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Nutritional Factors Associated with Thyroid Cancer and Nodules Using the Integrated Cancer Repository for Cancer Research (iCaRe2)

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Title:

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Abstract:

Introduction: The incidence of thyroid cancer in the United States has rising on average 3.1% each year over the last 10 years. Much of this increase is attributed to increased detection using ultrasound. Dietary habits can be an important modifiable risk factors for different types of cancer, but the association between dietary factors and thyroid cancer has not been well studied. The goals of this capstone were to: 1) review the literature for the association between dietary factors and thyroid cancer, 2) describe demographic and behavioral characteristics of patients with thyroid nodules and cancer in a hospital-based registry, and 3) conduct a case-control study comparing dietary habits of patients with thyroid cancer or thyroid nodules to a control (cancer-free) population.

Methods: A case-control study was conducted with 368 thyroid cancer cases and 475 thyroid nodule cases identified from the Thyroid Tumor and Cancer Collaborative Registry (TCCR), and 223 controls identified from the Great Plains Health Informatics Database (GPHID). Dietary habits of cancer cases and thyroid nodule cases were compared to the control group. Crude odds ratios (ORs), adjusted ORs, and 95% Cis were estimated using multivariable logistic regression.

Results: Thyroid cancer cases more likely to consume deli meat (OR=1.69 95%CI 1.03, 2.78), high sugar, low fiber cereals (OR=2.57 95%CI 1.46, 4.53) and mayonnaise (OR=1.65 95%CI 1.14, 2.39). Thyroid cancer cases were less likely to consume fried or scrambled eggs (OR=0.46, 95%CI 0.24, 0.90). Smoking and alcohol assumption did not impact the association between dietary habits and thyroid cancer.

Conclusion: Deli meat, high sugar/low fiber cereals and mayonnaise were more likely to be consume by thyroid cancer cases compared to the controls. These potential risk factors for thyroid cancer need to be explored further. The mechanism is not clear, but if these foods are found to increase risk it could lead to prevention opportunities.

Placement Site:

Name of the organization: Fred & Pamela Buffett Cancer Center (FPBCC)

Aim of the organization: The Fred & Pamela Buffett Cancer Center provides exceptional clinical care for cancer patients in Nebraska and conducts innovative research to both improve treatment and prevent cancer.

Background and Significance:

Thyroid cancer is a disease caused by abnormal cell growth in the thyroid gland. Most thyroid cancers are well-differentiated cancers including papillary cancer (80%), follicular cancer (10%), and Hűrthle (Hurthle) cell cancer (3%). (What Is Thyroid Cancer, 2018) In the United States, the 2018 estimates for thyroid cancer are approximately 53,990 new cases of thyroid cancer and 2,600 deaths per year. (Key Statistics for Thyroid Cancer, 2018) Thyroid nodules are the precursors for thyroid cancer. Nodules are extremely common in the United States, approximately one-half of the population by 60 years of age have thyroid nodules. However, only 5 to 10% of such nodules are malignant. (Thyroid Nodule FAQs, 2018)

Thyroid cancer is the fifth most common cancer diagnosed in females in the United States (U.S.). (American Cancer Society, 2017) Every three out of four diagnosed cases are women. (American Cancer Society, 2017) In the last decade, the incidence of thyroid cancer increased 3.1% each year. The mortality rates of thyroid cancer increased 0.7% each year during 2006 to 2015. (Figure1) (Figure 1-5 are in the Appendix A) Rates of thyroid cancer in Nebraska are comparable to the US. Between 2010 and 2014, the incidence of female thyroid cancer cases was 21 per 100,000 in Nebraska and 20.8 per 100,000 in the US. For males, the incidence was 6.7 per 100,000 in Nebraska and 7.0 per 100,000 in the U.S. (Table 1) The mortality rate is 0.7 per 100,000 in Nebraska and 0.5 per 100,000 in the U.S. for males and 0.5 per 100,000 in Nebraska and 0.5 per 100,000 in the U.S. for females. (Table 2) Whites have the highest risk of getting thyroid cancer, 7.7 per 100,000 males and 22.2 per 100,000 females. (Thyroid Cancer, 2018) Among males, the incidence of developing thyroid cancer is 7.2 per 100,000 in Asian/Pacific Islanders, 5.8 per 100,000 in Hispanics, and 4.0 per 100,000 in blacks and American Indian/Alaska Natives. (Thyroid Cancer, 2018) Among females, thyroid cancer incidence is 21.6

per 100,000 females in Asian/Pacific Islanders, Hispanics are 20.9 per 100,000 females, blacks are 13.9 per 100,000 females, and American Indian/Alaska Natives 11.8 per 100,000 females. (Thyroid Cancer, 2018) Incidence of thyroid cancer is highest in the 45 to 54 year old age group, 23.4% of new thyroid cases, all race/ethnic groups and gender, are in the 45 to 54 year old age group. (Figure 2) The median age of death from thyroid cancer is 73 years, and the 75 to 84 years old age group has the highest thyroid cancer related death, 27.2% of all cases. (Figure 4) In Nebraska, the age distribution of thyroid cancer incidence and mortality are shown in Figure 3 and Figure 5, 41.1% of new thyroid cancer cases occurred in 45-64 age year old group, 77.6% of deaths were 65 years or older.

Compared with other cancers, thyroid cancer is commonly diagnosed at a younger age. Papillary cancer is the most common type of thyroid cancer, and the 30-39 year age group has the highest incidence of papillary cancer , and rates in this age group are rising from 5.56 to 12.9 per 100,000 people between 2001 and 2010.(Jayarajah, Fernando, Prabashani, Fernando, & Seneviratne, 2018) Approximately 2% of thyroid cancers occur in children and teens. (Key Statistics for Thyroid Cancer, 2018)

There are several established risk factors for thyroid cancer. Non-modifiable risk factors include female gender, age (peak age 30-50 years in females and 60-80 years in males), hereditary conditions (several inherited genetic abnormalities and other diseases, such as familial medullary thyroid cancer, multiple endocrine neoplasia type 2, familial adenomatous polyposis, etc.), and family history of thyroid cancer. (Thyroid cancer risk factors, 2015) (Thyroid Cancer, 2017) Modifiable risk factors include a diet low in iodine, and radiation exposure to the head and neck at a young age. (Thyroid cancer risk factors, 2015) (Thyroid Cancer, 2017)

The results of a literature review on dietary habits and thyroid cancer are shown in Table 3 Appendix B. No association was found between all fish consumption and increased risk of developing thyroid cancer in Sweden, Norway and the United States.(Galanti et al., 1997; Horn-Ross et al., 2001) Two case-control studies showed salt water fish consumption may be a protective factor for thyroid cancer for both males and females in Kuwait and France, but the results were not significant. (Memon, Varghese, & Suresh, 2002; Truong, Baron-Dubourdieu, Rougier, & Guénel, 2010) Another study showed people with thyroid cancer were three times (95% CI 1.6-5.3) more likely to eat fish products compared to those without cancer. (Memon et al., 2002) Brackish water fish consumption (OR 0.43, 95% CI 0.20-0.93) was found as a significant protective factor for thyroid cancer. (Truong et al., 2010) Pork (OR=2.82, 95% CI 1.36-5.86) and chicken (OR=3.0, 95% CI 1.3-6.8) consumptions were significant risk factors for thyroid cancer. (Daniel et al., 2012; Markaki, Linos, & Linos, 2003; Memon et al., 2002) All meat consumption was measured in a study in Norway and Sweden and was insignificantly associated with thyroid cancer(Galanti et al., 1997) Cheese and butter intake were positively associated with thyroid cancer risk in Norway and Sweden, ORs were 1.7 (95% CI 1.1-2.7) for cheese consumers and 1.6 (95% CI 1.1-2.5) for butter consumers.(Galanti et al., 1997) Other dairy products, like milk, were not associated with thyroid cancer. (Galanti et al., 1997; Truong et al., 2010) Papillary cancer cases were 2.9 (95% CI 1.2-7.4) times more likely to consume multivitamins for 10 or more years compared to persons without thyroid cancer.(Mack, Preston-Martin, Bernstein, & Qian, 2002) An American cohort study found Vitamin C consumption was associated with increased risk (OR 1.34, 95% CI 1.02–1.76) of thyroid cancer.(O'Grady, Kitahara, DiRienzo, & Gates, 2014) Calcium (OR 0.55, 95% CI 0.35-0.89)), Vitamin A (OR 0.5, 95% CI 0.3-0.9), Vitamin C (OR 0.6, 95% ci 0.4-1.0), and Vitamin E (OR 0.5, 95% CI 0.3-

1.0) were protective factors for thyroid cancer.(Cho, Lee, & Kim, 2016; Galanti et al., 1997) Women with cancer had significantly higher total and food source iodine intake compared to the control group.(L.N., J.H., L.R., & F.H., 1990) Raw vegetables (OR 0.2, 95% CI 0.07-0.62), turnips (OR 0.6, 95% CI 0.3-1.0), and rutabagas (OR 0.5, 95% CI 0.2-0.9), were protective factors for thyroid cancer.(Bandurska-Stankiewicz, Aksamit-Białoszewska, Rutkowska, Stankiewicz, & Shafie, 2011; Mack et al., 2002; Markaki et al., 2003; Memon et al., 2002) Other factors, including all fruit (OR 1.2, 95% CI 0.8-1.8) and cauliflower (OR 1.8, 95% CI 1.0-3.2), were insignificantly associated with thyroid cancer.(Galanti et al., 1997; Memon et al., 2002) Two case-control studies found that people with thyroid cancer were 1.9 (95% CI 1.1-3.3) times and 1.86 (95% CI 1.01-3.43) times more likely to consume cabbage and cruciferous vegetables.(Memon et al., 2002; Truong et al., 2010)

In our study, we focused on different cooking methods for meat preparation, vegetable consumption, fruit consumption, dairy consumption, and other food consumption using data which was available in the registry database.

Interestingly, several studies have shown that smoking and alcohol consumption, typically risk factors for many cancers, may be inversely associated with thyroid cancer development. (Guignard, Truong, Rougier, Baron-Dubourdieu, & Guénel, 2007; Hwang et al., 2016; Mack et al., 2002; Meinhold et al., 2009; Myung, Lee, Lee, Kim, & Kim, 2017) Therefore, we also explored smoking and alcohol behaviors and the impact of these behaviors on the association between dietary factors and thyroid cancer or thyroid nodules.

Specific Aims:

Thyroid cancer responds well to treatment and can be cured with surgery. However, if dietary factors are associated with the development of thyroid cancer, it could potentially be prevented as dietary habits are a modifiable risk factor. Dietary habits may be risk factors or protective factors for thyroid cancer, and changes to dietary habits may provide primary prevention opportunities.

The specific aims of this study are to:

1) Describe the study population of thyroid cancer cases, high-risk thyroid nodules cases, and controls in X database;
2) Measure the association of dietary consumption factors (red meat, dairy, fish, vegetable, fruit, and other food) with thyroid cancer and thyroid nodules;
3) Estimate the impact of smoking and alcohol consumption on the association between dietary factors and thyroid cancer.

Data from the Thyroid Tumor and Cancer Collaborative Registry (TCCR) and Great Plains Health Informatics Database (GPHID) was used to conduct a case-control study.

Research Methods:

Study design and study population: A case-control study was conducted to address the specific aims. The Integrated Cancer Data Repository for Cancer Research (iCaRe2), a repository for all cancer-related data collection and managed by the Fred & Pamela Buffett Cancer Center at University of Nebraska Medical Center (UNMC), was used to identify the study population and obtain data. (Goldner, 2013) The iCaRe2 registry for all cancers and a control group began in November 2013, but data collection on thyroid cancer cases started earlier in 2008. The aim of the registry is to collect, manage, mine and share cancer-related data collected from cancer patients and a control group. The database includes the Thyroid Tumor and Cancer Collaborative Registry (TCCR) includes information for thyroid cancer and nodules. TCCR is a multicenter, web-based registry database to support the understanding of risk factors and natural history of thyroid cancer and nodules and to develop novel strategies for screening, detection, and treatment.(Shats et al., 2016) The Great Plains Health Informatics Database (GPHID) includes data for controls. The goal of GPHID is to establish a database including personal background information, medical and family details, dietary, and environmental exposure history for persons without cancer.

Eligibility criteria: Participants are adults 19 years of age and older who signed an informed consent to be included into the TCCR and GPHID. The final study population we used in this project was all participants who had answered dietary habits questions (frequency of food consumption) which were investigated in this study. Two case groups were people who had been diagnosed with thyroid cancer or thyroid nodules between February 2008 and June 2018. Data for cases was collected after people presented to clinic and were offered enrollment in to the registry. Controls had no history of being diagnosed with any type of cancer or any thyroid gland related disease, live in the Midwest and provided informed consent.

Data collection: Core data elements collected for cases and controls included demographic (date of birth, date of enrollment, age at diagnosis, birth country/state, gender, race/ethnicity, marital status, education – highest level, and household income), occupation and environment (current employment status and toxic exposures), family history and clinical data (family history of thyroid cancer, history of cancers and major diseases completed staging (pathologic and clinical) histologic type, site(s) of involvement, treatment (type, schedule, response), treatment outcome), lifestyle and dietary habits (physical activity, sleep patterns, tobacco/smoking habits (current and past), alcohol consumption (current and past), coffee drinking habits, and caffeinated beverages drinking habits, dietary habits, and vitamins/supplements intake), and genetic testing (genes tested/mutations found). Clinical data is only available for cases.

Sample size: The TCCR has data from 1,880 people, including 753 cancer cases (case group) and 1,127 thyroid nodule cases (high-risk group). The GPHID has 406 subjects (control group). As of June 2018, there were 368 thyroid cancer cases and 475 thyroid nodules cases in the TCCR and 223 healthy controls in the GPHID which met the eligibility criteria. (Figure 6 and Figure 7)

Figure 6. Framework of study population for TCCR

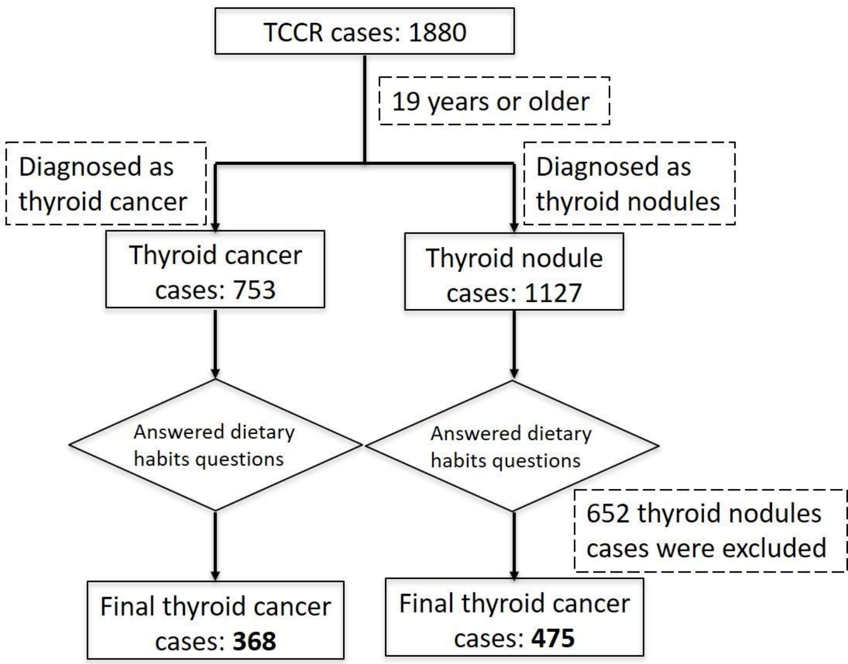
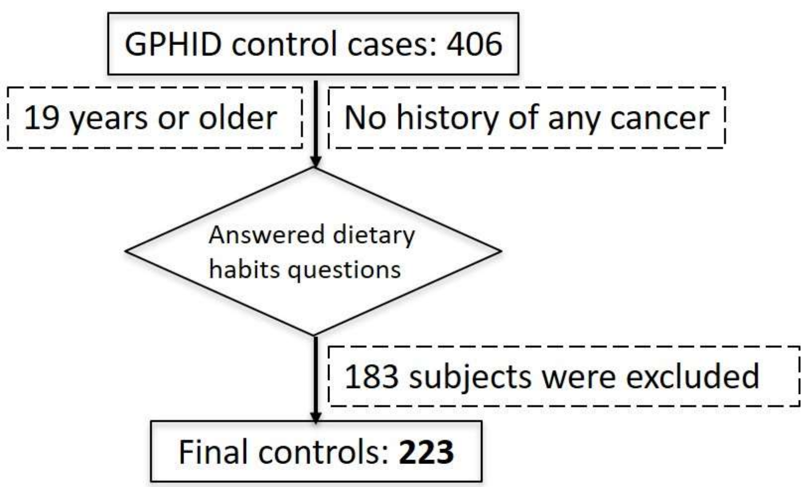


Figure 7. Framework of study population for GPHID



Statistical methods:

Descriptive statistics (frequencies, percentages, means, and standard deviation) were used to describe age at enrollment, gender, education, current BMI, smoking status, and drinking status among cancer cases, high-risk cases, and controls. Two sample t-test was used on continuous variables and Chi-square test was used on categorical variables to assess similarities and differences between the case and control groups. Single variable logistic regression model was used to compare the dietary consumption exposures (consumed the food or never consumed) between cases and controls, high-risk and control, and cases and high-risk. Food types with very low response rate were not analyzed. A low response rate is defined as the number of subjects answered the dietary habits questions in cancer (or high-risk) and control groups divided by total cancer (or high-risk) and control cases is less than 0.2. Multivariable logistic regression model was used to adjust for age at enrollment, gender, education, current BMI, and drinking status. Crude ORs and 95% CI were reported to estimate the associations between thyroid cases and controls and high-risk cases and controls. The presence of confounding was determined by assessing variables significantly related to both exposures (frequency of food consumptions) and outcome (cancer, high-risk, or control). Although we did not find that current BMI was a confounder in our data, previous studies of thyroid cancer and diet habits routinely adjust by BMI, therefore it was included in the final model. A p-value <0.05 was considered as significant.

Results:

Table 4. General characteristics of the thyroid cancer, thyroid nodules and control subjects

	Cancer(n=368)			High Risk(n=475)				Control(n=223)	
Characteristics	n	Mean (SD)	P (Cancer vs. Control)	n	Mean (SD)	P (HR vs. Control)	P* (Cancer vs. HR)	n	Mean (SD)
Diagnostic age	354	43.0 (15.7)							
Enroll age	368	47.1 (15.2)	<0.0001	475	53.1 (14.7)	0.6299	<0.0001	223	52.5 (13.5)
Characteristics	n	%		n	%			n	%
Gender			0.0006			<0.0001	0.0018		
Female	294	79.9		417	87.8			150	67.3
Male	74	20.1		58	12.2			73	32.7
Education			0.2870			0.0298	0.5401		
High school or lower	60	16.4		89	19.1			35	15.8
Associate degree or technical school	125	34.1		165	35.3			60	27.0
College graduate	108	29.4		134	28.7			74	33.3
Graduate or professional school	74	20.2		79	16.9			53	23.9
Current BMI			0.3630			0.0477	0.5817		
Underweight (Below 18.5)	7	2.01		10	2.3			2	0.9
Normal or Healthy Weight (18.5 – 24.9)	106	30.5		119	27.6			65	30.1
Overweight (25.0 – 29.9)	105	30.2		121	28.1			78	36.1
Obese (30.0 and Above)	130	37.4		181	42.0			71	32.9
Smoking Status			0.4531			0.9026	0.5959		
Current smoking	36	10.1		45	10.3			24	10.8
Past smoking	90	25.4		125	28.5			66	29.7
Never smoking	229	64.5		269	61.3			132	59.5
Drinking Status			0.0032			0.0038	0.8215		
Current drinking	221	63.1		278	63.5			167	76.3
Past drinking	47	13.4		64	14.6			23	10.5
Never drinking	82	23.4		96	21.9			29	13.2

* P* are the p-value of cancer group and high-risk group.

Table 4 shows the general characteristics of the thyroid cancer cases, thyroid nodule cases and control subjects. Two distinct case groups were identified, 368 persons with thyroid cancer (ICD-10 C73) which is referred to as the cancer group, and 475 persons with a thyroid nodule (ICD-10 E04) referred to as the high-risk group. The control group (n=223) was identified using the Great Plains Health Informatics Database (GPHID).

Age at diagnosis was only available for cases with thyroid cancer. For the cancer cases, age at diagnosis (43.0 years ± 15.7) and age at enrollment (47.1 years ±15.2) was significantly different ($p<0.0001$). Questionnaire data was obtained at age at enrollment. Age at enrollment differed by case control status. The age at enrollment of the cancer cases was 47.1 years old (SD 15.2), the high-risk cases was 53.1 years old (SD 14.7) and 52.5 years (13.5) for the control group. Cancer cases were significantly younger compared to the high-risk cases ($p<0.0001$) and control group ($p<0.0001$). There was no significant difference in age at enrollment between the high-risk cases and the control group. The percentage of case types by age at enrollment is shown in Figure 8.

The gender distribution of cancer cases, high-risk cases and the control group differed. All three groups were predominately females but there were more females in the cancer and high-risk groups compared to the control group (79.9% cancer case females, 87.8% high risk case females and 67.3% control group females) (Figure 9).

There was no significant difference between cancer cases and high-risk cases by education level, with college graduate or higher as 49.6% and 45.6% respectively. The control group was significantly more educated. However, there was a significant difference between high-risk group and control ($p=0.0298$), with college graduate or higher as 45.6% and 57.2% (Figure 10). There was no significant difference in current BMI between cancer cases and high-risk cases and between cases group and the control group. The percentage of overweight and obese was 67.6% in cancer cases, 70.1% in high-risk cases, and 69% in the control group (Figure 11). The percentage of people who ever smoked (current and former smokers) was similar among cancer cases, high-risk cases, and the control group (35.5%, 38.8%, and 40.5% respectively, p = 0.4531, 0.9026, and 0.5959). The distribution of alcohol drinkers (current drinking and past drinking) were similar between the case groups, 76.5% for cancer cases and 78.1% for high-risk cases. However, controls were more likely to drink. Never drinkers were only 13.2% in the control group compared to cancer cases (23.5%, p=0.0032) and high-risk cases (21.9%, p=0.0038) (Figure 12).

Table 5. Thyroid cancer and thyroid nodules (high-risk) according to different diet habits in logistic regression analysis

	Control	Cancer			High risk		
	(Consume the food / Total)	(Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)	(Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)
MEAT							
Sausage or bacon	194/214	315/349	0.96 (0.54-1.71)	0.97 (0.96, 0.99)	386/450	0.62 (0.37, 1.06)	0.58 (0.32, 1.04)
Deli meat/Cold Cuts	150/196	281/327	1.87 (1.19-2.95)	1.69 (1.03, 2.78)	319/402	1.18 (0.78, 1.78)	1.33 (0.84, 2.10)
Hot dogs	171/211	276/351	0.86 (0.56-1.32)	0.83 (0.52, 1.32)	353/445	0.90 (0.59, 1.36)	0.92 (0.58, 1.44)
Beef/ BBQ/ Grilled	196/212	324/351	0.98 (0.52-1.86)	0.83 (0.41, 1.70)	390/436	0.69 (0.38, 1.25)	0.72 (0.37, 1.42)
Beef/ Fried	111/173	1year/304	0.81 (0.55-1.19)	0.82 (0.54, 1.24)	213/372	0.75 (0.52, 1.09)	0.75 (0.50, 1.14)
Beef/ Baked	137/175	226/297	0.88 (0.56-1.38)	0.84 (0.52, 1.38)	292/384	0.88 (0.57, 1.35)	0.84 (0.52, 1.35)
Pork/ BBQ/ Grilled	137/177	220/292	0.89 (0.57-1.39)	0.92 (0.57, 1.49)	263/373	0.70 (0.46, 1.06)	0.85 (0.54, 1.34)
Pork/Fried	75/156	103/269	0.67 (0.45-1.00)	0.61 (0.39, 0.95)	131/331	0.71 (0.48, 1.04)	0.60 (0.39, 0.92)
Pork/ Baked	112/166	183/278	0.93 (0.62-1.40)	1.00 (0.64, 1.56)	220/351	0.81 (0.55, 1.20)	0.76 (0.50, 1.17)
Poultry/ BBQ/ Grilled	143/160	259/315	0.55 (0.31-0.98)	0.46 (0.25, 0.87)	342/400	0.70 (0.40, 1.25)	0.83 (0.44, 1.55)
Poultry/Fried	114/167	198/297	0.93 (0.62-1.40)	0.84 (0.54, 1.32)	226/363	0.77 (0.52, 1.13)	0.75 (0.49, 1.16)
Poultry/ Baked	171/195	271/309	1.00 (0.58, 1.73)	0.94 (0.52, 1.70)	352/402	0.99 (0.59, 1.66)	0.90 (0.51, 1.61)
Fish/ BBQ/ Grilled	95/165	110/267	0.52 (0.35, 0.77)	0.58 (0.38, 0.88)	172/346	0.73 (0.50, 1.06)	0.81 (0.54, 1.21)
Fish/ Fried	67/154	117/275	0.96 (0.65, 1.43)	1.14 (0.74, 1.76)	153/347	1.02 (0.70, 1.50)	1.08 (0.71, 1.65)
Fish/ Baked	114/173	151/290	0.56 (0.38, 0.83)	0.69 (0.46, 1.05)	224/362	0.84 (0.58, 1.23)	0.94 (0.62, 1.42)
Smoked Meats	93/165	152/285	0.89 (0.60, 1.30)	0.92 (0.60, 1.39)	170/350	0.73 (0.50, 1.06)	0.75 (0.50, 1.13)
VEGETABLE							
French fries, home fries, or hash brown potatoes	204/216	343/360	1.19 (0.56, 2.54)	0.90 (0.39, 2.09)	406/454	0.50 (0.26, 0.96)	0.46 (0.22, 0.96)
Vegetables (if preparation is unknown)	196/211	318/349	0.79 (0.41, 1.49)	0.99 (0.48, 2.04)	424/455	1.05 (0.55, 1.98)	1.11 (0.54, 2.32)

- Adjusted by age at enrollment, gender, education, current BMI, and drinking status.

Table 5. Continued

	Control	Cancer			High risk		
	(Consume the food / Total)	(Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)	(Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)
FRUIT AND FRUIT JUICE							
Fruit Juice	178/211	298/353	1.00 (0.63, 1.61)	0.97 (0.58, 1.61)	351/438	0.75 (0.48, 1.16)	0.82 (0.51, 1.34)
Fruit, fresh or frozen	215/218	355/360	0.99 (0.23, 4.19)	1.38 (0.29, 6.48)	459/463	1.60 (0.36, 7.22)	1.36 (0.28, 6.64)
GRAIN							
High sugar, low fiber cereals	180/212	333/356	2.57 (1.46, 4.53)	2.71 (1.46, 5.02)	412/460	1.53 (0.94, 2.47)	1.53 (0.91, 2.56)
White rice, pasta, bread	204/214	321/348	0.58 (0.28, 1.23)	0.69 (0.31, 1.52)	415/452	0.55 (0.27, 1.13)	0.63 (0.29, 1.34)
EGG, OIL and SAUSE							
Eggs fried or scrambled	200/212	314/355	0.46 (0.24, 0.90)	0.48 (0.23, 0.99)	399/453	0.44 (0.23, 0.85)	0.43 (0.21, 0.88)
Canola oil	142/199	238/338	0.96 (0.65, 1.41)	0.95 (0.63, 1.43)	305/428	1.00 (0.69, 1.44)	1.02 (0.68, 1.52)
Mayonnaise	127/203	251/342	1.65 (1.14, 2.39)	1.61 (1.08, 2.40)	302/427	1.45 (1.02, 2.06)	1.41 (0.97, 2.07)
Salad dressings	172/210	293/344	1.27 (0.80, 2.01)	1.28 (0.77, 2.10)	377/438	1.37 (0.88, 2.13)	1.38 (0.85, 2.24)
DAIRY							
Skim milk, on cereal or to drink	149/207	244/344	0.95 (0.65, 1.39)	0.97 (0.64, 1.47)	291/440	0.76 (0.53, 1.09)	0.81 (0.55, 1.20)
Cheese or cheese spread	196/210	333/353	1.19 (0.59, 2.41)	1.59 (0.70, 3.62)	421/453	0.94 (0.49, 1.80)	0.85 (0.41, 1.78)
OTHER							
Kelp/seaweeds	18/190	23/324	0.73 (0.38, 1.39)	0.67 (0.33, 1.36)	32/410	0.81 (0.44, 1.48)	1.08 (0.56, 2.10)
Soy products, tofu	63/191	107/327	0.99 (0.68, 1.45)	1.04 (0.69, 1.57)	138/420	0.99 (0.69, 1.43)	1.30 (0.87, 1.95)
Nuts	169/204	291/340	1.23 (0.77, 1.98)	1.31 (0.77, 2.22)	347/428	0.89 (0.57, 1.37)	1.04 (0.64, 1.71)

- Adjusted by age at enrollment, gender, education, current BMI, and drinking status.

In table 5, the reference for all food odds ratios were set as no consumption. Comparing cancer cases to the control group, with the exception of deli meats, meat consumption, including sausage or bacon, hot dogs, beef (grilled, fried, and baked), pork (grilled, fried, and baked), poultry (grilled and fried), fish (grilled and baked), and smoked meats, was reported less by cancer cases compared to controls. After adjusted for age at enrollment, gender, education, current BMI, and drinking status, the difference was significant for sausage or bacon (OR_{adj} 0.96, 95% CI 0.96-0.99), BBQ or grilled poultry (OR_{adj} 0.46, 95% CI0.25-0.87), and grilled fish OR_{adj} 0.58, 95% 0.38-0.88). The consumption of deli meats was associated with thyroid cancer OR_{adj} (1.69, 95% CI 1.03-2.78).

The odds ratios for vegetables white rice, pasta, and bread, fried or scrambled eggs, canola oil, skim mile, kelp/ seaweeds were less than 1.0, however only fried or scrambled eggs was significant OR_{adj} 0.48 (95% CI 0.23 - 0.99).

The adjusted OR for high sugar, low fiber cereals (OR_{adj} 2.71, 95% CI 1.46-5.02) and mayonnaise (OR_{adj} 1.61, 95% CI 1.08 to 2.40), were significant. Cases were more likely to eat these foods compared to controls.

High risk group and control group

Comparing thyroid nodule cases to the control group, with the exception of deli meats and fried fish, meat consumption, including sausage or bacon, hot dogs, beef (grilled, fried, and baked), pork (grilled, fried, and baked), poultry (grilled, fried, and baked), fish (grilled and baked), and smoked meat was reported less by thyroid nodule cases compared to controls. After adjusting for age at enrollment, gender, education, current BMI, and drinking status, the difference was significant for fried pork (OR_{adj} 0.60, 95% CI 0.39–0.92).

The odds ratios for French fries, home fries, or hash brown potatoes, fruit juice, white rice, pasta, and bread, fried or scrambled eggs, skim milk, and cheese were reported less by thyroid nodule cases compared to controls. Only French fries, home fries, or hash brown potatoes and fried or scrambled eggs were significant (OR 0.50, 95% CI 0.26 - 0.96 for French fries) and (OR 0.44, 95% CI 0.23 - 0.85 for fried or scrambled eggs). Consuming vegetables, fruit (not juice), high sugar, low fiber cereals, mayonnaise, salad dressings were risk factors for thyroid nodules. The crude odds ratios for mayonnaise was a significant risk factor for high risk group (OR =1.45, 95% CI 1.02 - 2.06). Kelp/seaweeds, soy products, nuts and canola oil did not have difference for thyroid nodules either before or after the adjustment.

Table 6. Comparing thyroid cancer and thyroid nodules (high-risk) according to different diet habits in logistic regression analysis

	Cancer (Consume the food / Total)	High Risk (Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)
MEAT				
Sausage or bacon	315/349	386/450	1.54 (0.99, 2.39)	1.60 (0.99, 2.58)
Deli meat/Cold Cuts	281/327	319/402	1.59 (1.07, 2.36)	1.24 (0.80, 1.91)
Hot dogs	276/351	353/445	0.96 (0.68, 1.35)	0.89 (0.61, 1.29)
Beef/ BBQ/ Grilled	324/351	390/436	1.42 (0.86, 2.33)	1.14 (0.65, 1.99)
Beef/ Fried	180/304	213/372	1.08 (0.80, 1.47)	1.22 (0.87, 1.72)
Beef/ Baked	226/297	292/384	1.00 (0.70, 1.43)	1.09 (0.73, 1.62)
Pork/ BBQ/ Grilled	220/292	263/373	1.28 (0.90, 1.81)	1.23 (0.84, 1.80)
Pork/Fried	103/269	131/331	0.95 (0.68, 1.32)	1.09 (0.75, 1.58)
Pork/ Baked	183/278	220/351	1.15 (0.83, 1.59)	1.36 (0.94, 1.97)
Poultry/ BBQ/ Grilled	259/315	342/400	0.78 (0.53, 1.17)	0.62 (0.40, 0.98)
Poultry/Fried	198/297	226/363	1.21 0.88, 1.67)	1.26 (0.88, 1.80)
Poultry/ Baked	271/309	352/402	1.01 (0.65, 1.59)	1.16 (0.71, 1.90)
Fish/ BBQ/ Grilled	110/267	172/346	0.71 (0.51, 0.98)	0.76 (0.53, 1.08)
Fish/ Fried	117/275	153/347	0.94 (0.68, 1.29)	1.14 (0.80, 1.64)
Fish/ Baked	151/290	224/362	0.67 (0.49, 0.92)	0.88 (0.62, 1.25)
Smoked Meats	152/285	170/350	1.21 (0.89, 1.66)	1.17 (0.83, 1.65)
VEGETABLE				
French fries, home fries, or hash brown potatoes	343/360	406/454	2.39 (1.35, 4.23)	1.94 (1.07, 3.53)
Vegetables (if preparation is unknown)	318/349	424/455	0.75 (0.45, 1.26)	0.88 (0.49, 1.60)

- Adjusted by age at enrollment, gender, education, current BMI, and drinking status.

Table 6. Continued

	Cancer (Consume the food / Total)	High Risk (Consume the food / Total)	Crude OR (95% CI)	Adjusted OR (95% CI)
FRUIT AND FRUIT JUICE				
Fruit Juice - Orange, apple, grape, pineapple, etc.	298/353	351/438	1.34 (0.93, 1.95)	1.14 (0.76, 1.72)
Fruit, fresh or frozen (not juices)	355/360	459/463	0.62 (0.17, 2.32)	1.49 (0.35, 6.40)
GRAIN				
High sugar, low fiber cereals (malt-o-meal, lucky charms, corn pops, frosted flakes, etc.)	333/356	412/460	1.69 (1.01, 2.83)	1.81 (1.02, 3.21)
White rice, pasta, bread	321/348	415/452	1.06 (0.63, 1.78)	0.93 (0.53, 1.64)
EGG, OIL and SAUSE				
Eggs fried or scrambled	314/355	399/453	1.04 (0.67, 1.60)	1.04 (0.65, 1.68)
Canola oil	238/338	305/428	0.96 (0.70, 1.31)	1.00 (0.71, 1.42)
Mayonnaise	251/342	302/427	1.14 (0.83, 1.57)	1.24 (0.88, 1.74)
Salad dressings	293/344	377/438	0.93 (0.62, 1.39)	0.94 (0.60, 1.45)
DAIRY				
Skim milk, on cereal or to drink	244/344	291/440	1.25 (0.92, 1.70)	1.21 (0.86, 1.68)
Cheese or cheese spread (if unknown which one)	333/353	421/453	1.27 (0.71, 2.25)	1.37 (0.70, 2.70)
OTHER				
Kelp/seaweeds	23/324	32/410	0.90 (0.52, 1.58)	0.65 (0.35, 1.21)
Soy products, tofu	107/327	138/420	0.99 (0.73, 1.35)	0.78 (0.56, 1.11)
Nuts	291/340	347/428	1.39 (0.94, 2.04)	1.29 (0.83, 1.98)

- Adjusted by age at enrollment, gender, education, current BMI, and drinking status.

In Table 6, the reference for all food odds ratios were set as no consumption. Comparing thyroid cancer group to the thyroid nodule group, deli meat, French fries, and high sugar, low fiber cereals consumptions were significant risk factors for thyroid cancer. The crude ORs were 1.59 (95% CI 1.07-2.36), 2.39 (95% CI 1.95-4.23), and 1.69 (95% CI 1.01-2.83). After controlling for age, gender, education, BMI, and drinking status, the adjusted ORs were 1.94 (95% CI 1.07-3.53) for French fries' consumption and 1.81 (95% CI 1.02-3.21) for high sugar, low fiber consumptions. BBQ and grilled fish or poultry and baked fish were protective factors for thyroid cancer. The crude ORs were 0.71 (95% CI 0.51-0.98) and 0.67 (95% CI 0.49-0.92) for fish (BBQ/grilled) and baked fish consumptions. The adjusted OR was 0.62 (95% CI 0.40-0.80) for BBQ/grilled poultry.

Discussion:

This study found that meat (pork, poultry, and fish) with different cooking methods (BBQ, grilled, fried, and baked), French fries and fried eggs consumed less in persons with thyroid cancer compared to the control group. In contrast, deli meat, high sugar, low fiber cereals, and mayonnaise consumption were risk factors of thyroid cancer. Thyroid cancer cases were significantly more likely to eat these foods. Age at enrollment, gender, education, BMI, and drinking status were adjusted in the final logistic regression model.

The data from Nebraska Department of Health and Human Services showed the incidence of thyroid cancer in female was 21 per 100,000 people compared to 6.7 per 100,000 people in male in Nebraska in 2014. The incidence of thyroid cancer in females was 3 times more common than in males (Incidence, 2014). The mechanism is still unclear, however the gender difference in the incidence of thyroid cancer might be explained by the difference of hormones between male and female (Myung et al., 2017). In our study population, there were more females than males.

Fish consumption has consistently been shown to be a protective factor in several previous case-control studies. One case-control study in Kuwait in 2002 showed consuming fish was negatively associated with thyroid cancer (Memon et al., 2002). Another study in France in 2010 found that brackish fish consumption was protective factor for thyroid cancer (Truong et al., 2010). Our study showed that fish that was BBQ, grilled or baked was protective, although these associations were not significant after adjustment.

In most previous studies, iodine intake was shown to reduce the risk of getting thyroid cancer (Cléro et al., 2012; Horn-Ross et al., 2001; Truong et al., 2010). Iodine was not measured in our study, but some food that are rich in iodine such as eggs, certain types of fish were included in our study.

Pork consumption and poultry consumption in different cooking methods were found negatively associated with thyroid cancer. However, these findings were inconsistent to two previous case-control studies. Memon (2002) found chicken was risk factor for thyroid cancer (OR=3.0, 95% CI 1.3-6.8) in Kuwait (Memon et al., 2002). Another study Markaki (2003) found pork was a positive association for thyroid cancer (OR=2.82, 95% CI 1.36-5.86) in Greece (Markaki et al., 2003). The possible reasons were first, our study was conducted in different population with different dietary habits (United States vs. Kuwait and Greece); secondly, our study population was three to four times larger than the sample size of the study in Greece; finally, the analysis variables were different. In our study, we researched the frequency of food consumption, however, other studies studied on the quantity of food consumption.

Some new results were found in this study. Fried eggs consumption was a protective factor for thyroid cancer. Deli meat, high sugar/low fiber cereals and mayonnaise consumptions were found as the risk factors for thyroid cancer. A study in Shanghai China found that women with higher levels of nitrite were at increased risk of thyroid cancer in females (Aschebrook-Kilfoy et al., 2012). The mechanisms of dietary fiber on metabolic health are not well understood. However, dietary fiber intake has been found to be negatively associated to cancer (Lattimer & Haub, 2010).

The strengths of this study were larger sample size compared to previous studies. The study population were 368 for cancer cases, 475 for high-risk cases, and 223 for controls. It is larger than most of previous case-control studies. In our study, different cooking methods of meat preparation were analyzed, including BBQ, grilled, baked, and fried for beef, pork, fish, and poultry. Meat preparation rather than the meat itself could be the important factor. We were able to adjust for demographic variables as well as potential confounders such as age, gender, education, BMI, and drinking status in the final model. There are some limitations in this study. First of all, the GPHID database is not a good control group for TCCR. From table 4, we found that the control group was significantly different from the cancer and high-risk cases by age at enrollment, gender, education level, current BMI, and drinking status. The control group is comprised of family and friends of cancer patients and was not selected only for thyroid cancer but to serve as the control group for iCARE2. The thyroid cancer and thyroid nodule groups were more similar to each other. Secondly, the age we used in this study was age at enrollment. The dietary habits of cancer cases could change between the age at diagnosis and the age at enrollment. The data was collected when patients enrolled into the project. Although the questionnaire asked, "what is your dietary habit before being diagnosed with thyroid cancer", the average age at enrollment was 4 years greater than age at diagnosis. This can cause a major problem with recall bias. As we know dietary habits can change over time with changes in age, education level, income, living environment, and health status, especially when people are diagnosed with cancer. The questionnaire responses may not reflect patients' diet habits before developing thyroid cancer. The TCCR was established in 2008. Patients diagnosed before 2008 were enrolled in the registry, years after the original diagnosis. All patients can be included into the registry if they signed the consent and met the eligibility regardless of age at diagnosis. Another limitation was most of previous studies researched the association between quantity of food consumptions and thyroid cancer. However, our questionnaire asked the frequency of food consumption only and not the quantity. It is easier to collect data on frequency compared to quantity and recall is a problem. We cannot compare the results with the previous studies which studies the quantity of food consumption. Finally, in some specific food consumptions the number of subjects who responded was small, less than 20%, limiting sample size for fruit, fresh or frozen, white rice, canola oil, and kelp/seaweeds.

Administrative Resources:

Resources needed include: computer, printer, copier, library access, and software (Microsoft Office and SAS).

Ethics:

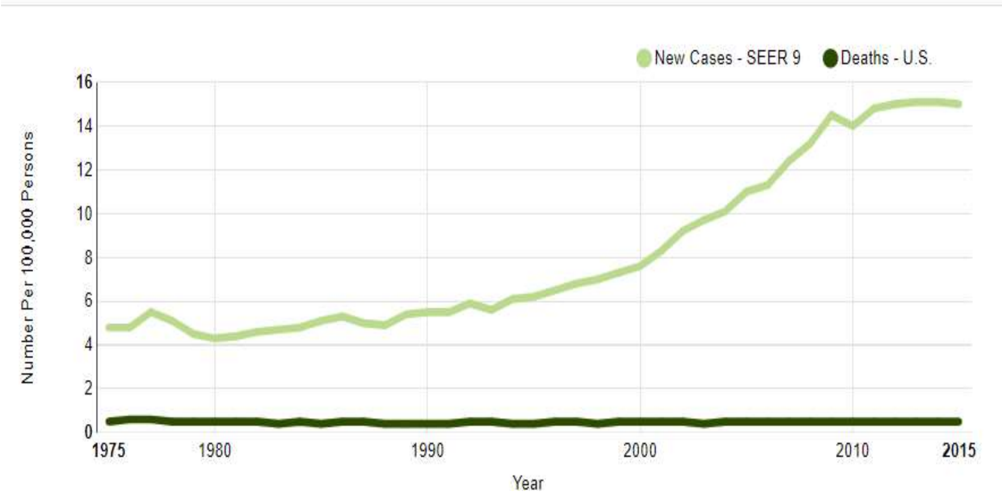
Participants' private information were protected in the entire process of SL/CE project. None of information which could link to the participant's identity would not be included in this study. All the data was stored and analyzed on the computers of UNMC or Fred & Pamela Buffett Cancer Center. It was supervised by the PI of TCCR and GPHID. There was no conflict of interest in this project. The TCCR and GPHID database were approved by the University of Nebraska Medical Center Institutional Review Board (IRB): IRB # 253-13 EP.

Conclusion:

In this study, Deli meat, high sugar/low fiber cereals and mayonnaise were risk factors for thyroid cancer. Fried pork, grilled poultry, fish (grilled, BBQ, or fried) and fried eggs were protective factors for thyroid cancer. Smoking and alcohol assumption did not impact the association between dietary habits and thyroid cancer. Nevertheless, these findings should be explored in larger epidemiological studies with better assessment of dietary habits. Further research on dietary consumptions as risk factors and protective factors for thyroid cancer or thyroid nodules is needed.

Appendix A:

Figure1. New cases and Deaths of thyroid cancer in the US. 1975-2015



(Cancer Stat Facts: Thyroid Cancer, n.d.)

Table1. Cancer incidence in the Nebraska and the US (2010-2014)

	Nebraska 2010-2014						US 2009-2013		
	male		female		total		male	female	total
	No.	Rate	No.	Rate	No.	Rate	Rate	Rate	Rate
All sites	24,354	508.2	22,664	416.6	47,020	454.4	511.3	418.2	461.9
Thyroid cancer	319	6.7	975	21.0	1,294	13.8	7.0	20.8	14.0

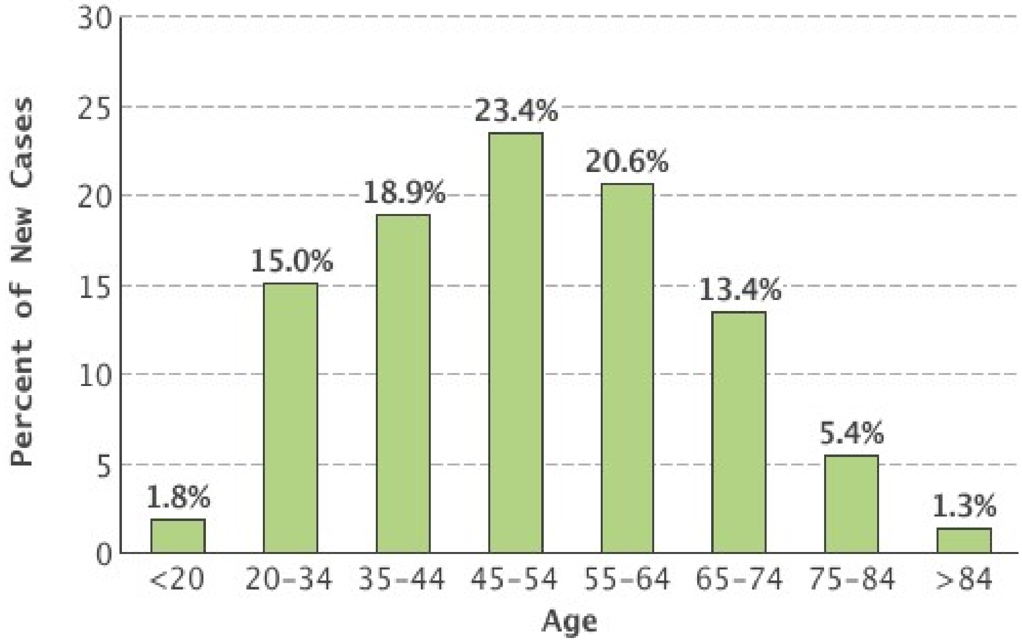
(Incidence, 2014)

Table2. Cancer mortality in the Nebraska and the US (2010-2014)

	Nebraska 2010-2014						US 2009-2013		
	male		female		total		male	female	total
	No.	Rate	No.	Rate	No.	Rate	Rate	Rate	Rate
All sites	9,091	196.6	8,114	138.1	17,205	162.6	204.0	143.9	168.9
Thyroid cancer	32	0.7	35	0.5	67	0.6	0.5	0.5	0.5

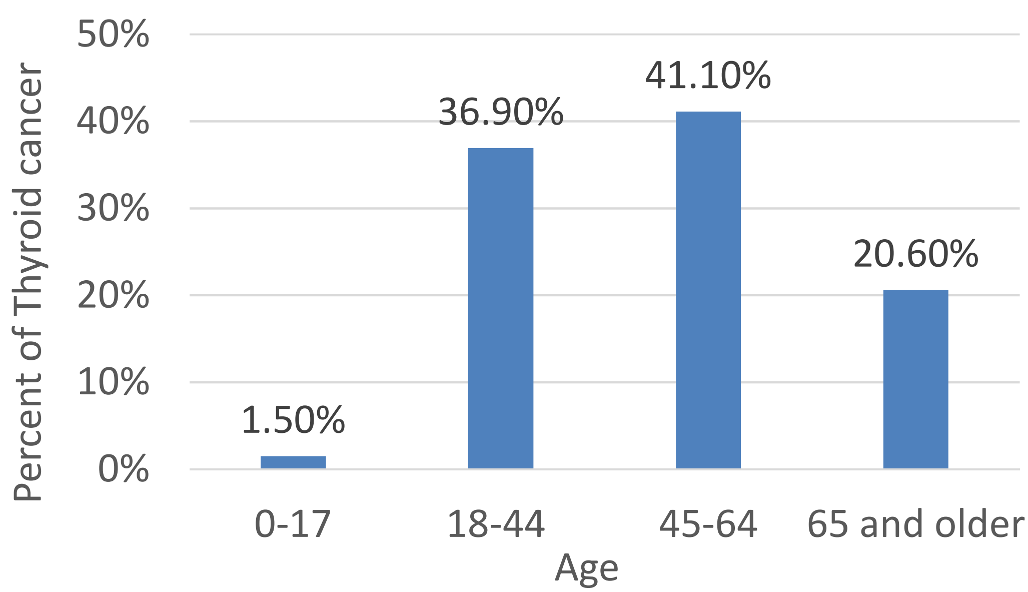
(Incidence, 2014)

Figure2. Age distribution of new thyroid cancer cases in the US.



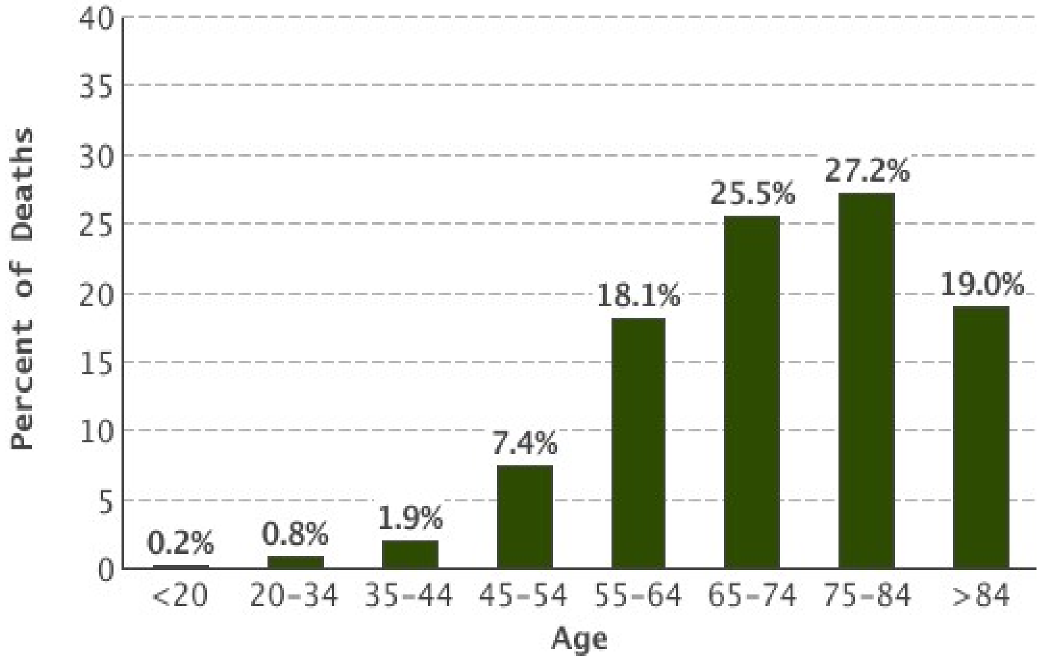
(Cancer Stat Facts: Thyroid Cancer, n.d.)

Figure3. Age distribution of new thyroid cases deaths in Nebraska during 2010-2014.



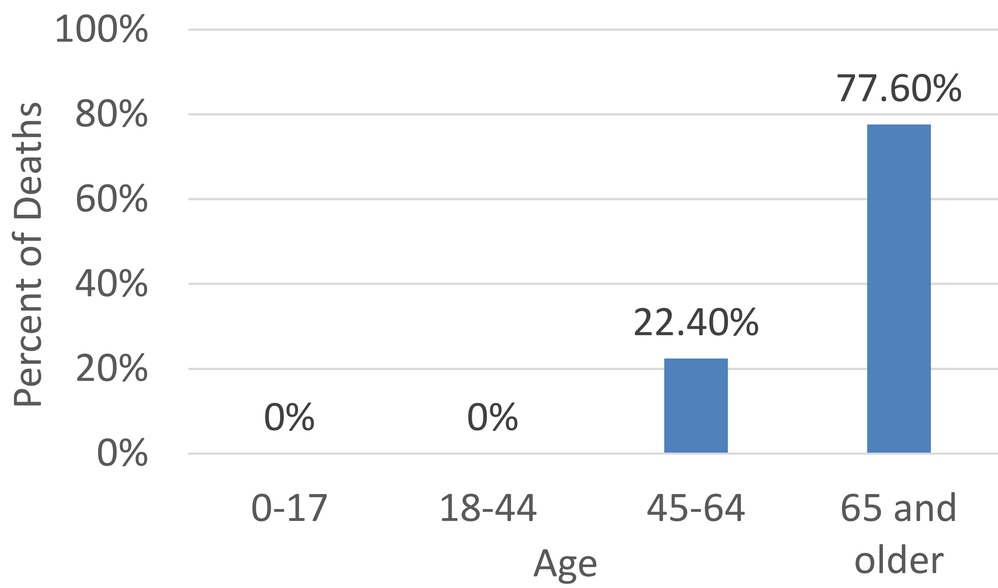
(Incidence, 2014)

Figure4. Age distribution of thyroid cancer caused deaths in the US.



(Cancer Stat Facts: Thyroid Cancer, n.d.)

Figure5. Age distribution of thyroid cancer deaths in Nebraska during 2010-2014.



(Incidence, 2014)

Figure8: Percentage of case types by age at enrollment

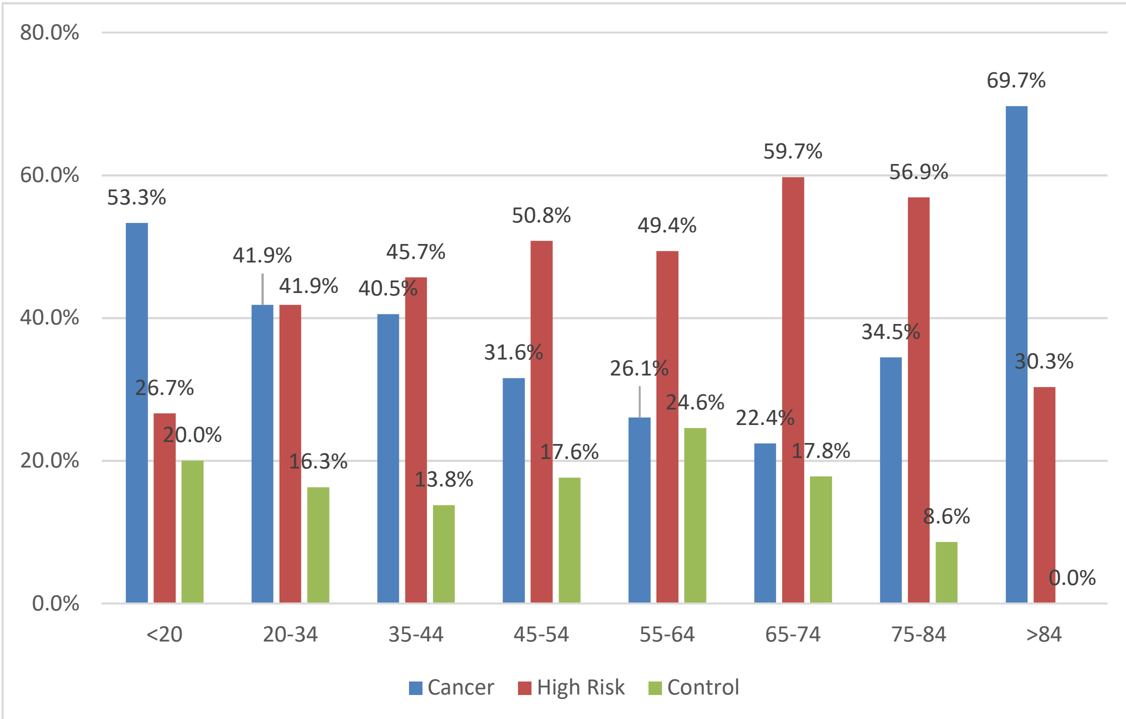


Figure9: Percentage of gender by case type

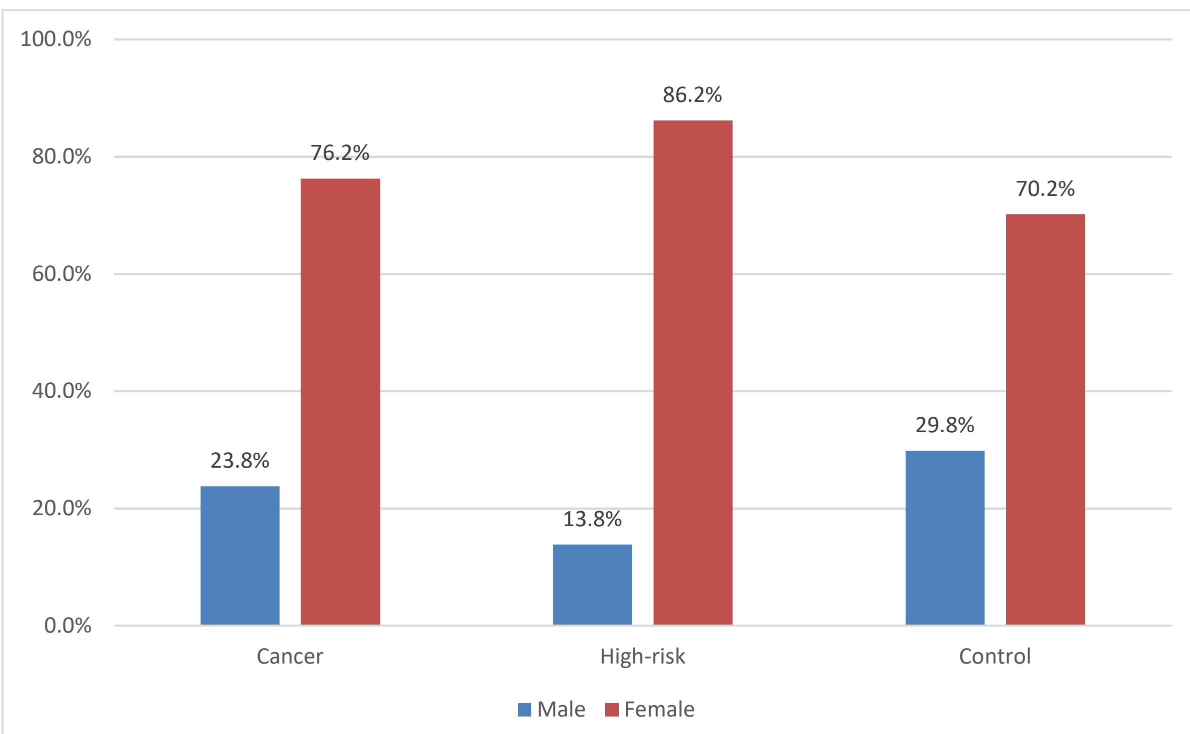


Figure10: Percentage of education level by case type

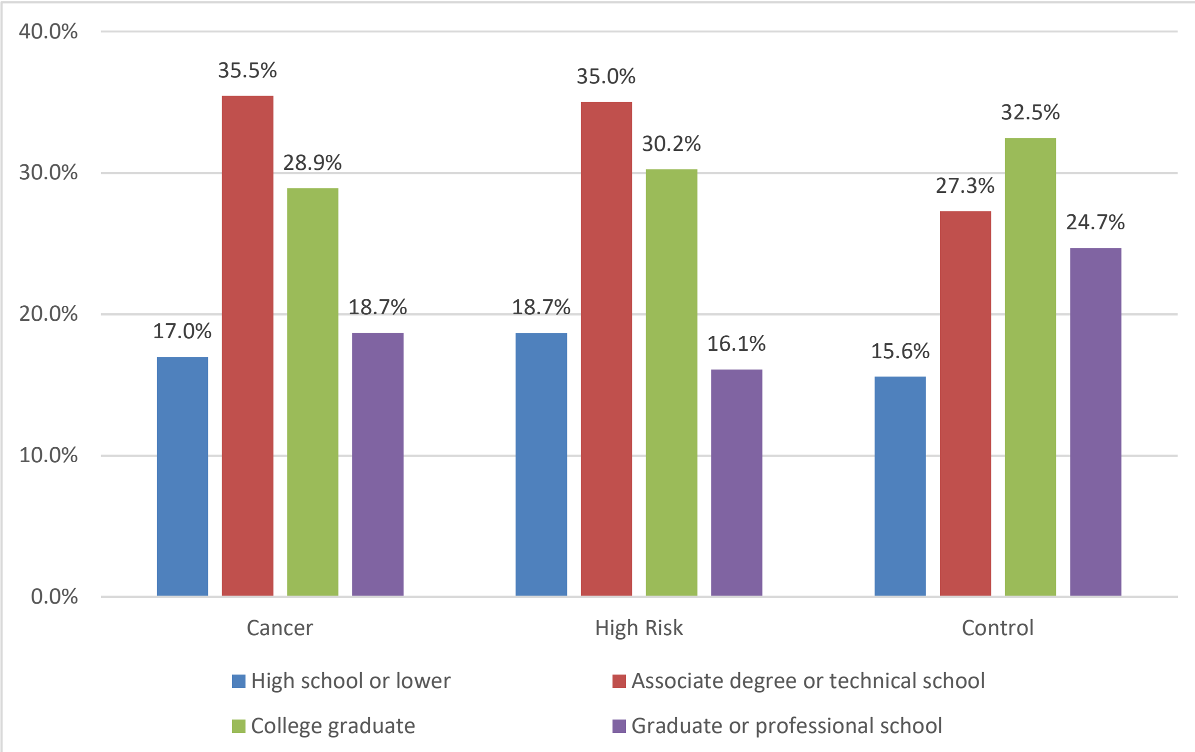


Figure11: Percentage of current BMI by case type

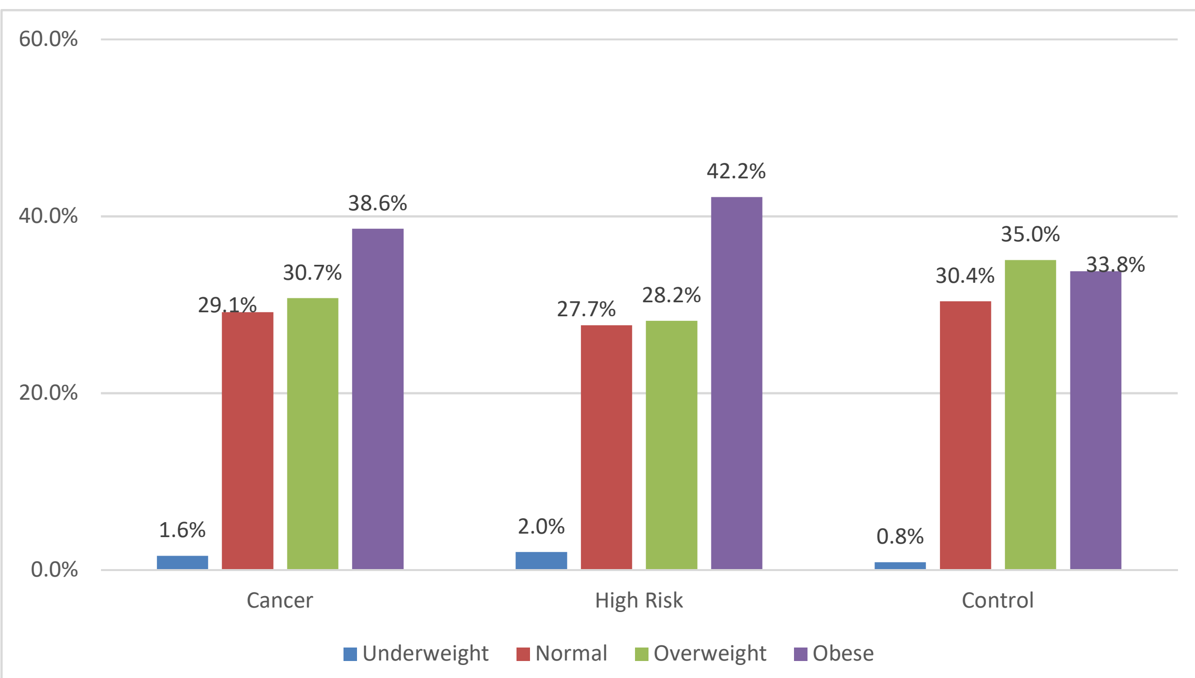
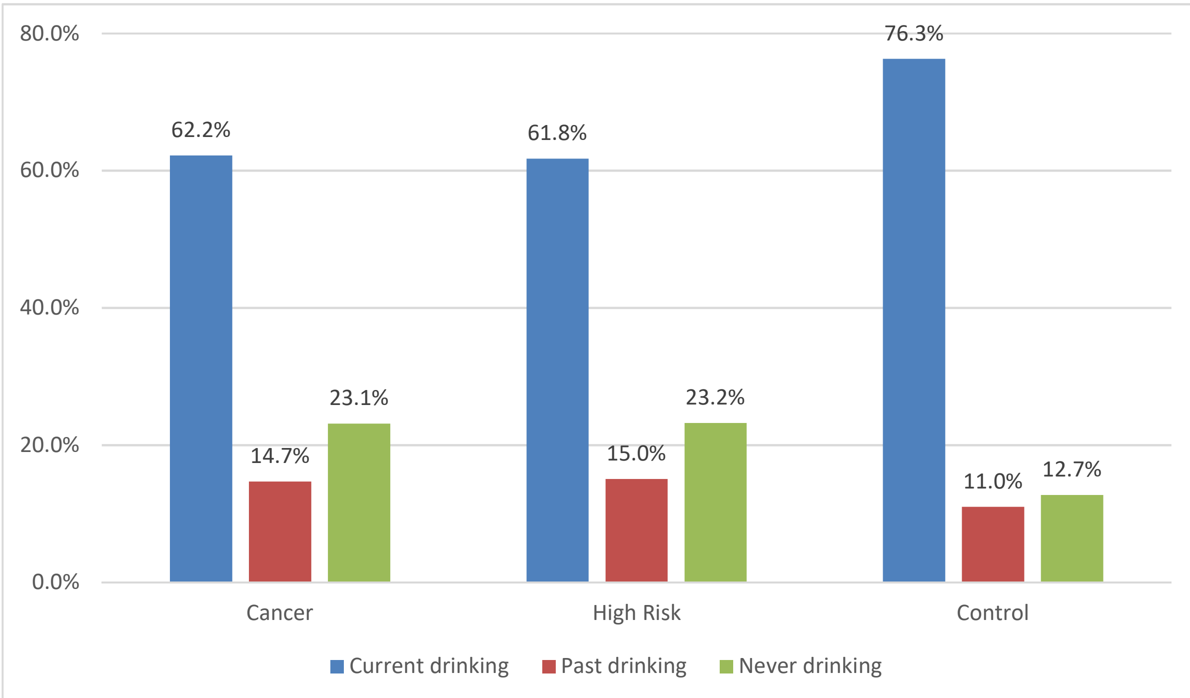


Figure12: Percentage of drinking status by case type



Appendix B:

Table 3. Literature review summary

	Author, year, country	Study design	Population, sample size	Age	Dietary pattern	Outcome	Result
Fish	Galanti et al., 1997 Sweden & Norway	case-control	Sweden (Case: 35 Male/130 Female; Control: 50 Male/198 Female) Norway (Case: 24 Male/57 Female; Control: 57 Male/135 Female)	18-75	all fish	OR=0.9 (0.6-1.5) both countries OR=1.1 (0.6-2.0) Sweden OR= 0.9 (0.4-2.0) Norway	No association
	Horn-Ross et al., 2001 U.S.	case-control	Case: 608 Female; Control: 558 Female	20-74	all fish	OR=0.87 (0.59-1.3) OR=1.1 (0.74-1.6)	Heavy all fish intake (>51.8 g per day) was associated with TC risk however median all fish intake was protective factor for TC, but they were insignificant.
	Memon et al., 2002 Kuwait	case-control	Case: 75 Male/238 Female; Control: 313	<=70	1. Fish 2. Fish products	1. OR=0.6 (0.3-1.0) 2. OR=3.0 (1.6-5.3)	
	Truong et al., 2010 France	case-control	Case: 293 Female; Control: 354 Female	>=18	1. Salt water fish 2. Brackish water fish	1. OR=0.79 (0.51-1.22) 2. OR=0.43 (0.20-0.93)	
	Daniel et al., 2011 U.S.	Cohort	492,186	50-71	HR=1.18 (0.90-1.55)		No association
Meat	Galanti et al., 1997 Sweden & Norway	case-control	Sweden (Case: 35 Male/130 Female; Control: 50 Male/198 Female) Norway (Case: 24 Male/57 Female; Control: 57 Male/135 Female)	18-75	All meat	OR=0.8 (0.5-1.3)	All meat consumption more than 20 protions per month inversely associated with TC risk in both Sweden and Norway, but it is insignificant.

	Memon et al., 2002 Kuwait	case-control	Case: 75 Male/238 Female; Control: 313	<=70	1. Chicken 2. Beef	1. OR=3.0 (1.3-6.8) 2. OR=2.6 (0.9-7.5)	
	Daniel et al., 2011 U.S.	Cohort	492,186	50-71	Red meat sausage		A positive trend for intake of processed red meat and the clear cell subtype (P-trend = 0.04). A statistically significant positive association for sausage intake and clear cell RCC (HRs and 95% CIs) across quintiles: 1.00 (reference), 1.21 (0.88, 1.68), 1.14 (0.83, 1.58), 1.56 (1.14, 2.14), and 1.54 (1.14, 2.12); P-trend = 0.002 (data presented in the text only)
	Markaki et al., 2003 Greece	case-control	Case: 31 Male/82 Female; Control: 43 Male/95 Female	25-60	pork	OR=2.82 (1.36-5.86)	p trend=0.001 adjusted for age, gender, BMI (kg/m2) and total energy intake (Kcal/month)
Dairy	Galanti et al., 1997 Sweden & Norway	case-control	Sweden (Case: 35 Male/130 Female; Control: 50 Male/198 Female) Norway (Case: 24 Male/57 Female; Control: 57 Male/135 Female)	18-75	1. Milk 2. Cheese 3. Butter	1. OR=1.0 (0.6-1.5) 2. OR=1.7 (1.1-2.7) Both OR=2.0 (1.2-3.4) SE OR=1.3 (0.6-2.9) NO 3. OR=1.6 (1.1-2.5) Both OR=1.8 (1.1-3.1) SE OR=1.3 (0.6-2.8) NO	Milk consumption is not associated with TC risk in both countries. Cheese and butter intake are positively associated with TC risk in both countries, but they are insignificant in Norway.
	Truong et al., 2010 France	case-control	Case: 293 Female; Control: 354 Female	>=18	Dairy products	OR=1.03 (0.67-1.59)	

Vegetable & Fruit	Galanti et al., 1997 Sweden & Norway	case-control	Sweden (Case: 35 Male/130 Female; Control: 50 Male/198 Female) Norway (Case: 24 Male/57 Female; Control: 57 Male/135 Female)	18-75	1. All fruit 2. All vegetable	1. OR=1.2 (0.8-1.8) 2. OR=1.2 (0.8-1.8) OR=0.9 (0.6-1.4)	Intake fruit can insignificantly increase risk of TC. Median all vegetable intake is positively associated with TC, however, heavy vegetable consumption intake is inversely associated with TC risk. Both of the results are insignificant.
	Mack et al. 2002 U.S.	case-control	Case: 292 Female; Control: 292 Female	15-54	Turnips or rutabagas	OR=0.6 (0.3-1.0) all thyroid cancer; OR=0.5 (0.2-0.9) papillary thyroid cancer	
	Memon et al., 2002 Kuwait	case-control	Case: 75 Male/238 Female; Control: 313	<=70	1. Cabbage 2. Cauliflower 3. Brussel sprouts 4. Broccoli 5. Fruit	1. OR=1.9 (1.1-3.3) 2. OR=1.8 (1.0-3.2) 3. OR=0.7 (0.1-4.3) 4. OR=0.9 (0.2-3.6) 5. OR=1.2 (0.6-2.5)	high
	Truong et al., 2010 France	case-control	Case: 293 Female; Control: 354 Female	>=18	Cruciferous vegetables	OR=1.86 (1.01-3.43)	women IODINE intake <96 µg/day
	Markaki et al., 2003 Greece	case-control	Case: 31 Male/82 Female; Control: 43 Male/95 Female	25-60	1. Tomato 2. Lemons	1. OR=0.3 (0.10-1.01) 2. OR=0.53 (0.24-1.15)	High intake 1. p trend=0.002 2. p trend=0.001 adjusted for age, gender, BMI (kg/m2) and total energy intake (Kcal/month)

	Zamora-Ros R et al., 2017 10 western European countries (Denmark, France,Germany, Greece, Italy, Norway, Sweden, Spain, The Nether-lands and the United Kingdom)	multicentre prospective cohort study	142,232 Male/333,876 Female	35-70	1. Total vegetable 2. Total fruit	1. OR=0.87 (0.69-1.08) 2. OR=0.88 (0.70-1.10)		
order paper through UNMC	Bandurska-S et al., 2011 Poland	case-control	Case: 33 Male/264 Female; Control: 75 Male/514 Fmale	/				
	Jung er al., 2013 Korea	case-control	Malignant Case: 111 Female; Control: 111 Female Benign Case: 115 Female; Control: 115 Female	20-70	Malignant 1. Raw vegetable Benign 2. Raw vegetable 3. Total vegetable	1. OR=0.20 (0.07-0.62) 2. OR=0.28 (0.10-0.76) 3. OR=0.11 (0.03-0.47)		
Vitamin & Food supplements	Mack et al. 2002 U.S.	case-control	Case: 292 Female; Control: 292 Female	15-54	Multivitamins	OR=0.8 (0.4-1.7) 0 to 2 years OR=1.6 (0.8-3.4) >10 years OR=2.9 (1.2-7.4) >10 y in papillary cancer		
	Young et al., 2016 Korea	case-control	Case: 113; Control: 226	>=30	Calcium	OR=0.55 (0.35-0.89)		
	O'Grady et al., 2014 U.S.	prospective cohort	287,944 Male/194,863 Female	50-71	Vitamin C	HR Q5 vs Q1=1.34 (1.02–1.76)	P trend=0.01	

	Galanti et al., 1997 Sweden & Norway	case-control	Sweden (Case: 35 Male/130 Female; Control: 50 Male/198 Female) Norway (Case: 24 Male/57 Female; Control: 57 Male/135 Female)	18-75	Sweden 1. Vitamin A 2. Vitamin C 3. Vitamin E Norway 4. Multivitamin preparations	1. OR=0.5 (0.3-0.9) 2. OR=0.6 (0.4-1.0) 3. OR=0.5 (0.3-1.0) 4. OR=3.4 (1.4-8.1)	Sweden female participants (regular vs. non-regular use) Norway female participanting in the study within 2 years from diagnosis (regular vs. non-regular use)
	Kolonel et al., 1990 U.S.	case-control	Case: 51 Male/140 Female; Control: 113 Male/328 Female	>=18	1. total iodine 2. food source iodine	1. p=0.01 2. p=0.01	Total and food source iodine intake are significantly difference between case and control women. Case women have higher iodine intake.

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Service Learning/Capstone (SL/CE) Experience Reflection:

I conducted my service learning in Fred & Pamela Buffett Cancer Center and used the iCare2 database. It is a multi-institutional resource maintained by the cancer center that covers small and rural hospitals and cancer centers. It collects data and biospecimens on cancer patients, high-risk individuals, and normal controls. These data and specimen were allowed for research on risk factors of cancer development and progression. The organization which I worked in is the data center of the whole iCaRe2 database in the University of Nebraska Medical Center. The work of the organization is to deal with all the data related work, such as application of data, database maintenance, cleaning data, summarizing the data and database, to support the clinical and colleges' research. The advantage of this operation is having a strong control of data. It covers the whole process of data analysis from data collection, entering data to database maintenance and distributing the data to people who apply them. It is very efficient and can find and fix problem in the first time. In the lab, the PIs have multiple labs. They would not go to each lab every day. Each lab has technicians, PhD students, and post-doctors. They would responsible for every day's work. They can help me to solve most questions. I improved my communication skills with people from different departments. I preferred to ask questions directly when something is not clear because colleagues and supervisors. They had more experience and might meet the same problem in the past, so they can help you to save time. I practice the skill of data management and organization through using Microsoft Excel and Tableau.

During this period, I think there was nothing that we did not expect before. We prepared very well at the beginning. Our committee members, including my supervisor Oleg Shats, met and discussed the work and timeline of my service learning work. All the data are under control, and we know the detail of the iCaRe2 database, such as the original sources of the data, the correct range of each data, the correct sample size information of different registries, etc. During working in the lab, my work is to check the TCCR specimen and move them to the new freezers. We compared the information in the excel sheet and on the labels. We thought there were some typo or mislabel, but more mistakes were found in these specimens after checking every box and freezer. We found the specimen database manager and lab technician and had a meeting to talk about how to figure the problems. I checked every box and mark them down. Then we keep contact through email to correct each problem together.

From June 12th to August 17th, I worked with Oleg Shats in their office for two months (100 hours). I summarized the data from iCaRe2 and used maps, plots, tables to present the geographic distribution, demographic information, and risk factors of developing different types of cancer. These graphs and dashboard were showed to Create graphs for clinicians, researchers, and database managers. It covered 9 topics and hundreds of variables from 15 registries (14 cancer registries and 1 control registry).

From August 22th to October 18th, I worked in the Dr. Kelly's lab (46 hours total) with Amy Wells to manage the specimens from patients of TCCR. I cooperated with Amy and Oleg to check thousands of TCCR specimen, then rearrange all them in new freezers, including relabeled and removed hundreds of errors. To do this work, you need to be very patient and careful. To check each tube one by one is very easy to miss the errors or make mistakes. In this process, I learned a good management system, like the open specimen, is very helpful for organizing a large sample size of specimens.

From October 3rd to October 29th, I shadowed the clinical research coordinators, Michelle and Krista, to see the consent process and iCaRe2 project enrollment (4 hours). I learned that communication skills were very important when you explained what this database was and what advantages and disadvantages the patients would meet when they participated into the project. Respect and protect patients' privacy were the first principle.

I finished the SL work and created dashboard for iCaRe2 database; helped the cancer center to organize their specimen; Researched the database and found the potential risk factors of dietary habits for thyroid cancer; and reported the flaws of the database. Finally, I presented my study and learning experience to the professional audiences.

The dashboard I created could be used in researching and data reviewing. With the developing of iCaRe2 database and update of the dashboard. In the future, people can review these graphs before deciding which variables or risk factors are associated to the events (cancer or high-risk). Database managers can monitor the overall sample size of each cancer registries through a more intuitive way. It is efficient for everyone with different purposes.

The greatest challenge was I had never used the software "Tableau" which was used to create dashboard. Every function was new for me. I have to use 100 hours to start it from zero to finish the whole work. So, I started from one registry TCCR which I was familiar with to decide the variables I would use, then start to create some simple graphs. After that I added more functions and tried complex plots. I also searched online and saw the videos on YouTube to learn how to use each function. My supervisor provided a lot of helps and we overcome every challenge we had met. Public health education helped me when I worked on the database. I could identify which variables and factors were important, and we wanted to show to the audiences. When I observed the consent process, I understood why respect and protect patients' privacy should be considering as the first principle.

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