Thyroid Cancer in Hawaii: Concern for Ethnic Disparity in the Filipino Population

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By

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We certify that we have read this thesis and that, in our opinion, it is satisfactory in scope and quality as a thesis for the degree of Master of Science in Biomedical Sciences (Clinical Research).

ABSTRACT

Background: Thyroid cancer is the most common endocrine malignancy. It is noteworthy that thyroid cancer is more common in particular geographic regions such as Hawaii. Additionally, there appears to be an ethnic predilection of thyroid cancer within particular groups such as the Filipino population in Hawaii. Outside the confines of ethnicity, other potential putative biologic determinants of aggression include genetic and protein alterations.

Objective: Due to the higher preponderance of thyroid cancer within distinct populations, our principal goal was to comprehensively assess if there was an ethnic disparity of survival in Hawaii.

Methods: This was a retrospective review of 622 patients with thyroid cancer treated at a tertiary care facility in Honolulu, HI from January 1, 1990 through December 2008. In addition, tissue biospecimens of 10 Filipino patients with papillary thyroid carcinoma from within the study cohort were subjected to DNA as well as protein characterization. A log-rank test was implemented to determine survival between the Filipino and non-Filipino cohorts. In order to model the survival of Filipinos vs. non-Filipinos adjusted for by age, gender, extra-thyroidal extension, and AJCC stage, regression analysis via the Cox proportional hazards model was utilized; hazard ratios with confidence intervals were computed.

Results: The entire cohort was comprised of 622 patients. There were 136 Filipinos (21.9%) and 486 non-Filipinos (78.1%). When compared as an individual group, the Filipinos (86.3%) had a worse mortality (unadjusted: P-value = 0.05) than the non-Filipinos (93.5%). Furthermore, when adjusted for age, gender, AJCC stage, and extra-thyroidal extension, Filipino ethnicity was still independently found to harbor a worse prognosis (P-value of < 0.039). The frequency of the BRAF somatic mutation was 10/10 (100%). The frequency of high expression for the eIF4Eprotein was 8/10 (80%).

Conclusion: In conclusion, we have reported for the **first time** that Filipino ethnicity is associated with a worse survival in thyroid cancer. Furthermore, our initial observation from the molecular analysis on thyroid cancer specimens demonstrated that the MAPK and mTOR signaling pathways may be a potential negative prognostic determinant.

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BRAF	murine sarcoma viral oncogene homolog
eIF4E	eukaryotic translation initiation factor 4E
IHC	immunohistochemistry
MAPK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
PCR	polymerase chain reaction
QMC	queen’s medical center
UH	University of Hawaii

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CHAPTER 1: INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, as an estimated 44,670 Americans will be diagnosed in 2010 (1). Nationally, its incidence is rapidly increasing and has doubled over the last decade (2). More significantly, in women its frequency has risen faster than any other cancer over the same time period (3). Risk factors include familial disposition, personal history of head or neck irradiation, female gender, and environmental exposure to nuclear fallout. The vast majority of patients will have papillary thyroid carcinoma, accounting for over 80% of all thyroid malignancies. Other less common histologic types are follicular, oncocytic, medullary, and anaplastic. Most thyroid cancer is amenable to surgical extirpation and associated with a favorable outcome; however, recurrence is more common than perceived affecting up to 30% of patients (4). Furthermore, 10% of patients will ultimately die of their disease (5). Historically, negative prognostic features of thyroid cancer have been identified to include older age, male gender, advanced stage, and extra-thyroidal extension (6). However, stratification by ethnicity has not been thoroughly undertaken. It is noteworthy that thyroid cancer is more common in particular geographic regions such as Hawaii (7). Additionally, there appears to be an ethnic predilection of thyroid cancer within particular groups such as the Filipino population in Hawaii. For example, data abstracted by the Hawaii Tumor Registry reveal that during the time period 1988-2007, amongst the 2324 patients diagnosed with thyroid cancer, 675 (29%) were Filipino. This ethnic proclivity has previously been noted in California where Filipinos in Los Angeles were found to have the highest

incidence rates of thyroid cancer; 4.44 cases per 100,000 males and 11.3 cases per 100,000 females (8). Outside the confines of ethnicity, other potential putative biologic determinants of aggression include genetic and protein alterations. BRAF (murine sarcoma viral oncogene homolog) is an oncogene that affects approximately 50% of patients with papillary thyroid carcinoma and is felt to be associated with a worse prognosis (9). It can also be prevalent in anaplastic thyroid carcinoma, although to a lesser degree (10). BRAF is the strongest activator of the mitogen-activated protein kinase (MAPK) pathway, which is thought to play a central role in thyroid tumorigenesis. This is a genetic alteration whereby in most instances, a somatic transversion point mutation (V600E) of exon 15 occurs (11). In addition to BRAF, the mammalian target of rapamycin (mTOR) cascade has been found to be important in the pathogenesis of multiple solid tumors. MTOR is essential to cellular growth, proliferation, and metabolism (12). It has been implicated in thyroid cancer formation and progression (13). Evidence suggests that when this serine/threonine kinase is activated via phosphorylation, it may portend a worse prognosis in distinct histologies (14). Increasingly, this venue has been utilized as a means of targeted therapy and has been an essential aspect for the armamentarium in selected tumors and is currently being evaluated in clinical trials for advanced thyroid cancer (15). More recently, eIF4E (eukaryotic translation initiation factor 4E) a complex located downstream to mTOR has garnered attention as a significant factor in neoplastic initiation as well as progression, involving

mechanisms of apoptotic evasion and angiogenic promotion (16). The presence of increased expression signifies activation of the mTOR pathway.

Due to the higher preponderance of thyroid cancer within distinct populations, our principal goal was to comprehensively assess if there was an ethnic disparity of survival in Hawaii. Specifically, we hypothesized that Filipinos diagnosed with thyroid cancer will have a worse prognosis when compared to non-Filipinos, which may be attributed to biologic factors. Therefore, we sought to 1) describe the ethnic disparity among thyroid cancer patients in Hawaii by analyzing demographic as well as clinical-pathologic variables from a comprehensive database, and in a cohort of Filipino patients, 2) examine BRAF as a conventional marker of aggressive thyroid cancer as well as, 3) evaluate eIF4E as a potential negative prognosticator.

CHAPTER 2: METHODS

Design. This was a retrospective review of 622 patients with thyroid cancer treated at a tertiary care facility in Honolulu, HI from January 1, 1990 through December 2008. In addition, tissue biospecimens of 10 Filipino patients with papillary thyroid carcinoma from within the study cohort were subjected to DNA as well as protein characterization. The institutional review board at the Queen's Medical Center (QMC) as well as the University of Hawaii (UH) approved the study.

Database. The database is compiled by the Oncology Data Registry at QMC, where outcome including survival is recorded. The demographic, clinical and pathologic data was transferred to a spreadsheet utilizing (Microsoft Excel, Redmond, WA).

Population. Conventional variables of 622 patients with thyroid carcinoma were examined. Patients were included if they were 15 years of age and older. Patients were excluded if they had lymphoma, melanoma, sarcoma, or metastatic involvement of the thyroid. Age, gender, ethnicity, tumor size, histologic type, American Joint Committee on Cancer (AJCC) stage, extra-thyroidal extension and vital status were recorded. The specific ethnic groups were categorized into Caucasian, Chinese, Japanese, Native Hawaiian, Pacific Islander, and Filipino. Ten Filipino patients with papillary thyroid carcinoma in which tumors that were pathologically confirmed (via QMC Department of Pathology) to possess extra-thyroidal extension were selected for genetic and protein characterization.

Statistical analysis. The analysis was performed employing (SAS 8.1, Cary, NC). For the outcome aspects of the study, Kaplan-Meier method was used to graphically illustrate five-year overall survival for all major ethnicities. A log-rank test was implemented to determine survival between the Filipino and non-Filipino cohorts. In order to model the survival of Filipinos vs. non-Filipinos adjusted for by age, gender, extra-thyroidal extension, and AJCC stage, regression analysis via the Cox proportional hazards model was utilized; hazard ratios with confidence intervals were computed. A t-test was used to ascertain if tumor size between the Filipino and non-Filipino groups were different. A log-rank test was applied to compare survival between the Filipinos and Caucasians. Significance level was set at 2-sided $P<0.05$ for all analyses.

DNA and protein characterization. BRAF mutational analysis was performed by Polymerase Chain Reaction (PCR) via standard protocol (Clarient Inc, Aliso Viejo, CA). Specifically, tissue blocks from thyroidectomy specimens previously archived and stored in paraffin wax after formalin fixation were made readily available. Laser capture microdissection to facilitate DNA isolation of neoplastic tissue was subsequently utilized. After DNA extraction, a real-time PCR reaction containing primers that flank codon 600 of BRAF with an internal probe specific for the mutated sequence was completed. A secondary reaction as an amplification control was executed on a wild-type sequence for BRAF. EIF4E (eukaryotic initiation factor 4E) activation was ascertained by immunohistochemistry (IHC). This was performed on formalin-fixed/ paraffin-embedded archived biospecimens utilizing PT link antigen retrieval with the

Envision^{TM} FLEX detection system (Dako Inc., Carpinteria, CA). The intensity was graded on a scale from 0 (absent) to 2 (high) using a mouse monoclonal antibody to the eIF4E protein (Santa Cruz Biotechnology Inc., Santa Cruz, CA).

CHAPTER 3: RESULTS

Subject characteristics. The entire cohort was comprised of 622 patients. There were 136 Filipinos (21.9%) and 486 non-Filipinos (78.1%). A comprehensive analysis of the data focusing on ethnicities revealed that the Filipino population was the group most commonly affected, as displayed in Figure 1. For the distinct ethnicities included in Table 1, it is noteworthy that the Filipino population had a median age of diagnosis (49.7 yrs) similar to all the groups (50.0 yrs). However, the Native Hawaiian group was diagnosed more than 5 years earlier than all the groups. Both the Caucasian and Pacific Islander groups had a 2:1 female to male ratio in comparison to the entire group (3:1). The vast majority of patients had differentiated thyroid carcinoma (papillary or follicular) n=580 (93%) while 14 had oncocytic, 8 medullary, 10 anaplastic, and 10 other. In regards to stage distribution, the Japanese had similar rates of stage III and IV disease (26.3%) when compared to the Filipinos (25.7%) and Pacific Islanders (25.6%). Extra-thyroidal disease was found to be most frequent in the Pacific Islander group (30.8%), nearly two-folds higher relative to the entire study cohort. A focused comparison between the Filipino and non-Filipino groups revealed similarities of age, gender distribution, tumor size, and extra-thyroidal extension as depicted in Table 2. Papillary and follicular thyroid carcinomas combined for over 90% of the histologic type for each group. The majority of patients from each cohort had early stage thyroid carcinoma. From a therapeutic standpoint, the proportion of Filipinos undergoing total thyroidectomy was 108/136 (79.4%) which was similar to the non-Filipinos 377/486 (77.6%).

Patient survival. With regard to outcome, overall five-year survival for all of the ethnicities was calculated to be 91.9%. Caucasians had the best survival (96.3%), followed by Chinese (91.6%), Japanese (90.5%), Native Hawaiians (89.3%), Pacific Islanders (88.2%), and Filipinos (86.3%) as shown in Figure 2. When compared as an individual group, the Filipinos (86.3%) had a worse mortality (unadjusted: P-value = 0.05) than the non-Filipinos (93.5%) as illustrated in Figure 3. Furthermore, when adjusted for age, gender, AJCC stage, and extra-thyroidal extension, Filipino ethnicity was still independently found to harbor a worse prognosis (P-value of < 0.039) as seen in Figure 4. Filipinos had a nearly 2-fold risk of death vs. their non-Filipino counterparts with a hazard ratio of 1.77. Figure 5 demonstrates that Filipinos had a worse survival than the Caucasians when compared against each other 86.3% vs. 96.3% (unadjusted with P-value 0.045. When adjusted for confounders, the significance disappears.

BRAF mutation. For the 10 Filipino patients with papillary thyroid cancer demonstrating extra-thyroidal extension, the frequency of the BRAF somatic mutation was 10/10 (100%). Table 3 provides the demographic and clinico-pathologic characteristics. Figure 6 illustrates an example of a PCR with a BRAF mutation.

EIF4E expression. For the 10 Filipino patients with papillary thyroid cancer demonstrating extra-thyroidal extension, the frequency of high expression for the eIF4Eprotein was 8/10 (80%). Table 4 provides the demographic and clinico-pathologic characteristics. Figure 7 illustrates an example of an IHC with high expression for eIF4E.

CHAPTER 4: DISCUSSION

This study demonstrated that there is an ethnic disparity of thyroid cancer survival in Hawaii with the Filipinos having a worse outcome in comparison to the non-Filipinos.

Thyroid cancer is not only increasing in overall incidence nationally but also locally. Our primary goal was to focus on the distinct ethnicities at a tertiary center in Hawaii and determine if particular groups such as the Filipinos have the highest incidence coupled with the worst outcome. We identified that the Filipino population comprised the largest percentage of patients affected by thyroid cancer (21.9%) and had the worst survival (86.3%). A previous matched-pair study found that patients with thyroid nodules who were Filipinos have a higher likelihood of malignancy. The authors reported that 50/72 (69.4%) Filipino patients had malignant nodules while for the non-Filipinos; the rate was only 28/72 (38.9%); the odds ratio for malignancy was 3.57 (16). Ethnicity in thyroid cancer has only recently been cited as a factor affecting clinical outcome. Kus and colleagues concluded that Filipino patients have a higher risk of recurrence as compared to their non-Filipino counterparts (17). They found that for Filipino patients, the recurrence rate was 25% compared with 9.5% for non-Filipino patients. However, their Filipino cohort consisted of only 36 patients. Therefore, our finding of a worse survival in the Filipino group consisting of 136 patients relative to the non-Filipino group in this study is compelling.

Because other variables such as age, gender, stage, and extra-thyroidal extension could serve as confounders, we performed a regression analysis to

further support that Filipinos as a group independently have a higher likelihood of dying. We found that their risk of death is nearly two-fold. Age, gender, advanced stage, and extra-thyroidal extension did not appear to be different in comparison to other groups. In particular, higher stages (III and IV) were found in one-fourth of Filipinos but this was comparable to the Japanese and Pacific Islander s. T4 status has been demonstrated to predict a worse survival. However, the proportion of Filipino patients with this variable was similar to the entire study group from 1990 through 2008; the Pacific Islander group had a rate of 30.8%. The overwhelming majority of patients in the study group had differentiated thyroid cancer (papillary or follicular) and therefore histologic type was not deemed a significant entity. The standard therapeutic tool utilized in managing thyroid cancer is surgery. There was no difference in the rates of total thyroidectomy between our 2 cohorts, thus indicating that substandard treatment could not be used as a reason to explicate the Filipino group's worse outcome. Environment cannot be used as an unequivocal inciting factor for the discrepancy in survival as Hawaii is a state in which individuals are exposed to similar conditions within the islands. However, further analysis regarding place of birth and length of time within the Philippines may be a valid field of study, as the Philippines are located within the Ring of Fire, a large area within the Pacific Basin affected by numerous volcanic eruptions. Even when the Filipino group (n=136) was compared with the Caucasian group (n=115), there was a significant difference in survival, 86.3% vs. 96.3 % respectively. When adjusted for confounders, the hazard ratio was over 2-fold (2.37) but was not significant

(P-value= 0.061), likely due to sample size. Although the adjusted survival was not significant, it still lends support to the concept that Filipino patients with thyroid cancer have a worse survival and should be expanded further to include larger cohorts.

Molecular analyses to account for thyroid cancer disparity in a diverse population containing unique ethnic groups such as Filipinos have been non-existent. This study was the first of its kind to examine biospecimens of thyroid cancer in Hawaii containing the Filipino group for various alterations in genes as well as proteins. The project recapitulated the importance of a major problem in thyroid cancer: ethnic disparity. Although the majority of patients afflicted with thyroid cancer in the United States are Caucasians, investigating non-Caucasians such as Filipinos may glean insight into disease biology. By analyzing biospecimens and the alterations of key oncogenes and proteins among multiple ethnicities, one is able to better characterize the individual tumor and thus potentially provide appropriate therapeutic recommendations that are tailored to the individual patient. For example, recognition of BRAF mutation in a distinct ethnic group may necessitate closer surveillance or more aggressive surgery; identification of increased expression of activated mTOR or its downstream effector eIF4E may serve as a surrogate marker of candidacy to receive targeted therapy with an mTOR antagonist. Although our molecular analysis consisted of only 10 samples from Filipino patients, we found a high frequency of BRAF and eIF4E alterations. This project has the potential to improve scientific knowledge by increasing awareness to investigators of other understudied ethnicities including Filipinos. It

may glean insight as to what the clinical and pathological characteristics that patients from different non-Caucasian ethnicities possess. Furthermore, it may provide the scientific community with an unexpected molecular profile with respect to BRAF mutation or eIF4E expression.

We recognize the limitations of this study. First, we do not have knowledge of the co-morbidities for both cohorts. Perhaps the Filipinos had a higher preponderance of concomitant processes such as diabetes mellitus or coronary heart disease which may complicate their thyroid cancer prognosis. Second, our registry does not collect cause of death and therefore does not record disease-specific mortality. The Filipinos may be dying from other afflictions beside thyroid cancer. Third, prior head or neck radiation and family history of thyroid cancer have been identified as adverse prognostic determinants; however the information was not captured within the database. Most important is that this is a retrospective review for which factors such as recall bias are inherently present. Because our institution is a tertiary center for the entire state of Hawaii, we may also have a referral bias.

As a result of our study as well as prior reports by Kus et al and Clark et al, Filipino ethnicity should be considered to portend a more adverse prognosis (17, 18). Therefore, these patients who develop thyroid cancer should be treated aggressively and closely monitored. Additionally, although it the pilot project analyzed only 10 biospecimens of Filipinos with thyroid cancer, it appears promising that BRAF and eIF4E may be more frequent in this distinct population and should be expanded to include other ethnicities.

In conclusion, we have reported for the **first time** that Filipino ethnicity is associated with a worse survival in thyroid cancer. Furthermore, our initial observation from the molecular analysis on thyroid cancer specimens demonstrated that the MAPK and mTOR signaling pathways may be a potential negative prognostic determinant. Therefore, our findings necessitate further investigation on a larger scale by including thyroid cancer patients in the entire State of Hawaii and elucidating if these biologic factors may account for ethnic disparity.

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Table 1: **Demographic and clinic-pathologic characteristics of subjects: distinct ethnicities.**

Ethnicity	Age	Female	Stage 1	2	3	4	Unknown	T4 Status
All n= 622	49.6	473 (76.0%)	303 (48.7%)	74 (11.9%)	99 (15.9%)	51 (8.2%)	95 (15.3%)	100 (16.1%)
Caucasian n= 115	48.2	77 (67%)	63 (54.8%)	11 (9.6%)	19 (16.5%)	7 (6.1%)	15 (13%)	17 (14.8%)
Chinese n= 46	52	40 (77%)	25 (54.3%)	6 (13%)	7 (15.2%)	4 (3.5%)	4 (3.5%)	8 (17.4%)
Japanese n= 133	54.7	103 (77.4%)	59 (44.4%)	19 (14.3%)	21 (15.8%)	14 (10.5%)	30 (22.6%)	24 (18.0%)
Hawaiian n= 84	45.6	64 (76.2%	45 (53.6%)	12 (14.3%)	9 (10.7%)	6 (7.1%)	13 (15.5%)	7 (8.3%)
Pac.Islander n= 39	47.9	26 (66.7%)	15 (38.5%)	6 (15.4%)	7 (17.9%)	3 (7.7%)	8 (20.5%)	12 (30.8%)
Filipino n= 136	49.7	104 (76.5%)	60 (44.1%)	15 (11%)	23 (16.9%)	12 (8.8%)	36 (19.1%)	23 (16.9%)

Table 2: Demographic and clinic-pathologic characteristics of patients: Filipino vs. non-Filipino.

	Filipino	**Non-Filipino**
Mean Age (yr)	**49.7**	**50.0**
Gender (female)	**104 (76.5%)**	**369 (75.9%)**
Tumor size (cm)	**2.4**	**2.2**
Histologic type		
Papillary	**107 (78.7%)**	**412 (84.8%)**
Follicular	**18 (13.2%)**	**42 (8.6%)**
Oncocytic	**2 (1.5%)**	**12 (2.5%)**
Medullary	**1 (0.7%)**	**7 (1.4%)**
Anaplastic	**3 (2.2%)**	**7 (1.4%)**
Other	**5 (3.7%)**	**6 (1.2%)**
Stages		
I	**60 (44.1%)**	**243 (50%)**
II	**15 (11.0%)**	**59 (12.1%)**
III	**23 (16.9%)**	**76 (15.6%)**
IV	**12 (8.8%)**	**39 (8.0%)**
Unknown	**26 (19.1%)**	**69 (14.2%)**
T4 disease	**23 (16.9%)**	**77 (15.8%)**

Table 3: BRAF oncogene mutation in representative Filipino cohort

Age (yrs)	Gender	Type	Size (cm)	Extension	Stage	BRAF
57	female	PTC	2.7	+	IVA	positive
55	male	PTC	3.5	+	III	positive
59	female	PTC	2.0	+	III	positive
55	male	PTC	5.0	+	III	positive
49	female	PTC	4.0	+	III	positive
35	female	PTC	1.4	+	I	positive
67	male	PTC	0.7	+	III	positive
45	female	PTC	1.2	+	III	positive
42	female	PTC	2.5	+	I	positive
87	male	PTC	1.6	+	III	positive

Table 4: eIF4E protein expression in representative Filipino cohort

Age (yrs)	Gender	Type	Size (cm)	Extension	Stage	eIF4E
57	female	PTC	2.7	+	IVA	2+
55	male	PTC	3.5	+	III	2+
59	female	PTC	2.0	+	III	2+
55	male	PTC	5.0	+	III	2+
49	female	PTC	4.0	+	III	2+
35	female	PTC	1.4	+	I	2+
67	male	PTC	0.7	+	III	2+
45	female	PTC	1.2	+	III	1+
42	female	PTC	2.5	+	I	2+
87	male	PTC	1.6	+	III	1+

Figure 1: Ethnic distribution of thyroid cancer in study cohort

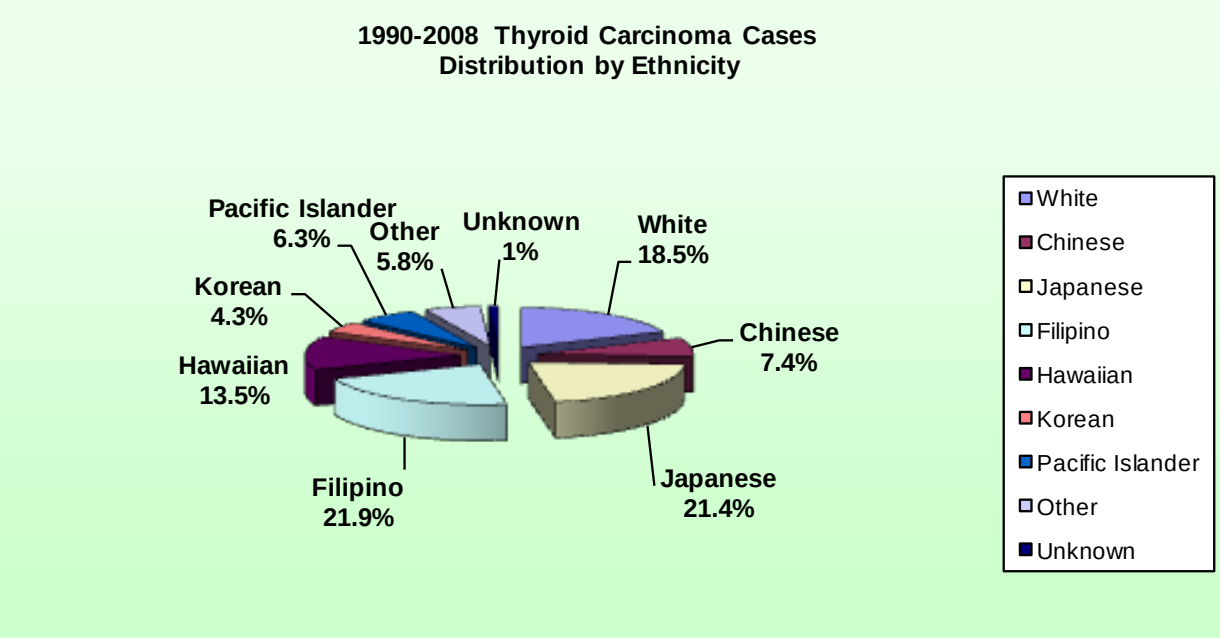


Figure 2: Overall survival stratified by ethnicity

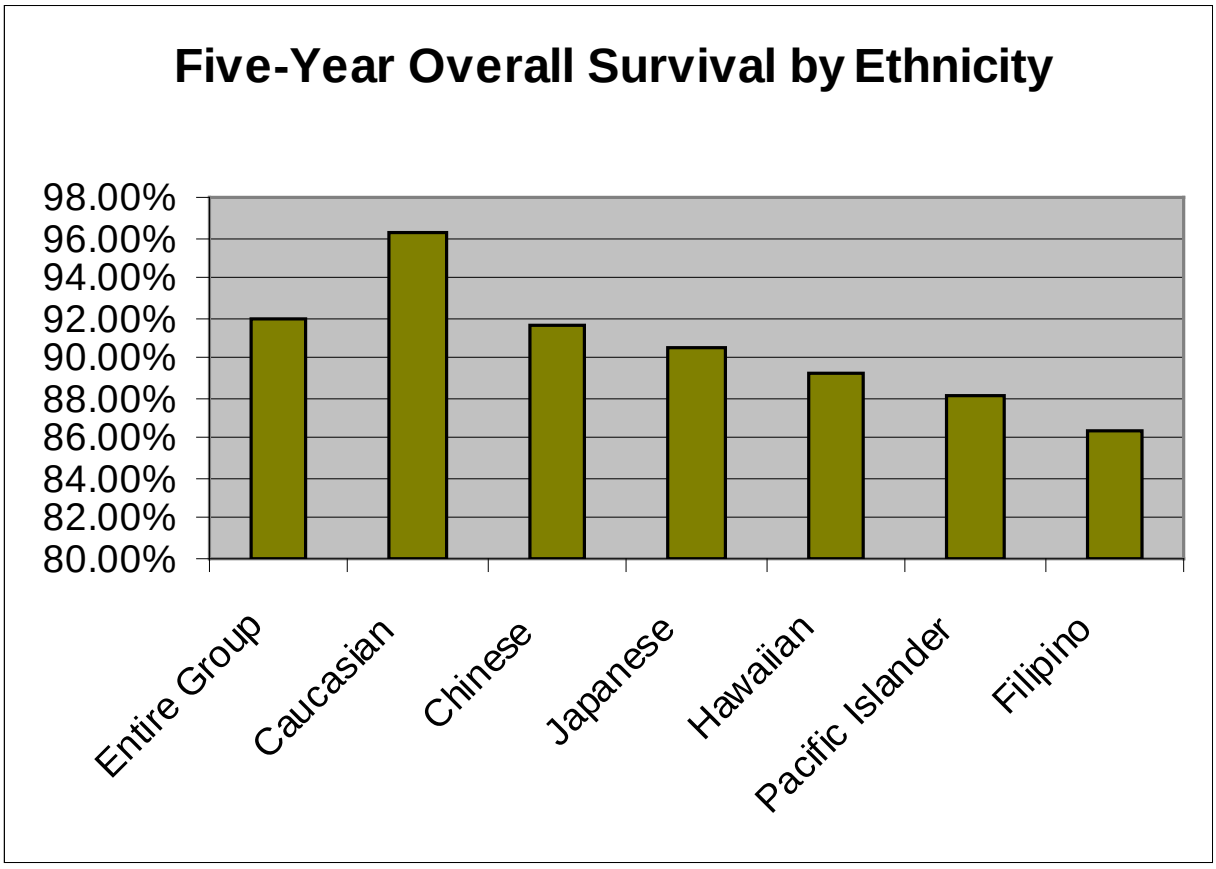
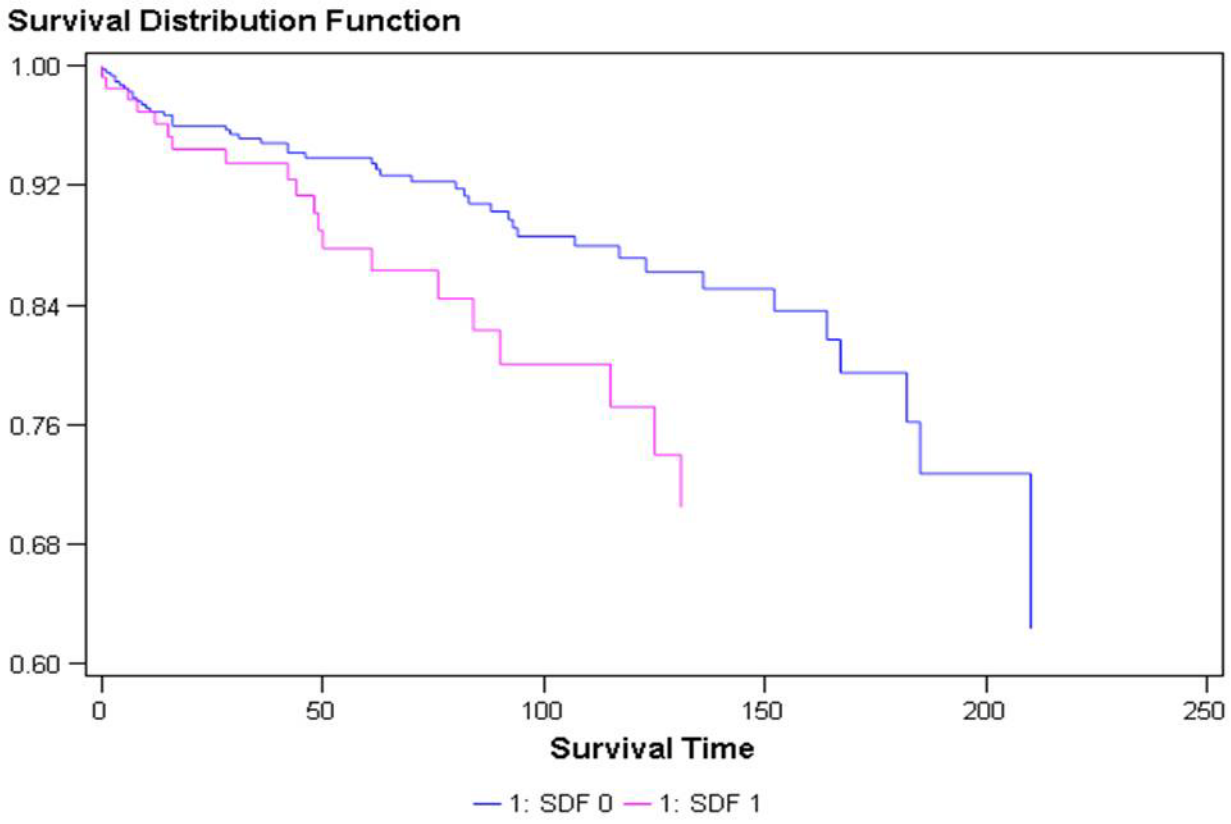
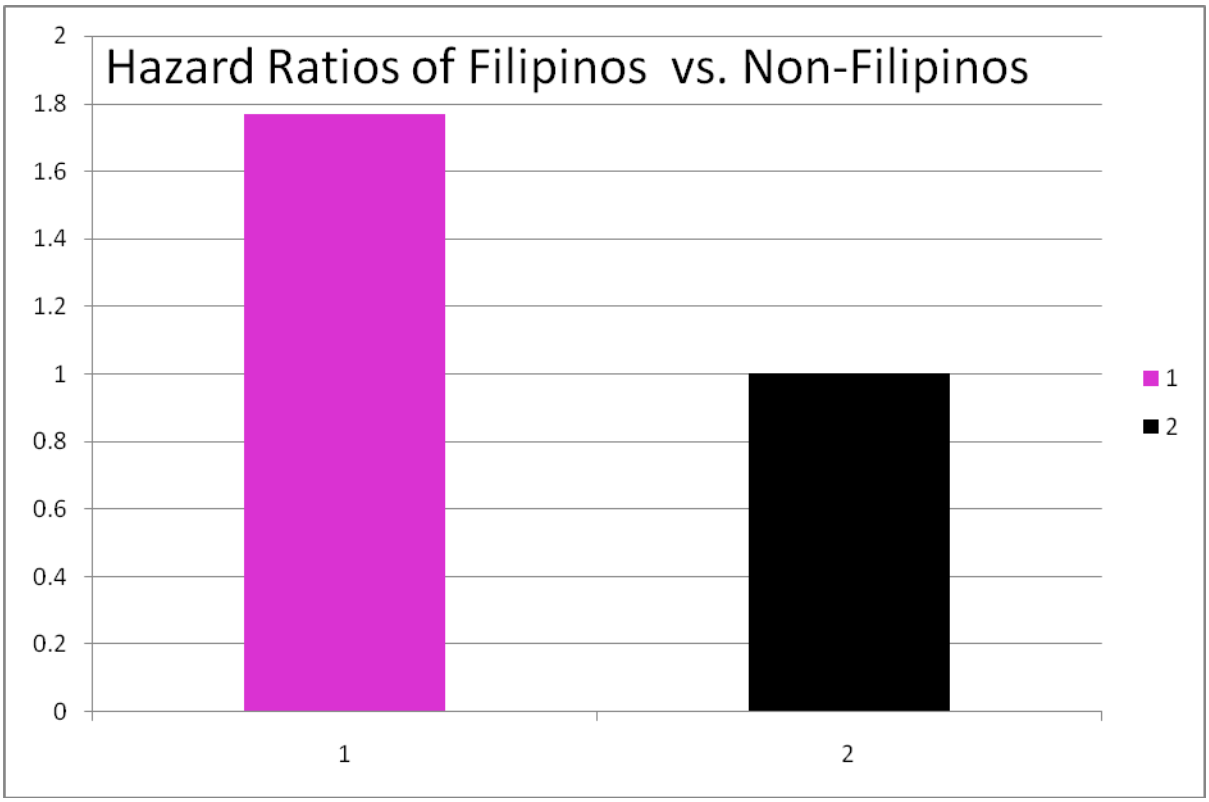


Figure 3: Survival comparing Filipinos vs. Non-Filipinos (un-adjusted)



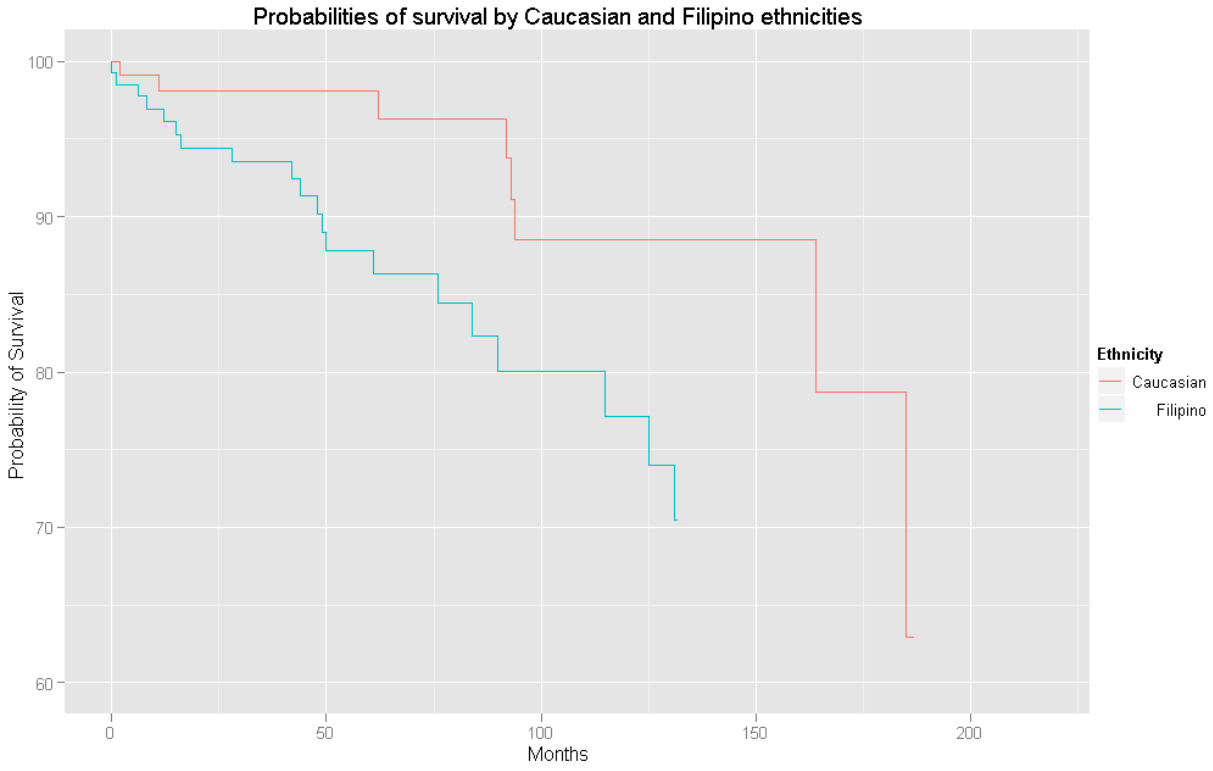
P value is 0.05 unadjusted. Filipinos (purple) had a worse survival than non-Filipinos (pink).

Figure 4: Hazard Ratios of Filipinos vs. Non-Filipinos (adjusted)



Filipinos (pink) independently have a worse outcome even when adjusted for age, gender, stage, and extra-thyroidal extension (P-value < 0.039)**.**

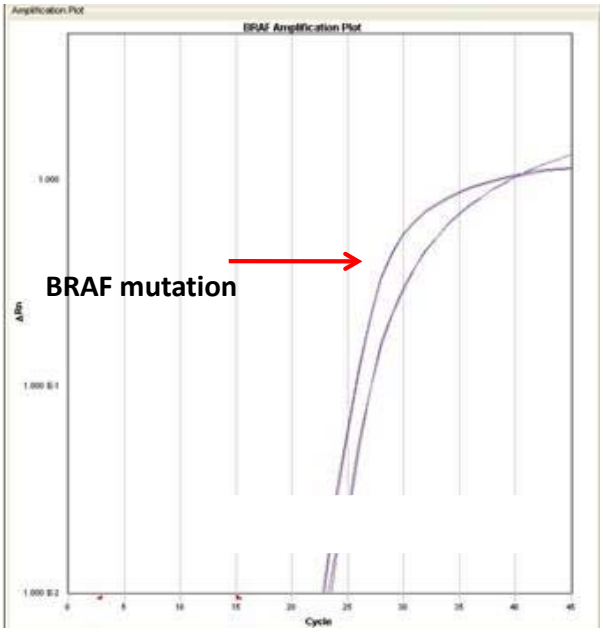
Figure 5: Survival comparing Filipinos vs. Caucasians



P value is 0.045 unadjusted and 0.061 adjusted. Filipinos (aqua) had a worse survival when compared to Caucasians (red).

Figure 6: PCR for BRAF oncogene

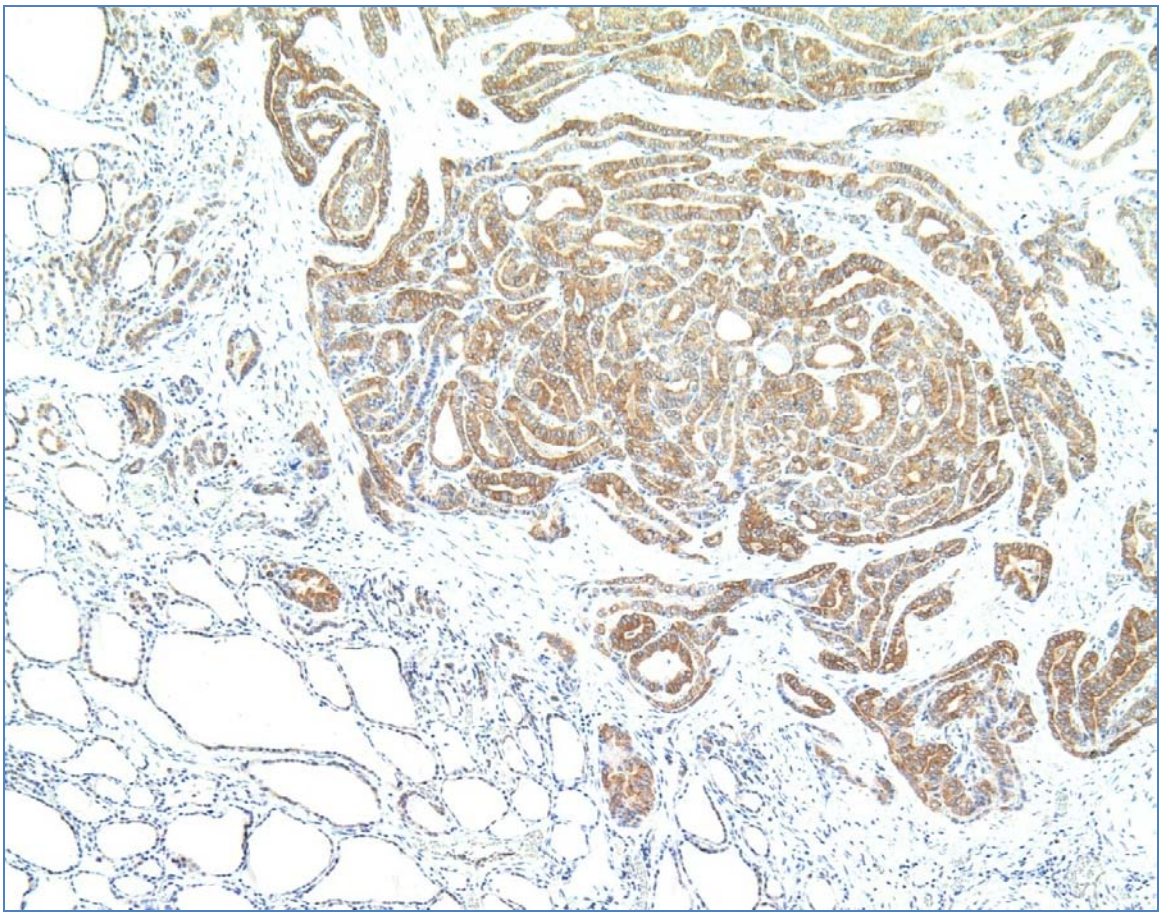
BRAF via PCR



Performed at Clarient Inc., Aliso Viejo, CA

Mutation signal for BRAF. Performed at Clarient, Inc., Aliso Viejo, CA.

Figure 7: IHC for eIF4E protein



High expression for eIF4E. Performed at QMC, Honolulu, HI.