Demographic, treatment, and survival patterns for Native Hawaiians with lung cancer treated at a community medical center from 1995 to 2001

Abstract: Lung cancer is the leading cause of death from cancer among persons of Native Hawaiian ancestry. Because a large number of Native Hawaiian patients with cancer are treated at this hospital, a single-institution review was conducted to compare recent nonsmall cell lung cancer (NSCLC) survival and treatment patterns in Native Hawaiian and non-Native Hawaiian patients. A total of 1,394 cases of NSCLC registered between January 1995 and December 2001 were reviewed; of those, 229 patients self-reported Native Hawaiian ancestry. Independent predictors of survival were determined by proportional hazards regression modeling. The median age at diagnosis for all cases of NSCLC, and for males and females separately, was significantly lower for Native Hawaiian vs. non-Native Hawaiian patients. Although there were no significant differences in the distribution of cancer stage, the median age at diagnosis at each stage was also significantly lower for Native Hawaiian vs. non-Native Hawaiian patients. A higher proportion of patients were women in the Native Hawaiian group. Differences in the time to receiving primary treatment, or the proportions receiving surgery, radiation therapy, or chemotherapy, for each stage of disease, were not significant. Controlling for age, gender, stage and Native Hawaiian ancestry was associated with an increased mortality risk. An observed higher mortality risk from NSCLC for Native Hawaiians was not associated with differences in treatment as appropriate for stage, nor with delays in treatment; this suggests other factors, including environmental or biological influences, as contributors to unfavorable lung cancer outcomes among Native Hawaiians. *Key Words*: histology, Pacific Islanders, oncology

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Introduction

Cancer is the second leading cause of mortality in Hawai'i, and, among those with cancer, persons of Native Hawaiian ancestry experience disproportionately higher mortality rates compared to other groups¹. These disproportionate rates among Native Hawaiians occur along with the lower life expectancy and higher standardized mortality^{2,3}. Moreover, Native Hawaiians have lower survival rates for similar cancers when compared to other ethnic groups in Hawai'i^{3,4}. Because a large number of Native Hawaiians are treated for cancer at this institution, and because data from this institution is being collected as part of the national cancer database, there is an opportunity to better understand and address the unequal burden of cancer borne by Native Hawaiians.

Nationally, lung cancer is the leading cause of cancer death for both men and women⁵. Lung cancer is also the most frequently diagnosed cancer in Native Hawaiian males, and the second most frequently diagnosed cancer in Native Hawaiian females⁴. Relative to other ethnic groups in Hawai⁴, there are disproportionately high incidence and

mortality rates from lung cancer for persons of Native Hawaiian ancestry, with males having mortality rates 1.4 -1.6 times higher than Filipino, Chinese, and Caucasian males, and nearly two times higher than Japanese males⁶. In studies of ethnic minorities on the Continental United States, differences in lung cancer mortality rates have been associated with significant socioeconomic disparities and differences in treatment. In one study, a lower rate of stageappropriate surgical treatment was associated with a higher mortality rate among African-American patients with lung cancer, even though survival rates in African-Americans who had received stage-appropriate treatments were similar to survival rates in Caucasians⁷. Another study found that patients with Stage I lung cancer were less likely to be treated if they were African-American or of lower socioeconomic status⁸. These findings suggest that the lower survival rate among African-American patients with earlystage NSCLC is largely attributable to the lower rate of appropriate treatments in this group.

Within this context, the present study analyzed data from a single large metropolitan hospital in Hawai'i (The Queen's Medical Center, Honolulu) to determine whether there were any observable differences in stage-specific treatments for lung cancer received by patients of Native Hawaiian ancestry compared to patients of non-Hawaiian ancestry. The study also sought to compare the mortality risk from lung cancer for Native Hawaiian and non-Native Hawaiian patients, controlling for known independent predictors of survival in lung cancer. We limited our observations to the most common type of lung cancer, non-small cell lung cancer (NSCLC), the type also most closely associated with smoking behavior.

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Method

Institutional review board approval was obtained prior to conducting this study. The Queen's Medical Center (QMC) Oncology Data Registry (ODR) collected data on 1,394 persons diagnosed with NSCLC from 1995 to 2001, accounting for approximately one-third of lung cancer cases registered in the state of Hawai'i during this period. The ODR collects data as part of the National Cancer Institute, Surveillance Epidemiology and End Results (SEER) program and the National Cancer Database (NCDB) program. The NCDB is a joint project of the Commission on Cancer (COC) of the American College of Surgeons (ACOS) and the American Cancer Society (ACS) and consists of a nationwide oncology outcomes database encompassing more than 1,500 hospitals in 50 states. Cancer staging conforms to the definitions provided by the American Joint Committee on Cancer (AJCC) Staging Manual, 5th edition9. Survival data was analyzed by the life-table or actuarial method (observed rate) as prescribed by the COC. Differences in proportions were evaluated for significance by the chi-square test. Proportional hazards regression modeling was used to determine individual predictors of mortality risk. All statistical analyses were performed using SPSS 10.2 (SPSS Inc., Chicago, IL). When appropriate, descriptive statistics and survival data were benchmarked to NCDB year 2000 demographic data.

Results

Age at diagnosis

Lung cancer accounted for 12% of all cancer cases registered at QMC during the period under study. The ethnic

Table 1. Racial Distribution of 1,394 Patients with NSCLC Treated at QMC from 1995 to 2001			
Ethnicity	Number (%)		
Caucasian	390 (28%)		
Japanese	325 (23%)		
Native Hawaiian	229 (16%)		
Filipino	171 (12%)		
Chinese	125 (9%)		
Korean	40 (3%)		
Samoan	19 (1%)		
Vietnamese	16 (1%)		
African-American	9 (0.6%)		
Other	79 (6%)		

distribution of NSCLC patients treated at QMC is shown in Table 1. Of the 1,394 patients diagnosed with NSCLC between January 1995 to December 2001, 229 patients were self-described as being of Native Hawaiian ancestry.

The differences in age at presentation between Native Hawaiian and non-Hawaiian patients were statistically significant for males, females, and both genders combined. The median age at diagnosis was 64 years for Native Hawaiian patients vs. 70 years for non-Native Hawaiian patients (p < 0.05). When genders were considered separately, the median age at diagnosis was 65 years for Native Hawaiian males vs. 70 years for non-Hawaiian males (p < 0.05), and the median age at diagnosis was 64 years for Native Hawaiian females vs. 70 years for non-Hawaiian males (p < 0.05), and the median age at diagnosis was 64 years for Native Hawaiian females vs. 70 years for non-Hawaiian females (p < 0.05).

Figure 1. Comparisons of Age Distribution. Peak lung cancer incidence for Native Hawaiian patients is between 60 and 69 years, compared to 70 and 79 years in non-Hawaiian patients and patients from the NCDB benchmark.



Age Distribution for NSCLC: Native Hawaiian vs. Non-Hawaiian at QMC, vs. NCDB 2000 Benchmark

[%] by Age Range

Pacific Cancer an	d Health	Studies
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Table 2. Median age at diagnosis for each AJCC stage			
	Median age at diagnosis, Native Hawaiian	Median age at diagnosis, Non- Native Hawaiian	p-value
Stage 1	67	73	< .05
Stage 2	64	71	< .05
Stage 3	63	69	< .05
Stage 4	63	69	< .05

Figure 1 shows the age distribution for NSCLC, comparing Native Hawaiian patients to non-Hawaiian patients at QMC and a national cohort of patients from the NCDB 2000 benchmark. There are higher proportions of patients of Native Hawaiian ancestry who presented with NSCLC between the ages of 30 to 39, 40 to 49, 50 to 59, and 60 to 69 years, with the peak incidence for NSCLC at 60-69 years of age in Native Hawaiian patients, compared to a peak incidence at 70 to 79 years for non-Hawaiian and NCDB patients.

Cancer stage and age

The proportions of patients presenting at the different stages of cancer are depicted in Figure 2. A marginally higher proportion of non-Native Hawaiian presented with Stage 4 cancer, but the differences were not significant. However, at each stage, the median age at diagnosis was significantly lower for the Native Hawaiian group compared to the non-Hawaiian group (Table 2).

Gender

Table 3 summarizes the gender distribution for NSCLC cases in Native Hawaiian and non-Hawaiian patients. Although men still make up the majority of NSCLC cases, the Native Hawaiian group has a significantly higher proportion of females compared to the non-Native Hawaiian group (46.7% vs. 39.2%, p < 0.05).

Histology

Lung cancer can be subclassified on the basis of histology. Traditionally, NSCLC is divided into adenocarcinoma, adenosquamous carcinoma, bronchioaveolar carcinoma, squamous cell carcinoma, large cell carcinoma, and undifferentiated carcinoma. The most common subtype in Native Hawaiian patients is adenocarcinoma (36%) followed by squamous cell carcinoma (20%). There was no significant difference in the distribution of cancer subtypes between Native Hawaiian and non-Hawaiian patients.

Time to Treatment and Treatments Received: The mean time to first primary treatment did not significantly differ between Native Hawaiian and non-Native Hawaiian patients (27.3 days vs. 28.0 days). The proportions of Native Hawaiians vs. non-Hawaiians receiving surgery, radiation, or chemotherapy were also not significantly different, even when data were examined by stage. Table 4 summarizes the types of treatments for NSCLC received by Native Hawaiian and non-Hawaiian patients for all stages combined.

Figure 2. Stage distribution for Native Hawaiian and non-Native Hawaiian NSCLC cases from QMC are not significantly different. Note: Compared to the NCDB benchmark, there are significantly fewer cases with unknown stage and more stage 3 cases in the Native Hawaiian cohort (p <0.05). Comparison of Stage Distribution for Native Hawaiians (NH), non-NH, and National Cancer Database (NCDB) 2000 Benchmark Data





Table 3. Gender distribution for Native Hawaiian vs. non- Native Hawaiian groups (QMC ODR 1995-2001)			
Count Percent	Male	Female	Total
Non-Native Hawaiian	708	457	1165
	60.7%	39.2%	
Native Hawaiian	122	107	229
	53.2%	46.7%	
Total	830	564	1394
	59.5%	40.5%	

Table 4. Primary treatments for NSCLC received by Native Hawaiian andnon-Native Hawaiian patients (all stages combined)

Treatment	Native Hawaiian	Non-Native Hawaiian
Surgery Only	33 (14.4%)	183 (13.1%)
Radiation Only	82 (35.8%)	560 (40.1%)
Chemotherapy Only	13 (5.7%)	73 (5.2%)
Surgery and Radiation	440 (19.2%)	286 (20.5%)
Chemotherapy and Radiation	11 (4.8%)	67 (4.8%)
Surgery, Radiation, and Chemotherapy	21 (9.2%)	146 (10.5%)
No treatment, or unknown	229 (10.9%)	79 (5.7%)

Table 5. Stage-specific median survival time for Native Hawaiian patients with NSCLC / Median Survival Time for Native Hawaiian patients with NSCLC at QMC: 1995-2001

Stage	Median Time (days)	Lower 95%	Upper 95%
Unknown (n=1)	322		
1 (n=49)	776	459	1034
2 (n=21)	532	368	856
3 (n=80)	314	272	391
4 (n=77)	123	90	169
Combined	296	250	329

Survival

Median survival time for Native Hawaiian patients at each cancer stage is summarized in Table 5. These survival figures account for all deaths, regardless of cause. This is known as the *observed* (or non-cause specific) survival rate. Alternatively, the survival rate accounting only for deaths attributable to lung cancer is known as the *adjusted* (or cancer-specific) survival rate. In this study, the *adjusted* and *observed* survival rates for NSCLC were similar, because lung cancer is usually the cause of death for patients with this diagnosis. In diseases with more favorable survival rates will tend to be higher than observed survival rates⁹.

Predictors of mortality risk

A Cox proportional hazards regression model for NSCLC survival was used to determine predictors of mortality in the study population. Table 6 summarizes the independent predictors of mortality determined from this model. As expected, earlier cancer stage was associated with a lower mortality risk, while increased age was associated with a significantly higher mortality risk. In this model, male gender was associated with a 1.12 times higher mortality risk even after controlling for other variables. This risk was statistically significant with confidence intervals (CI) set at 95% (p<0.05). The mortality risk was 1.23 times higher for individuals of Native Hawaiian ancestry compared to those of non-Native Hawaiian

ancestry, even after controlling for the independent effects of other identified factors influencing survival. When the model was adjusted so that the outcome in question was death from cancer, rather than death from any cause, Native Hawaiian ancestry remained a significant independent predictor of mortality in the model (RR 1.2, 95% CI 1-1.45).

Because the patients classified as non-Hawaiian in our study include a heterogeneous mixture of people of various ethnicities, it could be argued that the increased mortality risk ob-

served in Native Hawaiian patients may be attributable to a relatively lower risk of mortality in another ethnic subgroup. Therefore, we compared the mortality risk of Native Hawaiian patients against that of Caucasian patients, since Caucasians have served as a reference group in other studies examining relative mortality risk in ethnic minority groups^{7,8}. During the period from 1995 to 2001, there were 311 Caucasian patients with NSCLC treated at QMC. Compared to their Caucasian counterparts,

Native Hawaiian patients again demonstrated a statistically significantly higher mortality risk, controlling for the effects of age, gender, and stage. Table 7 summarizes the independent predictors of mortality when the data analysis was limited to include only Native Hawaiian and Caucasian patients.

Discussion

This study found a higher mortality from NSCLC among Native Hawaiian patients, relative to both non-Native Hawaiian and Caucasian patients, which was not explained by differences in age, gender, or stage at diagnosis. What else, then, can account for the higher mortality from NSCLC seen in patients of Native Hawaiian ancestry? In other studies of minority populations, it has been shown that factors related to interactions with the healthcare system played a role in survival, with either a delay in treatment or differences in the proportions of patients receiving stage-appropriate treatments as contributing to significant differences in outcome. Because hospital-based cancer registries contain detailed

Table 6. Independent predictors of mortality for 1,394 patients diagnosed with NSCLC at QMC between 1995 and 2001. CI= confidence interval

Term	Risk Ratio	Lower 95% Cl	Upper 95% Cl
Male Gender	1.12	1.05	1.19
Older Age	1.02	1.02	1.03
Hawaiian Ancestry	1.23	1.04	1.45
Stage 1	0.42	0.36	0.50
Stage 2	0.60	0.49	0.73
Stage 3	1.20	1.04	1.39
Stage 4	2.59	2.26	2.99

Table 7: Independent predictors of mortality determined from a proportional hazards regression model limited to Native Hawaiian and Caucasian patients diagnosed with NSCLC at QMC between 1995 and 2001. CI = confidence interval

Term	Risk Ratio	Lower 95% Cl	Upper 95% Cl
Male Gender	1.06	0.97	1.16
Older Age	1.02	1.01	1.03
Hawaiian Ancestry	1.11	1.01	1.23
Stage 1	0.37	0.28	0.49
Stage 2	0.52	0.38	0.71
Stage 3	1.17	0.95	1.46
Stage 4	2.49	2.03	3.10

information on the treatment of their patients, these databases can provide important information linking treatment to outcomes. We conducted an analysis of treatment and survival using a database from a single institution where a significant number of Native Hawaiian patients with cancer are treated. We did not find evidence supporting differences in the treatment of NSCLC between Native Hawaiian and non-Hawaiian patients that could explain differences in mortality risk. Specifically, the proportions of patients receiving surgery, radiation, or chemotherapy, for each stage of disease, and the time intervals between diagnosis and primary treatment were similar between Native Hawaiian and non-Hawaiian patients with NSCLC. Similar findings were reported in a study of American Indians in Washington State, where differences in treatment, stage of diagnosis, and residence in non-urban areas did not account for differences in survival outcome¹⁰. If differences in survival do not appear to be due to disparities in medical treatment, then other possibilities, including biological or environmental factors, should be considered.

Biological factors, including genetic polymorphisms of the genes encoding for enzymes that detoxify environmental carcinogens, may influence the risk of developing lung cancers in different ethnic groups¹¹⁻¹³. Such a factor may possibly explain the observed higher risk of developing lung cancer in Native Hawaiians who smoke, controlling for the number of pack-years of smoking¹⁴. However, this hypothesis may be difficult to substantiate, given that, in modern times, less than ten percent of the Native Hawaiian population can be classified as being of predominant Hawaiian ancestry. The genetic diversity across people who claim Native Hawaiian ancestry is likely to have diluted the effect of any genetic predisposition for developing lung cancer. That same argument can be applied if it is hypothesized that people of Native Hawaiian ancestry have biologically-related suboptimal responses to specific treatments such as chemotherapy or radiation therapy.

> Presently, people of Native Hawaiian ancestry may be more closely related through social, cultural, and geographic factors rather than genetics. This raises the possibility for environmental factors, potentially influenced by socio-demographic factors, contributing to earlier age at diagnosis, a gender predisposition for lung cancer in women, and poorer overall survival statistics. As an environmental factor, smoking has the greatest causal association with lung cancer.

> Tobacco is a potent carcinogen that accounts for the majority of all lung cancers^{15,16}. The risk for developing lung

cancer has been directly related to the quantity of cigarettes smoked¹⁷. The incidence of lung cancer follows demographic patterns in cigarette smoking, and exposure to smoking can vary significantly by ethnic subgroups. Different ethnic groups may also be differentially targeted as consumers by the tobacco industry. For example, a review of tobacco industry documents found that tobacco advertising and promotion strategies during the 1980s were specifically directed at Asians and Pacific Islanders^{18,19}.

This study found that patients of Native Hawaiian ancestry were being diagnosed with NSCLC at a younger age. This younger age at presentation was not associated with a difference in the proportions of patients diagnosed at the different stages of cancer. Rather, at each stage, the median age at diagnosis was significantly lower for Native Hawaiian patients compared to non-Hawaiian patients. In other words, Native Hawaiian patients appear to be developing lung cancer at an earlier age compared to non-Hawaiian patients, and that the lower mean age at presentation is not related to a disproportionate number presenting at any one stage of the disease.

In addition to stage, NSCLC can be sub-classified on the basis of histologic subtype. This study found the distribution of histologic subtypes of cancer in Native Hawaiian and non-Native Hawaiian patients to be similar, with the most common sub-type being adenocarcinoma. This sub-type is very strongly associated with tobacco use, and is the most common lung cancer in females^{15,16, 20}. Although there are slight variations in the biology and natural history of the various subtypes, cancer stage at the time of presentation is a more important predictor of survival²¹. In agreement with this observation, histological sub-type was not an important independent predictor of higher mortality risk in our multivariable analysis.

Given the earlier age at presentation shown in our study, it is possible that Native Hawaiians may be exposed to smoking earlier or with greater intensity. It has been reported that a significant proportion of Native Hawaiians, as well as other Asians and Pacific Islanders, start smoking at an earlier age²². The 2002 Behavioral Risk Factor Surveillance Survey (BRFSS) revealed that Native Hawaiians also have the highest proportions of current smokers (34%) compared to other ethnic groups in Hawaii (21% of Caucasians, 20% of Filipino, 16% of Japanese). However, this data has not been directly linked to data on cancer incidence. Smoking is also higher among other indigenous populations, including American Indians and Alaska Natives²³. These groups may also share the same high incidence rates for lung cancer seen in Native Hawaiians²⁴.

The finding that Native Hawaiians may be at risk for earlier presentations of lung cancer may assist in altering perceived susceptibility, perceived seriousness, and the perceived benefits of taking action²⁵. This conclusion is congruent with other studies that suggest primary prevention (e.g. prevention of smoking initiation) as a better policy aim than secondary or tertiary prevention, particularly since survival following a diagnosis of NSCLC is poor despite treatment^{26,27}. Education regarding earlier presentation enhances the likelihood of earlier diagnoses and interventions, including behavioral risk factor modification such as smoking cessation. Cancer education may also reduce the perceived barriers to seeking care, provide cues to action, and increase self-efficacy. Understanding three key factors may assist in the design of future health education curricula that target Native Hawaiians who smoke: the role of smoking in the pathophysiology of most lung cancers, improved outcomes that result from presenting at an earlier age, and poorer survival times among Native Hawaiians 28.

The analysis performed in this study was limited to data from a single hospital. Although this institution's registry collects data on a significant portion of the patients with cancer in the state of Hawai'i, the study mainly reflects the treatment and survival patterns at this institution; thus, its conclusions may not generalize to other centers. It is also worth noting that the study analysis is limited to patients that have already sought and received medical treatment. Therefore, the patients included in this study have already overcome a potential obstacle that can significantly affect cancer survival. Our statistics consequently do not reflect the potentially large group of Native Hawaiians who have cancer but have not engaged the healthcare system for various reasons. Therefore, it is possible that the true disparity in mortality risk may be significantly greater than determined by this study. This highlights the importance of a systematic data collection on cancer incidence and mortality for Native Hawaiians and other Pacific Islanders.

Although socioeconomic factors are obviously important contributors to differences in healthcare access, a focus group of Native Hawaiians with cancer have identified other factors that may also determine successful interactions with healthcare services and the maintenance of proactive health behaviors. Such factors include the incorporation of Hawaiian traditions and values, including the deep belief that strength is derived from spirituality and a reliance on family²⁹. Therefore, once the initial barrier to engaging the healthcare system is overcome, there are important factors, both positive and negative that need to be addressed in order to improve cancer-related outcomes among Native Hawaiians. In order for cancer prevention and control programs to be successful, information and treatment must be disseminated in a culturally compatible manner.

Conclusion

At one institution, patients who are of Native Hawaiian ancestry appear to present with NSCLC at a younger age, with a disproportionate number being female. Native Hawaiian ancestry was also associated with poorer survival, controlling for differences in age, gender, and stage distribution. However, the greater mortality risk experienced by Native Hawaiian patients was not associated with differences in the proportions receiving appropriate treatments or any delay in the delivery of primary treatments. This leads us to suspect other factors, including environmental or biological influences, as a possible explanation for the observed differences in presentation and survival, with smoking being the most plausible causative factor.

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