introduction: The effect of socioeconomic status (SES) on thyroid cancer treatment has not been studied extensively. The purpose of this study is to determine the impact of SES on the use of adjuvant radioactive iodine (RAI) after total thyroidectomy for papillary thyroid cancer (PTC). We hypothesize that patients of low SES are less likely to receive RAI after total thyroidectomy.

Methods: Case characteristics of 9011 patients with PTC ≥ 1 cm in size and undergoing total thyroidectomy were extrapolated from the Surveillance, Epidemiology and End Results database. Chi-square test and multivariate analyses were performed to compare demographics, clinicopathologic features, and use of RAI by county-level measures of SES.

Results: Low-SES patients were more likely to present with positive lymph nodes in the <45 -year age group and with advanced American Joint Committee on Cancer stage, positive lymph nodes, multifocal tumors, extra-thyroidal extension, and larger tumors in the ≥ 45 -year age group. Among patients <45 years of age, those from counties with a higher median household income and a higher SES composite score had significantly higher rates of RAI use (odds ratio [OR] 1.36 [95% confidence interval (CI) 1.09–1.70], $p=0.006$, and OR 1.29 [CI 1.11–1.49], $p<0.001$, respectively). Among patients ≥ 45 years of age, those residing in counties with higher education levels were associated with higher rates of RAI use (OR 1.27 [CI 1.05–1.54], $p=0.015$), while the association between SES composite score and RAI use approached statistical significance (OR 1.13 [CI 1.00–1.28], $p=0.053$).

Conclusions: This study demonstrates that low SES is associated with more advanced PTC at presentation and a lower rate of adjuvant RAI after total thyroidectomy, particularly among patients <45 years of age from areas with a low median household income. Future studies are needed to address these disparities, as well as to determine appropriate indications for the use of adjuvant RAI for PTC.

Introduction

SOCIOECONOMIC STATUS (SES) has been shown to be strongly associated with access to health care. It has been demonstrated that people with low SES have less access to preventative health services, primary care physicians, health screening, and treatment (1). For patients of low SES with cancer, this often translates into more advanced tumors at presentation and worse oncologic outcomes. This has been demonstrated in a variety of cancer sites, including lung, breast, and colon (1–3).

SES has also been shown to play an important role in thyroid cancer incidence, presentation, and outcomes. Previous studies have noted that areas with less access to health care (4) and lower SES (5) have a lower incidence of thyroid cancer, likely as a result of less surveillance in these communities. Low SES has also been associated with more ad-

vanced thyroid cancer stage at presentation (6,7). While the impact of SES on thyroid cancer incidence and stage at presentation has been reported, the effect of SES on thyroid cancer treatment has not been clearly elucidated.

Radioactive iodine (RAI) is widely used as adjuvant therapy after total thyroidectomy for well-differentiated thyroid cancer (8). While guidelines advocate the use of RAI for advanced or high-risk thyroid cancer (9), the use of RAI is controversial and significant variation in treatment patterns exists. The use of RAI varies by several factors unrelated to thyroid cancer stage or severity, including race/ethnicity, hospital type and case volume, and hospital region (10). The purpose of this study is to determine the impact of SES on the use of RAI for papillary thyroid cancer (PTC). We hypothesize that low SES is associated with lower rates of RAI use after total thyroidectomy for patients with PTC.

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Methods

Data sources and patient selection

The study design was a retrospective cohort analysis utilizing the Surveillance, Epidemiology, and End Results (SEER) database, a registry maintained and updated annually by the National Cancer Institute. Specifically, we employed the dataset named “Incidence – SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973–2009 varying).” This particular database contains incidence research records for 18 geographic areas that collectively span approximately 28% of the U.S. population. Since SEER is a public database without patient identifiers, this study was granted an exemption from the Baylor College of Medicine Institutional Review Board.

Eligible patients were identified using the *International Classification of Diseases for Oncology* (3rd edition), histology codes encompassing the clinically relevant subtypes of PTC. Thyroid cancer codes included were those for papillary carcinoma (8050) and papillary adenocarcinoma (8340–8344). Then, we further selected for cases with adequate data regarding staging, primary surgery, nodal management, and use of RAI. As the most recent American Joint Committee on Cancer (AJCC) (11) staging groups were gathered for patients after the year 2004, our study examines patients from 2004 to 2009. American Thyroid Association guidelines only recommend further evaluation of thyroid nodules above a threshold of 1 cm (9). Therefore, patients with tumors less than 1 cm in size were excluded from the study. As this study examined the use of adjuvant RAI, only patients undergoing total thyroidectomy were included in this study.

Our definitive case listing extrapolated from SEER included demographic variables such as patient age, sex, month and year of diagnosis, marital status at presentation, and race/ethnicity (non-Hispanic White, African American, Hispanic, and Asian). Clinicopathologic characteristics of the tumors included AJCC stage, tumor size in millimeters, tumor extension, histologic classification, number of examined and subsequently positive lymph nodes, and designation of lesions as solitary versus multifocal.

County-level data on SES were collected using SEER*Stat software as previously described by Li *et al.* (5). In brief, three county SES indicators (cost-of-living–adjusted median household income, proportion of residents with at least a high school education, and percentage of population with health insurance) were coded in quartiles and given equal weight to produce a composite SES score. For the analysis, these socioeconomic variables were categorized as either lowest quartile (“low”) or top three quartiles (“high”), as has been previously reported in other studies examining the effects of SES on cancer (5,12). The SES composite score was similarly divided into lowest quartile (“low SES”) or top three quartiles (“high SES”). SES composite scores such as the one used in this study have been used in other previously published studies using cancer registry databases to identify SES disparities in cancer (2,5,13,14).

Data analysis

The chi-square or Wilcoxon rank sum test was performed for comparisons of demographic and clinical characteristics between groups as classified by SES. Univariate logistic re-

gression was used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for each possible socioeconomic predictor for RAI treatment. To identify independent predictors for RAI treatment, multivariate analysis using a stepwise logistic regression model was used, with forward selection and backward elimination threshold at 0.3 and 0.1 alpha level, respectively. All statistical tests were two-sided, and $p < 0.05$ was taken as the level of statistical significance. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

A total of 11,198 patients with PTC diagnosed between the years 2004 and 2009 were identified from the SEER database. Among them, 9011 patients fit the inclusion criteria for this study. Table 1 shows the demographic, tumor, and treatment characteristics of patients included in this study by SES composite score. In the <45-year age group, there was no significant difference in sex, tumor size, tumor extension, solitary versus multifocality, regional nodes examined, and AJCC stage between the low- and high-SES groups. A statistically significant difference was noted in the racial/ethnic makeup of low- and high-SES patients, with a higher percentage of black and Hispanic patients in the low-SES group. Low-SES patients were also more likely to present with positive lymph nodes and to have >4 lymph nodes resected. In the ≥ 45 age group, low-SES patients were significantly more likely to present with advanced AJCC stage, positive lymph nodes, multifocal tumors, extrathyroidal extension, and larger tumors.

Univariate analysis of RAI use by socioeconomic variable can be found in Table 2. Patients <45 years of age residing in counties with a higher median household income and higher percent high school education had higher rates of RAI use, while no statistically significant association was found between RAI use and percent insured. RAI use was also significantly higher among patients in counties with a higher SES composite score. In the ≥ 45 group, patients from counties with a higher median household income and a higher county-level graduation rate had higher rates of RAI use. No significant association was noted between RAI use and insurance status or SES composite score.

Results of the multivariate analysis of RAI use by county-level median household income, percent high school education, and percent insured can be found in Table 3. Among patients <45 years of age, those from counties with a higher median household income had significantly higher rates of RAI use (OR 1.36 [CI 1.09–1.70], $p = 0.006$), while no significant association was noted between RAI use and percent insured or percent high school education. Among patients ≥ 45 , those residing in counties with a higher education level were associated with higher rates of RAI use (OR 1.27 [CI 1.05–1.54], $p = 0.015$), while county-level insured status was associated with a significantly lower rate of RAI use (OR 0.76 [CI 0.65–0.90], $p = 0.002$). No statistically significant association was noted between median household income and rate of RAI use.

Multivariate analysis of RAI use by SES composite score is found in Table 4. A higher SES score was associated with higher rates of RAI use in patients <45 years of age (OR 1.29 [CI 1.11–1.49], $p < 0.001$), while the association between

TABLE 1. DEMOGRAPHIC, PATHOLOGICAL, AND TREATMENT CHARACTERISTICS OF PATIENTS WITH PAPILLARY THYROID CANCER BY SOCIOECONOMIC STATUS AND AGE (SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS, 2004–2009)

Pathologic features	<45 years					≥45 years				
	Low SES		High SES		p	Low SES		High SES		p
	n	%	n	%		n	%	n	%	
Sex										
Male	217	19.5	491	18.2	0.354	441	28.5	1029	28.1	0.809
Female	894	80.5	2200	81.8		1109	71.5	2630	71.9	
Race/ethnicity										
White	583	52.5	1876	70.0	<0.001	941	60.8	2853	78.3	<0.001
Hispanic	363	32.7	360	13.4		332	21.5	285	7.8	
Black	78	7.0	193	7.2		128	8.9	229	6.3	
Asian	86	7.8	252	9.4		137	8.8	278	7.6	
Tumor size, mm										
Median (IQR)	23 (15–35)		22 (15–33)		0.290	23 (15–35)		21 (15–32)		0.002
11–20 mm	491	44.8	1225	46.1	0.635	682	44.7	1753	48.7	0.019
21–40 mm	438	39.9	1054	39.6		591	38.7	1321	36.7	
>40 mm	168	15.3	379	14.3		254	16.6	524	16.6	
Tumor										
Intrathyroidal	906	81.6	2220	82.6	0.477	1174	75.7	2869	78.4	0.035
Extrathyroidal	204	18.4	468	17.4		376	24.3	790	21.6	
Solitary vs. multifocal										
Solitary	575	52.7	1423	53.6	0.600	719	47.9	1845	51.7	0.013
Multifocal	517	47.3	1232	46.4		783	52.1	1723	48.3	
Regional node examined										
0–1	624	57.6	1592	60.6	0.091	1053	69.2	2524	70.1	0.521
>1	460	42.4	1037	39.4		468	30.8	1075	29.9	
Regional node positive										
0–1	386	65.0	1046	70.4	0.015	506	74.2	1283	78.7	0.018
>1	208	35.0	439	29.6		176	25.8	347	21.3	
AJCC staging										
I	1094	98.6	2666	99.1	0.162	506	32.6	1346	36.8	<0.001
II	15	1.4	23	0.9		390	25.2	942	25.7	
III						420	27.1	960	26.2	
IV						234	15.1	411	11.2	
Lymph node dissection										
>4 LNs removed	314	28.8	648	24.4	0.005	279	18.3	627	17.3	0.390
Others	776	71.2	2005	75.6		1246	81.7	2998	82.7	

AJCC, American Joint Committee on Cancer; IQR, interquartile range; LNs, lymph nodes; SES, socioeconomic status.

TABLE 2. UNIVARIATE ANALYSIS OF RADIOACTIVE IODINE USE IN PATIENTS WITH PAPILLARY THYROID CANCER IN ASSOCIATION WITH SOCIOECONOMIC STATUS

Socioeconomic status	<45 years					≥45 years				
	None		RAI		p	None		RAI		p
	n	%	n	%		n	%	n	%	
Median income										
Low	296	41.4	423	58.9	<0.001	427	40.7	623	59.3	0.020
High	1035	34.0	2001	66.0		1506	36.8	2589	63.2	
With insurance										
Low	426	36.7	732	63.3	0.251	573	36.5	998	63.5	0.282
High	905	34.8	1692	65.2		1360	38.1	2214	61.9	
HS education										
Low	430	38.8	678	61.2	0.005	611	39.6	931	60.4	0.047
High	901	34.0	1746	66.0		1322	36.7	2281	63.3	
SES										
Low	434	39.5	666	60.5	<0.001	600	39.3	927	60.7	0.098
High	897	33.7	1758	66.3		1333	36.8	2285	63.2	

HS, high school; RAI, radioactive iodine.

TABLE 3. MULTIVARIATE ANALYSIS OF RADIOACTIVE IODINE USE IN PATIENTS WITH PAPILLARY THYROID CANCER (MEDIAN INCOME, PERCENT WITH INSURANCE, PERCENT WITH HIGH SCHOOL EDUCATION)

Predictor	Use of RAI			
	<45 years OR [95% CI]	p	≥45 years OR [95% CI]	p
Median income				
Low				
High	1.36 [1.09–1.70]	0.006	1.16 [0.97–1.40]	0.104
With insurance				
Low				
High	0.89 [0.73–1.09]	0.272	0.76 [0.65–0.90]	0.002
HS education				
Low				
High	1.12 [0.88–1.40]	0.347	1.27 [1.05–1.54]	0.015
Solitary vs. multifocal				
Solitary				
Multifocal	1.27 [1.10–1.45]	<0.001		
Tumor				
Intrathyroidal				
Extrathyroidal	1.46 [1.21–1.77]	<0.001		
AJCC stage				
I				
II			1.27 [1.10–1.47]	0.001
III			1.45 [1.25–1.68]	<0.001
IV			1.44 [1.20–1.75]	<0.001

A stepwise procedure was used to select independent predictor for RAI treatment in the multivariate logistic regression model (entry threshold of 0.3 and stay threshold of 0.1). The median income, with insurance, and HS education variables were forced into the model. CI, confidence interval; OR, odds ratio.

SES score and RAI use in patients ≥45 years of age approached statistical significance (OR 1.13 [CI 1.00–1.28], $p=0.053$).

A total of 1168 patients were noted to have positive lymph nodes at the time of diagnosis, including 645 (17%) in the <45-year age group and 523 (10%) in the ≥45-year age group. On univariate analysis of RAI use by SES among patients with positive lymph nodes, no significant difference was noted between low- and high-income, insurance status,

or percent high school education groups in either the <45 or ≥45 age groups.

Discussion

This study demonstrates population-level SES disparities in the presentation and treatment of PTC. Patients <45 years of age in the low-SES group were more likely to present with lymph node involvement. No significant difference was

TABLE 4. MULTIVARIATE ANALYSIS OF RADIOACTIVE IODINE USE IN PATIENTS WITH PAPILLARY THYROID CANCER (SOCIOECONOMIC STATUS COMPOSITE SCORE)

Predictor	Use of RAI			
	<45 years OR [95% CI]	p	≥45 years OR [95% CI]	p
SES				
Low				
High	1.29 [1.11–1.49]	<0.001	1.13 [1.00–1.28]	0.053
Solitary vs. multifocal				
Solitary				
Multifocal	1.26 [1.10–1.45]	<0.001		
Tumor				
Intrathyroidal				
Extrathyroidal	1.47 [1.22–1.78]	<0.001		
AJCC stage				
I				
II			1.27 [1.10–1.47]	0.001
III			1.45 [1.25–1.68]	<0.001
IV			1.45 [1.20–1.75]	<0.001

noted in AJCC stage in this age group, reflecting that both groups had similar rates of distant metastases at presentation. Among those ≥ 45 years of age, low-SES patients were more likely to present with advanced AJCC stage, positive lymph nodes, multifocal tumors, extrathyroidal extension, and larger tumors compared with high-SES patients. These findings are in line with a previous report by Lim *et al.*, where thyroid cancer patients presenting to a county hospital had significantly more advanced stage at presentation compared with those presenting to a private hospital (6). Similar findings have been previously reported for a variety of other cancer sites, underscoring the presence of SES disparities in cancer surveillance, screening, and access to care.

This study demonstrates that SES has a significant impact on the use of adjuvant RAI for patients with PTC. Median household income appears to be the strongest determinant of the disparities noted in this study. Patients in the <45 -year and ≥ 45 -year age groups residing in counties with a higher median household income were significantly more likely to receive RAI on univariate analysis. After adjusting for demographic-, patient-, and tumor-related factors in a multivariate model, high median household income was associated with high RAI use in the <45 age group alone. A similar trend was noted when median household income, high school graduation rate, and insurance status were combined into an SES composite score. We found that high-SES patients <45 years of age had a 29% higher likelihood of receiving RAI than low-SES patients. While a similar association was noted between SES score and RAI in the ≥ 45 group, this finding did not reach statistical significance.

The finding that younger patients are more susceptible to SES disparities in use of RAI warrants further investigation. It has been demonstrated that young adult patients have less adherence to medical treatment for several chronic diseases, including cancer (15,16). Furthermore, young adults are almost twice as likely to lack health insurance compared with older adults, and the number of uninsured adults across all ages has increased over the last 10 years (17,18). A lack of health insurance reflects less access to care, and the financial burden of expensive medical care can limit a patient's adherence to treatment. In younger patients of low SES, this may be further exacerbated by lack of support networks and limited financial resources.

While the indications for adjuvant RAI remain controversial, its use has increased sharply over the last two decades (10). The American Thyroid Association guidelines recommend the use of RAI after total thyroidectomy in all T3 or greater primary tumors, and selective use in patients with intrathyroidal tumor >1 cm in size, or evidence of nodal metastases (9). However, it has been demonstrated that RAI use is influenced by several factors unrelated to disease severity (10,19). In a recent study using the National Cancer Database, Haymart *et al.* demonstrated that adjuvant RAI is more commonly used in high-volume hospitals and less commonly among African Americans, females, and patients without private insurance (10). They found that patient and tumor characteristics accounted for only 21% of variation in RAI use and that hospital characteristics accounted for 29% of variation in use. Differences in RAI use by geographic region of the United States (20), as well as a higher use of RAI by physicians with access to a tumor board (21), have also been demonstrated.

The present study identifies SES as an additional factor influencing the use of adjuvant RAI for PTC. The differences in RAI use noted in this study may reflect the difficulty that low-SES patients have in navigating multidisciplinary cancer care in general. Patients in low-SES communities often have limited financial resources and lack of support, preventing them from completing their recommended treatment course or follow-up care (16). This was demonstrated recently in patients with breast cancer, where rates of adherence to adjuvant tamoxifen were found to be significantly lower in patients of low SES (22).

It is important to note that the findings from this study do not necessarily suggest that low-SES patients with PTC are being undertreated. Given the lack of consensus on the use of RAI and significant treatment variation, it is also possible to interpret these findings as evidence of overtreatment among higher SES groups. A recent study by Nixon *et al.* demonstrated that early-stage and advanced-stage PTC patients not treated with RAI had a 5-year recurrence-free survival of $>97\%$ and $>90\%$, respectively (23). Another series of 1298 patients with differentiated thyroid cancer by Schwartz *et al.* showed no survival benefit of adjuvant RAI for low-risk thyroid cancer (24). These findings suggest that more aggressive treatment among patients in the high-SES groups may not be warranted, particularly when the risk of long-term complications (25) and second primary tumors (26,27) is not insignificant. Further research is needed to better define the indications for adjuvant RAI in the treatment of PTC.

This study has several limitations. Individual-level SES data are not collected in the SEER database, and the use of county-level socioeconomic determinants presents the possibility of ecological bias. However, several previous studies have demonstrated that regional measures of SES such as median household income correlate well with individual measures (11,28–30). Another limitation is the use of U.S. census data from 2000 to determine measures of SES. It is possible that county-level SES may have changed in the time leading up to or during the study period.

In conclusion, this study demonstrates that low SES is associated with more advanced PTC at presentation and a lower rate of adjuvant RAI after total thyroidectomy. Young patients from areas with a low median household income experience the lowest rates of adjuvant RAI use. Future studies are needed to address disparities in the presentation and treatment of PTC, to determine indications for the use of adjuvant RAI, and to ensure appropriate, evidence-based care across the socioeconomic spectrum.

Author Disclosure Statement

No competing financial interests exist.

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