RESEARCH

Racial/Ethnic Disparities in Thyroid Cancer Stratified by Risk Factors: A Literature Review

Kristiana Rood[1,2,3,**], Ria T. Laxa[1,**], Andrea Shields[4], Hae-Soo Kim[1,2], Salma Khan[1,2,3,5,*]

[1]Division of Biochemistry, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA. [2]Division of Otolaryngology, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA. [3]Center for Health Disparities & Molecular Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA. [4]Department of Pathology & Human Anatomy, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA. [5]Department of Internal Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92354, USA. Loma Linda University, Mortensen Hall, 11085 Campus St, Loma Linda, CA 92350.

*Corresponding author: Salma Khan: salmakhan@llu.edu. **Equally contributed.

ABSTRACT

In the United States, thyroid cancer incidence has increased dramatically within the last few decades. Recent research suggests that this incidence along with cancer stage and mortality vary by race/ethnicity, highlighting health disparities in the United States. There are several risk factors for thyroid cancer incidence that may contribute to these disparities. The goal of this literature review is to analyze whether these potential risk factors impact incidence and aggressiveness differently by race/ethnicity, implicating their possible role in influencing thyroid cancer disparities in the United States. Through PubMed searches, we have reviewed recent literature on U.S. populations. We found that chromosomal alterations/non-hereditary conditions, autoimmunity, thyroid nodules, and socioeconomic differences potentially impacted thyroid cancer incidence and aggressiveness by race/ethnicity, whereas sex disparities did not. Several potential risk factors showed some variations by race/ethnicity but either did not specifically examine their relationship to thyroid cancer or did not impact thyroid cancer incidence and aggressiveness. Other potential risk factors have not yet been studied regarding their influence on thyroid cancer incidence and outcomes for racial/ethnic groups in the United States. Therefore, we identify a critical need for subsequent research to examine these potential risk factors for different racial/ethnic groups and contribute to our understanding of racial/ethnic health disparities in the United States. We also present several research areas relating to thyroid cancer health disparities that require further study.

KEYWORDS: Thyroid cancer, health disparities, incidence, mortality.

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1. Introduction

Thyroid cancer incidence has increased dramatically over the last 30 years, and epidemiologists predict this cancer will become the fourth most prevalent cancer in the United States by 2030 (Krook et al., 2015; La Vecchia et al., 2015; Rahib et al., 2014; Reitzel et al., 2014; Weeks et al., 2018). One study found that by 2008, thyroid cancer had already been one of the top five cancers in Asian Indian/Pakistani, Chinese, Filipina, Korean, and Vietnamese women (Gomez et al., 2013). Furthermore, recent research suggests that this incidence varies by race/ethnicity (Table 1) (Magreni et al., 2015; Suresh et al., 2015; Weeks et al., 2018).

In the United States, thyroid cancer incidence rates are the highest in Non-Hispanic European Americans and the lowest in Non-Hispanic African Americans (Lim et al., 2017; Magreni et al., 2015; Reitzel et al., 2014; Tortolero-Luna et al., 2019; Weeks et al., 2018; Yu et al., 2010). However, when separating Asian Americans by subgroups, Vietnamese, Cambodian, and Filipino Americans are shown to have elevated thyroid cancer incidence rates; Filipino Americans, in particular, have higher thyroid cancer incidence rates than non-Filipino Asians and non-Hispanic European Americans (Gomez et al., 2013; Horn-Ross et al., 2011; Jin et al., 2016; Megwalu et al., 2021; Nguyen et al., 2017).

Table 1. Age-adjusted thyroid cancer incidence rates and 95% confidence intervals (CIs) by Asian subgroup and non-Hispanic (NH) Whites, 2009-2011* (Jin et al., 2016).

	Chinese		Filipino		Japanese		Korean		South Asian		Vietnamese		Asian Total		NH White	
	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)
Men	263	6.9 (6.1-7.8)	271	9.7 (8.5-11.0)	41	3.7 (2.6-5.2)	108	8.3 (6.8-10.1)	186	5.8 (4.9-6.8)	75	5.3 (4.1-6.7)	974	6.8 (6.4-7.3)	9,425	8.1 (7.9-8.3)
Women	920	20.8 (19.4-22.2)	1,108	28.5 (26.8-30.3)	153	(11.6 (9.7-13.9)	408	23.2 (21.0-25.6)	624	19.9 (18.3-21.7)	318	19.3 (17.2-21.7)	3,670	21.5 (20.8-22.2)	25,325	22.4 (22.1-22.7)

*Rates are average annual per 100,000 age-standardized to the 2000 US population; the Number of cases may not add up to the total due to rounding.

There are several risk factors for thyroid cancer incidence that may contribute to these disparities (Konturek et al., 2016; La Vecchia et al., 2015; Weeks et al., 2018). A recent study by Bogović et al. categorized the potential risk factors as either "high risk," "low risk," or "unclear" (Bogović Crnčić et al., 2020). High-risk factors included external radiation exposure (especially during infancy and childhood), chromosomal alterations, and hereditary conditions. Low-risk factors included thyroid imaging with iodine, iodine deficiency, high thyroid-stimulating hormone (TSH) level, autoimmunity, thyroid nodules, environmental pollutants, lifestyle/diet, and obesity/high BMI. The only unclear risk factor included was estrogen. Another recent study by Yildirim et al. mentioned metabolic syndrome and insulin resistance as important risk factors (Yildirim Simsir et al., 2020). Additionally, sex and socioeconomic status may also be considered risk factors. The goal of this literature review is to analyze whether these potential risk factors impact incidence and aggressiveness differently by race/ethnicity, implicating their possible role in

influencing thyroid cancer racial/ethnic disparities in the United States.

2. Materials and Methods

To review recent research, a PubMed search was used, including articles published since 2010. Each identified thyroid cancer risk factor, as informed by Bogović et al. (Bogović Crnčić et al., 2020) and Yildirim et al. (Yildirim Simsir et al., 2020), was used as a keyword: 'radiation exposure' or 'ionizing radiation', 'chromosomal alterations', 'non-hereditary conditions', 'hereditary conditions', 'iodine', 'TSH', 'autoimmunity', 'thyroid nodules', 'environmental pollutants' and 'geospatial', 'lifestyle and diet', 'BMI', 'metabolic syndrome', 'insulin resistance', 'sex', and 'socioeconomic'. Other keywords included: 'effects of', 'thyroid', 'thyroid cancer', 'United States', 'health disparities', 'risk factors', and 'race and ethnicity'. Articles were selected after screening titles and abstracts for relevancy, with a particular focus on research done in the United States. Afterwards, the full text for each article was acquired. Some potential risk factors - such as radiation exposure, autoimmunity, chromosomal alterations/non-hereditary conditions, hereditary conditions, and thyroid nodules - included publications since 2000 as the findings for these risk factors are less likely to change significantly within the last 20 years compared to the others. Each potential risk factor was reviewed for whether they may impact thyroid cancer incidence and aggressiveness differently by racial/ethnic group, if no difference exists, or if further research is necessary to examine their relationship to health disparities.

3. Risk factors potentially contributing to TC health disparities

3.1. Genetic Factors

Hereditary conditions influencing TC health disparities

Although more than 90% of thyroid cancers are sporadic, thyroid cancer has been shown to have a significant hereditary component with many hereditary forms exhibiting more aggressive courses. Hereditary thyroid neoplasms are divided into those that arise from follicular cells, familial non-medullary thyroid carcinoma (FNMTC) and those arising from calcitonin-producing C cells, familial medullary thyroid carcinomas (FMTCs).

FNMTCs are further divided into syndromes where non-thyroid tumors predominate, and those where non-medullary thyroid tumors predominate. The former includes familial adenomatous polyposis (FAP), Cowden Syndrome (CS), Carney complex (CNC), Werner syndrome (WS), McCune-Albright syndrome, Pendred syndrome, and DICER1 syndrome. The latter group includes pure familial papillary thyroid carcinoma (fPTC), fPTC with multinodular goiter, and fPTC with papillary renal cell carcinoma (Guilmette and Nosé, 2018).

Medullary thyroid cancer (MTC) is hereditary in 25% of cases, and commonly occurs as part of the multiple endocrine neoplasia II syndromes, although a heritable MTC-only syndrome is reported. Hereditary and sporadic MTC are both driven by mutations in the RET proto-oncogene; however, hereditary forms are more likely to present bilaterally and arise at an earlier age, with MENII carrying a near 100% lifetime risk of developing MTC (Guilmette and Nosé, 2018). Despite earlier presentation of hereditary MTC, one study found the overall 10-year survival to be 100% in hereditary MTC compared to 80% in sporadic MTC (Xu et al., 2012). Although hereditary MTC has been reported across varying ethnic groups, there

is little research investigating the racial distribution of hereditary MTC.

Familial adenomatous polyposis (FAP) is an autosomal disorder caused by a germline mutation in the adenomatous polyposis coli (APC) gene. Around 2-12% of patients with FAP develop PTC, with a 160-fold greater risk of developing PTC than unaffected individuals. More than 90% of the cases have a histologic variant, called cribriform-morular PTC (CMV-PTC), and they are more likely to affect females and present bilaterally. Overall, the prognosis is good and only 10% of CMV-PTC cases are aggressive (Guilmette and Nosé, 2018). FAP has been described in all races but there is little research comparing the prevalence between different racial groups. One study investigated the racial variation in APC mutations and found that the overall APC mutation rate was higher in Asians and African Americans compared to Europeans (Inra et al., 2015). Further research is indicated to evaluate whether the risk of thyroid cancer with FAP varies between racial/ethnic groups.

Out of all FNMTC, Cowden Syndrome (CS) is an autosomal dominant condition caused by a germline mutation in PTEN. Although other genes have also been implicated in CS, intact PTEN virtually excludes the diagnosis. Two-thirds of CS patients develop thyroid tumors, with the majority of follicular origin, including follicular adenoma and follicular carcinoma (Guilmette and Nosé, 2018). Although most of the patients with CS reported in the literature are European (Garofola et al., 2022), at present, the true racial distribution is not yet well described.

Carney complex (CNC) is a rare autosomal dominant syndrome with the majority harboring mutations in the PRKAR1a gene. Up to 75% have multiple thyroid nodules but they are at minimal risk for developing thyroid malignancy. Thyroid neoplasms within CNC patients are more likely to be found in young females and both follicular thyroid carcinoma and PTC can be seen (Guilmette and Nosé, 2018). There have been more than 750 reported cases with affected Europeans, Asians (from all continents), and African Americans described (Correa et al., 2015).

Werner syndrome (WS) is an autosomal recessive syndrome caused by WRN mutations leading to defects in DNA repair and replication that leads to premature aging. Thyroid cancer typically presents in the third decade, with a lower female to male ratio (2:1). They carry a three-fold increased risk for follicular carcinoma and a six-fold increased risk for anaplastic thyroid carcinoma (Guilmette and Nosé, 2018). There is a high prevalence of WS in Japan, where WS has been reported up to 1 in 20,000-40,000 live births compared to 1 in 100,000 births worldwide. In the United States the prevalence is estimated to be even less as 1 in 200,000 live births (Sickles and Gross, 2022). Up to 18% of Japanese patients with WS also develop thyroid cancer and Europeans have an increased risk of PTC. The median life expectancy of WS patients is approximately 54 years, with thyroid cancers and cardiac diseases being the most common causes of death (Guilmette and Nosé, 2018).

There are some cases of FNMTC in which genetics is not yet known. But it is believed that these cases are autosomal dominant and six potential chromosomal regions have been implicated. This category of FNMTC is diagnosed when three or more first-degree relatives have non-medullary thyroid cancer, usually PTC. The tumors are more likely to present at a younger age and have a more aggressive clinical course with a worse prognosis (Guilmette and Nosé, 2018). Further research is indicated on the racial distribution within all these various types of FNMTC.

3.2. Environmental Factors

3.2.1. Radiation exposure in TC health disparities

The radiosensitivity of the thyroid gland is well documented (Lubin et al., 2017). Radiation exposure in childhood is associated with a higher risk of thyroid cancer than radiation exposure in adults (Lee et al., 2019), and the risk increases from about 5 years after exposure (Furukawa et al., 2013). Radiation exposure in children increases their likelihood of developing papillary thyroid cancer later in life, which is the most common type of thyroid cancer (Bogović Crnčić et al., 2020; Yildirim Simsir et al., 2020). Children and adolescents exposed to radioactive iodine from the Chernobyl fallout have also shown a higher risk of thyroid cancer (Furukawa et al., 2013). This trend has also been seen in animal models. It was reported that more radiation-induced thyroid tumors developed in 10-day-old infant rats than in adult rats (Matsuu-Matsuyama et al., 2021). Another study demonstrated that the thyroids of 1-week-old neonatal rats are more sensitive to ionizing radiation at 12 Gy compared to those from adult rats (Matsuu-Matsuyama et al., 2021).

Increase in the use of imaging in medicine, such as CT examinations, is believed to play a role in the increased incidence of thyroid cancer in the United States (Yildirim Simsir et al., 2020). This means that differences in access to healthcare between patients of different ethnic groups may affect the population's exposure to radiation, and therefore incidence of thyroid cancer. For example, in the 1970s and 80s, there were many medical professionals who came to the United States from the Philippines. This group most likely had better access to CT examinations and had additional occupational exposure to ionizing radiation. In fact, one study reported that highly educated Filipinos had higher proportionate mortality due to thyroid cancer than less educated Filipinos (Nguyen et al., 2017). On the other hand, in a single hospital study of 1,024 female nurses and 2,631 non-nurse females with both groups receiving their annual health examinations over a period of two years, generally no difference was found in incidence of thyroid cancer between the two groups (Kim and Woo, 2016). This suggests more research is needed to determine if this increased incidence among Filipinos is due to job or socioeconomic status-related radiation exposure or if it is largely due to inherent biological factors within the Filipina population.

3.2.2. Iodine deficiency in TC health disparities

The thyroid gland uses iodine to make thyroid hormones. When the body is low on iodine and there is a decrease in the level of thyroid hormones, the pituitary gland produces more TSH to compensate. However, TSH is a growth stimulating factor for thyroid follicular cells. This suggests that diets with insufficient intake of iodine could play a role in follicular thyroid cancer (Bogović Crnčić et al., 2020). However, low iodine diets are necessary prior to radioactive iodine (RAI) treatment for thyroid cancer patients with a thyroidectomy (Nguyen et al., 2017). Studies showed that thyroid cancer patients on low-iodine diets before radioactive iodine (RAI) treatment experienced enhanced uptake and maximized destruction of thyroid cancer cells (Li et al., 2016; Nguyen et al., 2017). However, in Filipino Americans who have a higher intake of iodine-rich foods - such as seafood, dairy, grains, and eggs - treatment was less effective compared to other patients preparing for RAI treatment (Herrick et al., 2018; Nguyen et al., 2017). Another study analyzed the median urinary iodine concentration (mUIC) of individuals in the United States as a measure of dietary iodine (Herrick et al., 2018). Non-Hispanic Asian women of reproductive age had low mUIC, and therefore mild iodine deficiency, compared to non-Hispanic African

American women of reproductive age despite both populations consuming similar amounts of dairy and grains (Herrick et al., 2018). When looking at the total population of individuals ages 6 years and above, non-Hispanic Asians consumed more amounts of dairy and grains compared to non-Hispanic African Americans but continued to have lower mUIC (Herrick et al., 2018). Since Asian individuals tend to consume more rice than other racial groups, it is possible that differences in the type of grain consumed by ethnic groups could influence iodine levels (Herrick et al., 2018). Additionally, this study found that non-Hispanic Asians consumed higher amounts of soy products compared to other racial groups and suggests that substances in these soy products could inhibit iodine uptake by the thyroid (Herrick et al., 2018). These data suggest that differences in diet among racial/ethnic groups may impact dietary iodine levels and, therefore, RAI treatment outcome.

3.2.3. Environmental pollutants influencing TC health disparities

Populations are exposed to varying levels of harmful chemicals in the environment through water, air, food, or soil (Yildirim Simsir et al., 2020). A few of these chemicals – such as benzene, formaldehyde, and pesticides – have been linked to goiter and nodular goiter formation as well as papillary thyroid cancer (Bogović Crnčić et al., 2020; Yildirim Simsir et al., 2020). Another set of chemicals, nitrates, are commonly found in ready-made foods and, when at above-average levels, can affect iodine uptake and increase the risk of thyroid cancer (Bogović Crnčić et al., 2020). Additionally, polybrominated diphenyl ethers (PBDEs) found in many industrial materials may induce abnormal thyroid cell proliferation leading to a risk of thyroid cancer (Bogović Crnčić et al., 2020).

Considering residential segregation and racial/ethnic diversity by geographic level in the United States, a geospatial approach to cancer research could allow for a better understanding of whether environmental pollutants differentially impact certain racial/ethnic groups (Korycinski et al., 2018; Sahar et al., 2019). An example of this approach includes the application of geographic information science (GIScience) to cancer research. This allows researchers to analyze spatial data, visualize cancer and risk factor data on a map, and investigate geographic disease patterns and clusters (Sahar et al., 2019). Most geospatial cancer research studies have been published after 2010 and are affiliated with NCI-designated Cancer Centers (Korycinski et al., 2018). Additionally, despite this recently growing area of research, most of these studies have looked at other cancer types besides thyroid cancer – such as breast, prostate, and colorectal cancers (Korycinski et al., 2018). One study done in Vermont found no correlation between thyroid cancer incidence and proximity to tertiary healthcare centers or socioeconomic status (Hanley et al., 2015). However, the researchers note that Vermont has a population that is >95% European American and has >92% healthcare insurance coverage, providing little evidence for racial/ethnic minority groups (Hanley et al., 2015). Another study done in California found that disadvantaged communities, or DACs, had higher amounts of nitrate well contamination as well as a significant correlation between well contamination per square mile and thyroid cancer incidence (Tariqi and Naughton, 2021). In particular, there was a two times greater thyroid cancer incidence compared to non-DACs (Tariqi and Naughton, 2021). DACs tend to have a higher population density and amount of people per well, exposing a larger number of people to contaminated drinking water and suggesting that certain populations are disproportionately affected by environmental

factors (Tariqi and Naughton, 2021). These studies highlight the importance of further geospatial research on thyroid cancer to address geographic and racial/ethnic cancer disparities in the United States.

Another area of consideration regarding environmental pollutants and their possible contribution to thyroid cancer racial/ethnic disparities is birthplace. One study – although limited by birthplace data – has looked at whether birthplace alters incidence rates of thyroid cancer among Asians (Horn-Ross et al., 2011). Researchers found that US-born Chinese women had higher papillary thyroid cancer incidence rates than China-born Chinese women, and a reverse trend was observed among Filipino American and Japanese American women (Horn-Ross et al., 2011). Another study of five Asian female subgroups in California from 1988 to 2004 showed that Japan-born Japanese women had a significantly higher papillary thyroid cancer incidence rate compared to US-born Japanese women, and a reverse trend was observed among Chinese and Filipina American women (Horn-Ross et al., 2011). This study also found that foreign-born Chinese, Korean, Vietnamese, and Filipina American women had papillary thyroid cancer incidence rates that peaked at 70 years of age, whereas their US-born Asian subgroup counterparts peaked during reproductive and menopausal years (Horn-Ross et al., 2011). Overall, these findings suggest that exposures related to immigration and acculturation of these ethnic groups may have impacted their risk of thyroid cancer (Horn-Ross et al., 2011)(21). Further research is needed that includes other racial/ethnic groups and analyzes how these factors could affect thyroid cancer incidence.

3.3. Socioeconomic Factors

3.3.1. Radioiodine treatment

Within the last few decades, the use of RAI treatment for thyroid cancer has increased (Pasqual et al.). One study found that patients who had a thyroidectomy for low-risk papillary thyroid cancer were more likely to undergo RAI treatment if they had lower healthcare access (Marti et al., 2015). This includes those that are uninsured, in poverty, attained only a high school education, are non-English speaking, or unemployed. Additionally, racial/ethnic minority populations are more likely to be uninsured and have decreased access to high-quality care, whether due to geographic area or stereotyping by healthcare providers (Artiga S, 2021; National Research Council Panel on Race and Health in Later, 2004). This suggests that some racial/ethnic minority populations of the United States may experience inappropriate use of RAI treatment, an aggressive therapy for low-risk PTC (Marti et al., 2015).

When using RAI for differentiated thyroid cancer (DTC) treatment, one recent study found that RAI treatment increased the risk of leukemia and several types of solid cancer such as breast cancer, regardless of racial/ethnic group (Pasqual et al.). However, RAI treatment for DTC did not increase the risk of second thyroid cancer (Pasqual et al.). This indicates that RAI treatment may not be a risk factor for thyroid cancer which differentially impacts certain racial/ethnic groups. Further studies could examine the racial/ethnic variations in RAI treatment sensitivity or resistance to determine if these contribute to thyroid cancer health disparities.

3.3.2. Diagnostic differences in TC health disparities

Many literature suggest that thyroid cancer's racial/ethnic differences could be related to socioeconomic status and insurance coverage impacting dissimilar access to US-guided FNA and

computed tomography (CT) (Brown et al., 2010; Keegan et al., 2015; Morris et al., 2013; Reitzel et al., 2014; Roche et al., 2016; Stroup et al., 2012; Weeks et al., 2018; Zevallos et al., 2015). While thyroid cancer incidence has been increasing over time irrespective of socioeconomic status, a study in Texas reports a difference in the rate of increase between low and high socioeconomic status ethnic groups (Reitzel et al., 2014). In particular, the study found a low thyroid cancer incidence rate among low socioeconomic status Non-Hispanic African Americans and Hispanic Americans and a high thyroid cancer incidence rate among high socioeconomic status Non-Hispanic African Americans and Hispanic Americans (Reitzel et al., 2014). Similarly, a study in North Dakota found that counties with higher median income levels had increasing incidence rates, likely due to detection bias associated with increased access to physicians (Schwartz and Klug, 2019). Studies have also shown that among thyroid cancer patients, European Americans (vs. non- European Americans) have greater odds of having tumors <40mm, and this variability in diagnosis is likely due to differences between races in their access to medical care to detect these tumors; particularly, European Americans tend to have and seek more access to medical care than racial/ethnic minority patients (National Research Council Panel on Race and Health in Later, 2004; Weeks et al., 2018). However, once tumors increase to a size ≥40mm in other races/ethnicities, they become palpable, thus leading patients to seek medical attention similarly (Weeks et al., 2018).

Regarding insurance coverage, it has been found that insured patients were 45% more likely to be diagnosed with small tumors compared to the uninsured (Weeks et al., 2018). A study found that adolescent and young adult patients who were diagnosed between 2001 and 2010 had a worse overall survival if they had no medical insurance (Keegan et al., 2015). Another study found that age-adjusted thyroid cancer incidence rates were 2-3 times greater in uninsured Hispanic Americans than in uninsured European Americans (Weeks et al., 2018). The reverse incidence rate was found in insured Hispanic Americans compared to insured Non-Hispanic European Americans (Weeks et al., 2018). As mentioned previously, racial/ethnic minority populations are more likely to be uninsured (Artiga S, 2021; National Research Council Panel on Race and Health in Later, 2004), therefore these findings suggest that access to medical care and insurance could influence incidence rates among racial/ethnic groups differentially.

3.4. Metabolic Factors

Obesity, metabolic syndrome, and insulin resistance in TC health disparities

While there has been a rise in thyroid cancer incidence, the Centers for Disease Control and Prevention (CDC) reports that there has also been a rise in obesity in the United States; obesity prevalence has increased from 30.5% to 42.4% from 1999-2000 through 2017-2018, and the prevalence of severe obesity has increased from 4.7% to 9.2% (https://www.cdc.gov/obesity/data/adult.html). Besides being associated with a number of chronic diseases, such as diabetes mellitus and cardiovascular disease, studies have also shown that obesity puts individuals at a higher risk of thyroid cancer compared to those with normal weight (Bogović Crnčić et al., 2020; Clinckspoor et al., 2011; Franchini et al., 2022; Hales et al., 2020; Kushchayeva et al., 2022; Ma et al., 2022; Zhao et al., 2019). Studies found that high BMI was significantly associated with the risk of papillary, follicular, and anaplastic, but not medullary, thyroid cancers (Kitahara et al., 2016; Zhao et al., 2019). Furthermore, studies have shown that high BMI was associated with larger tumor size, multifocality, and

advanced tumor-node-metastasis (TNM) stage (Ma et al., 2022; Zhao et al., 2019). In addition to high BMI, a waist circumference ≥109 cm has also been found as a strong predictor of thyroid cancer (Lubin et al., 2017; Ma et al., 2022). While one cohort study found that higher BMI was not associated with more aggressive tumor features and recurrence or persistence, this study looked at a 93% European American population at a single institution, therefore, the results may have been limited by the lack of racial/ethnic and socioeconomic diversity (Paes et al., 2010).

In these ongoing studies, it is important to recognize that obesity impacts some ethnic/racial groups more than others. In particular, non-Hispanic African American adults have the highest prevalence of obesity (defined as a BMI of greater than or equal to 30) and severe obesity (defined as a BMI greater than or equal to 40) compared to other ethnic/racial groups (Hales et al., 2020). By contrast, non-Hispanic Asian adults have the lowest prevalence of obesity (Hales et al., 2020). Despite having lower BMI's than other racial/ethnic groups, Asian Americans tend to have high prevalence rates of metabolic syndrome, especially amongst Filipinos and Asian Indians (Palaniappan et al., 2011). Filipinos and Asian Indians also tend to have a higher prevalence of obesity than non-Hispanic European Americans (Palaniappan et al., 2011). This is particularly interesting considering the disproportionate impact Filipinos face from thyroid cancer as well. Therefore, further research is necessary to determine whether some factors which may impact obesity for a certain ethnic/racial group could impact that group's risk for thyroid cancer.

3.5. Behavioral Factors

Lifestyle and diet in TC health disparities

With the growing evidence that obesity may be associated with an increased risk of thyroid cancer, it is advised that individuals adopt a lifestyle that includes at least 60 min/day of moderate physical activity to reduce the incidence of obesity-related thyroid cancer (Franchini et al., 2022; Ma et al., 2022). Some studies in the United States have found that higher levels of physical activity could reduce the risk of some cancers (bladder, breast, colon, endometrial, esophageal adenocarcinoma, and gastric cardia) while increasing the risk for some other cancers (lung, ovarian, pancreatic, and renal cancer) (Friedenreich et al., 2021). However, these studies have not looked at the relationship between thyroid cancer, specifically, and physical activity (Friedenreich et al., 2021). Some research has been done to examine this relationship in Korea; less physical activity in women was associated with a decreased risk of thyroid cancer, and a positive correlation was found between physical exercise and thyroid cancer (Kim et al., 2021; Lee et al., 2020). Further research is needed to examine the relationship between physical activity and thyroid cancer among populations in the United States, especially since physical activity in the United States varies between racial/ethnic groups which could impact thyroid cancer outcomes. In particular, the CDC reports that Hispanic adults have the lowest physical activity outside of work and Non-Hispanic Asian adults have the highest.

Diets can vary by racial/ethnic group due to social and cultural differences between populations (Satia, 2009). Variations in iodine intake among racial/ethnic groups could be from differences in the consumption of seafood, dairy, grains, and eggs (Bogović Crnčić et al., 2020; Herrick et al., 2018; Nguyen et al., 2017). Nitrate/nitrite intake can vary among racial/ethnic groups due to consumption of processed foods and meats, which is more common in certain racial/ethnic groups than others (Said Abasse et al., 2022). In particular, one study found that Non-Hispanic European Americans were more likely than other racial/ethnic groups to consume excess processed meats (Gudenkauf and

Thrift, 2021). This study also found that Non-Hispanic African Americans had more cancer types attributable to processed meat consumption (Gudenkauf and Thrift, 2021). However, this study focused on Non-Hispanic European Americans, Non-Hispanic African Americans, and Hispanics while grouping all other racial/ethnic groups together. Further research is needed to examine differences in diet practices and nutrient intake among racial/ethnic subgroups since certain subgroups, such as Filipino Americans within the Asian American population, tend to have high consumption of processed foods. Social and cultural differences in diet could, therefore, place some racial/ethnic groups at a higher risk of thyroid cancer. It is worth noting that socioeconomic differences can play a role in access to ingredients and types of foods as well as how much physical activity individuals can realistically engage in due to barriers such as cost and time, placing minority populations at particular risk of thyroid cancer.

Some other lifestyle practices, such as smoking and alcohol consumption, could affect one's risk of thyroid cancer. In the United States, one study examining smoking found that e-cigarette users had a higher prevalence of several cancer types - including thyroid cancer - compared to traditional smokers (Chidharla et al., 2022). Smoking and alcohol consumption habits vary by racial/ethnic group, as well, and could be due to social and cultural factors. According to the CDC, cigarette smoking prevalence is the highest in Native Americans and Alaska Natives and lowest among Asian Americans - although within Asian subgroups, Koreans and Vietnamese have high smoking prevalence (Chartier and Caetano, 2010). Alcohol consumption tends to be most common in European Americans, lowest in Asian Americans, and similar amongst Native Americans, Hispanics, and African Americans; however Native Americans tend to have the highest prevalence of heavy and binge drinking (Chartier and Caetano, 2010). These variations in smoking and alcohol consumption habits could contribute to the thyroid cancer health disparities seen between racial/ethnic groups in the United States, however, further research is needed to examine these relationships.

3.6. Biological Factors

3.6.1. Thyroid-stimulating hormone (TSH) level in TC health disparities

Research suggests that thyroid stimulating hormone (TSH), also known as thyrotropin, mediates thyroid cell growth factors, such as IGF-I and insulin (Bogović Crnčić et al., 2020). Therefore, high levels of TSH may lead to an enlarged thyroid gland, or goiter (Bogović Crnčić et al., 2020; Yildirim Simsir et al., 2020). One study has found that higher levels of TSH is associated with a fourfold increase of thyroid cancer and a higher risk of advanced stage differentiated thyroid cancer (Bogović Crnčić et al., 2020). Another study has found that even minimal elevations of serum TSH over time could lead to increased thyroid volume and goiter (Yildirim Simsir et al., 2020). Obese individuals are at a higher risk of increased TSH levels and the development of goiter and papillary thyroid cancer (Yildirim Simsir et al., 2020). Therefore, it is not surprising that TSH suppression therapy following radioiodine treatment can reduce the recurrence rate of differentiated thyroid cancer (Bartenstein et al., 2014; Kim et al., 2014; Wang et al., 2022). However, further research is needed to look at whether levels of TSH vary by race/ethnicity in the United States.

3.6.2. Sex in TC health disparities

Thyroid cancer is one of the most rapidly increasing types of cancer in both women and men (Lim et al., 2017; Rahbari et al., 2010; Tortolero-Luna et al., 2019; Weeks et al., 2018). It is known that women are about three times more likely to be diagnosed with thyroid cancer than men, particularly through

the finding of small tumors (<40mm) (Rahbari et al., 2010; Weeks et al., 2018). This places thyroid cancer as one of the top ten most diagnosed cancers in women as of 2018 (Rahbari et al., 2010; Weeks et al., 2018). Furthermore, follicular and papillary thyroid cancers make up approximately 80% of thyroid cancer cases in women, and papillary thyroid cancer is three times more common in women than in men (Horn-Ross et al., 2011; Rahbari et al., 2010). However, it is also known that men have a higher mortality rate compared to women (Keegan et al., 2015; Rahbari et al., 2010; Tortolero-Luna et al., 2019). Additionally, men are more likely to have regional/distant stages of disease upon diagnosis, unfavorable clinicopathological characteristics such as angioinvasion, and a higher risk for recurrence of well-differentiated thyroid cancer (Gajowiec et al., 2021; Keegan et al., 2015; Zahedi et al., 2020). While some studies have been looking at differences between men and women in hormonal regulation, androgen receptor gene expression, and certain somatic mutations, further research is needed to find if there are any strong associations with thyroid cancer (Asban et al., 2019; Chou et al., 2020; Megwalu et al., 2021; O'Connell et al., 2021; Rahbari et al., 2010).

When looking at whether sex as a risk factor for thyroid cancer varies by race/ethnicity, one study found a ratio of female to male incidence rates of 3:1 to 4:1 across racial/ethnic groups, including European Americans, Hispanics, Asians, African Americans, and Native Americans (Weeks et al., 2018). It is likely that this higher incidence among women and the size of tumors upon diagnosis could be due to differences in access to medical care and women receiving more regular check-ups than men (Rahbari et al., 2010; Weeks et al., 2018). Generally, however, there is a uniform 3:1 ratio of sex disparities across all ethnicities, suggesting that sex is a risk factor for thyroid cancer that does not differentially impact certain racial/ethnic groups.

Based on these findings, it is of interest to investigate differences in sex hormone levels among racial/ethnic groups. For example, a study found that African American men had higher sex hormone binding globulin (SHBG) concentration and serum estradiol levels than Hispanic American and European American men (Rohrmann et al., 2007). Serum testosterone levels did not differ between African American men and European American men, however Hispanic American men had higher serum testosterone levels than the other racial/ethnic groups (Rohrmann et al., 2007). Another study looked at variations in hormone levels among overweight, glucose-intolerant, postmenopausal women (Kim et al., 2012). This study found that, among women not using estrogen, Non-Hispanic European Americans had higher baseline total and bioavailable estradiol and testosterone levels than Hispanics, as well as higher baseline bioavailable estradiol and lower levels of SHBG than African Americans (Kim et al., 2012). Therefore, while sex differences exist across all racial/ethnic groups, it is still possible that variations in androgen and androgen receptor levels between racial/ethnic groups could contribute to the racial/ethnic disparity in thyroid cancer. Future studies are required to investigate the correlation between androgen and thyroid cancer health disparities.

3.6.3. Autoimmunity in TC health disparities

Autoimmune diseases (AD) are caused by inflammation of organs due to production of antibodies against self-structures and cytotoxic action of T cells (Fröhlich and Wahl, 2017). AD is prevalent in the population and is more common in women (≥85%) than in men. Additionally, autoimmune thyroid disease (AITD) is one of the most common types (Fröhlich and Wahl, 2017). Graves' disease and Hashimoto's thyroiditis (HT) are

examples of thyroid autoimmune diseases (Umar et al., 2010).

In Graves' disease, hyperthyroidism (low TSH and elevated free T4 concentrations) is caused by thyroid-stimulating autoantibodies to the TSH receptor (TSHR) , which may lead to hyperfunction of the thyroid gland (Umar et al., 2010). After delivering a baby, some patients may develop forms of autoimmune thyroid dysfunction, such as Graves' disease (Inaba and Akamizu, 2000). Another is postpartum thyroiditis, which is also believed to be an autoimmune disorder, and its prevalence ranges from 3 to 8 percent of all pregnancies (Inaba and Akamizu, 2000). It is painless and occurs within 6 months after pregnancy, with a return to normal thyroid function typically within a year, although some patients develop permanent hypothyroidism as a result (Inaba and Akamizu, 2000). It is characterized by transient thyrotoxicosis followed by hypothyroidism or by one or the other occurring in the first year after parturition (Inaba and Akamizu, 2000). Diagnostic tests reveal that serum TSH is suppressed, associated with an increase in serum FT3 and FT4 levels (Inaba and Akamizu, 2000).

In HT, hypothyroidism (elevated TSH and low free T4 concentrations) is associated with thyroid peroxidase and thyroglobulin autoantibodies (McLachlan et al., 2007), and is thought to be caused by a TSH stimulation-blocking antibody (TSBAb) which blocks the action of the TSH hormone causing damage to the thyroid gland (Umar et al., 2010). Retrospective pathological studies and FNA cytological studies have shown an association between HT and papillary thyroid carcinoma (PTC) (Boi et al., 2017). Most pathological studies showed high prevalence of PTC in HT (Boi et al., 2017). In most FNAC studies, increased thyroid-stimulating hormone (TSH) levels were the main risk factor for malignancy (Boi et al., 2017).

Additionally, several studies have shown an association between chronic inflammation and increased risk of developing differentiated thyroid cancers (DTCs) (Pagano et al., 2018). This suggests that the inflammatory microenvironment is essential in cellular transformation and tumor progression (Pagano et al., 2018). It has been demonstrated that inflammatory cells within the cancer site and activation of oncoprotein-mediated signaling in epithelial cancer cells influence thyroid cancer progression (Pagano et al., 2018).

Racial disparities have been noted in autoimmune thyroid conditions (Table 2). A study has shown that African Americans and Asians are much more likely to develop Graves' disease than European Americans (McLeod et al., 2014). On the other hand, European Americans have a greater risk of developing HT compared to other ethnic groups (McLeod et al., 2014). When evaluating thyroid function and autoimmunity in African American and European American women during pregnancy and the postpartum period, another study found that African American women always had lower TSH values than European American women (Walker et al., 2005). These findings provide awareness of racial disparities in thyroid autoimmune disorders.

Table 2. Racial Disparities in Autoimmune Thyroiditis.

	European Americans (EA)	African Americans (AA)	Asian Americans
Graves' Disease (McLeod et al., 2014)	Less susceptible	More susceptible	More susceptible
Hashimoto Thyroiditis (McLeod et al., 2014)	More susceptible	Less susceptible	Less susceptible
Pregnancy/Postpartum (Walker et al., 2005)	Higher TSH values compared to AAs	Lower TSH values compared to EAs	-

3.6.4. Thyroid nodule size in TC health disparities

It is proposed that the dramatic increase in thyroid cancer incidence rates within the last few decades could be due to improved diagnostic techniques and the introduction of ultrasound-guided fine-needle aspiration (US-guided FNA) into the United States healthcare system in the 1990s, which aids in detecting tumors that are not easily discovered by palpation (La Vecchia et al., 2015; Lim et al., 2017; Tortolero-Luna et al., 2019; Weeks et al., 2018; Zevallos et al., 2015). More sensitive diagnostic procedures, such as CT or MRI scans (done for other medical problems), can detect nonpalpable, incidental thyroid nodules (ITNs) that might not otherwise have been found in the past (Fisher and Perrier, 2018). Imaging studies can detect up to 10 times more nodules than by palpation, most of which are benign (Fisher and Perrier, 2018).

Approximately 5 to 15% of nodules are found to be malignant (Alexander et al., 2012). For diagnostic purposes, nodules 1cm or larger in diameter prompt diagnostic US-guided FNA, which is the only method routinely used for thyroid nodule evaluation (Alexander et al., 2012; Yoon et al., 2014). However, about 15 to 30% of thyroid nodules evaluated by FNA are indeterminate, so it is unclear whether they are benign or malignant (Alexander et al., 2012). Indeterminate nodules are often referred for diagnostic surgery, though most of these nodules are shown to be benign (Alexander et al., 2012). This exposes these patients to a 2 to 10% risk of serious surgical complications, and they could require thyroid hormone replacement therapy for life to overcome hypothyroidism (Alexander et al., 2012). Future work is needed for better diagnostic tools in preoperative diagnosis of thyroid cancer.

Autopsy studies estimate that thyroid nodules may be present in up to 50% to 60% of all adults (Fisher and Perrier, 2018). Women are more frequently affected than men (4:1), and the prevalence of thyroid nodules in women increases with age (Fisher and Perrier, 2018). Studies have been done exploring ethnicities affected. Zheng et al. showed that thyroid nodules in African Americans had consistently lower rates of harboring malignancy compared to other groups (Zheng et al., 2022). Among different ethnic groups represented in the study, the prevalence of thyroid malignancy was 24.0% of African Americans, 52.1% of Caucasian Americans, 58.7% of Hispanic Americans, and 71.7% of Asian Americans (Zheng et al., 2022). Iwata et al. noted that African Americans have a much lower incidence of thyroid cancer than other ethnic groups despite presenting with larger nodules, and European Americans have a greater risk (Iwata et al., 2018). This study aimed to see if there was a true difference in the thyroid cancer rates between these ethnicities, or if socioeconomic status perhaps played a role (Iwata et al., 2018). They found that European Americans have a higher incidence not only due to diagnostic bias, but also due to a true difference in cancer prevalence (Iwata et al., 2018). Another study aimed to determine whether patients of Filipino descent are at increased risk of thyroid

cancer compared to matched controls (Clark et al., 2006). This group found that Filipino patients with thyroid nodules are at significantly increased risk. Thus, suspicion for malignancy should be high when evaluating these patients. Recently, we showed a differential expression of vitamin D binding protein (DBP) in two different ethnic groups, which was related to advanced stage thyroid cancer in Filipino Americans compared to European Americans (Mull et al., 2021); higher DBP expression in European Americans correlated to better prognosis. We further demonstrated that differential small non-coding RNAs may potentially influence the poor prognosis in Filipino Americans versus European Americans (Rood et al., 2021).

3.6.5. Chromosomal alterations/non-hereditary conditions influencing TC health disparities

Although germline mutations are very rare, somatic mutations play an important role in thyroid cancer oncogenesis. Several genetic alterations have been implicated in the development of thyroid cancer, including activation of signaling pathways by either recombination events or point mutations, with some mutations associated with more aggressive forms (Bogović Crnčić et al., 2020; Yildirim Simsir et al., 2020).

Somatic mutations can cause dysregulation of mitogen-activated protein kinases (MAPK), phosphoinositide 2 kinase-AKT (PI3K-AKT), and wingless-related integration site (WNT) cell signaling pathways (Singh et al., 2021). They are some of the most common pathways associated with thyroid cancer (Singh et al., 2021). Both MAPK and PI3K-AKT pathways are coupled to the cell membrane receptor tyrosine kinase (RTK), which leads to downstream intracellular signaling and ultimately activation and deactivation of genes related to cell growth, proliferation, and survival (Xing et al., 2013). The WNT pathway similarly leads to disordered cellular growth by preventing degradation of β-catenin, thus allowing its localization into the nucleus and subsequent activation of transcription factors involved in cellular proliferation and cell-cell adhesion (Pai et al., 2017). Activating point mutations of RAS and BRAF and rearrangements of RET/PTC and NTRK genes within the MAPK pathway, are common drivers of papillary thyroid cancer (PTC). In contrast, follicular thyroid cancer (FTC) frequently has alterations of the PI3K-AKT pathway such as activating mutations of PIK3CA, RAS, and AKT1, and deactivating mutations of PTEN. Other mutations such as p53 and TERT promoter mutations, and WNT/β-catenin pathway alterations have been implicated in thyroid cancer disease progression and dedifferentiation (Prete et al., 2020).

There are few studies comparing the prevalence of these mutations across different racial/ethnic groups. One study evaluated radioiodine refractory thyroid (RAIR) cancers and found that European race/ethnicity was associated with a reduced odds ratio of radioiodine refractoriness (Shobab et al., 2019). Additionally, 50% of patients with RAIR had mutations in the RAS/RAF pathway; however, the prevalence of RAS/RAF mutation within Europeans was not directly measured (Shobab et al., 2019). Another study performed whole-genome genotyping on European and African American patients with RAIR and found that the thyroglobulin, BRCA1, and the NSMCE2 haplotypes were uniquely associated with African Americans (Hurst et al., 2019). Differences in mutation can explain the established differences in the incidence of thyroid cancer among racial/ethnic groups. Different mutations also carry varying prognoses. Therefore, differences in chromosomal alterations between races/ethnicities can potentially contribute to the varying disease outcomes seen across racial/ethnic groups. Additional studies are indicated to further explore the demographics and other racial/ethnic groups with common thyroid cancer mutations.

4. Conclusions

Through this literature review, several risk factors are found to potentially impact thyroid cancer incidence and aggressiveness differently by racial/ethnic groups. Chromosomal alterations/non-hereditary conditions, autoimmunity, thyroid nodules, and socioeconomic differences are identified as factors that vary by racial/ethnic group and influence thyroid cancer incidence and outcomes. Some of these potential risk factors require further research to incorporate more racial/ethnic groups. The only risk factor that does not vary by racial/ethnic group is sex disparities. However, differences found in sex hormone levels between racial/ethnic groups may suggest their possible influence on thyroid cancer health disparities and necessitates further research. Some studies on iodine deficiency, environmental pollutants, obesity/metabolic syndrome/insulin resistance, and lifestyle/diet as risk factors for thyroid cancer suggest that certain racial/ethnic groups could be differentially impacted. Further research, however, is needed to specifically examine their relation to thyroid cancer or to clarify whether certain racial/ethnic groups are differentially impacted in the United States. Additionally, while some racial/ethnic disparities exist in regards to the use of RAI treatment, recent research suggests that this is not a risk factor for secondary thyroid cancer. Other potential risk factors - including radiation exposure, hereditary conditions, and TSH level - have not yet been studied regarding their potential influence on thyroid cancer incidence and outcomes for different racial/ethnic groups in the United States. These should be given priority in future research work.

5. Limitations

A limitation of our literature review is that we did not perform a meta-analysis of potential factors contributing to thyroid cancer health disparities. However, we are currently gathering insight into the factors that may contribute to the differences in the genetic and epigenetic pathways of health disparities. Additionally, the findings of our literature review are limited by the racial/ethnic groups that have been studied by the articles reviewed. In particular, some studies focused on two racial/ethnic populations only or may have grouped some racial/ethnic populations together. Therefore, it is possible that variations in the potential thyroid cancer risk factors between racial/ethnic groups may have been limited by the lack of diversity in some of these studies.

6. Future Directions

There are several areas of research which need to be addressed regarding thyroid cancer health disparities, as highlighted by this literature review. One such area of interest for our lab is the sex hormone-induced immune pathway in cancer cells. In future work, we will examine this pathway in relation to racial/ethnic groups in the United States to understand why Filipino Americans have higher TC incidence rates. Additionally, although biologic differences were thought to be responsible for the difference in the severity and progression of thyroid cancer, no genetic or molecular level differences were reported so far. This literature review contributes to our knowledge of the several factors that may be correlated to the differential miRNA expression we observe within ethnic groups. Future work may include taking these factors into account in our statistical analysis in a larger cohort of patients.

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Author's contribution

Conceptualization, KR, RL, SK; writing—original draft preparation, RL, KR, AS, HSK, SK; writing—review and editing, RL, KR, AS, HSK, SK; supervision, SK; funding acquisition, SK. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent

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