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Thyroid carcinoma: correlation of the extent of disease at presentation and risk of death and recurrence with race/ethnicity and income differences

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THYROID CARCINOMA: CORRELATION OF THE EXTENT OF DISEASE AT PRESENTATION AND RISK OF DEATH AND RECURRENCE WITH RACE/ETHNICITY AND INCOME DIFFERENCES

by

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ABSTRACT

Background: Many research publications indicate that racial minorities and people in lower socioeconomic status are negatively affected by a higher morbidity and mortality rate in many diseases, including many cancers such as thyroid cancer. Although these disparities may be attributed to multiple factors, it is unclear whether a biological predisposition and/or the differences in levels of health care education, intervention and resources result in people of low-income levels and minorities presenting with higher risk and advanced stage of cancer. This commonly results in poorer prognoses, response to therapy, and outcomes. Even though thyroid cancer has had a progressive annual increase in incidence rates in the last thirty years across all demographic categories, the overall survival rate remains excellent. However, previous publications suggest that minorities and those in lower socioeconomic classes may present with higher-risk thyroid cancer cases. The goal of this research is to determine if socioeconomic status (SES) and race/ethnicity (R/E) influence the stage of the cancer and predict the risk of recurrence from thyroid cancer. To investigate, we performed an examination of our comprehensive THYROid CAncer REgistry (ThyroCARE) at Boston Medical Center, an urban tertiary care hospital with a diverse population, many of whom are from minority and international backgrounds, for the effect of SES and R/E on the initial staging and response to treatment.

Methods: A thyroid cancer registry was designed with the intent to capture both retrospective and prospective individual patient data at BMC. ThyroCARE resides in a browser-based Research Electronic Data Capture (REDCAP) program and contains 1,208 discrete data points related to initial and ongoing patient management. Patients were consented either in person or after receiving research documents through mail. Data is captured via individual record review and recorded in REDCAP. Analyses were performed with SPSS software. A total of 1305 BMC patients who have had treatment for thyroid cancer were consented and enrolled into the IRB approved *BMC Thyroid Cancer Registry* starting in 2010 with enrollment currently ongoing. Demographic, social history, and medical information were retrieved from the patients via IRB-approved surveys and a review of EPIC medical charts. An estimate of each patient's median household income was determined by using their zip code and public data from the 2019 United States Census and American Community Survey that correlates income and zip codes. The information collected was then used to measure the initial and current risk of thyroid cancer, and the staging of the cancer across race/ethnicity and income level in the State of Massachusetts.

Results: Overall, there was no overall significant difference of thyroid cancer subtype with R/E but subset analysis show Black/African Americans have a lower prevalence of classic PTC and higher prevalence of follicular variant of PTC while Hispanics and Asians show the reverse with a higher proportion of classic PTC and lower proportion of FVPTC. When income level and R/E were compared, Black/African American and Hispanic/Latino patients had the greatest representation in the low-income bracket while Asian American and White/Caucasian patients had the greatest representation in the high-income bracket.

However, there was no statistical difference seen when initial ATA risk of tumor recurrence and AJCC staging classification for risk of mortality were distributed across R/E or income level. A difference was seen in current ATA risk that reflects response to therapy as Asian American and Hispanic/Latino patients had a greater representation in the intermediate risk of recurrence category. Furthermore, low-income level patients had the least representation in the current ATA low risk recurrence group.

Conclusion: In this safety net population of patients traditionally composed of patients who are non-Caucasians, have a low income and immigrant status, there was no statistical difference seen in the initial ATA risk and AJCC staging classification when distributed across levels of income or R/E. The initial presentation and extent of disease was not associated with R/E or income level. There is a difference in current ATA risk which reflects response to therapy. There was no significant difference in R/E in the ATA low or high current risk groups but, in contrast, the ATA intermediate risk demonstrated a higher prevalence of Asian and Latino/Hispanic patients. We hypothesize that this difference can be attributed to the higher percentage of Asian and Latino/Hispanic patients with classical papillary thyroid cancer, a tumor subtype with a higher potential for local invasion and lymph node metastases for these R/E groups. Future studies will examine if the difference in response to therapy is due to R/E or difference of tumor subtypes.

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LIST OF ABBREVIATIONS

ACS..... American Community Survey

AJCC.....American Joint Committee on Cancer

ATA .....American Thyroid Association

ATC..... Anaplastic thyroid carcinoma

BMC..... Boston Medical Center

DTC.....Differentiated thyroid carcinoma

FNA..... Fine needle aspiration

FTC .....Follicular thyroid carcinoma

FVPTC……...……Follicular variant of PTC

HHI ..... Household Income

I-131 .....Isotope iodine 131

LN .....Lymph node(s)

MTC.....Medullary thyroid carcinoma

PDTC ..... Poorly differentiated thyroid carcinoma

PTC .....Papillary thyroid carcinoma

R/E .....Race/Ethnicity

RAI..... Radioactive iodine

rhTSH.....Recombinant human thyroid stimulating hormone

SES.....Socioeconomic status

T3 ..... Triiodothyronine

T4 .....Thyroxine

Tg ..... Thyroglobulin

TgAb ..... Thyroglobulin antibody

TRH.....Thyrotropin releasing hormone

TSH ..... Thyroid stimulating hormone

Thyroid CA .....Thyroid cancer, carcinoma

US .....Ultrasound

WBS .....Whole body scan

WDTC.....Well-differentiated thyroid carcinoma

ZCTA .....Zip code tabulation area

INTRODUCTION

The Thyroid Gland and Pathophysiology of Thyroid Carcinomas

The thyroid is a butterfly-shaped endocrine gland located in the anterior neck, directly below the laryngeal prominence, and wraps around the trachea. With coordinated direction from the hypothalamus and pituitary gland, each respectively secreting thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH), the follicular cells of the thyroid gland release the hormones thyroxine (T4) and triiodothyronine (T3), with the bulk of T4 being converted to the more biologically active T3 peripherally via de-iodination. Thyroid hormones function to increase the metabolism of nearly all nucleated cells responsible for stimulation of increased heart rate, respiratory rate, heat production, and growth/development in the human body *(Armstrong et al, 2020)*. In addition to follicular cells, the thyroid also contains parafollicular cells, also known as C-cells. C-cells are of neuro-crest origin and migrate into the thyroid during fetal development. In the presence of elevated serum calcium levels, C-cells release the hormone calcitonin to counter the hypercalcemic effects of parathyroid hormones and maintain blood calcium levels at homeostasis *(Das et al, 2017)*.

Malignancy and tumor formation in the thyroid often begin when genetic material in the nucleus mutate or become damaged, causing uninhibited growth of thyroid cells. Based on the histological characteristics discovered during diagnostic workup, thyroid cancer (Thyroid CA) types are commonly categorized into three different groups. Cancers originating from follicular cells form differentiated thyroid carcinoma (DTC) which comprise of follicular thyroid carcinoma (FTC), Hurthle cell carcinoma, and papillary

thyroid carcinoma (PTC). The next group is anaplastic thyroid carcinoma (ATC), which differs from DTC in that the malignant cells of ATC are undifferentiated and have very little similarity to normal thyroid cells. Lastly, cancers derived from the parafollicular cells, or C-cells, are known as medullary thyroid carcinomas (MTC) *(Grimm et al, 2017)*. DTC is the most common form of thyroid malignancy, with PTC comprising nearly 85% of thyroid cancer cases followed by FTC and Hurthle cell carcinoma making up 10-15% of thyroid cancer cases. Most DTC cases present clinically as well-differentiated thyroid carcinomas (WDTC), which are commonly associated with an excellent prognosis and high survival rates. PTC is categorized as a classic type (80%) and follicular variant type (20%). However, it is important to note that WDTC can mutate to more aggressive variants of thyroid CA such as tall cell variant, sclerosing variant, insular, poorly differentiated thyroid carcinoma (PDTC) and ATC (Figure 1).

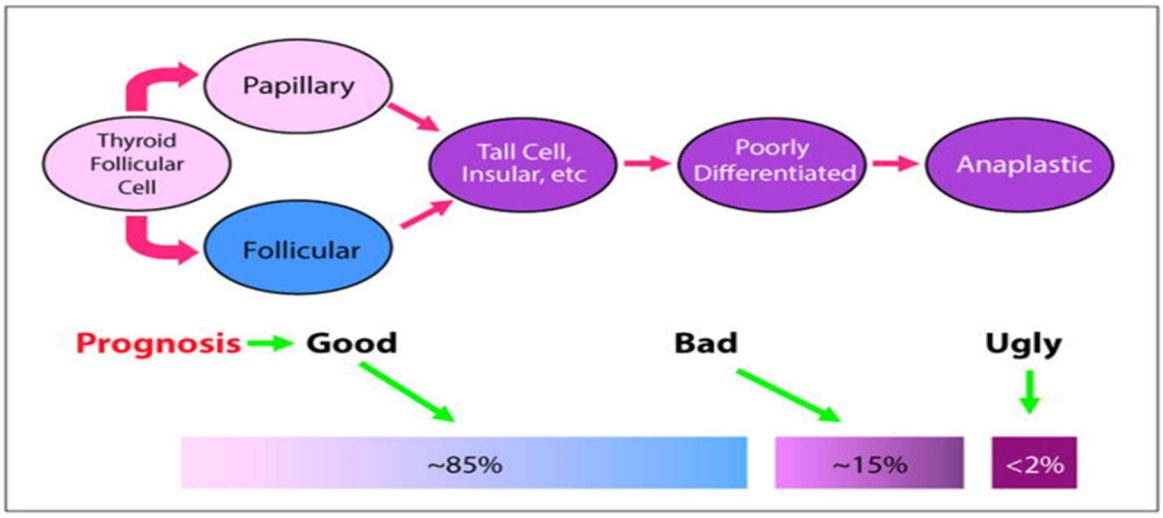

Figure 1. DTC Tumor Progression Model. Figure taken from *American Journal of Pathology* (2002). Thyroid CA originating from follicular cells can progress from well-differentiated form to more aggressive variants, poorly differentiated, and un-differentiated forms that carry a poorer prognosis.

Etiology

The inactivation of tumor suppressors and/or the transformation of normal proto-oncogenes to cancer forming oncogenes are common causes in various cancers. In thyroid CA, a mutation in the *BRAF* proto-oncogene (BRAFV600E) make up nearly 55% PTC, while the next most common mutation in the *RET* proto-oncogene makes up nearly 8% of PTC *(The Cancer Genome Atlas Network, 2014).* Although definitive etiologic factors for thyroid CA have not been established, it is universally agreed that childhood neck exposure to radiation is a common trigger for mutation of thyroid cells *(Schneider et al, 2005)*

BRAFV600E is the most common mutation found in PTC and known to be linked to tumors with more aggressive characteristics *(White et al, 2017)*. Research has suggested that BRAFV600E mutations are predictive of lymph node (LN) invasion, primarily in the lateral cervical LN. Furthermore, it is associated with invasion with extrathyroidal extension and high risk of local recurrence *(Virk et al, 2012)*. In contrast, a *RAS* gene mutation is commonly linked to the follicular variant of PTC (FVPTC) and FTC, making up about 30-45% of FVPTC cases. Unlike BRAFV600E mutations, *RAS* positive tumor lack the same aggressive characteristics and is associated with an excellent prognosis. In many *RAS* positive cases, less aggressive measures and even non-surgical long term monitoring are used to treat the cancer *(Xing, 2016)*.

Epidemiology and Prognosis

For the year 2020, cancer statistics published by the American Cancer Society reported a total of 52,890 new thyroid CA cases. Of which, 12,720 cases were diagnosed

in males and 40,170 cases were diagnosed in females. Thyroid CA is considered a rare malignancy, making up 1% of new cancer cases in males and 4% of new cancer cases in females. However, it is the fifth most common cancer in females as they are three times more likely to be diagnosed with the disease compared males. The cause of the disproportionate occurrence in females remains unknown. Thyroid CA is also more prevalent in younger age groups with The American Cancer Association reporting it to be the most common diagnosis for people between 15 to 29 years of age *(Siegel et al, 2020)*. In the last thirty years, there has been a dramatic increase of thyroid CA incidence rates across all age and race groups. This phenomenon may have been attributed to an increase in access and availability of medical care and intervention, as well as the introduction of more sensitive disease detection techniques to include microcarcinomas *(Weeks et al, 2018)*. However, the last few years saw a decrease of incidence rates in males and the stabilization of incidence rates in females, as the response to potential over-diagnosing has been to implement more conservative diagnostic practices *(Morris et al, 2016).*

Thyroid CA, overall, has been known to have a great prognosis, primarily with DTC having an excellent prognosis. PTC, the dominant thyroid CA type, has a 100% five-year survival rate when the cancer is localized in the thyroid, and an 83% five-year survival rate if there is metastasis. FTC and MTC share a five-year survival rate of nearly 100% when the cancer is localized, however, when there is metastasis the five-year survival rate falls to 63% and 40% respectively. ATC has the poorest prognosis and survival rate with a 31% five-year survival rate if localized to the thyroid but 4% in the presence of metastasis *(Cleveland Clinic, 2020)*. Although classical PTC is associated with an overall excellent

survival rate and prognosis, it should be noted that various pathological and background characteristics such as an older age at diagnosis, large tumor size, poorly differentiated histological features, and more aggressive variants such as tall cell and sclerosing variants can lead to a poorer prognosis *(Limaiem et al, 2021)*. Whether race/ethnicity (R/E) and lower socioeconomic status (SES) can lead to a poor prognosis remains a topic of controversy.

Clinical Evaluation and Diagnosing

Thyroid CA commonly presents as a palpable neck nodule during routine physical examination but can also be discovered incidentally through neck imaging for an unrelated medical issue. Although thyroid nodules increase in prevalence with advancing age with 50% of people older than 65 years will have a nodule, only about 5% of thyroid nodules are malignant. As the tumor grows, patients may begin to experience symptoms of neck pain, hoarseness, and difficulty swallowing. Initial tests for thyroid abnormalities are done via a thyroid function blood panel, measuring for abnormal levels of TSH, free T4 and T3 which occurs in an overactive or toxic adenoma that has a very low risk of cancer *(Lee et al, 2020)*.

Along with diagnostic blood tests, a diagnostic neck ultrasound (US) is recommended to be performed by the American and international thyroid nodule guidelines to visualize the thyroid gland and local lymph nodes, searching for the presence of other nodules or abnormal nodes, and to risk assess each nodule based on malignant characteristics. Suspicious thyroid nodules imaged via an US commonly show signs of

increased vascularity, small areas of calcium deposits, taller than wide morphology, irregular, or invasive margins and a dark or hypoechoic appearance *(Haugen et al, 2016).* When diagnostic imaging of a thyroid nodule demonstrates sonographic characteristics suspicious for malignancy and an absence of blood test showing hyperthyroidism, a biopsy of the thyroid nodule is done via fine needle aspiration (FNA). FNA is commonly performed with the guidance of an US probe. When the probe locates the neck nodule, a small needle will then be inserted into the nodule to remove small samples of nodular tissue. A cytology evaluation of the cells can then confirm if the nodule is positive and suspicious for thyroid CA.

Treatments and Disease Management

Surgery is the primary and considered the most effective option in the treatment and management of thyroid CA. A lobectomy is performed in WDTC measuring less than four centimeters in length (<4 cm) and if there is no evidence of an aggressive form of thyroid CA on cytology, no evidence of extrathyroidal extension of tumor, no abnormal neighboring LN and absence of nodules in the contralateral lobe. As an incomplete surgery is now considered insufficient treatment in higher risk thyroid CA, where the tumor is greater than four centimeters (>4cm) and extension of the cancer extends beyond the thyroid capsule or with metastatic nodes, the preferred form of thyroid surgery is a total thyroidectomy *(Nguyen et al, 2015)*. During a total thyroidectomy, the complete thyroid gland is surgically removed. Patients may also have an initial lobectomy and soon after, a completion surgery in which the contralateral lobe is removed. Due to the high probability

of multiple tumor distribution across the thyroid lobes, a total thyroid thyroidectomy is recommended to prevent malignancy in the residual functional tissue especially if additional nodules are found in the contralateral lobe *(Tuttle et al, 2018)*.

As LN metastasis is common in many cases of thyroid CA, surgeons can elect to perform a LN dissection during surgery. In higher risk cases of thyroid CA, during a total thyroidectomy the surgeon may perform dissection of the central neck compartment LN in Level VI even if the LN are not suspected to be cancerous. Although the dissection of non-cancerous central neck nodes remains a controversial medical topic, it is thought that due to the location of the central lymph nodes in the lower neck, they are prone to metastasis during recurrence of thyroid CA and are removed during total thyroidectomy for preventative purposes. This type of dissection is known as a prophylactic LN dissection *(Bonnet et al, 2009)*. If LN suspicious of malignancy are detected pre-operatively via neck palpation or diagnostic imaging such as a neck US, MRI, or PET/CT scan, then those nodes are deemed as clinically evident for metastatic disease and can be confirmed with a FNA biopsy. Clinically evident LN can also be discovered during surgery, or intra-operatively, in which case the surgeon comes across LN with metastatic appearances, such as enlarged node with blue or black discoloration. In the event clinically evident LN are observed before and during surgery, the surgeon will execute a therapeutic LN dissection. Therapeutic LN dissections are done in both the central neck compartment and in sections of the lateral neck, commonly in Levels II-IV *(Medscape: Neck Dissection Classification, 2020)*.

Due to the sensitive location of the thyroid gland in the neck, it is difficult to remove all thyroid tissue during surgery without risking injury to nearby structures, such as the parathyroid glands and the recurrent laryngeal nerves. For this reason, a post-operative treatment of radioactive iodine (RAI) will commonly be administered four to six weeks after a total thyroidectomy of high-risk thyroid CA as adjuvant therapy to destroy remnants of the normal thyroid gland left after surgery and to suppress the potential growth of secondary tumors *(Oncolink, 2020)*. In preparation for RAI administration, patients are put on an iodine restricted diet for one week, depleting the body of iodine and maximizing the uptake of RAI therapy once it is administered. Patients may also have two separate injections of thyrogen (rhTSH), a recombinant form of human TSH that will stimulate serum TSH and increase the amount of radioactive iodine uptake by the residual benign and malignant thyroid tissue. Once patients have completed an iodine withdrawal diet and rhTSH injections, a therapeutic dose of RAI in the form of isotope iodine-131 (I-131) is administered orally. When absorbed into the body, I-131 will travel to and will be taken up by the residual benign and malignant thyroid tissue where the radioactivity will ablate the residual tissue to prevent recurrence. One week after treatment, a post-therapy whole body scan (WBS) is performed to check for the uptake of I-131 and locate possible radioiodine tracer uptake in proximal LN and, most importantly, areas outside the neck for potential distant metastasis. Administration of RAI therapy is done only for patients of WDTC and sometimes PDTC but not ATC that has been shown to have very poor uptake of I-131 *(Nagaiah et al, 2011)*.

After surgery and RAI therapy, long-term observation is critical to detect thyroid CA recurrence. This is achieved through repeat neck US, diagnostic WBS, and measurement of thyroglobulin (Tg) levels. Tg is a glycoprotein produced by the thyroid gland, which is precursor molecule to produce thyroid hormones, T4 and T3, but Tg also acts as a tumor marker, measuring potential thyroid CA recurrence. Furthermore, many patients of DTC receive sufficient levothyroxine to cause a TSH suppression after surgery and RAI therapy. TSH suppression serves to prevent Tg production and the regrowth of thyroid tissue that may cause recurrence *(Eghtedari et al, 2020)*.

Thyroid Cancer – Clinicopathologic Staging and Risk Stratification

To best determine the route of treatment and disease management after a diagnosis of thyroid CA, physicians will routinely stage the cancer using medical information acquired during diagnostic workup and from post-surgery pathology reports. This can be medical information from pre-operative US and FNA as well as post-surgical pathology and procedure reports, such as RAI therapy.

To help determine the possibility of disease recurrence after treatment, The American Thyroid Association (ATA) developed a risk stratification method to assess initial risk after thyroidectomy and RAI therapy and updates risk over the long-term observation of patients' response to therapy (Figure 2). The risk measurement is scaled on low, intermediate, and high-risk rankings. This type of risk staging considers the size of the largest tumor, the number of LN and size of largest metastatic LN, whether the metastatic LN were discovered clinically or pathologically, the variant(s) of the thyroid

CA, and if extent of the cancer is intra-thyroidal or extra-thyroidal. For example, microcarcinomas (<1 cm) that are intra-thyroidal without metastatic nodes would be staged as low risk, and cancers of tall cell or sclerosing variant with microscopic invasion into surrounding fat tissue and adjacent skeletal muscle, or metastasis to lateral neck LN, would be staged as intermediate. It is important to note that cases of ATC, PDTC, metastatic LN greater than 3 centimeters, incomplete tumor resection, and distant invasion of disease will automatically be classified as having an initial ATA high risk *(American Thyroid Association Guidelines, 2020)*.

To determine the current ATA risk, patients are followed clinically over the course of at least one year where their TSH, Tg, and thyroglobulin antibodies (TgAb) are measured along with a neck US. This helps determine the patients' response to therapy and can be used to assess whether the ATA risk is stable/unchanged, downgraded for an excellent response, or upgraded due to evidence of disease recurrence. As the clinical course of thyroid CA can change over time, observing changes in patients' responses to therapy using thyroid laboratory tests, and neck US during each follow-up is highly recommended by the ATA. Results from these tests should be used along with the ATA risk stratification guidelines to continuously update patients' existing ATA risk. This is vital to aid physicians and patients in determining prevention measures or further treatment.

Category	ATA 2009 Cooper *et al.* (2009)	ATA 2015 Haugen *et al.* (2016)
ATA low risk	1. No local and distant metastases 2. All macroscopic tumor resected 3. No tumor invasion of locoregional tissues or structures 4. No aggressive histology or vascular invasion 5. If RAI given no RAI uptake outside thyroid bed on the first posttreatment WBS	PTC fulfilling all ATA 2009 criteria and additionally Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in the largest dimension Intrathyroidal, encapsulated follicular variant of PTC (NIFTP)* Intrathyroidal, well differentiated FTC with capsular invasion and/or minimal (<4 foci) vascular invasion Intrathyroidal papillary microcarcinoma, unifocal or multifocal, including BRAF V600E mutated (if known)
ATA intermediate risk	1. Microscopic invasion of the tumor into the perithyroidal soft tissues at initial surgery 2. Cervical lymph node metastases or RAI uptake outside thyroid bed on WBS done after remnant ablation 3. Tumor with aggressive histology (tall cell, insular, columnar cell variant)	ATA 2009 criteria 1 and 3 and additionally: hobnail PTC variant PTC with vascular invasion Multifocal papillary microcarcinoma with ETE and BRAF V600E mutated (if known) Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm, in largest dimension
ATA high risk	1. Macroscopic tumor invasion into the perithyroidal soft tissues (gross ETE) 2. Incomplete tumor resection 3. Distant metastases 4. Tg out of proportion to what is seen on posttreatment WBS	ATA 2009 criteria 1–3 and additionally Postoperative serum Tg suggestive of distant metastases Pathologic N1 with any metastatic lymph node >3 cm in largest dimension FTC with extensive vascular invasion (>4 foci of vascular invasion)

*The 2015 ATA GL did not discussed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).
ETE, extrathyroidal extension; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; RAI, radioiodine; WBS, whole body scan.

Figure 2. American Thyroid Association (ATA) Risk Stratification Guidelines. Figure taken from the ATA. The 2009 and 2015 ATA risk stratification guidelines for staging the risk of thyroid CA. Both guidelines are used to assess the initial and current risk of thyroid CA patient's post-surgery and/or RAI post-therapy scan in ThyroCARE.

There is a thyroid CA-specific discrepancy between the risk of recurrence and the risk of death. There are many patients with a high risk of tumor recurrence, usually as local metastatic nodes that do not have an increased risk of death *(Haugen et al, 2016)*. As mentioned prior, the ATA risk stratification predicts the risk of recurrence but, physicians will also stage cancer with the AJCC system as a predictor of mortality. DTC, PDTC, and ATC are staged using a system developed by the American Joint Committee on Cancer

known as the AJCC system (Figure 3). The AJCC uses a numerical clinical staging system of Stage I, II, III, and IV, taking into the account the size of the tumor, the involvement of lymph nodes, and the degree of invasion and presence of metastases, commonly referred to as TNM staging. TNM staging is used along with the AJCC numerical staging as a predictor of mortality amongst thyroid CA patients. Additionally, AJCC staging also considers the age of the patient at the time of diagnosis, for example, in the AJCC 8th edition, the classification for Stage I applies to all DTC and PDTC patients under the age of 55, unless there is evidence of distant metastases for which they will be classed as Stage II. This rule does not apply to patients of ATC as they are automatically classed as Stage IV regardless of age (Figure 3). The major differences between the AJCC 8th edition and the 7th edition are low risk patients now include patients up to 55 years old instead of 45 years and tumor size up to 4 cm instead of 2 cm (Figure 3). The results of the AJCC 8th edition are to downgrade staging and risk of death of small < 4 cm tumors.

It is important to note that there is no direct relationship between AJCC/TNM staging and ATA risk stratification. A patient with an ATA intermediate or high-risk thyroid CA will not necessarily have advanced AJCC staging. Note the similarities and differences between ATA risk stratification and AJCC/TNM Staging. Both the ATA and AJCC guidelines consider the size of the tumor(s), the involvement of LN, and distant metastasis when respectively determining disease risk and staging. However, unlike AJCC Staging, the ATA guideline considers aggressive histology, such as tall cell, insular or columnar variants of DTC, lymphovascular invasion, the number and size of positive LN involved, incomplete tumor resection, level of Tg, and the presence of BRAFV600E

mutation to determine risk. The AJCC on the other hand, considers the age of the patient at diagnosis when determining stage of the disease. For example, a 40-year-old patient may be diagnosed with DTC showing features of poor differentiation, which automatically classes them as high initial ATA risk. However, using the 8th Edition of AJCC Staging, if the tumor is localized to the thyroid and considering the patient is under the age of 55 at diagnosis, such a patient will be classed as AJCC Stage I.

AJCC 7th Edition (Age ≥ 45 years old)					AJCC 8th Edition (Age ≥ 55 years old)			
STAGE	T	N	M	DESCRIPTION	T	N	M	DESCRIPTION
I	T1	N0	M0	≤ 2 cm tumor confined to the thyroid	T1, T2	N0	M0	≤ 4 cm tumor confined to the thyroid
II	T2	N0	M0	2-4 cm tumor confined to the thyroid	T1, T2 T3a,T3b	N1 Any N	M0 M0	Tumors of any size with central or lateral neck lymph nodes Or >4 cm tumor or gross extrathyroidal extension into strap muscles
III	T3 T1,T2,T3	N0 N1a	M0 M0	>4 cm tumor or minimal extrathyroidal extension, Or central neck lymph node metastasis	T4a	Any N	M0	Tumors of any size with gross extrathyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve
IV a	T4a T1,T2,T3,T4a	N0,N1a N1b	M0 M0	Tumors of any size with gross extrathyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve Or lateral neck lymph node metastasis	T4b	Any N	M0	Tumors of any size or lymph node status with gross extrathyroidal extension into prevertebral fascia, encasing major vessels
IV b	T4b	Any N	M0	Tumors of any size or lymph node status with gross extrathyroidal extension into prevertebral fascia, encasing major vessels	Any T	Any N	M1	Distant metastasis
IV c	Any T	Any N	M1	Distant metastasis				

Figure 3. American Joint Committee on Cancer (AJCC) 7th and 8th Edition AJCC/TNM Staging Guidelines. Taken from the AJCC, 2018. This figure shows the composite of TNM and AJCC staging. The 8th edition is the most up-to-date guideline and was used in this research to stage patients after surgery and RAI post-therapy WBS.

Thyroid Carcinoma and the Importance of Access/Availability to Healthcare

Extensive research has demonstrated a need for equal access and availability to adequate healthcare as it has shown minorities and lower SES groups are negatively affected by a lack of proper health resources and health literacy. The disparity in health resource can lead to higher risk presentation of diseases and poorer prognoses in these groups. With the sharp uptick in thyroid CA incidence rates in the past thirty years across all demographics, it is important to measure for disparities in disease and outcomes in various R/E and SES groups to see if the same issue applies to a disease like thyroid CA which is known to have a high survival rate and great prognosis.

In 2014, a retrospective cohort study at the University of California Los Angeles (UCLA), Section of Endocrinology was performed to assess the R/E and SES disparities in WDTC during presentation and outcome *(Harari et al, 2014)*. The study proposed that R/E minorities suffered from disproportionate rates of morbidity and mortality when it came to chronic diseases. By conducting a retrospective assessment of 25,945 patients from varying R/E and SES backgrounds in the California Cancer Registry, researchers found that minorities presented with higher rates of metastatic thyroid CA when compared White/Caucasian patients. Amongst the minority groups, Black/African American patients had the lowest overall survival rates while Hispanic/Latino and Asian/Pacific Islander patients had higher overall survival rates. Patients with the lowest SES had greater presentation of metastatic thyroid CA compared to the highest SES patients. Furthermore, patients that were uninsured, could not afford insurance, or had Medicaid had a greater

probability of advanced stage thyroid CA at presentation compared to patients that had access to private insurance.

In contrast to the UCLA study, a 2010 retrospective assessment on the effects of race on thyroid CA and an equal access healthcare system *(Brown et al,2010)*, was performed with a total of 4625 Black/African American and White/Caucasian patients being identified as having no difference in age at presentation of disease, tumor size, use of surgery and RAI treatment. The study proposed that Black/African American patients are more likely to present with thyroid CA at later age, and with larger tumor dimensions compared to White/Caucasian patients. Both groups were provided with equal access to care through a Department of Defense medical facility from 1986 to 2008. The results saw that Black/African American patients had similar presentation and disease survival rates as White/Caucasian patients. Furthermore, it was discovered that Black patients receiving treatment at this facility showed lower rates of LN involvement.

Although the relationship between initial presentation and recurrence of thyroid CA with R/E and SES disparities remains a controversial topic of research, it is nonetheless a crucial and valuable topic that needs further investigation. Identification of disparities in healthcare is important to implement medical, political, or social interventions to narrow the gaps between R/E and SES groups.

Objective

The purpose of this current research is to examine patients of Boston Medical Center (BMC), a health safety-net hospital, with a highly diverse patient population for a

difference in presentation and prognosis of thyroid CA based on R/E and SES using a large IRB-approve thyroid CA registry, ThyroCARE.

In 2006 in the State of Massachusetts, Governor Mitt Romney introduced The Massachusetts Health Care Reform, also referred to as "Romneycare", a landmark healthcare legislation that increased insurance coverage to residents of Massachusetts to almost universal levels *(Miller, 2012)*. With the expansion of healthcare coverage throughout the State allowing for greater access to healthcare, a sharp increase was seen in the rate of thyroid CA surgeries especially within non-White minority groups *(Loehrer, 2017)*. With R/E and SES disparities being mitigated through the introduction of Romneycare and now the Obama Affordable Care Act, aka "Obamacare", establishing ThyroCARE at safety net hospital such as BMC is ideal to assess if there is a difference in thyroid CA presentation and outcome in various R/E and SES groups.

METHODS

Study Population, Data Source and Collection

To help determine the relationship between R/E and SES with the initial extent of disease and potential for cancer recurrence, 1305 patients from BMC were enrolled and consented by March 31st, 2021, to have medical information pertaining to their thyroid CA treatment recorded in an IRB approved thyroid CA registry, ThyroCARE. In total, the current registry contains 900 (69.0%) White/Caucasian patients, 133 (10.2%) Black/African American patients, 163(12.5%) Latino/Hispanic patients, 67 (5.1%) Asian patients, 3 (0.2%) American Indian/Alaskan Native patients, and 39 (3.0%) patients that identified as mixed race, other, unknown/uncertain, or declined to disclose their race. The registry was set up with REDCap data collection instruments and used to record demographic variables and social histories such as age at diagnosis, R/E, gender, and current zip code. The registry also recorded information about the patients' thyroid CA history and treatment including surgery, RAI therapy and post-therapy WBS, thyroid-related pathology reports, post-operative US, thyroid laboratory tests, ATA initial and current risk stratification, and AJCC staging. Patients' medical information were gathered from BMC's electronic medical record, EPIC. Patients records after 01/01/2000 associated with ICD 9 (193) or ICD 10 (C73) diagnosis codes were identified by the BMC Data Warehouse. Since 01/01/2016, the BMC Data Warehouse is queried annually for new patients. To help determine current ATA risk, post-operative thyroid laboratory results for TSH, Tg, and TgAb and post-operative US were recorded and observed overtime.

Collection of patients' zip codes was used to estimate their level of income based on their area of residence. A zip code-income composite was done for each patient by using the zip code-income data retrieved from the 2019 United States Census and American Community Survey's (ACS) zip code tabulated area (ZCTA) income estimation *(United States Census Bureau ZCTAs, 2019)*.

Initial Staging After Surgery and RAI-TX Post Therapy Scan

To determine initial ATA risk and AJCC staging after surgery and RAI treatment, reviews of patients' surgical reports, post-operative pathology reports, and RAI therapy WBS reports were conducted. The surgical and operative reports detail the type of thyroid surgery that was performed, such a unilateral lobectomy, sub-total thyroidectomy, or a total thyroidectomy and give insight on whether a LN dissection was necessary. As mentioned earlier, with many cases of thyroidectomies, surgeons may include a prophylactic LN dissection to prevent the spread of cancer to the central neck compartment LN. Other times, if metastatic LN are confirmed pre-operatively during diagnostic imaging and FNA or by direct observation by the surgeon, a therapeutic LN neck dissection will be performed. These metastatic LN may have a black or dark blue discoloration and can be confirmed with a frozen section rapid pathology test during surgery.

The information from the post-surgery pathology report was used to gather details on characteristics of the cancer such as the number of tumors, size of the tumor(s), the cancer variant(s), the degree of invasion within and outside of the thyroid and other non-malignant thyroid pathology such as thyroiditis or adenomatous goiter (benign thyroid

nodules). If LN were removed during surgery, a pathology report can also confirm the number of LN removed, if any of the LN were metastatic, the size of the largest metastatic LN, and if there was extra-nodal extension. The vital information gathered from these reports was used alongside the ATA risk stratification system and the 8th edition of the AJCC cancer staging system to help determine an initial risk of thyroid CA recurrence and stage of the disease.

In many cases of DTC and in rare cases of PDTC, patients may opt to have RAI ablation therapy several months after a thyroidectomy which will include a RAI post-therapy WBS. The significance of a post-therapy WBS is to see if the I-131 is taken up in areas of thyroid remnants left after surgery, in metastatic LN, or outside of the neck area, a sign of distant metastases. Uptake in residual thyroid tissue is normal, however, there may be uptake in the cervical or mediastinal LN that can suggest metastases not seen at surgery. There may also be uptake of I-131 in the lungs, liver, and bones that are not physiological and suggestive of distant disease. The information from the RAI therapy and post-therapy scan was also used alongside the ATA risk stratification and AJCC staging guidelines to determine initial ATA risk and AJCC staging after RAI post-therapy scan. If uptake of I-131 reveals metastatic LN or distant disease, the patient's current ATA risk will be upgraded.

Determining ATA Current Risk

As earlier elaborated, ATA risk is a clinical predictor of thyroid CA recurrence. ATA current risk is established at least one year after the ATA initial risk, which is done

after surgery and administration of RAI therapy. To determine if there is a change from the ATA initial risk, observation begins during post-surgery follow-up with diagnostic neck US, WBS, and thyroid laboratory tests measuring serum levels of TSH, Tg, and TgAb. Results and impressions from a neck US can reveal any suspicious lesions, structures or lymph nodes that may require further examination. As Tg levels act as a tumor marker for DTC after total thyroidectomy, abnormally high levels of serum Tg is usually an indicator of recurrent thyroid malignancy. Ideally, a patient who has had treatment for DTC would have negative US results and low to undetectable levels of Tg and TgAb at follow-up. If this is the outcome, initial ATA low risk patients will maintain their low-risk status and initial ATA intermediate or high-risk patients can be downgraded to a lower current ATA risk. However, if imaging results and laboratory tests show concerning structures and abnormal serum Tg levels, initial ATA intermediate and high-risk patients may maintain their status and in cases where follow-up examinations confirm the recurrence of cancer, initial ATA low and intermediate-risk patients can be upgraded to high current ATA risk. An upgrade in ATA risk is normally seen with recurrent disease of LN, recurrent disease in residual thyroid tissue, or distant metastasis, all of which show evidence of a structural incomplete response to treatment (Figure 4).

	Total thyroidectomy and RAI ablation Haugen *et al.* (2016)	**Total thyroidectomy alone** Momesso *et al.* (2016)	**Lobectomy alone** Momesso *et al.* (2016)
Excellent response	Negative imaging Suppressed Tg < 0.2 ng/mL or TSH-stimulated Tg < 1 ng/mL, Undetectable TgAb	Negative imaging Nonstimulated Tg < 0.2 ng/mL or Stimulated Tg < 2 ng/mL, Undetectable TgAb	Negative imaging Stable nonstimulated Tg < 30 ng/mL
Biochemical incomplete response	Negative imaging Suppressed Tg ≥ 1 ng/mL or Stimulated Tg ≥ 10 ng/mL or Rising TgAb levels	Negative imaging Nonstimulated Tg > 5 ng/mL or Stimulated Tg > 10 ng/mL or Increasing Tg values over the time with similar TSH levels or Rising TgAb levels	Negative imaging Nonstimulated Tg > 30 ng/mL or Increasing Tg values over the time with similar TSH levels or Rising TgAb levels
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without TgAb	Structural or functional evidence of disease regardless of Tg or TgAb	Structural or functional evidence of disease regardless of Tg or TgAb
Indeterminate response	Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable, but < 1 ng/mL Stimulated Tg detectable, but < 10 ng/mL or TgAb stable or declining in the absence of structural or functional disease	Nonspecific findings on imaging studies or Faint uptake in thyroid bed on RAI scanning or Nonstimulated Tg 0.2–5 ng/mL or Stimulated Tg 2–10 ng/mL or TgAb levels stable or declining in the absence of structural or functional disease	Nonspecific findings on imaging studies or TgAb levels stable or declining in the absence of structural or functional disease

Figure 4. Guidelines for Determining Response to Therapy for Thyroid CA. Taken from the ATA, 2018. Observation guidelines for thyroid CA patients to help determine their response to therapy and current ATA risk one year after implementation of treatment.

Statistical Analysis

Once demographic, social history, and pathological information of thyroid CA diagnosis and treatment for the 1305 patients were recorded into REDCap, the data collected was downloaded into MS Excel files and statistically analyzed with IBM SPSS Statistics ®.

After establishing a relationship between R/E and income level by breaking down the income status of all ThyroCARE patients into four levels, cancer types were then distributed across R/E and the four levels of income. The statistical distribution was also

performed for AJCC staging, ATA initial risk, and ATA current risk across R/E and the four levels of income. Chi-square analysis was performed for each distribution against p-value <0.05.

RESULTS

Among the 1305 patients currently enrolled in ThyroCARE, 900 are White/Caucasian (69%), 163 are Hispanic/Latino (12.5%), 133 are Black/African American (10.2%), 67 are Asian (5.1%), 3 are American Indian/Alaskan Native (0.2%), with the remaining 39 patients categorized as other/unknown (3%). Please note that American Indian/Native Alaskan patients, mixed race patients, and patients with other/unknown R/E are not considered for this current research because of the small number of subjects in these categories. Furthermore, as DTC comprise nearly 95% of thyroid CA and the ATA stratification guidelines only apply to DTC, rarer and uncommon thyroid CA types such as thyroid lymphoma, MTC, squamous cell carcinoma, or unknown cancer types due to lacking pathological information, are not included in this research.

Table 1 details the distribution of thyroid CA types across R/E. The only statistical significance seen is in the relative prevalence of PTC and the FVPTC when distributed across different R/E. Of the 813 patients that presented with classical PTC, the greatest in-group prevalence was among Hispanic/Latino patients with 72.8% that is significantly higher than other R/E *($p = 0.000$)*. Black/African American patients had the highest in-group prevalence of FVPTC with 36.3% that is significantly higher than other R/E *($p = 0.001$)*.

Table 1. Cancer Type Versus Race and Ethnicity.

Cancer Type		RACE/ETHNICITY				Total	p-value**
		White	Black	Hispanic	Asian		
Papillary (Classical)	Count	575	60	134	44	813	0.000
	% within R/E	67.3%	48.4%	72.8%	68.8%	66.3%	
Papillary follicular variant	Count	179	45	32	14	270	0.001
	% within R/E	20.9%	36.3%	17.4%	21.9%	22.0%	
Papillary tall cell variant	Count	10	0	0	1	11	0.281
	% within R/E	1.2%	0.0%	0.0%	1.6%	0.9%	
Papillary sclerosing variant	Count	14	3	1	1	19	0.598
	% within R/E	1.6%	2.4%	0.5%	1.6%	1.5%	
Follicular Carcinoma	Count	36	6	4	3	49	0.571
	% within R/E	4.2%	4.8%	2.2%	4.7%	4.0%	
Hurthle cell Carcinoma	Count	15	3	7	0	25	0.200
	% within R/E	1.8%	2.4%	3.8%	0.0%	2.0%	
***Medullary Thyroid Carcinoma**	Count	12	2	2	0	16	0.784
	% within R/E	1.4%	1.6%	1.1%	0.0%	1.3%	
Anaplastic thyroid carcinoma	Count	2	1	1	0	4	0.664
	% within R/E	0.2%	0.8%	0.5%	0.0%	0.3%	
Poorly differentiated thyroid carcinoma	Count	8	4	2	1	15	0.188
	% within R/E	0.9%	3.2%	1.1%	1.6%	1.2%	
***Thyroid lymphoma**	Count	3	0	0	0	3	0.727
	% within R/E	0.4%	0.0%	0.0%	0.0%	0.2%	
***Squamous cell carcinoma**	Count	1	0	1	0	2	0.561
	% within R/E	0.1%	0.0%	0.5%	0.0%	0.2%	

*Uncommon tumor types not included in overall statistical analysis
** Difference across R/E groups

To determine a relationship between R/E and income status, a statistical distribution of income levels across R/E was performed. As mentioned earlier, each patient's income level was determined by their zip code as reported in the 2019 United States Census/ACS ZCTA dataset. The median household income and mean household income (HHI) of all patients in ThyroCARE are respectively $83,519 and $85,92, with a standard deviation of $31,853. Since there is a normal distribution of HHI with similar median and means income for ThyroCARE patients, income status was broken into four levels using the standard deviation. Level I is less than -1 standard deviation below the mean (<$54,068), level II is 0 to -1 standard deviation below the mean ($54,068-$85,92), level III is 0 to +1 standard deviation above the mean ($85,92-$117,775), and level IV is greater than +1 standard deviation above the mean (>$117,775). From the distribution of R/E versus income levels seen in Table 2, there is a difference in income levels between Black/African American and Hispanic/Latino patients when compared to Asian and White/Caucasian patients. Statistical significance is seen in level I income among Black/African American and Hispanic/Latino patients, both groups having the highest representation in the lowest level income group *($p<0.00001$)* and the least representation in the highest income level group compared to Asian and White/Caucasian patients. In contrast, a statistical significance in the highest-level income level group is noted as Asian and White/Caucasian patients have the greatest representation in this level *($p = 0.0201$)*, and the least representation in the lowest level income group.

Table 2. Income Level Versus Race and Ethnicity.

			RACE/ETHNICITY				Total	p-value*
			White	**Black**	**Hispanic**	**Asian**		
Income Level	**I**	Count	68	30	51	5	154	p<0.00001
		% within R/E	7.7%	22.7%	27.4%	7.6%	12.2%	
	II	Count	322	71	93	39	525	p<0.00001
		% within R/E	36.5%	53.8%	50.0%	59.1%	41.5%	
	III	Count	350	21	23	14	408	p<0.00001
		% within R/E	39.7%	15.9%	12.4%	21.2%	32.3%	
	IV	Count	141	10	19	8	178	p = 0.0201
		% within R/E	16.0%	7.6%	10.2%	12.1%	14.1%	
Total		Count	881	132	186	66	1265	
		% within R/E	100.0%	100.0%	100.0%	100.0%	100.0%	
*Difference across R/E groups								

When distributing initial ATA risk across R/E as shown in Table 3, no significant difference is seen amongst the groups of White/Caucasian, Black/African American, Hispanic/Latino, and Asian patients when it comes to risk at presentation of disease post-treatment. Although the prevalence of ATA initial high risk may appear to be greater in non-White patients compared to White/Caucasian patients, this finding was not statistically

significant *(p = 0.571).* The absence of a significant association of ATA initial risk and R/E suggests there is no difference in the risk of tumor recurrence across R/E.

ATA initial risk was also distributed across the four levels of income as seen in Table 4. Much like the distribution across R/E, there was no data of significant difference in ATA initial risk between the R/E groups. The results showed a lower in-group percentage of ATA initial high-risk cases amongst the highest-level income group compared to the other levels, however, this proved to be statistically insignificant *(p = 0.282).* The absence of a significant association of ATA initial risk and income quartiles suggests there is no difference in the risk of tumor recurrence across low to high income levels.

Table 3. Distribution of ATA Initial Risk Across Race and Ethnicity.

		RACE/ETHNICITY				Total	p-value*
		White	Black	Hispanic	Asian		
ATA Initial Low Risk	Count	479	75	82	35	671	0.061
	% within R/E	54.4%	56.8%	44.1%	53.0%	53.0%	
ATA Initial Intermediate Risk	Count	247	29	63	20	359	0.133
	% within R/E	28.0%	22.0%	33.9%	30.3%	28.4%	
ATA Initial High Risk	Count	113	19	31	9	172	0.571
	% within R/E	12.8%	14.4%	16.7%	13.6%	13.6%	
Total	Count	881	132	186	66	1265	
	% within R/E	100.0%	100.0%	100.0%	100.0%	100.0%	
*Difference across R/E groups							

Table 4. Distribution of ATA Initial Risk Across Income Levels.

ATA Initial Risk Stratification		INCOME LEVEL					
		I	II	III	IV	Total	p-value*
ATA Initial Low Risk	Count	80	264	228	99	671	0.325
	% within Income Level	51.9%	50.3%	55.9%	55.6%	53.0%	
ATA Initial Intermediate Risk	Count	40	151	115	53	359	0.884
	% within Income Level	26.0%	28.8%	28.2%	29.8%	28.4%	
ATA Initial High Risk	Count	22	81	51	18	172	0.282
	% within Income Level	14.3%	15.4%	12.5%	10.1%	13.6%	
TOTAL	Count	154	525	408	178	1265	
	% within Income Level	100.0 %	100.0 %	100.0%	100.0%	100.0%	
*Difference across income groups							

Patients in this current research were staged using AJCC 8th Edition guidelines with AJCC stage IVA and IVB collectively grouped together as AJCC stage IV. The AJCC guideline was distributed across R/E as seen in Table 5, and from the raw data it appears Black/African American patients had a higher in-group percentage of AJCC stage IV cancers and Asians had a higher in-group percentage of AJCC stage III cancers. However, statistical difference in AJCC stage IV and stage III cancers were shown to be insignificant (respectively, $p = 0.378$ and $p = 0.155$). Overall, the distribution of AJCC staging 8th

Edition across R/E did not show significant difference suggesting that the risk of death does not increase with R/E.

Distribution of AJCC staging across the four levels of income is shown in Table 6. When examining the raw data in AJCC stage IV versus income level, there is a sequential decrease of stage IV cancers and a sequential increase of stage I/II cancers from the lowest level of income to the high level of income, suggesting a greater prevalence of more aggressive stage IV cancers in patients with the lowest level income versus patients with the highest level of income. However, statistical analysis showed there was no significant difference statistically in this data *($p = 0.601$).* Overall, no significant difference was noted between AJCC staging and income levels suggesting that the risk of death is not associated with low to high income levels.

Table 5. Distribution of AJCC Staging 8th Edition Across Race and Ethnicity.

AJCC 8th Staging 8th Edition		Race/Ethnicity				Total	p-value*
		White	Black	Hispanic	Asian		
AJCC-8 Stage I	Count	710	102	151	51	1014	0.738
	% within R/E	80.6%	77.3%	81.2%	77.3%	80.2%	
AJCC-8 Stage II	Count	86	13	21	9	129	0.730
	% within R/E	9.8%	9.8%	11.3%	13.6%	10.2%	
AJCC-8 Stage III	Count	11	1	3	3	18	0.155
	% within R/E	1.2%	0.8%	1.6%	4.5%	1.4%	
AJCC-8 Stage IV	Count	31	7	4	1	43	0.378
	% within R/E	3.5%	5.3%	2.2%	1.5%	3.4%	
Total	Count	881	132	186	66	1265	
	% within R/E	100.0%	100.0%	100.0%	100.0%	100.0%	
*Difference across R/E groups							

Table 6. Distribution of AJCC Staging 8th Edition Across Income Levels.

AJCC 8th Staging 8th Edition		Income Level				Total	p-value*
		I	II	III	IV		
AJCC-8 stage I	Count	115	418	333	148	1014	0.208
	% within Income Level	74.7%	79.6%	81.6%	83.1%	80.2%	
AJCC-8 stage II	Count	18	51	45	15	129	0.700
	% within Income Level	11.7%	9.7%	11.0%	8.4%	10.2%	
AJCC-8 stage III	Count	7	20	12	4	43	0.968
	% within Income Level	4.5%	3.8%	2.9%	2.2%	3.4%	
AJCC-8 stage IV	Count	7	20	12	4	43	0.601
	% within Income Level	4.5%	3.8%	2.9%	2.2%	3.4%	
Total	Count	154	525	408	178	1265	
	% within Income Level	100.0%	100.0%	100.0%	100.0%	100.0%	
*Difference across income groups							

After treatment for thyroid CA, surgery and/or RAI therapy, at least one year observation is required to assess response to therapy and current ATA risk via US and Tg, and TgAb laboratory tests. The current ATA risk and response to therapy to each patient is assessed during each follow-up for disease management, and if there are evident changes in the course of disease, then ATA risk and response to therapy will be updated. In Table 7, the distribution of ATA current risk across R/E is shown, and current ATA low risk and

high risk do not show significant difference statistically (respectively, $p = 0.685$ *and* $p = 0.497$) with R/E. However, when intermediate ATA current risk was distributed across R/E, a significant difference was seen between the groups. Asian and Hispanic/Latino patients had the greatest in-group prevalence of current ATA intermediate risk versus White/Caucasian and Black/African American patients, with the latter having the lowest representation in the current ATA intermediate risk group. This can be explained by higher percentage of Hispanic/Latino and Asian patients presenting with classical PTC. As mentioned earlier, classical PTC has a greater risk of highly aggressive BRAFV600E gene mutation, which present with more extrathyroidal extension of tumor and metastatic LN, hallmarks of ATA intermediate tumor. This can explain why Asian and Hispanic/Latino patients make up a higher percentage of current ATA intermediate risk cases after treatment.

When ATA current risk was distributed across the four income levels as shown in Table 8, no significant difference was seen in current intermediate and high risk, however, the data is significant when it comes to ATA current low-risk patients. The results show a stepwise increase between the four levels of income with the lowest income level having the least percentage of current ATA low risk cases and the highest income level having the highest percentage of current ATA low risk cases ($p<0.0001$). Although it was earlier noted that there was a significance in representation of Black/African American and Hispanic/Latino patients in the lowest income level group, in this case, the issue of income level may be impartial to race as deeper analysis of the members in the lowest level income

group in current ATA low risk reveals it comprises of nearly 40% White/Caucasian patients.

Table 7. Distribution of ATA Current Risk Across Race and Ethnicity.

ATA Current Risk		RACE/ETHNICITY				Total	p-value*
		White	Black	Hispanic	Asian		
ATA Current Low Risk	Count	583	91	118	41	833	0.685
	% within R/E	66.2%	68.9%	63.4%	62.1%	65.8%	
ATA Intermediate Risk	Count	69	4	22	10	105	0.007
	% within R/E	7.8%	3.0%	11.8%	15.2%	8.3%	
ATA Current High Risk	Count	97	16	26	5	144	0.497
	% within R/E	11.0%	12.1%	14.0%	7.6%	11.4%	
Total	Count	881	132	186	66	1265	
	% within R/E	100.0 %	100.0 %	100.0%	100.0 %	100.0%	
*Difference across R/E groups							

Table 8. Distribution of ATA Current Risk Across Income Level.

ATA Current Risk		Income Level				Total	p-value*
		I	II	III	IV		
ATA Current Low Risk	Count	83	331	286	133	833	0.000
	% within Income Level	53.9%	63.0%	70.1%	74.7%	65.8%	
ATA Current Intermediate Risk	Count	13	54	26	12	105	0.152
	% within Income Level	8.4%	10.3%	6.4%	6.7%	8.3%	
ATA Current High Risk	Count	21	65	43	15	144	0.373
	% within Income Level	13.6%	12.4%	10.5%	8.4%	11.4%	
Total	Count	154	525	408	178	1265	
	% within Income Level	100.0 %	100.0%	100.0%	100.0%	100.0%	
*Difference across income groups							

DISCUSSION

The present retrospective research is a study in the correlation between R/E and SES with staging and risk of recurrence through a thyroid CA registry of BMC patients, ThyroCARE. Of the 1305 patients that have been enrolled into the registry, the present research only considered patients with DTC, patients of differing cancer types or lacking pathological data to conclude a diagnosis of DTC were excluded.

DTC Distribution by R/E

The distribution of cancer types across R/E revealed that, overall, there was no significant difference statistically in cancer types and R/E, inferring no direct correlation between R/E and cancer type which is contrary to various past research that suggested R/E minority groups presented with more aggressive tumor types. Performing a subset analysis with the distribution of tumor subtypes within individual R/E, Black/African American patients have a greater prevalence of FVPTC, a variant that has much higher survival rates and response to treatment versus classical variant of PTC. Asian and Hispanic/Latino patients had a greater prevalence of classical PTC, known to have 60% BRAFV600E mutation associated with tumor invasion and metastases which reduces response to therapy

Initial ATA Risk of Recurrence and AJCC Stage by R/E and Income

Based on the overall median and mean HHI of ThyroCARE's patients, income status was divided into four levels, I, II, III, and IV. It is revealed that Black/African American and Hispanic/Latino had over-representation in the in level I, the lowest income

level group, while Asian American and White/Caucasian patients had the highest representation in level IV, the highest income level.

The distribution of initial ATA risk, or risk of recurrence, across R/E did not reveal a significant difference statistically. Past research publications have indicated that racial minorities suffer from more advanced stage diseases primarily due a lack in access and availability to health resources, however, the findings in this research do not support this concept. Similar to Brown *(Brown, SR et al,2010)*, where access to care was equal despite R/E or income, there was no difference in initial ATA risk of recurrence. This is further supported when AJCC staging is distributed across R/E with the results showing there was no significant difference statistically, inferring that minority R/E groups do not present with more advanced stage thyroid CA with an increased risk of death.

As stated with distribution of R/E across income levels of ThyroCARE patients, Black/African American and Hispanic/Latino patients were most represented in the lowest income level while Asian and White/Caucasian patients had the greatest representation in the highest income level. Past research would suggest that Black/African American and Hispanic/Latino patients in the lowest income level would present with the advanced stage disease and highest risk, however, no significant difference was seen when ATA initial risk was distributed across income levels. No significant difference was seen when AJCC staging was distributed across income levels as well, further suggesting no distinct correlation between R/E and income levels with the AJCC stage of disease and ATA initial risk of recurrence.

Current ATA Risk of Recurrence by R/E and Income

Current ATA risk of recurrence is a measure of persistent disease after initial treatment. This is a measure of response to therapy. The distribution of current ATA risk across R/E did not reveal a significant difference statistically in between R/E when it came to current intermediate risk and current high risk. However, a significant difference was seen in current ATA intermediate risk in Asian and Hispanic/Latino patients as these two groups had the greatest in-group prevalence if intermediate risk cases while Black/African American patients had the least prevalence in this category. This difference can be explained by the higher prevalence of the FVPTC in Black/African American patients which tends not to have invasion or metastatic LN compared to other tumor subtypes. Likewise, when ATA current risk was distributed across income levels, there was no data suggesting a significant difference statistically in the relationship between income levels and current ATA intermediate risk and current ATA high risk, representing income status having no association with response to therapy and outcome of disease. However, a difference was seen in the current ATA low risk group with a stepwise increase of in-group percentage starting from the lowest income level group to the highest income level group. This data suggests that the greater the patients' income status, the greater their chances of having good response to therapy that would lead to a current low risk status. It is important to note that this may not be associated with R/E and income, as a further analysis of the R/E in the lowest income patients from the current ATA low risk group shows a greater number of low-income White/Caucasian patients compared to low-income Black/African

American and Hispanic/Latino patients. It is not possible to distinguish in this dataset whether the difference in response is due to tumor subtypes or income.

This current research has several strengths, including (1) the capability to collect and organize a large amount of patient data related to thyroid CA that can be used for various research and publications, (2) BMC is a large, urban safety-net hospital, allowing for a diverse population sample and can help answer key questions relating to R/E and SES when it comes to thyroid CA, (3) ThyroCARE is the first cancer registry that researches specifically thyroid CA and contains more than 1300 elements and is more detailed than any other thyroid CA registry, (4) ThyroCARE contains details of more than 1300 patients, inclusive of foreign-born patients, which is large for an uncommon cancer, and (5) Massachusetts has a long history of near-universal access to care since 2007 which helps remove this influence on the results. Furthermore, ThyroCARE is ongoing and continues to add more patients. Nevertheless, this research also comes with limitations that need to be discussed. First, the current registry contains a greater number of White/Caucasian patients than any other R/E group at 68%. This can mean an under-representation of other R/E in the data. However, this issue can be mitigated as the registry continues to grow and enroll more patients. Second, as number of patients in the registry are foreign born, had thyroid surgery many years in the past, or presented for ongoing treatment at BMC with incomplete medical history, they did not have enough pathological data in their records to determine the type of thyroid CA they were diagnosed with or extent of disease at presentation. As a result, these patients were not considered in this current research. Third, although annual follow-ups are highly recommended by providers, a number of patients

entered into ThyroCARE either have inconsistent follow-up monitoring or were lost to follow-up which can have an effect on long-term response data. Lastly, as this research is currently isolated to BMC, it is limited to a single institution.

This research has demonstrated that there is no association with AJCC 8th edition staging and risk of death based on R/E and income. There is an independent association between various R/E and income levels with risk of cancer recurrence and response to therapy. The presentation of disease type did not show significant difference statistically that would suggest minority R/E groups suffer from more advanced or aggressive thyroid CA variants, in fact, Black/African American patients showed a greater prevalence for FVPTC, which has a very good response to therapy and high survival rates overall. The higher prevalence of classic PTC, which is affiliated with a higher risk of extrathyroidal invasion and metastatic LN, in Latino/Hispanics and Asians likely explains the higher representation of these R/E groups within the ATA current intermediate risk of recurrence. Future studies will need to confirm this observation and determine the cause of increased prevalence of lower risk follicular variant of PTC in Black African Americans and high-risk classic PTC in Latino/Hispanics and Asians. Future research through ThyroCARE can also examine the difference in behavior of tumor subtypes such as classical PTC and FVPTC when independent of R/E and income level influences.

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