Penetrance of a Rare Familial Gene Predisposing to Papillary Thyroid Cancer

THESIS

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By

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Abstract

Background and Aims

Thyroid cancer is increasing in incidence, with over 63,000 cases diagnosed in the United States in 2015 (DeLellis, 2004). Non-medullary thyroid cancer (NMTC) arises from follicular cells of the thyroid gland and accounts for over 90% of all thyroid cancers (Czene, Lichtenstein, & Hemminki, 2002). Approximately 5-7 % of NMTC is familial (FNMTC) and generally affects multiple generations, appear with a younger age of onset, and may predispose to a greater risk of malignancy and recurrence (Sippel, Caron, & Clark, 2007). FNMTC is clinically defined as two or more first-degree relatives with NMTC and appears to follow an autosomal dominant inheritance pattern (Sippel, Caron, & Clark, 2007). A known predisposition to thyroid cancer based on family history may alter surveillance and treatment recommendations.

The aim of this study was to determine the age-specific thyroid cancer risk of individuals in a large family with FNMTC due to a 4q32 C>A mutation. Determining the penetrance will help facilitate clinical management and counseling of at-risk individuals in this family, and appropriate surveillance recommendations for mutation-positive individuals in this family. A second aim was to determine the age-specific risk for benign thyroid disease in these individuals.

Methods

This study includes one large family that previously participated in a gene hunting study as a result of their family history of NMTC. Each participant was assessed on their clinical history of thyroid disease and/or cancer, status of the familial gene mutation, age at diagnosis, treatment, and family history. Additional demographic information including age, sex, medical history, outside exposures, and thyroid pathology/imaging were obtained when possible. Data were obtained for a total of 115 individuals within this large family. Germline 4q32 mutations were detected in 34 of 68 tested individuals. We investigated the association between the 4q32 mutation, thyroid cancer, and benign thyroid disease. Penetrance, or age-specific risk, of thyroid cancer and thyroid disease was determined using the Kaplan-Meier method of segregation analysis and accounting for ascertainment bias.

Results

We report the clinical characteristics of a large family of individuals with a 4q32 mutation including cancer diagnoses and benign thyroid disease. Within this family, individuals who tested positive for the 4q32 mutation have a 68.9% (95% CI, 46.45%-88.69%) risk of developing thyroid cancer by age 70. Females with a 4q32 mutation have a 82.9% (95% CI, 50.05%-98.87%) risk of developing cancer by age 70 compared to a 57.2% (95% CI 28.77%-88.06%) risk for males. Individuals who tested positive for the 4q32 mutation have a 65.3% (95% CI 45.96%-83.77%) risk of developing benign thyroid disease by age 70.

Conclusion

The 4q32 A>C mutation significantly increases the risk for thyroid cancer in individuals with the mutation compared to those without it. Predictive testing for the known mutation in this family can identify individuals at increased risk who could benefit from increased thyroid surveillance. Current recommendations for individuals with the 4q32 mutation in this family are to begin surveillance of the thyroid at the age of 10 with annual ultrasound and discuss the benefits and risks associated with a prophylactic thyroidectomy with their endocrinologist.

I would like to dedicate this to my wonderful husband for his continued love and encouragement.

Acknowledgments

I would like to thank Dr. Albert de la Chapelle and his team for their dedication to this research, the National Cancer Institute for funding this project through the P01 NCI award, and the participants of the study for their contribution. I would also like to thank the faculty, advisors and committee members for their support and guidance with this project!

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Fields of Study

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Chapter 1: Background

Thyroid cancer is the most common malignancy of the endocrine system and accounts for 3.8% of newly diagnosed cancers annually (SEER, 2016). The incidence of thyroid cancer is rapidly increasing in America, from 7.6 to 14.9 per 100,000 between 2000 and 2012. Annually, approximately 62,450 new cases of thyroid cancer were diagnosed in the United State in 2015, compared to roughly 22,000 in 2004 (DeLellis, 2004; 2). Thyroid cancers are often highly curable if detected early and have a survival rate of 97.9% (SEER, 2016).

The thyroid is a butterfly shaped gland located in the front of the neck, consisting of two lobes and an isthmus. The two most common types of cells found in the thyroid are follicular cells, which utilize iodine to make hormones and regulate our metabolism, and C cells, which produce calcitonin to control the use of calcium in our bodies. Thyroid cancer most commonly presents with a lump in the neck, difficulty swallowing, voice changes, or discomfort in the neck region. Ultrasound imaging can be used to determine the size and shape of a lesion and whether it is fluid-filled or solid. These results could be utilized to determine the likelihood of malignancy. If a thyroid lesion is suspicious, physicians use ultrasounds to navigate fine needle aspiration (FNA). FNA removes cells from a lesion so they can be viewed under a microscope. Patients with a suspicious

ultrasound or FNA may undergo a partial or complete thyroidectomy. Some patients may require radioactive iodine treatments post-surgery to eliminate residual thyroid cancer cells and to enable the ability to monitor for recurrence using Tg levels. Individuals who undergo thyroidectomy require lifelong daily replacement of their thyroid hormones. Tumor staging is dependent on the primary tumor size, metastasis (regional and distant) and patient's age. Several tumor-staging criteria exist (e.g. TNM, AGES, MACIS, AMES) and each takes into account different factors to establish the stage of disease. Other screening options include measuring hormone levels of thyroid stimulating hormone (TSH), thyroglobulin (Tg) and in medullary thyroid cancer, calcitonin. Tg levels are often used as a follow-up to screen for recurrence in patients who have previously had their thyroid removed.

Thyroid carcinomas are categorized into several groups: papillary (PTC), follicular (FTC), medullary (MTC), undifferentiated (anaplastic), Hurthle cell and a subgroup of rare morphologies (i,e. squamous, mucoepidermoid, and oncocytic carcinomas). MTC are derived from C cells, while the remaining non-medullary (differentiated) subtypes originate from follicular cells. In general, some follicular cancers may be linked to iodine deficiency, while some papillary cancers may be linked to radiation exposure. The majority of thyroid cancers is papillary in origin and often remains small and localized. Together, papillary and follicular histologies account for approximately 90% of thyroid cancers (DeLellis, 2004). While they are both well differentiated, PTC has a better prognosis compared to FTC, with an estimated 5 year mortality of 1-2% and 10-20%,

respectively (SEER, 2016). MTC has a mortality rate of approximately 25-50% in 5 years and the most severe undifferentiated, anaplastic cancers have a high mortality above 95% in 5 years (SEER, 2016).

The increase in thyroid cancer incidence, particularly small PTCs, may be, in part, due to increased awareness about benign thyroid disease and cancer and increased use of thyroid ultrasounds and other imaging modalities (Davies, Ouellette, Hunter, & Welch, 2010; Davies & Welch, 2006; Welch & Black, 2010). Higher socioeconomic status (SES) is another factor associated with increased thyroid cancer incidence, increasing PTC diagnosis by more than 2.5 times compared to those with lower SES (Altekruss, Das, Cho, Petkov, & Yu, 2015). Many individuals being diagnosed with early stage thyroid cancers today may have never had any clinical problems from their cancer and would have gone undiagnosed in the past. A study in Finland examined 36 thyroid glands and detected small papillary thyroid cancer post-mortem in over a third of patients who died from non-thyroid related causes (Harach, Franssila, & Wasenius, 1985). Determining whether the increase in incidence is a result of over-surveillance associated with increased detection of subclinical disease, or a true increase in the incidence makes it challenging to identify which patients need treatment and whether or not surgery is appropriate. Incidental PTC may be a result of increased imaging, which may lead to treatment of cancers that would not have caused symptoms or death, if left untreated (Welch & Black, 2010).

A combination of genetic, environmental and hormonal factors likely contributes to the formation of thyroid cancer. The thyroid gland relies on iodine from the environment and therefore is "vulnerable to the genotoxic effects (DNA damage) of radioactive iodine and to the nongenotoxic effects (TSH stimulation) resulting from iodine deficiency" (DeLellis, 2004).

A thyroid cancer risk factor is anything that can increase the chance of developing a thyroid cancer. Risks include:

- Age (between 20-55 years old)
- Gender (female to male ratio is ~3:1)
- Radiation exposure (especially during childhood)
- Low intake of iodine
- Ethnicity (increased risk to Caucasian and Asian populations)
- Clinical history of thyroid disease (i.e. goiter)
- Family history of thyroid disease or thyroid cancer
- A germline mutation in a predisposing gene

The observed higher incidence of thyroid cancer in women may be attributed to factors such as age of menarche and hormone replacement therapy, although little is known about the gender disparity. Breast, peritoneum, omentum and mesentery, thyroid, gallbladder, and anorectum are the five cancer types in which females have a higher

incidence than males (Nilubol, Zhang, & Kebebew, 2013). While women have a higher incidence of thyroid cancer, men typically have more advanced cancer and are diagnosed at an older age. A study of 61,523 patients with NMTC diagnosed between 1988 and 2007 in the SEER registry found that affected males had significantly more aggressive histology and were more likely to have undifferentiated thyroid cancer. Males also had more advanced disease at presentation (larger primary tumor size, higher rates of extrathyroidal extension, regional lymph node metastasis, and distant metastasis) (Nilubol, Zhang, & Kebebew, 2013). While the specific cause cannot be determined, this may be related to less surveillance in men, for which earlier detection could identify the cancer at a less advanced stage.

Radiation exposure includes nuclear explosions (i.e. Chernobyl), power plant accidents, or radiation therapy during childhood, specifically prior to the 1960s when radiation of the head and neck was commonly used to treat acne, adenoid hypertrophy, tinea capitis, and thymus enlargement (Davies & Welch, 2006). Individuals exposed to such radiation can experience thyroid cancer several years after the incident. The Chernobyl accident exposed individuals to high concentrations of 131I and 132I, which is absorbed and stored in the thyroid (DeLellis, 2004). Although the risk of thyroid cancer development increased for all exposed individuals, children had a much larger risk because they have a larger uptake of iodine compared to adults. Somatic RET rearrangements may be caused by radiation which causes double stand breaks and can result in the development of PTC (DeLellis, 2004). In contrast, the incidence of papillary thyroid cancer is lower in regions

of adequate or high intake of iodine. Previous findings suggest that follicular cancer is associated with low iodine intake because of dyshormogenetic goiter that occurs from an imbalance hormones related to iodine intake and TSH levels (DeLellis, 2004).

Ethnicity differences have been noted in a variety of populations with an increased incidence of thyroid cancer in Sweden, France, Japan and the United States (DeLellis, 2004). Hawaii and Iceland have the highest reported rates of thyroid cancer, possibly associated with their volcanic environments (DeLellis, 2004; Malandrino et al., 2013).

Benign thyroid diseases are common in the general population and treatment of these diseases with thyroidectomies remains controversial. Thyroid nodules have an incidence of about 4-7% in the U.S. population by physical exam and 30-67% by imaging or autopsy studies (Cooper et al., 2009; Tufano, Noureldine, & Angelos, 2015). However, only approximately 5-20% of these nodules are malignant (Herz, Hu, Shilatifard, 2014; Cooper et al., 2009). Treatment of nodules, particularly solitary nodules in the context of other risk factors (e.g. radiation exposure, gender, and family history) remains uncertain (Cooper et al., 2009). While an association exists between Hashimoto's thyroiditis and PTC, causation has yet to be confirmed (Anand, Singh, Kushwaha, Hussain, & Sonkar, 2014). Treatment of PTC with Hashimoto's remains the same as a diagnosis of only PTC (Anand, Singh, Kushwaha, Hussain, & Sonkar, 2014).

A total of 228 patients with benign thyroid disease (nontoxic solitary thyroid nodule, nontoxic multinodular goiter, toxic multinodular goiter, toxic adenoma, and Grave's disease) underwent complete thyroidectomies and incidental thyroid cancer was detected in 33 of the individuals (Askitis et al., 2013). The majority of incidental thyroid cancers occurred in individuals who did not have toxic thyroid disease (Askitis et al., 2013). While autoimmune thyroid disease may play a role in the development of thyroid cancer, no clear association has been established.

Thyroid cancer can be categorized as either sporadic or familial. While the majority of cases are sporadic, approximately 5-7% of thyroid cancers are familial (Nagy & Ringel, 2015; Haugen et al. 2016). FNMTC is clinically defined as two or more first-degree relatives with NMTC and appears to follow an autosomal dominant inheritance pattern (Sippel, Caron, & Clark, 2007). When compared to sporadic NMTC, FNMTC may be more aggressive, present with an earlier age of onset, and often result in multifocal and bilateral tumors (Sippel, Caron, & Clark, 2007). In some studies, these familial cancers have a higher rate of lymph node metastasis and extrathyroidal invasion (Sippel, Caron, & Clark, 2007).

Genetics

The underlying genetic cause of thyroid cancer varies based on histology. The genetic cause of MTC is well known. Hereditary MTC is caused by mutations in the RET proto-oncogene that cause multiple endocrine neoplasia 2A (MEN2A) syndrome characterized

by MTC, parathyroid hyperplasia and pheochromocytoma, and multiple endocrine neoplasia 2A (MEN2B) syndrome characterized by MTC, pheochromocytoma, mucosal neuromas, and tall, asthenic habitus.

Meanwhile, the genetic causes of familial non-medullary thyroid carcinoma (FNMTC) are less understood and can be divided into two groups. The first includes familial syndromes in which thyroid cancer is one of several component tumors, such as Cowden syndrome, familial adenomatous polyposis (FAP), Carney complex and Werner's syndrome (Nagy & Ringel, 2015). The second category includes familial syndromes characterized primarily by NMTC such as FNMTC, FNMTC associated with papillary renal cell carcinoma, and FNMTC with multinodular goiter (Nosé, 2008).

Though efforts have been made to identify a highly penetrant underlying genetic factor predisposing to NMTC, FNMTC is often described as a polygenic disorder comprised of multiple low to moderate penetrance susceptibility genes and incomplete penetrance (Bauer, 2013). The majority of FNMTC families display an autosomal dominant inheritance pattern with variable expressivity. When compared to the general population, individuals with a strong family history of thyroid cancer have increased risks of developing thyroid cancer at an earlier age and with a more aggressive phenotype (Sippel, Caron, & Clark, 2007; Bauer, 2013).

As one of the most heritable forms of all cancers, first degree relatives of an affected individual have an 8- to 10-fold risk of developing disease which suggests that there must be underlying germline mutations that have not yet been discovered (Czene, Lichtenstein, & Hemminki, 2002; Bauer, 2013; Goldgar et al., 1994). A population-based study found thyroid cancer to have one of the highest familial relative risks, excluding MTC and proposing high familial risk in NMTC (Goldgar et al., 1994). A large study assessing heritability of various cancers determined thyroid cancer to have the highest risk susceptibility accounted for by genetic effects (53%), with the next highest identified in all endocrine glands combined (28%) (Pal et al., 2001). A large study of the Norwegian Cancer Registry supported the significant increase in familial occurrence of NMTC in both males and females (Frich, Glattre, & Akslen, 2001). These studies indicate a strong contribution of genetic factors and heritability in thyroid cancer predisposition. Families with multiple affected relatives and early ages of onset are being studied in efforts to identify a causative germline mutation.

While a large proportion of germline genetic inheritance for FNMTC remains uncharacterized, research is ongoing to identify additional causative genes within families with a high incidence of thyroid cancer. Identifying the genetic cause(s) of FNMTC provides the ability to define the cancer risks more clearly. It also promotes predictive testing for at-risk individuals to determine who could benefit from early cancer surveillance and may provide molecular targets for therapy of thyroid cancers when they do develop.

Enhancer Elements

Enhancers are short DNA sequences that can activate transcription of associated genes and regulate tissue-specific gene expression. They contain specific DNA elements that are recognized by tissue-specific transcription factors to enable activation of target genes (Herz, Hu, Shilatifard, 2014). Strong correlations have been identified with transcription factor binding on enhancers and increased nucleosome depletion or turnover (Herz, Hu, Shilatifard, 2014). Mutations in enhancers disrupt the regulation of transcription factors and co-factors of associated genes and may be the cause tissue-specific carcinogenesis (Herz, Hu, Shilatifard, 2014; Mansour et al., 2014). Specifically, mutations in enhancers may result in silencing of tumor suppressor genes or activating oncogenes (Herz, Hu, Shilatifard, 2014). "Specific enhancer mutations have been correlated with various disease-linked genes for multiple conditions (X-linked deafness, Hirschprung's disease, Crohn's disease, multiple sclerosis). Some studies observing colon cancer risk and enhancer "landscape provide evidence that enhancer inactivation of tumor suppressor genes or enhancer activation of oncogenes might contribute to tumorigenesis" (Herz, Hu, Shilatifard, 2014). As the importance of enhancer status increases, Weedon et al suggest integrating genome sequencing and epigenetic annotation of the disease relevant cell type to uncover new noncoding elements associated with disease (Weedon et al., 2014).

We have previously described a large multi-generational family with FNMTC who participated in an IRB-approved study that performed genome-wide linkage analysis of

39 families with FNMTC (He et al. 2013). The family includes 13 known cases of thyroid cancer at that time, with two ATC cases, early onset of PTC, and a high rate of benign thyroid disease. A strong linkage peak at 4q32 was detected in this single family but not in any others. Further gene hunting investigation of this region identified a specific intergenic 4q32 A>C single nucleotide mutation that segregated with all but one of the tested individuals who developed PTC (He et al. 2013). Gene expression and functional studies suggest this mutation occurs in an enhancer element and is likely the causative factor predisposing to thyroid cancer in this family (He et al. 2013). This novel mutation was not identified in any of the other 38 NMTC families in the study, in any other thyroid cancer patients in a large endocrine neoplasia biorepository at The Ohio State University, or in public databases (He et al. 2013). Herein, we attempt to characterize the phenotypic implications and penetrance of the 4q32 A>C mutation.

Chapter 2: Methods

This study described herein was conducted in order to determine the lifetime penetrance of benign thyroid disease and thyroid cancer due to the 4q32 A>C mutation in this family. Participation in the study was offered to individuals who participated in the original study, as well as all other family members who were interested. An invitation letter was sent describing our study and requesting their consent to participate. The letter, questionnaires (medical and family history), consent forms, and medical records request forms were approved by the local institutional review board and were mailed and/or emailed to the study participants. Participants were encouraged to invite family members who were not part of the original study to participate and share clinical data. The survey was open for six months to obtain as many participants as possible. At-risk individuals in this family were offered the opportunity to undergo free genetic testing to determine whether or not they inherited the 4q32 mutation regardless of their decision to participate in the research study.

Personal and family history information was collected from all participants via questionnaires. Specific information regarding demographics (e.g. age, sex, and ethnicity), major medical concerns, family medical history, screening practices, history of thyroid cancer and benign thyroid disease, and surgery history was requested from

participants. We inquired about the specific timing and cause of any thyroid evaluation, screening and/or surgery. Additional risk factors pertaining to thyroid cancer, such as therapeutic radiation at a young age and other work related exposures, were also ascertained. Cancer diagnoses and information regarding reported thyroid disease was confirmed with medical records when possible. Mutation status and additional data were extracted from the Division of Human Genetics database to confirm who was affected and unaffected in the family.

Statistical Analysis

All 34 mutation positive individuals in the family were used in the penetrance analysis of thyroid cancer in this family. In general, penetrance at mean age is defined as the proportion of affected mutation carriers in a cohort. In order to determine penetrance of thyroid cancer at different ages, or age-specific penetrance, cumulative risk was estimated using the inverted Kaplan-Meier function with age at diagnosis as the survival variable. Individuals with the 4q32 mutation who have not been diagnosed with thyroid cancer were censored at their age at thyroidectomy, current age or age at death. Moreover, stratified penetrance analysis was performed within male and female groups. Inverted Kaplan-Meier survival curves representing cumulative risk, and their 95% confidence intervals (95%CI) were computed.

The diagnosis of Hashimoto, Graves' disease, nodules, hyperthyroidism, and hypothyroidism were grouped under "benign thyroid disease". Similarly, the age-specific

penetrance of benign thyroid disease and the 95% CI were calculated using the inverted Kaplan-Meier method with all the 34 mutation positive individuals.

Cumulative risk of thyroid cancer and benign thyroid disease in mutation negative individuals and their 95% CI were also estimated with inverted Kaplan-Meier method.

Chapter 3: Results

A total of 31 individuals provided complete study materials. Data including mutation status and health history of an additional 84 individuals was abstracted from the Division of Human Genetics database and previous studies of this family, as well as by reports of the participating individuals. Data of this large family included a total of 115 individuals, 68 of which underwent molecular testing or were known obligate carriers of the 4q32 A>C mutation (Table 1). Of that subgroup, 34 tested positive for the 4q32 mutation and 34 tested negative (Table 2).

	MALE	FEMALE	TOTAL
Participants	50	65	**115**
Tested participants	25	43	**68**

Table 1. Demographics of participants

	MALE	FEMALE	TOTAL
Mutation POSITIVE	17	17	34
Mutation NEGATIVE	8	26	34
Total Tested	**25**	**43**	**68**

Table 2. Demographics of individuals tested for the 4q32 mutation

Of the known individuals who tested positive for the 4q32 mutation or were known obligate carriers, 14 were diagnosed with thyroid cancer, three of which were diagnosed after a prophylactic thyroidectomy. Of note, one individual not included in the penetrance analysis was diagnosed with ATC, but did not undergo genetic testing; therefore his mutation status remains unknown.

	MALE	FEMALE	TOTAL
Mutation +	6	7	13
Mutation -	0	2	2
Not Tested	1	1	2
TOTAL diagnosed (dx)	**7**	**10**	**17**
Avg age of dx (years)	45.14	36.2	40.67

Table 3. Demographics of individuals diagnosed with thyroid cancer

The risk of developing thyroid cancer in individuals who tested positive for the 4q32 mutation in this family is 68.9% to age 70. Age specific risks for thyroid cancer for mutation positive individuals from this family are 6.1% by age 20, 12.9% by age 30, 25.7% by age 40, 36.3% by age 50, 41.6% by age 60, and 68.9% by age 70 (Table 4).

POSITIVE group (n=34 and 14 events)		
Cancer risk to age	Cumulative Risk	95% CI
10	0.0%	(0.0%, 0.0%)
20	6.1%	(1.6%, 22.2%)
30	13.0%	(5.0%, 31.0%)
40	25.7%	(13.0%, 47.1%)
50	36.3%	(20.3%, 59.3%)
60	41.6%	(24.3%, 64.7%)
70	68.9%	(46.5%, 88.7%)

Table 4. Cumulative risk of thyroid cancer in individuals with the 4q32 mutation

The risk to develop thyroid cancer, independent of gender, for an individual with a 4q32 mutation within this family is 68.9% by age 70. Overall, among those with a 4q32 mutation, we estimate that the risk to develop thyroid cancer in men is 57.2% and in women is 82.9% by age 70.

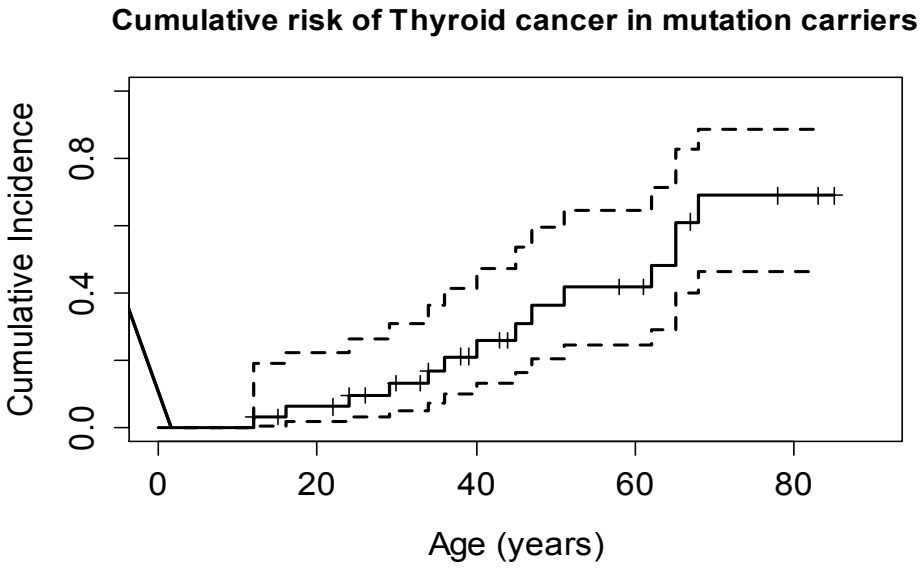

Figure 1. Cumulative risk of thryoid cancer in individuals with the 4q32 mutation, with 95% CI

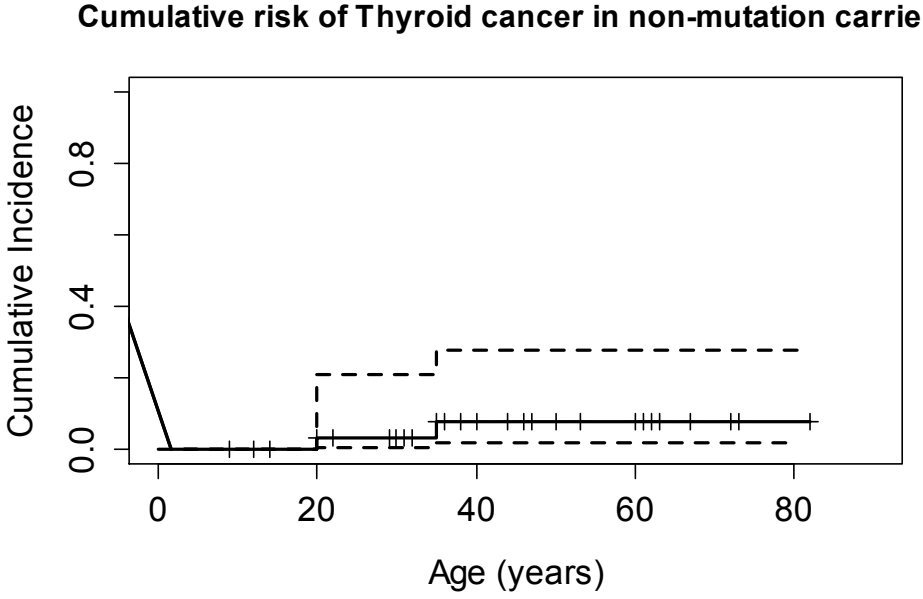

Figure 2. Cumulative risk of thryoid cancer in individuals without the 4q32 mutation

NEGATIVE group (n=34 and 2 events)		
Cancer risk to age	Cumulative Risk	95% CI
10	0.0%	(0.0%, 0.0%)
20	3.2%	(0.5%, 20.8%)
30	3.2%	(0.5%, 20.8%)
40	7.6%	(1.9%, 27.7%)
50	7.6%	(1.9%, 27.7%)
60	7.6%	(1.9%, 27.7%)
70	7.6%	(1.9%, 27.7%)

Table 5. Cumulative risk of thryoid cancer in individuals without the 4q32 mutation

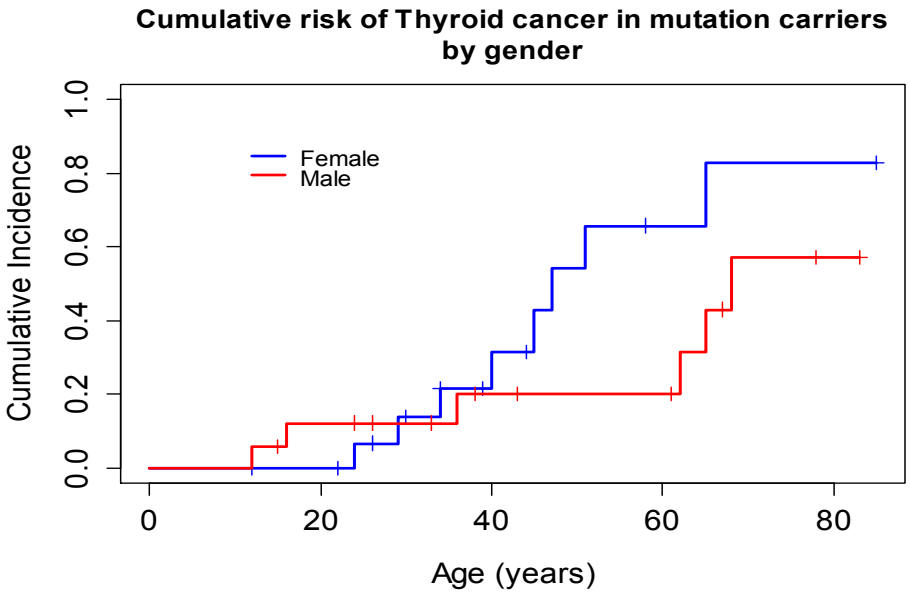

Figure 3. Cumulative risk of thryoid cancer in individuals with the 4q32 mutation by gender

POSITIVE group Female (n= 17 and 8 events)		
Cancer risk to age	Cumulative Risk	95% CI
10	0.0%	(0.0%, 0.0%)
20	0.0%	(0.0%, 0.0%)
30	13.9%	(3.6%, 45.0%)
40	31.5%	(12.8%, 64.7%)
50	54.3%	(27.9%, 84.6%)
60	65.7%	(37.4%, 91.4%)
70	82.9%	(50.1%, 98.9%)

Table 6. Cumulative risk of thryoid cancer in female individuals with the 4q32 mutation

POSITIVE group Male (n= 17 and 6 events)		
Cancer risk to age	Cumulative Risk	95% CI
10	0.0%	(0.0%, 0.0%)
20	12.2%	(3.2%, 40.5%)
30	12.2%	(3.2%, 40.5%)
40	20.1%	(6.9%, 51.0%)
50	20.1%	(6.9%, 51.0%)
60	20.1%	(6.9%, 51.0%)
70	57.2%	(28.8%, 88.1%)

Table 7. Cumulative risk of thryoid cancer in male individuals with the 4q32 mutation

The median age of thyroid cancer diagnosis of individuals with the 4q32 mutation was 42 years old with a wide range of 12-68 years.

Although thyroid cancer and benign thyroid disease may not be independent factors in this large family because we are unable to identify how and if one diagnosis might affect the other, the penetrance of benign thyroid cancer was analyzed. The risk to develop benign thyroid disease, independent of gender, for an individual with a 4q32 mutation within this family is 65.3% by age 70. Overall, among those with a 4q32 mutation in this

family, we estimate that the risk to develop benign thyroid disease in men is 49.8% and in women is 80.0% by age 70.

The median age of benign thyroid disease in individuals with the 4q32 mutation was 33 years old with a wide range of 14-58 years.

POSITIVE group (n=34 and 16 events)		
Cancer risk to age	Cumulative Risk	95% CI
10	0.0%	(0.0%, 0.0%)
20	9.8%	(3.3%, 27.4%)
30	20.3%	(9.6%, 39.8%)
40	40.5%	(24.6%, 61.5%)
50	50.4%	(32.6%, 71.3%)
60	65.3%	(46.0%, 83.8%)
70	65.3%	(46.0%, 83.8%)

Table 8. Cumulative risk of benign thryoid disease in individuals with the 4q32 mutation

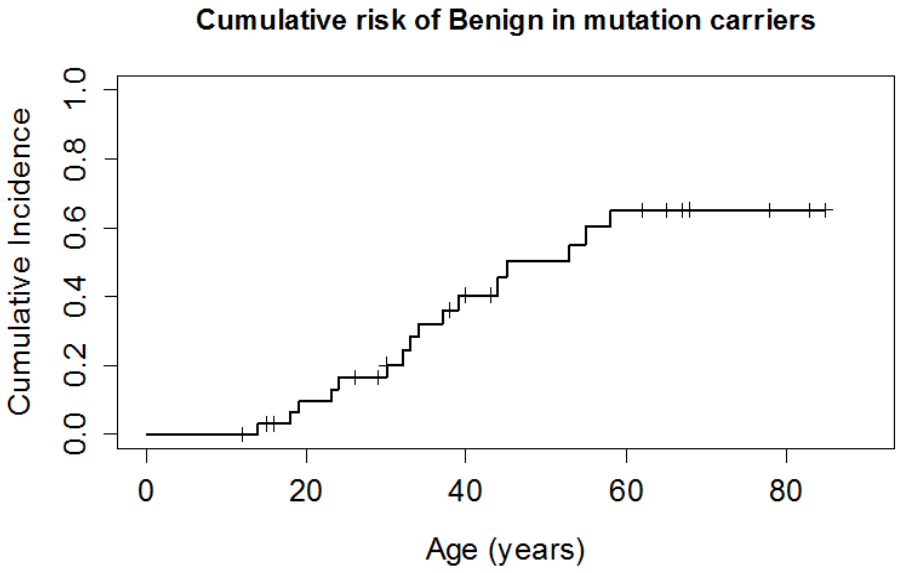

Figure 4. Cumulative risk of benign thryoid disease in individuals with the 4q32 mutation

NEGATIVE group (n=34 and 18events)		
Cancer risk to age	Cumulative Risk	95% CI
10	2.3%	(0.4%, 19.1%)
20	6.2%	(1.6%, 22.6%)
30	22.3%	(11.6%, 42.2%)
40	38.1%	(23.0%, 58.4%)
50	56.0%	(37.9%, 75.7%)
60	70.7%	(51.6%, 87.4%)
70	70.7%	(51.6%, 87.4%)

Table 9. Cumulative risk of benign thryoid disease in individuals without the 4q32 mutation

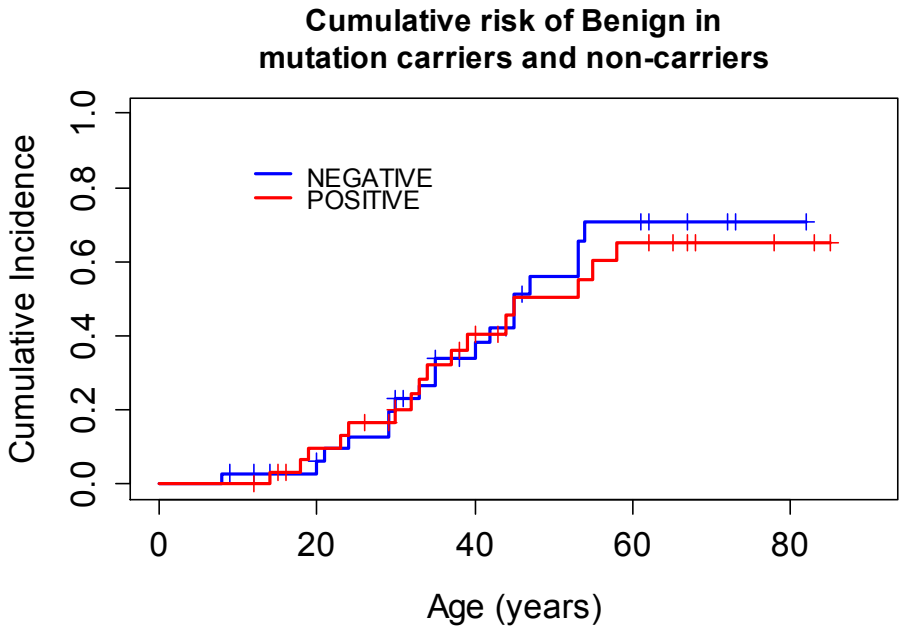

Figure 5. Cumulative risk of benign thyroid disease in individuals with a mutation compared to individuals without the 4q32 mutation

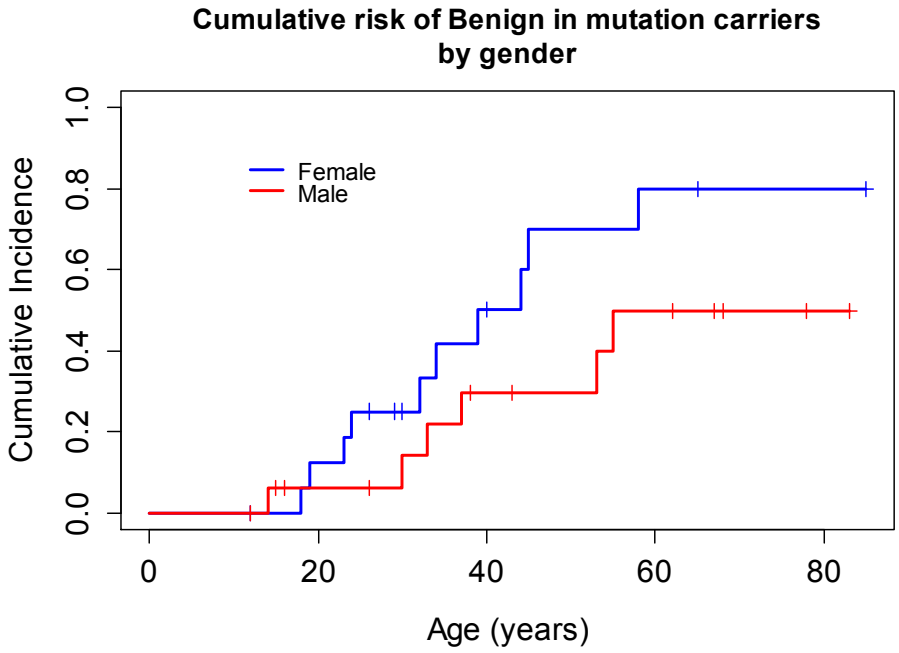

Figure 6. Cumulative risk of benign thryoid disease in individuals with the 4q32 mutation by gender

Two individuals diagnosed with PTC tested negative for the 4q32 mutation, representing phenocopies. A phenocopy is an individual who presents with a particular phenotype that may mimic the phenotype of another group for which there is a known genotype. This may suggest influence of additional factors, such as modifier genes and environmental factors. These individuals may have also been detected due to the intensive screening occurring in this family, which may lead to detection of thyroid cancers that may have never become clinically relevant.

Additional cancers reported in this family included prostate, liver and two basal cell carcinomas diagnoses in a total of four individuals who did not develop thyroid cancer,

which does not appear to be an increased risk over the expected number of other cancers in this family. Of these individuals, one tested positive for the mutation, two tested negative and one has not undergone genetic testing. We obtained thyroid cancer screening information from all study participants and of those who tested negative, many individuals discontinued screening. Most individuals who tested positive were recommended to have annual thyroid blood work and ultrasound to monitor for changes in their thyroid beginning at the time they tested positive. Of the 34 individuals who tested positive for the mutation, 24 have undergone thyroidectomies and the remaining 10 have either not reported surgery, or have their thyroid intact. Of the group who underwent thyroidectomies, 16 reported a history of benign thyroid disease, unusual imaging or cancer suspicion, 7 underwent surgery relatively soon after identifying a positive mutation status, and 1 cause remains unknown.

Chapter 4: Discussion

This study demonstrates that individuals with the 4q32 mutation in this family are at significantly increased risk to develop thyroid cancer. Our data predicts that those with the 4q32 mutation have a 68.9% risk to develop thyroid cancer by age 70, and a 65.3% risk to develop benign thyroid disease (e.g. Hashimoto, Graves' disease, nodules, hyperthyroidism, or hypothyroidism) by age 70.

Penetrance is the age-specific risk associated with a specific phenotype. It provides important information regarding a predisposition to individuals who test positive for the associated gene mutation. Such information impacts the medical management and treatment decisions of at-risk individuals. Determining the penetrance for a particular mutation may be inflated due to ascertainment bias of the selected cohort (Nosé, 2008).

The 4q32 mutation in this family is inherited in an autosomal dominant pattern and is present in at least four generations. Of those who tested positive for the mutation and were diagnosed with thyroid cancer, 8 are female and 6 are male. This nearly 1:1 ratio supports the autosomal dominant inheritance by representing males and females nearly

equally, compared to the 3:1 female to male ratio observed in the general population, and suggests a strong genetic cause of thyroid cancer in this family.

The 4q32 mutation located in a long-range enhancer element leads to reduced enhancer activity and reduced transcription factor binding. While the target of the enhancer element in this NMTC family remains to be determined, this private mutation is believed to be the causative precursor to thyroid cancer for affected family members (He et al. 2013).

Two individuals in this family were diagnosed with thyroid cancer, yet tested negative for the 4q32 mutation. The lifetime risk to develop thyroid cancer in the U.S. is approximately 1.1%, so while these individuals may fall within this general population risk of developing thyroid cancer, they may also share other risk factors with their family members that increased their risk to develop cancer (DeLellis, 2004). One of these phenocopies was diagnosed with PTC at age 35 after the detection and further analysis of thyroid nodules. She is the daughter of a mutation positive female. Her mother was not diagnosed until age 65 and recently tested positive for the 4q32 mutation. Our second phenocopy is related to the family through her father, who did not undergo genetic testing but she is known not to carry the 4q32 mutation. Her mother, not a biological relative to this family, was diagnosed with PTC at age 51 so she may have inherited other risk factors from that side of the family. Still, this phenocopy was diagnosed with separate foci of PTC, thyroiditis and nodular hyperplasia at age 21, which is much younger than

expected. The cause of her increased risk remains unknown, as it may have resulted from her mother's diagnosis of PTC, or other risk factors from her father's family history. This represents a good example of the heterogeneity of thyroid cancer because this individual may have factors impacting her diagnosis that were inherited by her mother and/or father. These risk factors, in addition to other possible influences and modifier genes likely pushed her risk passed the threshold, causing an early diagnosis of PTC, as well as benign thyroid disease.

The high risk of thyroid cancer in this family may be in part due to over-surveillance that led to more incidental findings of benign thyroid disease and thyroid cancer. The family history caused heightened awareness of thyroid cancer and an increase in the thyroid palpation and ultrasounds compared to the general population. This may have resulted in earlier ages of diagnosis and it is possible that some cases of PTC in this family may have never been diagnosed if increased surveillance had not been implemented.

Two individuals in this family were diagnosed with ATC, a very rare and aggressive form of thyroid cancer. These individuals are siblings; the sister is an obligate carrier and the brother had a 50% chance of having the mutation, but unknown mutation status. It is uncertain whether these individual's ATC diagnoses began as unrecognized PTC and de-differentiated over time to develop into ATC. While some ATC may be derived from PTC, it is unknown why these two individuals developed this rare and aggressive form of

thyroid cancer but it is possibly due to the 4q32 mutation and other modifying risk factors in this family (Xing, 2007).

The earliest age of onset of thyroid cancer in an individual with a 4q32 mutation in this family is 12 years. This young man was diagnosed with an atypical follicular lesion at age 12 upon a left lobectomy, which led to a right lobectomy detecting PTC with a follicular variant. His older brother was screened shortly thereafter and multi-centric PTC in both lobes was detected at age 15. The third brother was not diagnosed with thyroid cancer, but did have nodules detected at age 14 and ultimately had his thyroid removed at age 24 given his positive mutation status and family history. All three sons tested positive for the 4q32 mutation. In addition, their mother underwent a partial thyroidectomy at age 39 due to a diagnosis of Hashimoto's thyroiditis, ultimately removing the remainder of her thyroid prophylactically in her 40s. Now with children of their own, her sons are concerned about when to begin thyroid surveillance for their children.

The benign thyroid disease risk in individuals with the mutation in this family is very similar to that of the individuals who tested negative for the mutation, 65.3% and 70.7% respectively. This may suggest that this mutation is likely contributing the higher predisposition to develop thyroid cancer and not necessarily impacting the benign thyroid disease risk. This may be an important distinction to make in the individuals of this family who develop benign thyroid cancer that may be unrelated with a positive mutation status.

The variability in the clinical presentation of disease may be attributed to other modifying genes or environmental factors that cannot be evaluated at this time. However, given this high penetrance, increased thyroid cancer surveillance is indicated for mutation-positive individuals in this family. Screening should begin at a younger age in individuals with a known 4q32 mutation given the earlier age of onset of thyroid cancer (12 years old). For many hereditary cancers, it is reasonable to begin surveillance 5 to 10 years prior to the earliest age of diagnosis, proposing beginning surveillance between the ages of 2 to 7 in those individuals who test positive for this mutation (Sippel, Caron, & Clark, 2007; Bauer, 2013). It may be more reasonable for this family to follow similar guidelines provided by NCCN for Lynch syndrome, suggesting surveillance every 2 to 5 years prior to the earliest diagnosis if the diagnosis occurred prior to age 25. This proposes surveillance to begin between ages 8 to 10 in those who test positive for the mutation (Goldgar et al., 1994).

While PTC has a high survival rate and is generally a slow growing cancer, this family does have two cases of very aggressive ATC; therefore the decision to pursue surveillance versus a prophylactic thyroidectomy is uncertain. In patients with MEN2, children who test positive undergo thyroidectomies because of the high risk of MTC and the higher mortality rate (Moline & Eng, 2011). Provided that individuals in this family have a high predisposition to develop PTC and two relatives diagnosed with ATC, they must carefully consider if and when to undergo prophylactic thyroidectomies.

We integrated information provided by individuals from this family, with the goal of understanding the penetrance and assisting genetic counselors and medical professionals to provide the most appropriate level of care to these individuals. Specific counseling and surveillance recommendations may change and improve as we learn more about this private mutation, or other factors associated with their risks. The results of this study indicate that the surveillance and treatment recommendations for those with a 4q32 mutation should be closely determined by physicians who are made aware of this information. Although specific guidelines cannot be provided at this time, small nodules in these individuals can be detected by increased surveillance using ultrasound and FNA. An enlargement in nodule size can be detected by serial ultrasound and undergo further evaluation for determination of malignancy risk. While some individuals in the family have undergone prophylactic thyroidectomies, the benefit of earlier detection of these small malignancies is unclear. The patient must weigh the risk of surgery with the possible benefit of earlier detection.

Prophylactic thyroidectomy risks include surgery complications, lifetime thyroid replacement therapy, possible financial burden and surveillance for recurrence if thyroid cancer is detected (Davies & Welch, 2006). Although small, surgical complications may result in permanent hypoparathyroidism and damage to the recurrent laryngeal nerves (Davies & Welch, 2006).

In addition to surveillance implications, these results also have counseling implications. Individuals undergoing genetic testing and surveillance should fully understand the risks and limitations associated with testing positive for the 4q32 mutation. A discussion between the patient and physician will be required to reach an optimal decision on the precise timing and interval of surveillance. Genetic counseling to discuss inheritance and the possibility of the mutation being passed down to future generations is also warranted to most effectively prepare families. It is important to note that individuals who test negative for the 4q32 mutation in this family can still develop thyroid cancer and have a 7.6% (95% CI, 1.9%-27.7%) risk of developing thyroid cancer by age 70. Although we cannot compare the thyroid cancer risk in the individuals without the mutation in this family to that of the general population, the lower end of the CI (1.9%) is similar to the general population risk of 1.1% to develop thyroid cancer. Individuals who test negative for this mutation should continue to be aware of changes in their thyroid and discuss appropriate care with their physicians.

Strengths of this study include the detailed information provided by each participant, including specific information on the timing of their imaging and/or surgeries, other co-morbidities, exposures, and general demographics. Most participants also provided thorough information regarding the clinical history of their relatives. The standardized 4q32 testing, which was analyzed by the same laboratory provided consistency and reassurance in determining accurate mutation status. Confirmation of thyroid surgeries and pathology as often as was possible to validate the reported participant information is

another strength of this study. Unfortunately, while participants were willing to share their records, some medical records were unavailable due to the length of time that has passed since the event.

Limitations of this study include the small sample size and while we had information on 115 individuals, a smaller proportion (68 participants) underwent genetic testing or were known to be obligate mutation carriers. Another challenge is the fact that this is a private mutation found in a single family. Thus, the estimated penetrance of this mutation determined from this study cannot be generalized to the population.

Additionally, prophylactic thyroidectomies censor whether or not individuals would have developed thyroid cancer and/or benign thyroid disease. Assessing an accurate thyroid cancer risk for this family is a challenge because of the heightened awareness of the phenotype and increased surveillance paired with their prophylactic surgery decisions. Other limitations included the lack of some clinical data and non-uniform treatment (i.e. independent decisions made regarding the appropriate timing of thyroid removal). Combined, these factors may bias the penetrance estimate and should be taken into consideration when discussing treatment options.

In conclusion, our results demonstrate elevated thyroid cancer and benign thyroid disease risks for individuals with a 4q32 mutation in this large family. Individuals in this family who test positive for this mutation have 68.9% likelihood to develop thyroid cancer by

age 70 and 65.3% to develop benign thyroid disease by age 70, and should discuss medical management guidelines with their endocrinologist.

References

Altekruse, S., Das, A., Cho, H., Petkov, V., & Yu, M. (2015). Do US thyroid cancer incidence rates increase with socioeconomic status among people with health insurance? an observational study using SEER population-based data. *BMJ Open, 5*(12), e009843-2015-009843.

American Cancer Society. (n.d.). Overview of bladder cancer. Retrieved from http://www.cancer.org/cancer/thyroidcancer/index.

American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper, D. S., Doherty, G. M., Haugen, B. R., Kloos, R. T., Lee, S. L., et al. (2009). Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid: Official Journal of the American Thyroid Association, 19*(11), 1167-1214.

Anand, A., Singh, K. R., Kushwaha, J. K., Hussain, N., & Sonkar, A. A. (2014). Papillary thyroid cancer and hashimoto's thyroiditis: An association less understood. *Indian Journal of Surgical Oncology, 5*(3), 199-204.

Askitis, D., Efremidou, E. I., Karanikas, M., Mitrakas, A., Tripsianis, G., Polychronidis, A., et al. (2013). Incidental thyroid carcinoma diagnosed after total thyroidectomy for benign thyroid diseases: Incidence and association with thyroid disease type and laboratory markers. *International Journal of Endocrinology,* 451959.

Bauer J.B. (2013). Endocrine tumor syndromes and their genetics: Clinical behavior and genetics of nonsyndromic, familial nonmedullary thyroid cancer. Bethesda, MD: Karger.

Brito, J. P., Yarur, A. J., Prokop, L. J., McIver, B., Murad, M. H., & Montori, V. M. (2013). Prevalence of thyroid cancer in multinodular goiter versus single nodule: A systematic review and meta-analysis. *Thyroid: Official Journal of the American Thyroid Association, 23*(4), 449-455.

Czene, K., Lichtenstein, P., & Hemminki, K. (2002). Environmental and heritable causes of cancer among 9.6 million individuals in the swedish family-cancer database. *International Journal of Cancer. 99*(2), 260-266.

Davies, L., & Welch, H. G. (2006). Increasing incidence of thyroid cancer in the united states, 1973-2002. *Jama, 295*(18), 2164-2167.

Davies, L., Ouellette, M., Hunter, M., & Welch, H. G. (2010). The increasing incidence of small thyroid cancers: Where are the cases coming from? *The Laryngoscope, 120*(12), 2446-2451.

DeLellis, R. A. (2004). Pathology of genetics and tumours of endocrine organs. Lyon: IARC Press.

Frich L., Glattre E, Akslen LA. (2001). Familial occurrence of nonmedullary thyroid cancer: a population-based study of 5673 first-degree relatives of thyroid cancer patients from Norway. *Cancer epidemiology, biomarkers & prevention.10*(2):113-7.

Goldgar D.E., Easton D.F., Cannon-Albright L.A., et al. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *Journal of National Cancer Institute. 86*(21):1600-8.

Guerra A., Di Crescenzo V., Garzi A. et al. (2013). Genetic mutations in the treatment of anaplastic thyroid cancer: a systematic review. *BMC Surgery, 13*(Suppl 2): S44.

Harach H.R., Franssila K.O., & Wasenius V.M. (1985). Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer. 56*(3):531-8.

Haugen, B. R., Alexander, E. K., Bible, K. C., Doherty, G. M., Mandel, S. J., Nikiforov, Y. E., et al. (2016). 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid: Official Journal of the American Thyroid Association, 26*(1), 1-133.

He, H., Li, W., Wu, D., Nagy, R., Liyanarachchi, S., Akagi, K., et al. (2013). Ultra-rare mutation in long-range enhancer predisposes to thyroid carcinoma with high penetrance. *PloS One, 8*(5), e61920.

Herz, H. M., Hu, D., & Shilatifard, A. (2014). Enhancer malfunction in cancer. *Molecular Cell, 53*(6), 859-866.

Kilfoy, B. A., Zheng, T., Holford, T. R., Han, X., Ward, M. H., Sjodin, A., et al. (2009). International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer Causes & Control: CCC, 20*(5), 525-531.

Malandrino, P., Scollo, C., Marturano, I., Russo, M., Tavarelli, M., Attard, M., et al. (2013). Descriptive epidemiology of human thyroid cancer: Experience from a regional registry and the "volcanic factor". *Frontiers in Endocrinology, 4*(65).

Mansour, M. R., Abraham, B. J., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, A. D., et al. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science, 346*(6215), 1373-1377.

Moline J. & Eng C. (2011). Multiple endocrine neoplasia type 2: an overview. *Genetics in medicine. 13(*9):755-64

Nagy, R., & Ringel, M. D. (2015). Genetic predisposition for nonmedullary thyroid cancer. *Hormones & cancer, 6*(1), 13-20.

Nilubol, N., Zhang, L., & Kebebew, E. (2013). Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. *Thyroid: Official Journal of the American Thyroid Association, 23*(6), 695-702.

Nosé V. (2008). Familial non-medullary thyroid carcinoma: an update. *Endocrine Pathology: 19*(4):226-40.

Pal, T., Vogl, F. D., Chappuis, P. O., Tsang, R., Brierley, J., Renard, H., et al. (2001). Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: A hospital-based study. *The Journal of Clinical Endocrinology and Metabolism, 86*(11), 5307-5312.

Sippel, R. S., Caron, N. R., & Clark, O. H. (2007). An evidence-based approach to familial nonmedullary thyroid cancer: Screening, clinical management, and follow-up. *World Journal of Surgery, 31*(5), 924-933.

Surveillance, Epidemiology, and End Results Program. (n.d.). Retrieved January 4, 2016, from http://seer.cancer.gov/.

Tufano R.P., Noureldine S.I., & Angelos P. (2015). Incidental thyroid nodules and Thyroid cancer: considerations before determining management. *JAMA Otolaryngology–Head & Neck Surgery, 141*(6):566-72.

Weedon M.N., Cebola I., Patch A.M. et al. (2014). Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nature Genetics, 46*(1):61-4.

Welch H.G., & Black, W.C. (2010). Overdiagnosis in cancer. *Journal of the National Cancer Institute, 102*(9):605-13.

Xing, M. (2007). BRAF mutation in papillary thyroid cancer: Pathogenic role, molecular bases, and clinical implications. *Endocrine Reviews, 28*(7), 742-762

Yarchoan, M., LiVolsi, V. A., & Brose, M. S. (2015). BRAF mutation and thyroid cancer recurrence. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 33*(1), 7-8.

Appendix A: Questionnaires

Ohio State Familial Thyroid Cancer Study
Participant questionnaire

Today's date: **DEMOGRAPHIC SECTION:**

1.) Name: _____ 2.) Date of birth (mm/dd/yyyy): _____
3.) Birthplace: _____
4.) Gender: □ Male □ Female
5.) Marital Status: □ Married □ Single □ Divorced □ Separated
6.) Occupation: _____
7.) Highest Level of Education (Choose one):
- □ Less than high school
- □ High school graduate
- □ Technical school graduate
- □ College graduate
- □ Advanced degree beyond college

8.) Ethnicity:
- □ Asian
- □ Black/African-American
- □ Mid-Eastern
- □ Hispanic or Latino
- □ White
- □ Native Hawaiian/Pacific Islander
- □ American Indian/Alaskan Native

GENERAL MEDICAL HISTORY:

9.) Weight: _____ pounds Height: _____feet _____ inches
10.) Do you currently smoke cigarettes? □ Yes □ No
If yes, 10a.) How many packs of cigarettes do you smoke per day? _____
10b.) How many years have you smoked cigarettes? _____
11.) Have you smoked cigarettes in the past? □ Yes □ No
If yes, 11a.) How many packs of cigarettes did you smoke per day? _____
11b.) How many years did you smoked cigarettes? _____
12.) How many drinks of alcohol do you consume daily on average?
(A standard drink is equal to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces [1 shot] of liquor)
□ 1 drink or less per day □ 2 drinks daily □ More than 2 drinks per day

13.) Have you had or do you now have any of the following conditions?
Circle all that apply

Alzheimer's, senile dementia	Dental problems	High cholesterol
Anemia	Diabetes – juvenile (type I) or adult (type II)	Irregular heart beat
Arthritis: rheumatoid or osteo	Drug dependence: (Alcohol, Nicotine, other)	Kidney failure, chronic
Asthma	Endometriosis	Liver disorder (Cirrhosis, Hepatitis)
Autoimmune disease	Fibrocystic breast disease	Ovarian cysts
Benign breast biopsies	Stomach/intestinal problems	Parkinson's disease
Breast cysts/aspirations	Genetic condition	Psychiatric disorder
Breast lumps	Glaucoma/cataracts	Skin lumps or bumps
Changes in moles	Heart attack	Skin lesions removed
Colitis	Heart disease	Stroke
Colorectal Polyps	High blood pressure	Uterine fibroids
Congenital abnormalities		

13a.) For anything circled above, please explain what the diagnosis was; age at diagnosis, # times (e.g. 2 breast biopsies), and other information such as how it was treated (surgery, etc..)

Condition	Age at diagnosis	# of times	Other information

14.) Please list any other major medical problems (not listed above) with which you have been diagnosed:

_____
_____
_____
_____
_____

FEMALE SECTION ONLY:

15.) What age were you when you had your first period? _____

16.) Have you ever taken oral contraceptives (birth control pills)? □ Ye s □ No
If yes, 16a.) At what age did you start taking this? _____
16b.) Are you currently taking this medication? □ Yes □ No
16c.) How many months or years did/have you taken this medication?

17.) How many pregnancies have you had? _____

18.) What age were you when you had your first child? _____

19.) Have you had any miscarriages? □ Yes □ No
If yes, 19a.) How many? _____

20.) Have you gone through menopause? □ Yes □ No
If yes, 20a.) At what age? _____
20b.) Was the cause of your menopause:
□ Natural
□ Chemical (due to a drug or chemotherapy)
□ Surgical (due to having your ovaries removed)

21.) Have you ever taken hormone replacement therapy? □ Yes □ No
If yes, 21a.) At what age did you start taking this? _____
21b.) Are you currently taking this medication? □ Yes □ No
21c.) How many months or years did/have you taken this medication?

THYROID & CANCER HISTORY:

22.) Have you ever had any type of cancer? If so, please list the specific type(s) and indicate age(s) of diagnosis.

_____

23.) Do you have any history of benign thyroid disease (e.g. goiter, grave's disease, toxic adenoma, or thyroiditis)? □ Yes □ No

23a.) If yes,what kind of thyroid disease?

- □ Overactive thyroid gland
- □ Underactive thyroid gland
- □ Nodule or enlarged thyroid gland
- □ Other (please specify)
- □ N/A

23b.) What was the age of diagnosis? _____

23c.) How was this diagnosed (e.g. ultrasound, biopsy, etc.)? _____

23d.) What was the treatment plan and was it followed strictly? _____

23e.) Any complications or recurrences? _____

24.) Have you ever been treated for a thyroid disease? □ Yes □ No

24a. If yes, which treatments did you have (check all that apply)?

- □ Thyroid hormone therapy (eg. Synthroid, Eltroxin, Cytomel)
- □ Antithyroid drug therapy (eg. PTU, Tapazole)
- □ Thyroid surgery
- □ Radioiodine therapy
- □ Other (please specify)

25.) Please describe any form of radiation exposure in the past

Age when exposure began / *Exposure duration*

- □ X-ray pre-1960's (e.g. acne or tonsil treatment) _____
- □ Therapeutic (e.g. to treat thyroid cancer, goiter, etc.) _____
- □ Environmental (e.g. exposures at work) _____
- □ Other (please specify) _____ _____
- □ N/A

26.) Are you currently taking thyroid medication? □ Yes □ No

If yes, please indicate.

- □ Thyroid hormone therapy (eg. Synthroid, Eltroxin, Cytomel)
- □ Antithyroid drug therapy (eg. PTU, Tapazole)

28.) Is there any additional information that you think is relevant to your medical history that has not yet been mentioned? _____

Family History for OSU Familial Thyroid Cancer Study

Name: _____ **Date Completed:** _____

Relationship:	Name: Last, First, MI	Are they living?	Current age or age at death:	Have they have cancer? If yes, what kind?	How old were they when cancer was found?	Do/did they have benign thyroid disease (Goiter, nodules, etc..)
Your Wife/Husband/Partner:						
Your Mother:						
Your Father:						
Your Sister/Brother:						
Your Sister/Brother:						
Your Sister/Brother:						
Your Sister/Brother:						
Your Sister/Brother:						

Family History for OSU Familial Thyroid Cancer Study
Your Children

Name: _____ **Date Completed:** _____

Relationship:	Name: Last, First, MI	Are they living?	Current age or age at death:	Have they have cancer? If yes, what kind?	How old were they when cancer was found?	Do/did they have benign thyroid disease (Goiter, nodules, etc..)
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						
Your Son/Daughter:						

Family History for OSU Familial Thyroid Cancer Study
Your Mother's Relatives

Name: _____ **Date Completed:** _____

Relationship:	Name: Last, First, MI	Are they living?	Current age or age at death:	Have they have cancer? If yes, what kind?	How old were they when cancer was found?	Do/did they have benign thyroid disease (Goiter, nodules, etc..)
Your Mother's Mother:						
Your Mother's Father:						
Your Mother's Brother/Sister:						
Your Mother's Brother/Sister:						
Your Mother's Brother/Sister:						
Your Mother's Brother/Sister:						
Your Mother's Brother/Sister:						

Family History for OSU Familial Thyroid Cancer Study

Your Father's Relatives

Name: _____ **Date Completed:** _____

Relationship:	**Name: Last, First, MI**	**Are they living?**	**Current age or age at death:**	**Have they have cancer? If yes, what kind?**	**How old were they when cancer was found?**	**Do/did they have benign thyroid disease (Goiter, nodules, etc..)**
Your Father's Mother:						
Your Father's Father:						
Your Father's Brother/Sister:						
Your Father's Brother/Sister:						
Your Father's Brother/Sister:						
Your Father's Brother/Sister:						
Your Father's Brother/Sister:						

Family History for OSU Familial Thyroid Cancer Study

General Family Background

Name: _____

Relationship:	Country of Origin:	Religion:
Mother's Mother		
Mother's Father		
Father's Mother		
Father's Father		

Notes: _____

_____

_____