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Urban/Rural Disparities of Thyroid Cancer Using the Integrated Cancer Repository for Cancer Research (iCaRe2)

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Capstone Title: Urban/Rural Disparities of Thyroid Cancer Using the Integrated Cancer Repository for Cancer Research (iCaRe2)

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Abstract:

Background and objective: Multiple studies have shown that the place of residence and the distance to travel from one's residence to nearby health care providers impact cancer diagnosis and treatment. The stage of cancer at the time of diagnosis is paramount for cancer treatment and affects survival. Disparities in cancer treatment exist which affect the outcome disproportionately to certain segments of the population. To date, much of the focus has been on the racial and socioeconomic disparities in the management of thyroid cancer. The effect of geography and location (urban-rural status) on thyroid cancer stage diagnosis has not been well studied. Therefore, the purpose of this study was to- 1) To investigate geographic disparities in thyroid cancer stage at the time of diagnosis. 2) To identify the factors affecting the stage of thyroid cancer at the time of diagnosis.

Methods:

A cross-sectional study was conducted with the sample of 800 thyroid cancer patients using the integrated Cancer data Repository for Cancer Research (iCaRe2) database. Residents in urban or rural counties at the time of diagnosis were categorized by 2013 Rural-Urban Continuum Codes and mapping between FIFS and Zip codes. The distance between the patient's residence and the case reporting hospital, University of Nebraska Medical center (UNMC) was characterized as short(<=12.5miles), intermediate (>12.5 to <50 miles) or long(>=50miles). The American Joint Committee on Cancer (AJCC) the tumor-node-metastasis (TNM) staging 7th edition, was used for staging of differentiated thyroid cancer. We dichotomized the stages as early (Stage I) and late (stage II) for thyroid cancer patients' less than 45 years old. For patients over 45 years old, we have dichotomized the stage as early (Stage I and II) and late (stage III, IV). Patients' demographics and clinicopathological features were compared between the Urban and Rural populations using the chi-square test. We performed a multivariable logistic regression model to look at the association factors between location of residence and outcome variable (stages of thyroid cancer at diagnosis (early vs. late stage)), after adjusting for age at diagnosis and gender.

Results:

The odds of late-stage thyroid cancer diagnosis compared to early-stage diagnosis were 1.6 (95% CI, 1.04 to 2.4) times higher among patients 45 years and older living in rural counties compared to urban counties, after adjusting for age at diagnosis and gender (p=0.032).

Similarly, among patients 45 years and older, the odds of late versus early stage at diagnosis were 2.0 (95% CI, 1.2-3.2) times greater for thyroid cancer patients living long distance (>= 50 miles) versus short distances (<= 12.5 miles) to the reporting hospital, after adjusting for age at diagnosis and gender (p=0.01).

Conclusion:

Multiple studies have been conducted regarding racial disparities to improve its outcome among various populations. However, the disparities of patients living in rural areas who face travel burden and medical access to health that can affect thyroid cancer outcomes have been overlooked. In our study, we found that patients 45 years and older living in rural areas and longer distance from the diagnosing reporting hospital have higher odds of being diagnosed at advanced stages of thyroid cancer compared to those living in urban areas.

INTRODUCTION

BACKGROUND

Thyroid cancer is the most common endocrine malignancy which makes up 2.3% of newly diagnosed cancer in the United States (US) with an estimated 43,800 new cases in 2022, (*Statistics of Thyroid Cancer (SEER, 2022)*, n.d.). Although incidence of thyroid cancer kept increasing from 1995 to 2008, the incidence remained stable and plateaued between 2010-2019 ((*Statistics of Thyroid Cancer (SEER, 2022)*, n.d.) (Figure 2). This initial increase was attributable to an increase in surveillance via use of more sensitive diagnostic modalities like ultrasonography, computed tomography (CT) or Magnetic resonance imaging (MRI). Also, there has been increased follow up surveillance of the incidental thyroid nodules (McDow et al., 2020). The rising rate included multifactorial risks, including biological or genetic factors, environment exposure, medical comorbidity, and lack of treatment adherence.

The incidence of thyroid cancer varies with age, gender, and race/ethnicity (Weeks et al., 2018). 20-49 years old Hispanic females had an increasing trend in incidence without deceleration after 2009, whereas elderly non-Hispanic white females had a decrease in incidence rate but stable mortality rate (Kotwal et al., 2019). The incidence rate of Thyroid Cancer was 14.1 per 100,000 in 2014-2018, and the mortality rate was 0.5 per 100,000 in 2015-2019 (Key Statistics for Thyroid Cancer (American Cancer Society, 2022)). Thyroid cancer rates in Nebraska (2014-2018) were comparable with US (2013-2017). Based on gender, incidence and mortality rate of thyroid cancer was 23.6 and 0.3 per 100,000 females in Nebraska (2014-2018), 21.1 and 0.5 per 100,000 females in the US (2013-2017), 7.4 and 0.5 per 100,000 males in Nebraska and 7.3 and 0.5 per 100,000 males in US respectively (Table 8 and 9). Among males, whites have the highest risk of getting thyroid cancer with an incidence rate of 7.5 per 100,000 compared to 6.8 per 100,000 in Asian and Pacific Islanders, 6.3 per 100,000 in Hispanics, and 3.3 per 100,000 in blacks and 3.3 per 100,000 in American Indian and islanders. Among female, incidence of thyroid cancer is 9.7, 21.4, 21.2, 11.1 and 11.3 per 100,000 among white females, Asian and Pacific Islander, Hispanic females, black females, and American Indian/Alaska Natives females respectively (USCS Data Visualizations - CDC, 2022).

In Nebraska, despite 41.7% of thyroid cancer happened among age 45-64, 75% of death occurred among 65 years and older (Figure 4, 5 and 6) (Department of Health et al., 2021). In US, thyroid Cancer is most diagnosed among age groups 45-54 and 45-64 among all races and gender (Department of Health et al., 2021)(Figure 3). Females are three times more likely to be diagnosed with thyroid cancer (National Comprehensive Cancer Network, Guidelines for Patients Details, 2022, n.d.). Radiation exposure to the head and neck at a young age and family history of thyroid cancer or related syndromes (familial adenomatous polyposis (FAP) and multiple endocrine neoplasia (MEN)) are common risk factors for developing thyroid cancer (*National Comprehensive Cancer Network, Guidelines for Patients Details, 2022*, n.d.). In the US, about 90% of thyroid cancers are papillary or follicular type, while anaplastic and medullary cancers account for less than 5% (Siegel et al., 2022). Thyroidectomy with or without postoperative administration of radioactive iodine therapy (RAI) represents the mainstay of treatment of Differentiated Thyroid Cancer (Shah et al., 2017).

Social determinants of health care (SDHs) are defined as differences in the health outcomes among specific populations (Gruszczynski et al., 2021). Disparities exist across the entire spectrum of cancer care (cancer occurrence, diagnosis, treatment, prevention, and research participation). In recent years, there has been a flood of research in cancer specialty on the new treatments from the pharmaceutical industry and government-sponsored organizations which have led to an increase in cancer survival, and quality of life. However, more studies are consistently describing a wider gap not only across racial/ethnic minorities but also in medically underserved populations including those living in rural areas. Several studies recently have validated that underserved populations are less likely to receive a standard of care recommended for the type and stage of cancer. The consequential disparities can be minimized if we provide equitable access to the standard of care. Hence, the complex mechanisms and systems that play a role in widening the disparities among disadvantaged populations, must be addressed. Clinical interventions such as social workers', establishing patient navigation system and use of local community leaders and advocates via faith-based organizations (Churches) can reduce disparities (*AACR Cancer Disparities Progress Report 2022 | Cancer Progress Report*, n.d.). Since 2009, the American Society of Clinical Oncology (ASCO) has issued a policy statement on cancer care disparities and also has updated 2019 statement to overcome long-standing disparities in cancer care. The statement outlines both principles and recommendations with an effort to guide the future by establishing a dedicated Health Equity committee which can foster awareness and address inequities in access to care ("Erratum: Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline (American Society of Clinical Oncology (2020) DOI: 10.1200/JCO.20.00642)," 2020; Patel et al., 2020)

Much of the cancer studies related to inequalities have been descriptive. These have suggested that thyroid cancer's racial/ethnic differences could have arisen from differential access to diagnostic modalities like ultrasound guided or computed tomography (CT) fine needle aspiration (FNA), a discrepancy in socioeconomic status, and differences in insurance coverage. Whites have higher Age Adjusted Incidence Rate (AAIR) for Stage I and stage II cancers, whereas Asians and Hispanics have significantly higher incidence for stages III and IV cancers (Weeks et al., 2018). Young people have a low chance of dying from differentiated thyroid cancer (*Thyroid Cancer*

Stages, American Cancer Society, 2022, n.d.). Risk factors for an adverse thyroid cancer outcome include male sex, increased age, lymph nodes metastasis, large size tumors, and histologically undifferentiated cancer, including medullary and anaplastic (Rose et al., 2013).

Although the cancer incidence rate declined similarly in metropolitan and rural areas, the cancer mortality rate declined less in the rural populations (Hashibe et al., 2018). Observational studies have reported higher incidence among urban residents compared to rural, affirming the concept of epidemic of overdiagnosis than epidemic of the disease (Udelsman & Zhang, 2014). The existing gap may depend on race, geography, health care access (availability and affordability of screening/ diagnosis and treatment), and education level (McDow et al., 2020) (Weeks et al., 2018). Therefore, there have been substantial barriers to health care access among rural and urban residents, which need further research to validate prior studies.

Cancer stage at diagnosis determines treatment options. Staging at diagnosis is a strong predictor of survival (Lee et al., 2019; *Statistics of Thyroid Cancer (SEER, 2022)*, n.d.). Thyroid cancer has been grouped into localized, regional, and distant stages with 65.4% diagnosed at the local, 29% at the regional and 3% at the distant stage where the cancer has already metastasized (*Statistics of Thyroid Cancer (SEER, 2022)*, n.d.). 5-year relative survival for localized, regional, and distant metastatic type thyroid cancer are 99.9%, 98.3% and 53.3% respectively (*Statistics of Thyroid Cancer (SEER, 2022)*, n.d.). The American Joint Committee on Cancer (AJCC) TNM Staging 7th ed. (2010), has defined thyroid cancer based on stages I (1) through IV (4), TNM system as the extent of the tumor (T), spread to nearby lymph nodes (N) and to distant sites (metastasis) (M) (Table A).

Table A: AJCC Prognostic Staging Groups (7th ed, 2010)

AJCC Prognostic Staging	T	N	M
Differentiated: Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Differentiated: 45 years and older			
Stage I	T1	N0/Nx	M0
Stage II	T2	N0/Nx	M0
Stage III	T3	N1a	M0
Stage IVa	T4a	N1b	M0
Stage IVb	T4b	Any N	M0
Stage IVc	Any T	Any N	M1

Data on geographical disparities in the United States on thyroid cancer stages at diagnosis is lacking, despite multiple studies. Descriptive studies conducted on thyroid cancer mainly concentrated on race, gender, socioeconomic status, and stage at diagnosis.

We hypothesize that there is an association between urban and rural residence (exposure) and the stage of thyroid cancer (outcome) at the time of diagnosis.

AIM: The primary purpose of this study is to identify the association between the urban/ rural status of residence and stage of thyroid cancer at diagnosis. We also aim to identify an association between a secondary exposure, the distance of patient residence from a health care, with thyroid cancer stage at diagnosis.

HYPOTHESIS

Null hypothesis: There is no difference in thyroid cancer diagnosis by stage in rural versus urban residence.

Alternative hypothesis: The rural residents will have a more advanced stage of thyroid cancer at the time of diagnosis than urban residents.

MATERIALS AND METHODS:

A retrospective cross- sectional study was conducted to assess the specific aims. In this study, the integrated Cancer Repository for cancer research (iCaRe2) database was used to identify patients diagnosed with primary thyroid cancer in the state of Nebraska, Iowa, North Dakota, South Dakota, Kansas, and Missouri who presented to the University of Nebraska Medical Center (UNMC) between (2000-2021). The iCaRe2 is a multi-institutional resource created and maintained by the Fred and Pamela Buffett Cancer Center to collect and manage standardized, multi-dimensional, longitudinal data and bio-specimens on consented adult cancer patients, high-risk individuals, and normal controls (*The Integrated Cancer Repository for Cancer Research (ICaRe2) - ICaRe2*, n.d.). The database comprises many cancers in its registry and one of them is Thyroid Tumor and Cancer Collaborative Registry (TCCR) which is the interest of our study. It collects data on adults aged 19 years and older, diagnosed with Thyroid Cancer or Thyroid Nodules. It includes data on socio-demographic characteristics, lifestyle, clinical data, quality of life, medical history and family history of cancer and major diseases (Shats et al., 2016). The county characteristics using Rural-Urban 2013 Continuum Codes (RUCC) and mapping between FIFS and Zip codes with the population-based design used to categorize patients into rural and urban residence. We have defined access to care by the distance to a medical facility. The distance between the participants' residence and the reporting hospital (UNMC) was classified as short (<=12.5miles), intermediate (>12.5 to <50 miles) or long (>=50 miles).

UNMC IRB determined that the project does not constitute human subject research as defined in 45CFR46.102. Therefore, it is not subject to the federal regulations and does not require IRB review.

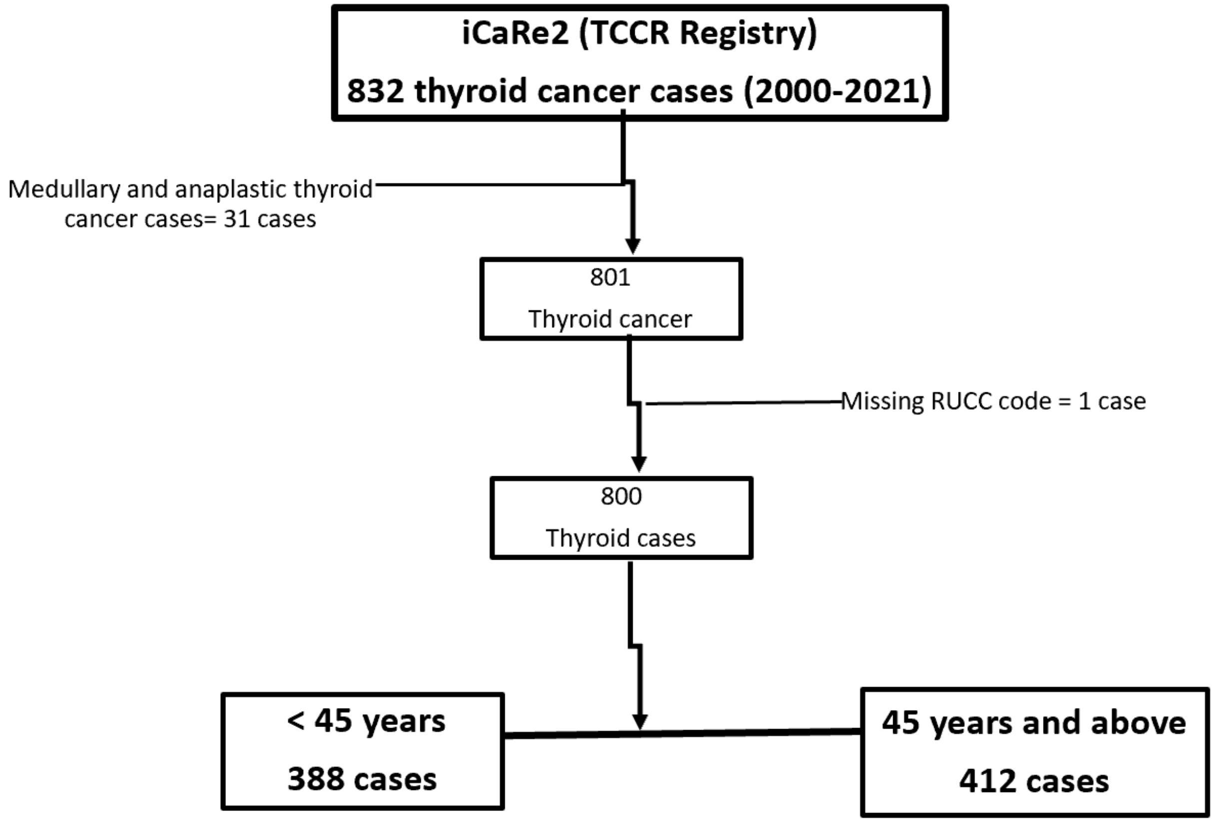
Eligibility Criteria

We used the integrated Cancer data Repository for Cancer Research (iCaRe2) database to identify patients who were diagnosed with primary thyroid cancer in the state of Nebraska, Iowa, North Dakota, South Dakota, Kansas, and Missouri presented to the University of Nebraska Medical Center (UNMC) between (2000-2021). Study participants are adults 19 years and older who have provided consent to be enrolled into the TCCR (Shats et al., 2016; *The Integrated Cancer Repository for Cancer Research (ICaRe2) - ICaRe2*, n.d.).

For this study, we have included differentiated thyroid cancer based on histological diagnosis (papillary, follicular and hurthle cell origin). We have excluded undifferentiated thyroid cancers (anaplastic and medullary type) and participants with missing data on county of residence. We included 800 thyroid cancer patients who met the eligibility criteria for our study in the statistical analysis (Figure 1).

Data Collection- The TCCR core data elements collected for thyroid patients include socio-demographic features like age, date of enrollment, age at diagnosis, county of residence, gender, race/ethnicity, education, and household income (Shats et al., 2016; *The Integrated Cancer Repository for Cancer Research (ICaRe2) - ICaRe2*, n.d.). Under lifestyle, tobacco/smoking habits (ever smoker or never), alcohol consumption (current and past), lifestyle (dietary habits, vitamins/supplements intake, coffee drinking habits, physical activity, and sleep patterns) are included. Under clinical data, first symptom, history of cancers, and major disease, surgical and hospitalization history, imaging studies done, staging (pathological and clinical) histological type, sites of involvement are also incorporated. Treatment (type, schedule, response), laboratory test results, functional/medical changes after treatment, treatment outcome and vital status have been included in the dataset and so in our study ((Shats et al., 2016; *The Integrated Cancer Repository for Cancer Research (ICaRe2) - ICaRe2*, n.d.).

Figure 1. Framework of Study Population for TCCR Registry.



iCaRe2, TCCR Registry, Year (2000-2021), Site (UNMC), States- Nebraska and the neighboring states (Iowa, Kansas, Missouri, North Dakota, South Dakota).

STATISTICAL ANALYSIS

We assessed differences in patients' characteristics at diagnosis across geographic categories of rural and urban using a chi-square test. Frequency and percentages for demographics, education, lifestyle, and clinical characteristics were used to describe the categorical variables which are shown in Table 2. We used a multivariable logistic regression model to look at the association of location of residence and distance from hospital with the outcome variable, stage at diagnosis while adjusting for age at diagnosis and gender. Our primary outcome is the stage at diagnosis. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging 7th

edition, was used for staging of differentiated thyroid cancer. Based on the staging criteria of AJCC 7th edition, we created two groups from the total subject population- less than 45 years at the diagnosis and 45 years and older. 1) In less than 45 years old, stage I is classified as early and Stage II as late. 2) In 45 years and older group, the stage variable was dichotomized as early (Stages I and II) and late (Stages III and IV). Crude (unadjusted) and adjusted odd rations (ORs) and 95% confidence intervals (CIs) were reported to assess the association of predictor variables and outcome variables. We considered a P value of <0.05 to be statistically significant for analysis. Statistical analysis was done by using the SAS 9.4 version.

FOUNDATIONAL AND CONCENTRATION COMPETENCY

EPIMPH2 Apply appropriate study design and data collection methods to answer specific epidemiology questions and address public health issues. Data was requested and collected from iCaRe2(TCCR) registry, and an observational study was designed to see the geographical disparity among thyroid cancer cases.

EPIMPH3 Analyze datasets using computer software. The descriptive statistics and the association of predictor variables to outcome variables have been analyzed by using computer software SAS version 9.4.

MPHF21 Perform effectively on an interprofessional team.

I have been communicating with my Capstone committee members through emails, zoom calls to take their feedback regarding study design, statistical analysis. Their expertise has been instrumental in the success of this project. This experience has provided me with the opportunity to interact with my committee members on a professional level.

RESULTS

The demographics and the clinicopathological features of total thyroid cancer patients were analyzed and compared between rural and urban populations (Table A). Among 800 study participants, 570 (71%) were urban, and 230 (29%) were rural residents.

The age at diagnosis was more frequent among age category 19-44 years in both urban and rural residents, with statistical significance of p value =0.04. Participants were mostly of non – Hispanic white race in both geographical locations, urban (89%), rural (98%). Thyroid cancer patients were more likely to be female (76.2%) whole cohort. Obesity was slightly higher among rural residents (50.4%) compared to urban residents (45.3%) but there was no statistical difference between rural and urban populations while using BMI as a variable (p=0.18). Rural residents had less college education (57.8%) than urban residents (47.1%) and was statistically significant (p=0.02). Regarding smoking status, 40.3% of urban residents had ever smoked (over 100 cigarettes compared to 26.9% rural residents, however with statistical significance (p=0.003). Overall, we found that 97.2% of patients had no distant metastasis. The distribution was similar across rural and urban residents. The percentage of Thyroid cancer patients with absent lymph nodes was higher among urban versus rural (66.2% vs 60%). The higher percentage of tumor size (>4cm) in rural residents (31.05%) than urban residents (26.7%). Majority of patients underwent total or near total thyroidectomy in both categories (71.1% in urban and 64.3% in rural) and there was no statistically significant difference between and followed by Radioiodine ablation therapy was more common in rural residents (55.9%) compared to urban population (52.9%).

Thyroid cancer has a very good prognosis with over 98% survival. The prognosis is more favorable in <45 years than higher ages in previous study and registries. AJCC 7 prognostic staging is also different based on age with age < 45 years vs in 45 years and above. So, to avoid any skewed results, we analyze our hypothesis separately in these 2 different cohorts- age under 45 years and age 45 and above.

The demographics and clinicopathological features of Thyroid Cancer patients for < 45 years old groups were compared between Urban and Rural populations (Table 1). Among 388 study participants, 290 (74.7%) were Urban and 98 (25.26%) were rural residents. Thyroid Cancer patients were more likely to be female (82.2%). Participants were mostly of white race in both geographical locations-urban (90.6%), rural (95.7%). Rural residents had less college education (48.6%) than urban residents (38.9%) with 25% missing data on education. Regarding smoking status, 35.3% of urban residents had ever smoked (over 100 cigarettes) compared to 23.53% rural residents. Also, there were 40% of data missing regarding smoking status. Obesity was higher among rural residents (49.4%) compared to urban residents (41.2%) and was the only variable that had a statistically significant difference between rural and urban populations under the 45 years cohort ($p = 0.04$). Race, gender, education type and smoking variables were not statistically significantly different when compared to rural versus urban ($p => 0.5$) (Table 1)

Overall, we found that 96% of patients were diagnosed at an early stage (Stage I), and only 4% were diagnosed at a late stage. Also, most patients were in the early stage in both cohorts (96% in urban and 95% in rural) and were not statistically significantly different among rural and urban residents. Most patients underwent total or near-total thyroidectomy in both categories (72.9%) in urban and 63.3% in rural). The percentage of Thyroid Cancer patients with absent lymph nodes was higher in both urban and rural residents (60% vs 55%). Overall, we found that 97.35% of patients had no distant metastasis. The distribution was similar across rural and urban residents (Table 1).

TABLE A: **Demographics and Clinicopathological variables of total thyroid cancer patients' vs urban vs rural cohort**

Variables	Urban, N (%) 570(71.25)	Rural, N (%) =230(28.7)	Total, N (%) =800(100%)	P value
Age at Diagnosis				0.04
19-44 years.	290(50.8)	98(42.6)	388(48.5)	
45-64years	212(37.1)	92(40.0)	304(38.0)	
65-95 years	68(11.9)	40(17.3)	108(13.5)	
Race				
Non-Hispanic whites	506 (89.2)	222 (97.8)	728 (91.8)	
Others	61 (10.7)	4 (1.8)	65 (8.1)	
Missing	3	4	7	
Gender				0.16
Female	427(74.9)	183(79.5)	610(76.2)	
Male	143(25.09)	47(20.43)	190(23.7)	

BMI				0.18
Normal	138(25.3)	41(19.16)	179(23.5)	
Overweight	160(29.3)	65(30.3)	225(29.6)	
Obese	247(45.3)	108(50.4)	355(46.7)	
Missing	15	16	41(5.1)	
Education				0.02
Graduate	115(28.2)	41(27.8)	156(28.1)	
College Graduate	100(24.5)	21(14.29)	121(21.8)	
Less college	192(47.1)	85(57.82)	277(50.0)	
Missing	163	83	246(30.7)	
Smoking				0.003
Ever Smokers	152(40.3)	36(26.09)	188(36.5)	
Never Smokers	225(59.6)	102(73.9)	327(63.5)	
Missing	193	92	285(35.6)	
Metastasis				0.14
No	525(97.7)	208(95.8)	733(97.2)	
Yes	12(2.23)	9(4.15)	21(2.79)	

missing	33	13	46(5.7)	
Lymph Node				0.2
Absent (NO)	365(66.2)	136(60.1))	501(64.4)	
Central(N1a)	99(17.9)	47(20.8)	146(18.7)	
Lateral(N1b)	87(15.7)	43(19.0)	130(16.7)	
Missing	19	4	23(2.8)	
Tumor size				0.3
0.1-2.0(T1)	284(52.0)	101(46.1)	385(50.3)	
2.1-4 (T2)	116(21.2)	50(22.8)	166(21.7)	
>4.0 (T3/T4)	146(26.7)	68(31.05)	214(27.9)	
Missing	24	11	35(4.3)	
Procedure type				0.1
Total/near total thyroidectomy	379(71.1)	130(64.3)	509(69.2)	
Lobectomy	120(22.5)	58(28.7)	178(24.2)	
Others	34(6.3)	14(6.9)	48(6.53)	
Missing	37	28	65(8.1)	

Therapy type				0.45
RAI therapy/1131	292(52.9)	122(55.9)	414(53.8)	
Others	259(47.0)	96(44.0)	355(46.1)	
Missing	19	12	31(3.8)	

[b]Body mass index (BMI) <18.5kg/m2 was defined as underweight, BMI between 18.5and 24.9kg/m2 was defined as normal, BMI between 25-29.9kg/m2 as overweight and BMI>=30kg/m2 as obese (CDC,2017). excluded underweight BMI due to a very low sample.

[c]smoking status was based on patients who had smoked over 100 cigarettes in their lifetime

[d] from the chi-square test

TABLE 1: Characteristics of patients within subgroups (age < 45 years = 19-44 years)

Variables	Urban, N(%)=290(74.7)	Rural, N(%) =98(25.26	Total, N (%)=388(100%)	P value
Gender				0.17
Female	234(80.69)	85(86.73)	319(82.2)	
Male	56(19.31)	13(13.27)	69(17.7)	

Race				
White	262 (90.6)	91 (95.7)	353(91.9)	
Black/African Americans	6(2.08%)	1 (1.05)	7(1.8)	
Others	20(6.8)	3 (3.25)	23(5.9)	
Missing	2	3	5(1.2)	
BMI[b]				0.04
Normal	91(32.3)	18 (18)	109(28.9)	
Overweight	74(26.3)	30(31.5)	104(27.6)	
Obese	116(41.2)	47(49.4)	163(43.3)	
Missing	9	3	12	
Education				0.05
Graduate	61(27.9)	10(13.89)	71(24.4)	
College Graduate	72(33.3)	27(37.5)	99(34.1)	
Less college	85(38.9)	35(48.6)	85(38.9)	
Missing	72	26	98(25)	
Smoking[c]				0.07
Ever Smokers	71(35.3)	16(23.53)	87(32.3)	
Never Smokers	130(64.6)	52(76.4)	182(67.6)	
Missing	89	30	119(31)	

Variables 19-44 years	Urban, N(%) =290(74.7)	Rural, N (%) =98 (25.26	Total, N (%) =388(100%)	P value
AJCC7 stage				0.49
Stage I=early	270(96.43)	92(94.85)	362(96%)	
Stage II, =late	10(3.57)	5(5.15)	15(3.9)	
Missing	10	1	11(2.8%)	
Distance to Center				.001
Short<=12.5miles	110(37.9)	0	110(28.35)	
intermediate. >12.5-<50miles	117(40.3)	2	119(30.6)	
Long>=50miles	63(21.7)	96(97.9)	159(40.9)	
Metastasis				
No	272(96.8)	96(98.97)	368(97.35)	
Yes	3(1.07%)	1(1.03%)	4(1.06%)	
Unknown	6(2.14%)	0	6	
Missing	9	1	10	
Lymph Node				0.6
Absent (NO)	169(60.1)	53(54.6)	222(58.7)	
Central(N1a)	64(22.7)	24(24.7)	88(23.2)	
Lateral(N1b)	48(17.08)	20(20.6)	68(17.9)	
Missing	9	1	10	
Tumor size				0.9
0.1-2.0cm(T1)	138(49.2)	48(50)	186(49.4)	
2.1-4 cm(T2)	64(22.8)	21(21.8)	85(22.6)	
>4.0 cm(T3/T4)	78(27.8)	27(28.1)	105(27.9)	
Missing	10	2	12	
Procedure type				0.7
Total/near-total thyroidectomy	202(72.9)	64(68.8)	266(71.8)	
Lobectomy	64(23.10)	25(26.8)	89(24.0)	
Others	11(3.9)	4(4.3)	15(4.05)	
Missing	13	5	18	

Notes.

[b]Body mass index (BMI) <18.5kg/m2 was defined as underweight, BMI between 18.5and 24.9kg/m2 was defined as normal, BMI between 25-29.9kg/m2 as overweight and BMI>=30kg/m2 as obese (CDC,2017). excluded underweight BMI due to a very low sample.

[c]smoking status was based on patients who had smoked over 100 cigarettes in their lifetime

[d] from the chi-square test

Table 4: Characteristics of patients within subgroups (Equal to or above 45 Years age)

Variables.	Urban N=280 (67.9%)	Rural N=132 (32.04%)	Total N=412 (100%)	P Value[d]
Diagnosis age				0.19
45-64 years	212 (75.7)	92 (69.7)	304 (73.7%))	
65-95 years	68 (24.2)	40 (30.3)	108 (26.2)	
BMI[b]				0.8
Normal	47 (17.8)	23 (19.3)	70 (18.2)	
Overweight	86 (32.5)	35 (29.4)	121 (31.5)	
Obese	131 (49.6)	61 (51.2)	192 (50.1)	
Missing	16	13	29	
Gender				0.26
Female	193 (68.9)	98 (74.2)	291 (70.6)	
male	87 (31.07)	34 (25.7)	121 (29.3)	
Race				
White	244 (87.7)	131 (99.9)	375 (91.4)	
African Americans	24 (8.6)	1 (0.76)	25 (6.10)	
Others	10 (3.6)	0	10 (3.6)	
Missing	2		2	
EDUCATION				0.3
Graduate	39 (20.6)	11 (14.6)	50 (18.9)	
College graduate	43 (22.7)	14 (18.6)	43 (22.7)	
Less college	107 (56.6)	50 (66.6)	107 (56.6)	
Missing	91	57	148 (36)	
AJCC 7 Stage				0.034
Early: Stage (I, II)	156 (58.2)	59 (46.8)	215 (54.57)	
Late: Stage (III, IV)	112 (41.7)	67 (53.1)	179 (45.43)	
Missing	12	6	18	
Procedure type				0.23

Total/near-total thyroidectomy	181 (70.7)	69 (63.3)	250 (68.49)	
lobectomy	56 (21.88)	33 (30)	89 (24.3)	
others	19 (7.4)	7 (6.42)	26 (7.12)	
missing	24	23	47 (11)	
Therapy Type				0.27
RAI therapy/I131	116 (42.9)	61(48.8)	177(44.8)	
Others	154 (57.7)	64(51.2)	218(55.1)	
Missing	10	7	17	
Smoking[c]				0.01
Ever smokers	81 (46.02)	20 (28.5)	101 (41.06)	
Never smokers	95 (53.9)	50 (71.4)	145 (58.9)	
missing	104	62	166 (40)	
Tumor size				0.05
0.1-2.0 cm(T1)	147 (55.06)	53 (42.4)	200 (51.0)	
2.1-4.0cm(T2)	52 (19.4)	29 (23.2)	81 (20.6)	
>4cm(T3/T4)	68 (25.4)	43 (34.4)	111 (28.3)	
missing	13	7	20	
Lymph Nodes				0.23
Absent (No)	196 (72.5)	83 (64.34)	279 (69.9)	
Central neck (N1a)	35 (12.9)	23 (17.8)	58 (14.5)	
Lateral neck (N1b)	39 (14.4)	23 (17.8)	62 (15.5)	
Missing	10	3	13	
Distant metastasis				0.1
No	253 (96.5)	112 (93.3)	365 (95.5)	
Yes	9 (3.4)	8 (6.67)	17 (4.45)	
Missing	18	12	30	
Distance to center				<.0001
Short<=12.5 miles	187 (66.7)	0	187 (45.3)	
Intermediate>12.5-<50 miles	53 (18.93)	16 (12.1)	69 (16.7)	
Long>=50miles	40 (14.2)	116 (87.8)	156 (37.86)	

[b]Body mass index (BMI) <18.5kg/m2 was defined as underweight, BMI between 18.5and 24.9kg/m2 was defined as normal, BMI between 25-29.9kg/m2 as overweight and BMI>=30kg/m2 as obese (CDC,2017). excluded underweight BMI because of a very low sample.

[c]Smoking status was based on patients who had smoked over 100 cigarettes in their lifetime

[d] from the chi-square test

Table 4 shows the demographics and clinicopathological features of Thyroid Cancer patients for 45 years and older groups, which were compared between Urban and Rural populations. Among

412 study participants, 280 (67.9%) were Urban and 132 (32.04%) were rural residents. The age at diagnosis was more frequent among age category 45-64 years in both urban and rural residents. Thyroid Cancer patients were more likely to be female (70.6%). Participants were mostly of white race in both geographical locations-urban (87.7%), rural (99.9%). Obesity was slightly higher among rural residents (52%) compared to urban residents (49.6%) but there was no significant difference between rural and urban populations while using BMI as variable ($p = 0.8$). Rural residents had less college education (66.6%) than urban residents (56.6%).

Overall, we found that 54.5% of patients were diagnosed at an early stage, being 46.8% in rural counties and 58.2% in urban counties. Rural residents were more likely to be diagnosed at late stage (III, IV) (53.1%) of thyroid cancer at the time of diagnosis than urban residents (41.7%) and were statistically significant ($p = 0.034$). Majority of patients underwent total or near-total thyroidectomy in both categories (70.7% in urban and 63.3% in rural) and there was no significant difference between rural and urban populations by procedure type ($p=0.23$). Radioactive iodine therapy was more common in the rural population (48.8%) compared to the urban population (42.9%). Regarding smoking status, 46.0% of urban residents had ever smoked (over 100 cigarettes) compared to 28.5% of rural residents ($p = 0.01$). However, there was 40% of data missing regarding smoking status. We found a higher percentage of tumor size (>4cm) in urban residents (34.4%) than rural residents (25.4%). The percentage of Thyroid Cancer patients with absent lymph nodes, was higher among urban versus rural residents (72.5% vs 64.3%). Overall, we found that 95.5% of patients had no distant metastasis. The distribution was similar across rural and urban residents. In addition, rural residents were more likely to be living long distances (87.8%) from the reporting hospital compared to urban counterparts (14.2%) and were statistically significant ($p<0.0001$).

Table 5: Factors associated with late-stage diagnosis in multivariable Logistic Regression analysis (45 years and older at the time of diagnosis)

Rural/Urban Category	Significant Variables	Unadjusted, OR (95%CI)	P value	Adjusted OR (95% CI)	P* value
Urban		**Reference**			
Rural		**1.5 (1.03-2.42)**	**0.034**	**1.6 (1.04-2.4)**	**0.032**
	Gender				
	Male	**Reference**			
	Female	**0.56 (0.36-0.8)**	**0.009**	**0.53 (0.34-0.8)**	**0.005**
	Age at Diagnosis				
	65-95 years	**Reference**			
	45-64 years	**0.55 (0.3-0.8)**	**0.010**	**0.56 (0.35-0.89)**	**0.014**

*Analyses were adjusted for diagnosis age, gender.

Abbreviations: CI confidence interval; OR odds ratio.

The odds ratio (OR) of a late versus early stage at diagnosis (Stage III, IV versus I and II) was 1.6 with a 95% confidence interval (CI) between 1.04 to 2.4 p=0.032 (Table 5) among rural residents than urban in 45 years and older patients with a diagnosis of thyroid cancer. So, age 45 year and older and living in rural counties have 60% more likely to be diagnosed at a late-stage than those living in urban counties, after adjusting for age at diagnosis and gender.

Odds of late-stage thyroid cancer versus early-stage were 0.53 times (or 47%) lower among females than males. Also, the odds of late-stage thyroid cancer for age 45-64 years were 0.56 times (or 44%) lower than those diagnosed at age 65 to 95 years.

However, Body Mass Index (BMI) was not associated with the log odds of being diagnosed at late-stage thyroid cancer in a multivariable logistic regression model with p value=0.06 (Table B).

Table B: Analysis of Maximum Likelihood Estimates

Parameter		Estimate	Standard Error	P value
Intercept		0.099	0.43	0.5
RU2013_CAT	Rural	0.21	3.3	0.06
AGEGRP	45-64	-0.28	0.12	0.03
GENDER	Female	-0.3	0.11	0.008
BMI	Normal weight	-0.01	0.19	0.94
BMI	Obese	0.27	0.14	0.06

The change in estimate (CIE) =0.23 (adjusted effect)-0.22 (unadjusted effect)/0.23=0.04% which is less than 10%. So, age at diagnosis and gender are not confounders.

The p value for the interaction term (rural * (45-64) years is not significant (p=0.29). So, there is no interaction between rural and age group. The p value for the interaction term (female * rural) is also not significant (p value=0.10). So, there is no interaction between rural and female.

Table 6: Association between distance from medical facility subgroups and Late stage at diagnosis (stage III and IV) in multivariable Logistic Regression analysis (for 45 years and over at the time of diagnosis).

Distance to Center	Significant Variables	Unadjusted OR (95%CI)	P value	Adjusted [a] OR (95%CI)	P *value
Short<=12.5miles		**Reference**			
Long>=50miles		**1.9 (1.2-3.0)**	**0.02**	**2.0 (1.2-3.2)**	**0.01**
	Gender				
	Male	**Reference**			
	Female	**0.56 (0.36-0.8)**	**0.009**	**0.50 (0.31-0.79)**	**0.0036**
	Age at Diagnosis				
	65-95	**Reference**			
	45-64	**0.55 (0.3-0.8)**	**0.010**	**0.58 (0.35-0.95)**	**0.032**

[a] Analyses were adjusted for diagnosis age, gender.

Abbreviations: CI confidence interval; OR odds ratio.

The odds of a late stage at diagnosis were 2.0 (95% CI, 1.2-3.2) times greater for thyroid cancer patients living long distance (>= 50 miles) to the reporting hospital as compared to short distance (<=12.5miles) after adjusting for age and gender (Table 6). Odds of late-stage thyroid cancer versus early-stage were 0.50 times (or 50%) lower among females than males. Also, the odds of late-stage thyroid cancer for age 45-64 years were 0.58 times (or 42%) lower than those diagnosed at age 65 to 95 years.

DISCUSSION

This study found that the patients who were diagnosed with a thyroid cancer at 45 years of age and over, at the time of diagnosis and living in rural geography, have a higher risk of diagnosing at the late-stages (stages III and IV) of thyroid cancer based on AJCC 7th edition classification as compared to those living in urban areas. The odds of diagnosing late-stage thyroid cancer were 1.6 times higher among patients living in rural counties compared to urban counties, after adjusting for age at diagnosis and gender, with a 95% confidence interval (CI) between 1.04 to 2.4. Also, the patients living over 50 miles from the medical facility had higher odds of being diagnosed with late-stage thyroid cancer than those living within 12.5 miles at the time of diagnosis.

Our study confirmed the disparities at the stage of diagnosis on geographic boundaries for thyroid cancer. Patients living in rural areas will probably face travel burdens (long distance to travel, require time off from their work, or accommodation issue) which will affect their medical access and the ultimate outcome. Similar disparities were reported across other cancer spectrum (Johnson et al., 2021). However, Johnson et al. reported the study on five different cancers, including thyroid cancer. A systematic meta-analysis suggested that breast cancer patients had 1.19 times the odds (95% CI, 1.12-1.27) of late-stage diagnosis among those residing in rural compared to urban areas (Nguyen-Pham et al., 2014). Similarly, Segel at al. reported a lower rate of early-stage pancreatic cancer at diagnosis in rural counties (Segel et al., 2020).

Disparities in stage at diagnosis across the geographical boundaries were also reported outside of the United States (US) across five most common cancers (lung, stomach, colorectum, esophagus, breast cancers) in an observational study conducted in China by Zeng et al. The persistent diagnostic disparity was demonstrated between rural and urban areas (Zeng et al., 2021).

Our multivariate analysis of thyroid cancer patients also revealed that women were 47% less likely to be diagnosed with late-stage thyroid cancer compared to men who are residing in rural areas. Weeks et al. in their study identified that women with thyroid cancer are diagnosed with small tumors (< 4 cm). Similarly, an adverse thyroid cancer outcome to male sex, increased age, lymph nodes metastasis, large size tumors, and histologically undifferentiated cancer, including medullary and anaplastic, has been reported (Rose et al., 2013). Women were found to have frequent healthcare providers visits and receive frequent check-ups more often than males and may constitute an early diagnosis of smaller size tumor (Weeks et al. 2018). However, our study did not show any significant outcome based on tumor size and lymph node metastasis.

From the thyroid cancer registry in Nebraska (2014-2018), the incidence of thyroid cancer in females was 23.6 per 100,000 and 7.4 per 100,000 for males in the state of Nebraska (Table 9) (Department of Health et al., 2021). Similarly, our study population also has a higher percentage of females, so further investigation is needed to better understand higher incidence among females in relation to medical access versus biological, hormonal, or genetic factors.

Beyond 55 years, there are increasing trends in the case fatality rate (Mazurat et al., 2013). So, increasing age is associated with both increased recurrence and mortality of thyroid cancer. Our multivariable analysis found that thyroid cancer patients for those aged 45 to 64 years were less likely to be diagnosed at a late stage compared to 65 to 95 years. Prior studies on well-differentiated thyroid cancer with regional or distant metastasis have a survival rate dependent on age (Haymart, 2009; Mazurat et al., 2013).

Under the 45 years of age cohort, rural residents and those living long distance from the medical facility were not associated with late-stage diagnosis for thyroid cancer. However, under 45, we found that 96% of patients were diagnosed at an early stage (Stage I), and only 4% were diagnosed at late stage (stage II). Also, most patients were in the early stage in both cohorts (96% in urban and 95% in rural) and were not statistically significant. So, further analysis was not done, and would likely skew due to very small sample size in the late stage. Thyroid cancer patients under 45 years can have distinctly different prognosis than those aged 45 years and over. Henceforth, age is an important prognostic marker for well -differentiated thyroid cancer. Studies have shown that patients aged 20-44 years have a low risk of tumor recurrence and a low risk of overall mortality (Haymart, 2009).

We have found the higher percentage of rural residents were obese than urban residents among <45years old. The nationally representative cross-sectional sample studying rural/urban disparities showed that the odds of obesity were higher in rural compared to urban areas (odds ratio=1.3, p<.001). In addition, Masone et al., suggested that obesity and excess body weight were related to increased risk of thyroid cancer (Masone et al., 2021).

Regarding geographic differences in thyroid cancer incidence and survival, McDow showed both a higher incidence and long-term survival for thyroid cancer in urban areas compared to rural areas (McDow et al., 2020). Considering high survival rates in thyroid cancer, approaching 98%, we opted not to consider the survival in our current study. However, this can be a topic of future investigation and would probably need a larger sample size.

In thyroid cancer, tumor size and histology differed significantly among race and insurance status, with non-white being less associated with small sized thyroid cancer compared to white population. Similarly, medicaid and uninsured patients were less associated with thyroid cancer less than 4 cm and papillary type (Weeks et al., 2018).

Even though overall survival of thyroid cancer is much more favorable than other cancer types, our study reinforces the need for better access to healthcare, especially for elderly and rural populations, so that thyroid cancer can be diagnosed and treated at an early stage before it progresses. Through our study, we realized that living in a rural area is an independent predictor of diagnosis at a later- stage of thyroid cancer. Also, male sex, and age group 65 and over have independent risk factors for diagnosing at a later stage, which will probably affect the outcomes. This suggests that further research will be needed on factors affecting the early diagnosis of thyroid cancer beyond access to care.

Limitation

This study is an observational study. So future studies are needed to explore whether the association between the independent covariates and the stage at diagnosis determine causality. This cancer registry only represents the patients that are being seen at UNMC, a single medical center in the state of Nebraska, with some referral from neighboring states (Iowa, Kansas, Missouri, North Dakota, South Dakota). This is not a representation of all thyroid cancers in the state of Nebraska, and/ or neighboring states. So, we cannot generalize the findings from our study to the entire Nebraska state population or the US populations.

We didn't incorporate education and smoking in the multivariable regression model because over 20% of data were missing, and it will probably skew the results. However, prior studies have shown that cigarette smoking was associated with decreased risk of incidence of thyroid cancer in men but not in women (Cho et al., 2018).

When examining thyroid cancer incidence trends in Surveillance Epidemiology and End Results (SEER), high income counties have experienced high thyroid cancer incidence because of advancement of diagnostic technologies like USG guided Fine needle aspiration cytology (FNAC), access to MRIs leading to more biopsies among those who are rich. However, the confounding association with education and socioeconomic status may coexist and can be a topic of research in the future.

Other barriers for disparities in thyroid cancer that were not considered in this study included ethnicity or race. TCCR registry represents only English-Speaking residents and exclusively 90% of the registry were non-Hispanic whites. Thyroid cancer incidence trend still increasing in young Hispanic and Black, although overall trend plateaued, and further deceleration appeared in non-Hispanic Whites and elderly (Kotwal et al., 2019).

Our study confirmed that the patients living over 50 miles from the medical access had an increased likelihood of presenting at late-stage thyroid cancer. In the future, we can further categorize each patient's residence by metro, non-metro (adjacent to population >=200,000), small rural town and isolated rural town and can further quantify the nature and magnitude of disparities.

In this study, we use the American Joint Committee on Cancer (AJCC) TNM staging 7th edition for patients with differentiated thyroid Cancer. We have included patients who are diagnosed with thyroid cancer since 2000, when staging was done using AJCC 7th edition. However, from 2018, the American Joint Committee on Cancer (AJCC) 8th edition has been in practice. One of the population-based retrospective reviews showed that 20% of patients were downstage from the 7th edition to the 8th edition. (Gan et al., 2019). It would be interesting to do a similar study with the AJCC 8th edition in the future and see if the association with rural/urban disparity still exists regarding the stages of thyroid cancer.

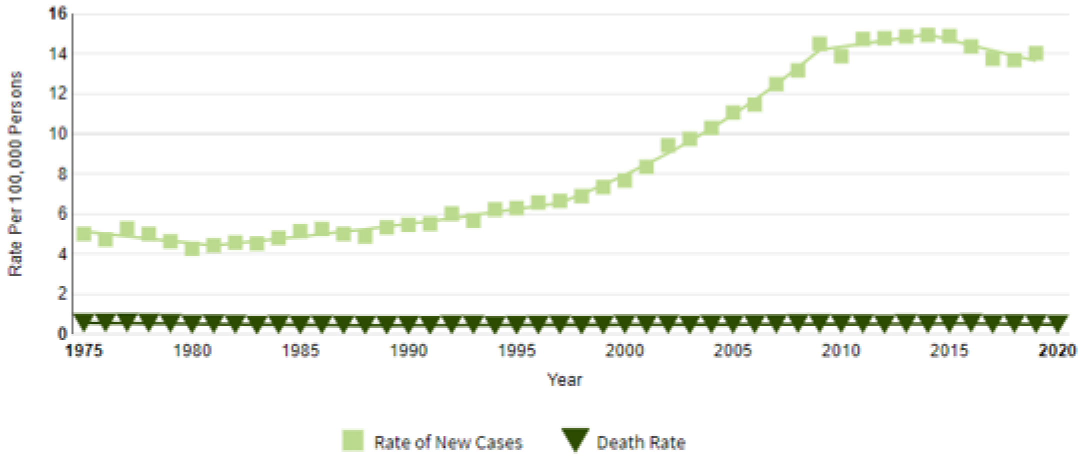
Conclusion:

Our study results show that rural residents and residents living a long distance from reporting medical facilities are associated with later stages of diagnosis. Being male sex and age above 65 have increased chances of thyroid cancer diagnosis at a later stage. Health disparities will further exacerbate the differences in outcome of cancer across the disadvantaged populations (rural residents) and hence, geography will continue to affect cancer outcomes.

This study will open a public health, social and political discussion to consider prioritizing and allocating more resources in the disparities areas, including building a new health facility or preventing closure of existing facilities via the state and federal public health policies.

Implementation of strategies that use patient navigation, faith-based organization (churches) and local community engagement, and social services can improve health access and will reduce disparities.

Figure 2. New cases and Deaths of thyroid cancer in the US. 1975-2020



(Statistics of Thyroid Cancer (SEER, 2022), n.d.)

Table 8. Cancer incidence in Nebraska (2014-2018) and US (2013-2017)

	NEBRASKA (2014-2018)						US 2013-2017		
	Male		Female		Total		Male	Female	Total
	No	Rate	No	Rate	No	Rate	Rate	Rate	Rate
All sites	26,447	509.1	24,893	440.5	51,341	468.0	488.5	422.2	448.7
Thyroid cancer	370	7.4	1,116	23.6	1,486	15.4	7.3	21.1	14.3

Nebraska cancer registry, 2021

Table 9. Cancer mortality in Nebraska (2014-2018) and the U.S(2013-2017)

	NEBRASKA (2014-2018)						US (2013-2017)		
	Male		Female		Total		Male	Female	Total
	No	Rate	No	Rate	No	Rate	Rate	Rate	Rate
All sites	9,138	182.8	8,226	132.9	17,364	154.1	189.5	135.7	158.3
Thyroid cancer	24	0.5	20	0.3	44	0.4	0.5	0.5	0.5

Nebraska cancer registry, 2021(Department of Health et al., 2021)

Figure 3. Age distribution of thyroid incidence in the United States.

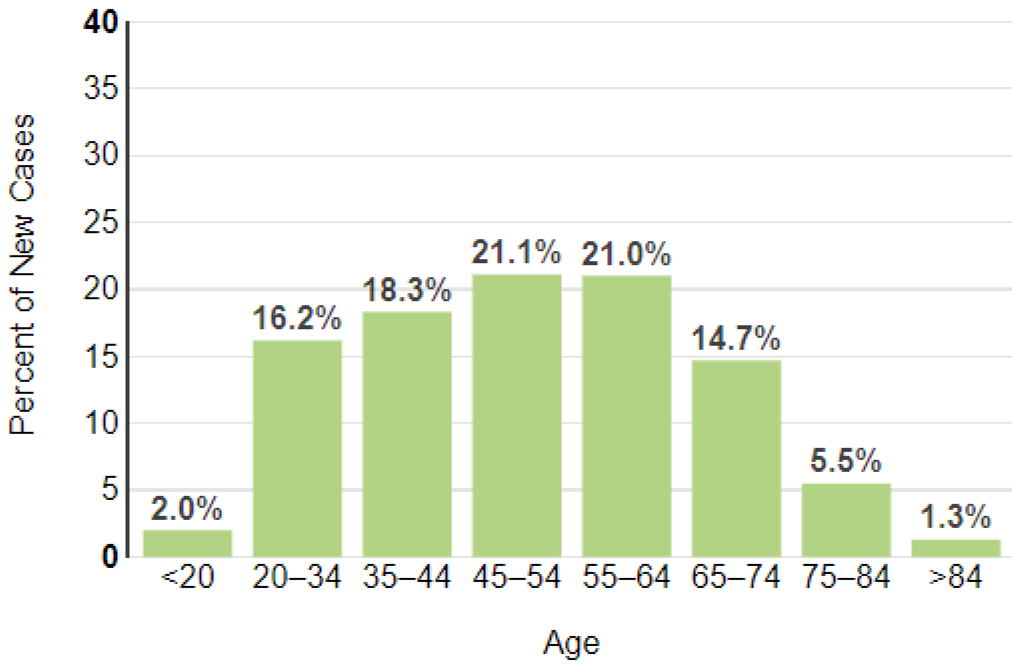
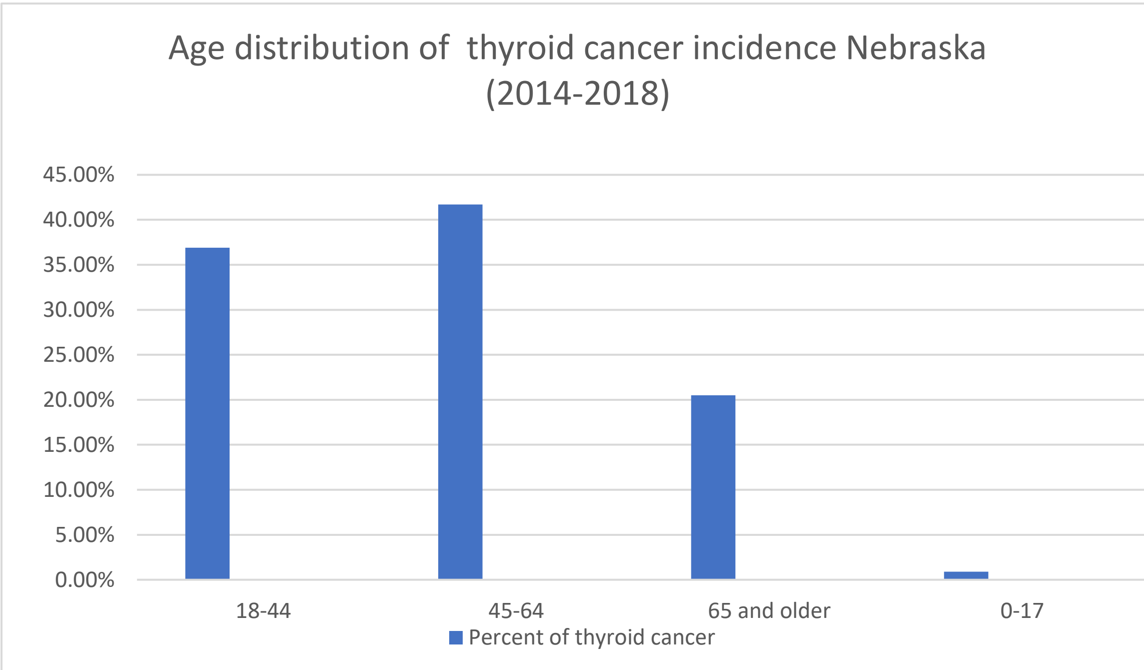
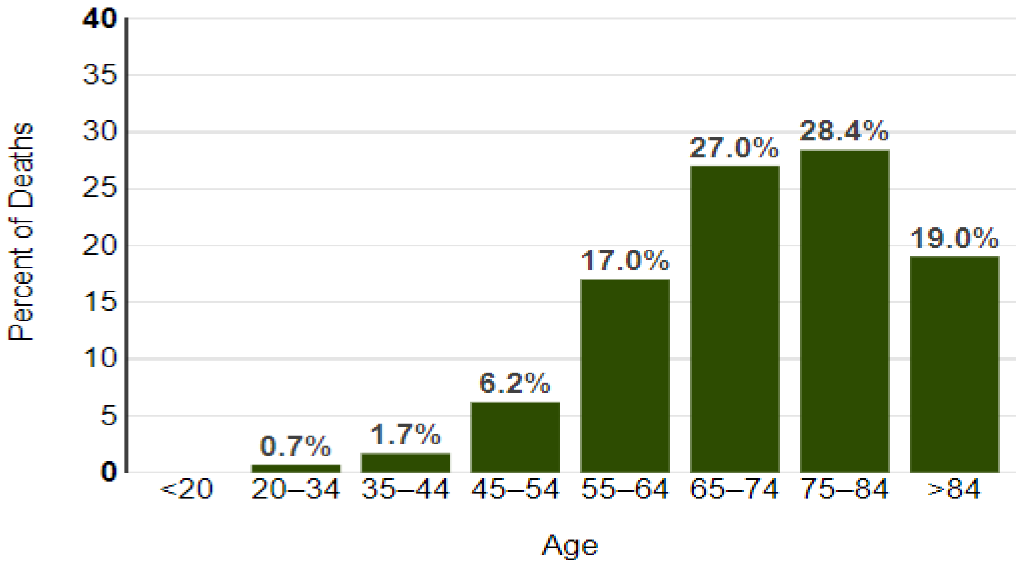


Figure 4.



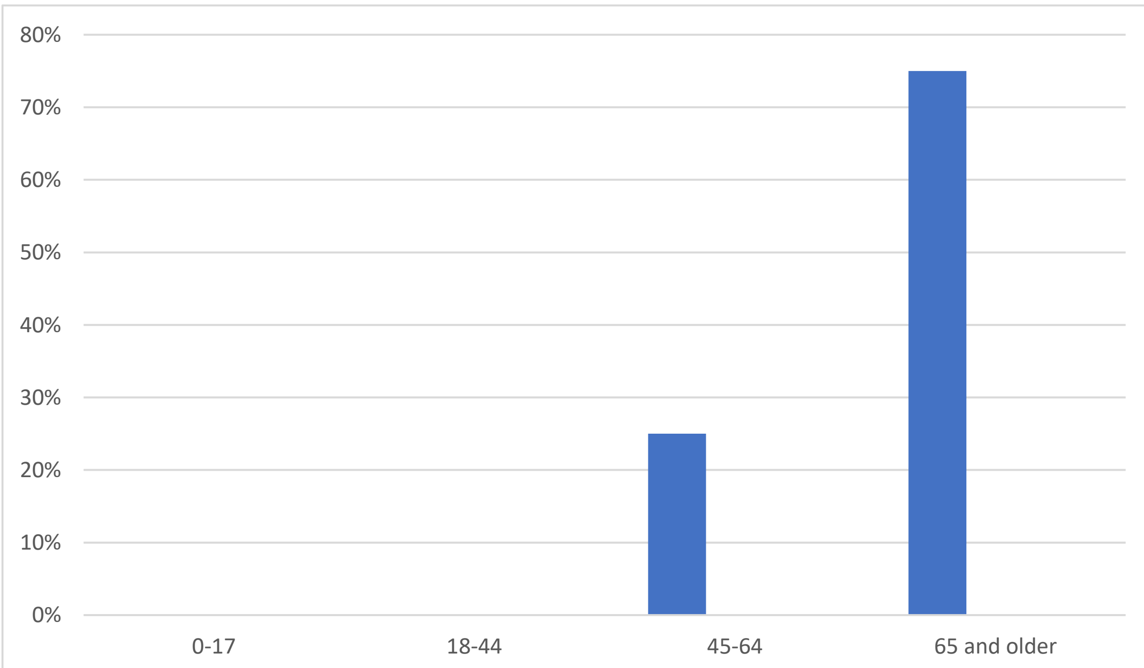
Nebraska Cancer Registry, 2022

Figure 5. Percent of death by age group: Thyroid Cancer (US)



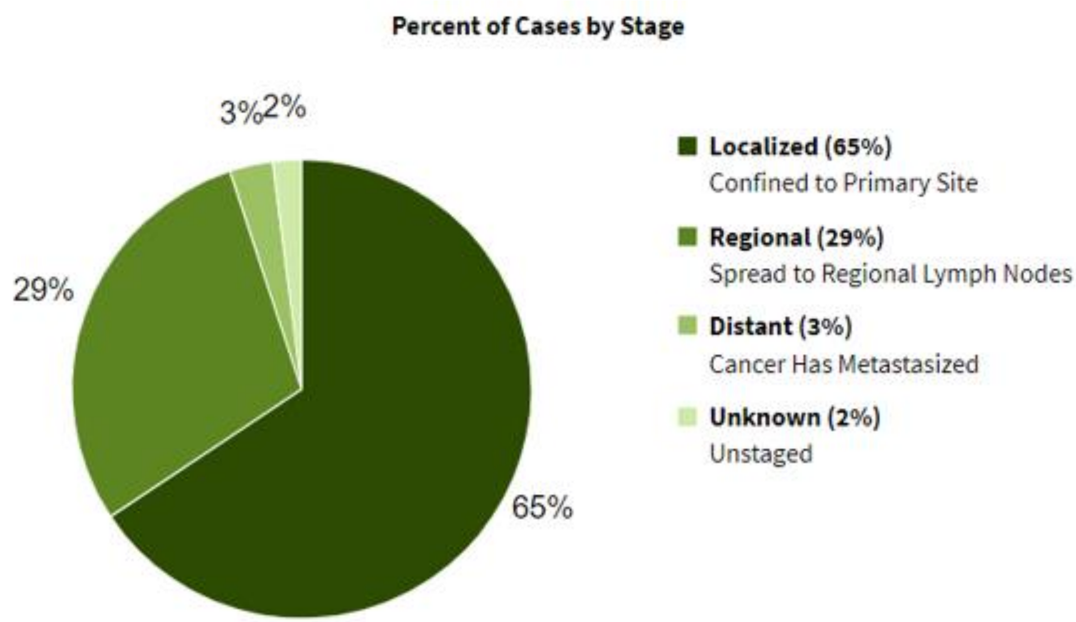
Statistics of Thyroid Cancer (SEER, 2022), n.d.)

Figure 6. Percent of death by age group: Thyroid Cancer, Nebraska (2014-2018)

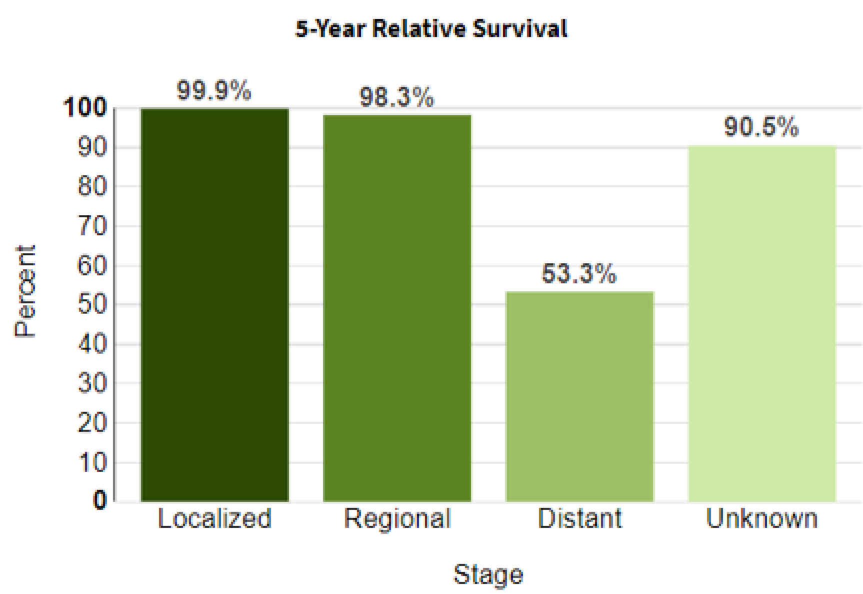


Nebraska cancer registry, 2021

Figure 7. Percentage of Thyroid cancer and 5-year relative survival by stage at diagnosis



Statistics of Thyroid Cancer (SEER, 2022), n.d.)



(Statistics of Thyroid Cancer (SEER, 2022), n.d.)

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