COLORECTAL CANCER SURVIVAL AMONG AMERICAN INDIAN AND ALASKA NATIVE PEOPLE IN THE PACIFIC NORTHWEST

By

Paneen S. Petersen

A THESIS

Presented to the Department of Public Health & Preventive Medicine
and the Oregon Health & Science University
School of Medicine
in partial fulfillment of
the requirements for the degree of

Master of Public Health

November 2011

Department of Public Health and Preventive Medicine

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

Paneen S. Petersen

has been approved

Thomas Becker, MD, PhD

Jodi Lapidus, PhD

Victoria Warren-Mears, PhD, RD, LD

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LIST OF ABBREVIATIONS

AI/AN	American Indian and Alaska Native
CDRI	Cancer Disease Registry of Idaho
CRC	Colorectal Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IHS	Indian Health Service
NAACCR	North American Association of Central Cancer Registries
NCI	National Cancer Institute
NHW	Non-Hispanic White
NPAIHB	Northwest Portland Area Indian Health Board
NTR	Northwest Tribal Registry
OSCaR	Oregon State Cancer Registry
SEER	Surveillance, Epidemiology and End Results
WSCR	Washington State Cancer Registry

ACKNOWLEDGEMENTS

Foremost, I would like to express my sincere gratitude to Dr. Thomas Becker, for the continuous support of my educational endeavors, for his patience, motivation, and humor. I would also like to thank the rest of my thesis committee: Dr. Jodi Lapidus, and Dr. Victoria Warren-Mears.

My sincere thanks also goes to Megan Hoopes for providing me a summer internship opportunity with the Northwest Portland Area Indian Health Board (NPAIHB), and for letting me pursue my interest in cancer survival with the Northwest Tribal Registry Project. Other people at the NPAIHB have been very helpful in my work, in addition to being pleasant to be around: Dr. Thomas Weiser, Eric Vinson, Chris Sanford, and Clarice Charging.

I received scholarship support for my studies from the NPAIHB's Northwest Native American Research Center for Health (NARCH); a program made possible by funding from the Indian Health Service and National Institutes for Health. I would like to thank them for their generous investment in my epidemiologic training.

To my friends in Alaska who supported me with care packages, thank you for the smoked salmon, bowhead whale, dried sheefish, and pilot bread.

Last but not least, I would like to thank my family. Especially CoCo and Pingo.

ABSTRACT

Background – Colorectal cancer is the second leading cause of cancer-related deaths and the third most common cancer in both men and women within the U.S. American Indian and Alaska Native (AI/AN) population. The calculation of cancer incidence, mortality, and survival for an overall AI/AN population in the U.S. obscures the heterogeneity in cancer burden within the AI/AN population at local or regional levels. Studies at state and regional levels have documented variation in colorectal cancer mortality within the AI/AN population. AI/AN people have also been reported to be more likely to be diagnosed at later stages of colorectal cancer as well as having a greater risk of colorectal cancer mortality than non-Hispanic White people. Local level or regional data on cancer survival are more informative for state and tribal communities in the development of strategies for the control of cancer.

Methods – Using data with improved AI/AN racial ascertainment from record linkages performed between the Northwest Tribal Registry and Oregon, Washington, and Idaho state cancer registries, we compared invasive colorectal cancer survival between AI/AN and non-Hispanic White (NHW) races. We used Kaplan-Meier estimates and a multivariable Cox proportional hazards model to analyze the association of race with survival for AI/AN and NHW cases of invasive colorectal cancer in Washington, Idaho, and Oregon. Cases included diagnoses from January 1, 1998, through December 31, 2006 and follow-up of cases from January 1, 1998, through December 31, 2007.

Results – Four hundred fifty-three *(*453) AI/AN cases and 37,433 NHW cases were included for analysis. Cases from Washington made up the largest percentage of AI/AN cases in the Pacific Northwest. AI/AN cases tended to be diagnosed at an earlier age than

NHW cases. Unadjusted Kaplan-Meier estimates indicated that AI/AN experience poorer 1- and 5-year survival than NHW. After adjusting for age, sex, and stage of diagnosis, the risk of colorectal cancer-related death after diagnosis of invasive colorectal cancer was greater in AI/AN cases compared to NHW cases (hazard ratio 1.34, 95% CI 1.14-1.57). The adjusted 1-year survival proportion for AI/AN (0.88, 95% CI 0.86-0.90) was lower than NHW (0.91, 95% CI 0.90-0.92). The adjusted 5-year survival proportion for AI/AN (0.48, 95% CI 0.42-0.54) was lower than NHW (0.57, 95% CI 0.56-0.59). Male cases experienced poorer survival than female cases in both AI/AN and NHW races, but this difference was not statistically significant.

Conclusions – Our study suggests that AI/AN people experience poorer survival than NHW people after invasive colorectal cancer diagnosis in the Pacific Northwest. The disparity between races in risk of death from invasive colorectal cancer persists after adjustment for age, sex, and stage of diagnosis.

INTRODUCTION

According to the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program cancer surveillance data, approximately 142,570 cases of colorectal cancer were diagnosed in the United States in 2010 (National Cancer Institute, 2011). Colorectal cancer is the second leading cause of cancer-related deaths in the U.S. and the third most common cancer in both men and women (U.S. Cancer Statistics Working Group, 2010). This ranking is also reflected in the overall American Indian and Alaska Native (AI/AN) population, but colorectal cancer incidence and mortality has been reported to be lower in AI/AN relative to the total U.S. population (Swan & Edwards, 2003). However, AI/AN have also been reported to be more likely to be diagnosed with Stage III or IV colorectal cancer as well as having a greater risk of colorectal cancer mortality than non-Hispanic Whites (Chien, Morimoto, Tom, & Li, 2005).

The U.S. AI/AN population is not a homogenous group with respect to culture, language, or health behaviors. The United States government currently recognizes five hundred sixty-four distinct tribes within the contiguous United States and Alaska (Bureau of Indian Affairs, 2010). Grouping all AI/AN into one category obscures important differences in the health risk profiles of AI/AN subgroups (Steele, Cardinez, Richardson, Tom-Orme, & Shaw, 2008). Similarly, the calculation of cancer measures for an overall AI/AN population in the United States obscures the heterogeneity in cancer burden within the AI/AN population at local or regional levels (Swan & Edwards, 2003). Studies at state and regional levels have documented variation in colorectal cancer incidence and survival within the AI/AN population (Bleed, Risser, Sperry, Hellhake, & Helgerson,

1992; Brown, Lanier, & Becker, 1998; Harwell, Miller, Lemons, Helgerson, & Gohdes, 2006). A linkage study utilizing SEER and Indian Health Service (IHS) records reported colorectal cancer incidence rates (per 100,000 persons per year) in AI/AN people that showed as much as 5-fold variation regionally for the period 1999-2004 (Perdue et al., 2008). The overall colorectal cancer incidence rate in the same SEER study was 9% lower in the AI/AN population relative to non-Hispanic Whites (NHW) (Perdue et al., 2008).

Measures of incidence, mortality, and survival are integral to cancer surveillance and form a basis for cancer research as well as for cancer prevention and control (Swan & Edwards, 2003). Accuracy and completeness of data are key issues that affect the quality of cancer surveillance within the AI/AN population. The SEER program reports coverage of only 43% of the U.S. AI/AN population (National Cancer Institute, 2011). A lack of full population coverage and small AI/AN case numbers can create instability in rates of incidence, mortality, and survival (Swan & Edwards, 2003). Furthermore, misclassification of race in population-based cancer registries has been reported to result in an underenumeration of AI/AN cases (Becker et al., 2002; Espey et al., 2008; Frost, Taylor, & Fries, 1992; Hoopes, Taualii, Weiser, Brucker, & Becker, 2010; Johnson et al., 2009; Puukka, Stehr-Green, & Becker, 2005; Wiggins et al., 2002). AI/AN people tend to be misclassified in administrative data more frequently than other racial/ethnic groups (Boehmer et al., 2002). Previous cancer studies have used record-linkages between Tribal or Indian Health Service and population-based cancer registries to improve AI/AN racial ascertainment in cancer data (Becker et al., 2002; Foote, Matloub, Strickland,

Stephenson, & Vaughan-Batten, 2007; Hoopes et al., 2010; Johnson et al., 2009; Partin et al., 1999; Perdue et al., 2008; Sugarman, Holliday, Ross, Castorina, & Hui, 1996).

In 2003, the Northwest Portland Area Indian Health Board (NPAIHB) Northwest Tribal Registry (NTR) Project began collaborating with the Cancer Disease Registry of Idaho (CDRI), the Oregon State Cancer Registry (OSCaR), and the Washington State Cancer Registry (WSCR) to permanently correct AI/AN race data. NTR staff performed record linkages using an AI/AN patient list obtained from the Portland Area Office of the Indian Health Service (IHS). Records from the Seattle Indian Health Board have supplemented the NTR patient listing since 2008. NTR linkages have been performed annually since 2003 to improve racial data within each of the three state cancer registries. In a previous NTR linkage study, AI/AN race misclassification was assessed and cancer incidence and incidence-based mortality were calculated for the Pacific Northwest (Idaho, Oregon, and Washington). During the period 2003-2007 in the Pacific Northwest, their results showed a significantly higher incidence of colorectal cancer among Washington AI/AN people (56 per 100,000) compared to Washington non-Hispanic White people (44 per 100,000). During the same period, incidence-based mortality was found to be highest among Pacific Northwest AI/AN people living in Idaho. Observed variations in incidence and incidence-based mortality in the Pacific Northwest region affirmed that local level cancer data, when available, are more informative for state and tribal communities in the development of strategies for the prevention and control of cancer.

The objective of the present study was to calculate and compare invasive colorectal cancer survival between AI/AN and NHW races in the Pacific Northwest using

data with improved AI/AN racial ascertainment from the NTR linkages performed with the CDRI, the OSCaR, and the WSCR. Net survival is a useful measure when comparing survival between populations with different life expectancies, and serves to filter out the effect of mortality from causes other than the disease in question. Two methods used to calculate net survival are cause-specific survival and relative survival. Relative survival is commonly used in the analysis of cancer registry data to avoid potential bias from the misclassification of cancer-related causes of death. When cause of death is extracted from death certificates (a source routinely used by cancer registries), an underestimation of cancer mortality has been shown to occur (Begg & Schrag, 2002). The calculation of relative survival is dependent upon obtaining the expected survival of a comparable population, typically from published life tables. The Centers for Disease Control and Prevention's National Center for Health Statistics publishes life tables for White and Black races, but not from other racial groups such as AI/AN people. Cause-specific survival is the alternative approach, and although it is subject to potential bias from cause of death misclassification, it may provide more accurate survival estimates for minority racial subgroups such as AI/AN (Howlader et al., 2010). In this study we used a cause-specific survival approach for analysis.

METHODS

This analysis is a population-based study of cancer-specific survival in invasive colorectal cancer cases from Oregon, Washington, and Idaho. Data used for this study include racial data from the three state cancer registries that was enhanced through record-linkages with the Northwest Tribal Registry (NTR). The NTR is a listing of the

AI/AN population within the Portland Indian Health Service administrative area (Idaho, Oregon, and Washington) that is maintained and regularly updated by the Northwest Portland Area Indian Health Board's (NPAIHB) Registry Project.

Study Population

The purpose of this study was to compare invasive colorectal cancer survival between NHW people and AI/AN people in the Pacific Northwest. Included for analysis were male and female subjects classified as NHW or AI/AN, living within Idaho, Oregon, or Washington at time of diagnosis, and diagnosed with invasive cancer with the colon or rectum as primary cancer site per the SEER Site Recode for ICD-O-3 Definition (National Cancer Institute, 2003). Cases included diagnoses from January 1, 1998, through December 31, 2006 and follow-up of patients from January 1, 1998, through December 31, 2007. The total number of AI/AN and NHW invasive colorectal cancer cases was 42,927. Unstaged cases (n=1821) were excluded from analysis, as well as cases whose duration of survival could not be determined because of missing data (n=3220). This resulted in 11.7% of cases being excluded from analysis.

Data Sources

Northwest Tribal Registry (NTR)

The Northwest Tribal Registry (NTR) is derived from the Portland Area Indian Health Service (IHS) registration file, and includes all AI/AN who received services from a federally operated IHS or tribal health care facility in the area between 1986 and December 2009. IHS eligibility is based on tribal membership or descent from an

enrolled member of a federally recognized tribe, therefore all patient records in the NTR are of documented AI/AN ancestry. NTR data have been supplemented with the AI/AN patient registry of the largest urban Indian health clinic in the Pacific Northwest through a partnership with the Seattle Indian Health Board.

State Cancer Registries for Idaho, Oregon, and Washington

The Washington State Cancer Registry (WSCR), Cancer Data Registry of Idaho (CDRI), and Oregon State Cancer Registry (OSCaR) have been active as population-based cancer registries since 1992, 1992, and 1996, respectively. Cancer case information is reported to the three state cancer registries from a variety of sources that include hospitals and other health care facilities, pathology laboratories, ambulatory surgery centers, freestanding radiation and oncology centers, other state cancer registries, vital statistics, and medical clinics and health care providers who diagnose and/or treat cancers or conditions that meet the criteria for reporting. Each of the three state registries has achieved certification of adherence to quality control standards set by the North American Association of Central Cancer Registries (NAACCR) for the period 1997 to 2007 (NAACCR, 2010). Data from each of the registries were matched against state death certificate files to improve ascertainment of vital status and cause of death prior to linkage with the Northwest Tribal Registry. Data collected by the state cancer registries include: (a) patient and facility demographics information; (b) cancer identification; (c) staging or extent of disease information at the time of diagnosis; (d) treatment information; (e) follow-up information including vital status, date of last contact, and tumor status.

Portland Area Indian Health Board Northwest Tribal Registry Project Cancer File

In 2010, the Northwest Tribal Registry Project used probabilistic linkage software Link Plus (version 2.0; Atlanta, GA), developed by the Centers for Disease Control and Prevention, to compare the AI/AN patient list of the NTR against cancer cases from the CDRI (1992-2008), the OSCaR (1996-2009), and the WSCR (1992-2009). The most recent complete year of cancer data for all three state cancer registries at the time the 2010 linkages were performed was 2007. The same match parameters were used in the NTR linkages with each of the cancer registries. Matches deemed uncertain by the linkage software were reviewed manually by two NTR Project staff members and categorized as "true" or "false". A de-identified dataset with a limited number of covariates was retained for analysis from each of the three state cancer registries. Data retained by the NTR Project include both matched and non-matched cancer cases, with a race classification variable that indicates post-linkage corrected race. All NTR matched cases, plus non-matched records coded as AI/AN in the state cancer registries were treated as AI/AN race in analysis. Data received from the NTR Project were not further evaluated for racial misclassification in our study.

Definition of Variables

Survival time (in months) was calculated from the variables date of diagnosis and date of last contact. For the purposes of this study, we created a binary variable to reflect colorectal cancer (CRC)-related death. CRC-related death was defined as true in colorectal cancer cases where cause of death was coded as colorectal cancer, as in cases

where cause of death was coded as any type of cancer for those patients where colorectal cancer was the only reported lifetime neoplasm. Primary site and histology data were coded according to the ICD-O-3 (World Health Organization, 2000). Cause of death was based on SEER Cause of Death Recode definitions (National Cancer Institute, 2004). Stage of disease at diagnosis was coded in all cases according to SEER Summary Staging 2000 (Young Jr, Roffers, Ries, Fritz, & Hurlbut, 2001). We were able to use SEER Summary Staging 2000 for stage of disease coding in all cases, even those diagnosed before 2000, because no revisions were made in the guidelines for colorectal cancer staging from the previous manual (Phillips, 2003). Key variable definitions are in Table 2.

Statistical Analysis

Descriptive analysis of data included frequency distributions of race, age, sex, stage of diagnosis, year of diagnosis, and state of residence at time of diagnosis. When comparing distributions to assess potential confounders to survival, we used chi-square analysis with an alpha level of 0.05 to test differences between AI/AN and NHW proportions. The student's t-test with an alpha level of 0.05 was used to test the difference between mean age at diagnosis between AI/AN and NHW cases.

The Kaplan-Meier method was used to calculate cancer-specific survival, providing an estimate of the likelihood of surviving one, and five years after invasive colorectal cancer diagnosis. Duration of survival was measured in months until the event of death where cause of death was coded as colorectal cancer, or any cancer death in cases where colorectal cancer was the only reported neoplasm in the patient's lifetime.

Survival time was censored at the date of a patient being lost to follow-up, date of death from causes not considered as CRC-related death, or on December 31, 2007, whichever occurred first. Univariate analysis included calculating Kaplan-Meier survival curves for race, age at diagnosis, stage of diagnosis, state of residence, and year of diagnosis.

Multivariable Cox Proportional Hazards regression models were explored to assess for confounding and two-way interactions between race, sex, age at diagnosis, year of diagnosis, and state. A final Cox PH model used for predicting survival estimates was constructed using the change-in-estimate approach (Hosmer, Lemeshow, & May, 2008) in which variables were selected for inclusion in the model based on their degree of effect on the magnitude of association between race and risk of CRC-related death. Model fit and proportional hazards assumptions were tested graphically and statistically. Cox-Snell pseudo R-squared values were calculated to compare overall model fit between model candidates. Schoenfield residuals were also examined to assess model fit. Scaled Schoenfield residuals were examined to assess the proportional hazards assumption. Difference in Betas were examined to assess influential observations.

Adjusted KM survival estimates were plotted for comparing subgroups and were calculated using the final Cox PH model. Relative risk for colorectal cancer-related death between subgroups was assessed with hazard ratios from the final Cox PH model. Hazard ratios (HRs) in the final model were adjusted for age at diagnosis, stage of diagnosis, and sex. Age was entered as a continuous variable in Cox PH models. HRs are presented with 95% confidence limits with statistical significance of differences determined by HRs differing significantly from 1.0 ($p<.05$). All data management and statistical analyses were conducted using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

We included 453 AI/AN invasive colorectal cancer cases and 37,433 NHW invasive colorectal cancer cases diagnosed between January 1, 1998 and December 31, 2006. Demographic characteristics are shown in Table 3. A statistically significant difference ($p<0.0001$) in mean age at diagnosis was observed between AI/AN and NHW cases. AI/AN and NHW mean age at diagnosis was 64.0 years (s.d. 13.2 years) and 69.6 years (s.d. 13.2 years) respectively. More AI/AN cases tended to be diagnosed at regional and distant stages compared to NHW, but this difference in distribution by stage was not statistically significant between AI/AN and NHW at an alpha 0.05 level. Similar proportions of male and female cases were observed in both races. The proportion of cases between Idaho, Oregon, and Washington differed significantly between AI/AN and NHW races ($p<0.0001$), with a larger percentage of AI/AN cases in Washington. The proportion of cases by year of diagnosis did not differ significantly between AI/AN and NHW cases.

Table 4 presents unadjusted Kaplan-Meier survival estimates. The 1- year unadjusted survival estimates for AI/AN and NHW are similar for both sexes combined. When stratified by sex, males have slightly higher 1-year survival proportions than females in both races. AI/AN females have a marginally lower 1-year survival than NHW females. The 5-year unadjusted survival estimates show significantly poorer survival in AI/AN cases for both sexes combined. When stratified by sex, AI/AN have poorer 5-year survival compared to NHW in both males and females. However, the difference in 5-year survival is not statistically significant between AI/AN females and NHW females.

Unadjusted Kaplan-Meier survival curves were plotted for comparisons by race and sex. Figure 1 presents plots of invasive colorectal cancer survival estimates by race for both sexes combined in the Pacific Northwest for the period 1998-2007. The log rank p-value (0.0024) shown in Figure 1 indicates a statistically significant difference in unadjusted survival estimates between races for both sexes, with AI/AN experiencing poorer survival than NHW. Figure 2 and Figure 3 show comparisons of Kaplan-Meier survival curves between AI/AN and NHW by sex. A significant difference between female AI/AN and female NHW was not observed, but the difference in survival between male AI/AN and male NHW was statistically significant (Log rank p=0.0021).

In the exploration of multivariable Cox Proportional Hazards regression models to calculate adjusted survival estimates, we found that race, age at diagnosis, year of diagnosis, and state were all statistically significant predictors of colorectal cancer-related death. Of these variables, stage of diagnosis explained the greatest amount of variation. A variable for a two-way interaction between sex and age was statistically significant and considered for inclusion in the final model, but the effect of the interaction term on the association between race and survival was minimal and it was subsequently left out of the final model. The final Cox PH model selected to calculate adjusted survival estimates included variables that had the greatest effect in changing the association between race and risk of death. These variables were age and stage of diagnosis. State and year of diagnosis, although statistically significant, altered the association between race and risk of colorectal cancer-related death less than 1% when included in the model. The variable for sex was not statistically significant and did not alter the association between race and risk of colorectal cancer-related death, but was included in the final model because of

potential clinical importance. The final Cox PH model therefore included age, sex, and stage of diagnosis. Scaled Schoenfield residuals indicated mild violations of the proportional hazards assumption in the final model for age and stage of diagnosis.

Table 5 presents the survival estimates calculated from the final Cox PH model where the association between race and survival was adjusted for age, sex, and stage of diagnosis. In both sexes combined the 1- and 5- year survival proportions for AI/AN (88%, 48%) are poorer than the 1- and 5- year survival proportions for NHW (91%, 57%). When stratified by sex the survival proportions are lower in AI/AN compared to NHW in both males and females. AI/AN have statistically significantly less favorable 5-year survival proportions in both males and females. Statistically significant differences were not observed between males and females within each race for 1- and 5- year survival proportions.

When NHW is used as the reference race, AI/AN cases had an unadjusted hazard ratio (HR) for risk of CRC-related death of 1.28 after invasive colorectal cancer diagnosis (95% CI 1.09, 1.51). Table 6 presents adjusted hazard ratios calculated from a Cox PH model for CRC-related death after invasive colorectal cancer diagnosis for the period 1998 to 2007 in the Pacific Northwest. Calculations were made with a model that included the independent variables sex, age, and stage of diagnosis. AI/AN cases have a 34% increase in risk of death compared to NHW cases. Females have a 2% reduction in risk of death, but this difference in risk is not statistically significant from that of males. The effect of age on risk of death can be interpreted as for every five-year increase in age the risk of death after invasive colorectal cancer diagnosis increases approximately 10.2%. Those diagnosed at 80 years old have 1.79 times the risk of CRC-related death of

those diagnosed at 50 years old. Cases diagnosed at a regional stage have nearly a 3-fold risk of CRC-related death when compared to those diagnosed at a local stage. Cases diagnosed at the distant stage have 17.6 times the risk of CRC-related death compared to those diagnosed at a local stage.

Figure 4 shows a comparison of plots of adjusted survival estimates for AI/AN and NHW in both sexes combined, with 95% confidence limits. The impact of a small sample size of AI/AN cases is reflected in the wider confidence bands. The confidence limits do not overlap after 10 months of survival time, and the disparity between survival probabilities for AI/AN and NHW increases with time.

Figure 5 and Figure 6 present plots comparing adjusted survival estimates by sex between AI/AN and NHW, with 95% confidence limits. Survival curves are similar between males and females, and both sexes show poorer survival in AI/AN compared to NHW. AI/AN survival estimates have wider confidence bands than NHW estimates, yet there is no overlap between confidence limits. The difference in survival estimates between races in both sexes is distinct after 10 months of survival time and this difference increases with time.

DISCUSSION

The most important finding from our data is that invasive colorectal cancer survival is generally poorer among AI/AN cases compared to NHW cases in the Pacific Northwest during the period 1998 to 2007. When NHW is used as the reference race, AI/AN cases had an unadjusted hazard ratio (HR) for risk of CRC-related death of 1.28 (95% CI 1.09, 1.51). After adjusting for age, sex, and stage of diagnosis the HR for

AI/AN cases remained statistically significantly elevated at 1.34 (95% CI 1.14, 1.57). Survival estimates adjusted for sex, stage, and age indicated that 1-year proportions were similar between AI/AN and NHW cases, but 5-year survival was worse in male, female and both sexes combined for AI/AN cases.

We found that age, stage of diagnosis, sex, state, and year of diagnosis are all statistically significant predictors in a Cox PH model for risk of CRC-related death. However, stage of diagnosis has the greatest effect. Cases diagnosed at a regional stage have nearly a 3-fold risk of death when compared to those diagnosed at a local stage. Cases diagnosed at the distant stage have 17.6 times the risk of death compared to those diagnosed at a local stage. Age at diagnosis also increased the risk of CRC-related death among those diagnosed with invasive colorectal cancer. Those diagnosed at 80 years old have 1.79 times the risk of death of those diagnosed at 50 years old. Sex was not a statistically significant predictor for risk of death, but females tended to have better survival than males in our data.

Comparative Studies

A study of site-specific cancer survival among two cohorts of American Indian cases from the Seattle-Puget Sound Cancer Registry diagnosed during the period 1974 to 1989 showed poorer colorectal cancer survival among American Indians even after adjustment for difference in age, stage of diagnosis, lack of cancer treatment, and residence in a non-urban county (Sugarman, Dennis, & White, 1994). The cohort in that study that represented both SEER-coded AI/AN plus AI/AN who were registered with the Portland Area IHS but coded as other races in SEER had an age and stage adjusted

HR for death of 1.2 (95% CI 1.0-1.6) and 5-year survival proportion of 39.7%. Differences between age and stage adjusted hazard ratios for risk of death in AI/AN colorectal cancer cases in western Washington during that period were not statistically significantly different from Whites. The study also did not find a significant difference in stage of diagnoses between AI/AN and Whites. However, that study calculated survival proportions using deaths from all causes, included in situ stage, and cases represented only 13 counties in western Washington.

Similar survival proportions in Alaska Natives when compared to Whites in the western Washington SEER registry were found among colorectal cancer cases during the period 1969 to 1993 (Brown et al., 1998). The study of the Alaska region calculated survival using the life table method, and adjusted for sex, age, stage of diagnosis, and year of diagnosis. The 1-year and 5-year survival proportions for Alaska Natives were calculated at 77% and 42%, respectively. Alaska Natives cases on average were diagnosed 3 years younger but were otherwise similar to the SEER White cases with respect to histological type, stage of diagnosis, site (distal or proximal), or percent undergoing treatment (Brown et al., 1998).

A study of cancer incidence and survival among AI/AN during the period 1982 to 1987 used a linkage between the Montana Central Tumor Registry and IHS records (Bleed et al., 1992) to capture miscoded AI/AN cases in the tumor registry. That study used an unpublished age- and sex- specific life table of all American Indians in the United States in 1980 to calculate site-specific relative cancer survival. One- and 5-year survival proportions for AI/AN were compared to AI/AN in Montana, AI/AN in New Mexico and Arizona, as well as U.S. Whites. Survival was relatively poorer among

AI/AN when compared to U.S. Whites, but the authors cautioned interpretation of their results because a small number of cases. Stage of diagnosis data were not used in that study, and can be an important determinant of survival.

A previous study of cancer survival among AI/AN in the Pacific Northwest calculated survival from all cancer sites, using Kaplan-Meier estimates of survival and a Cox PH model to estimate hazard ratios for subgroups of AI/AN in the Northwest (Becker, Lambert, Pukka, Stehr-Green, & Johnson, 2005). Their data indicated that poor survival in AI/AN from all cancers combined was associated with age, stage, and lack of surgery or chemotherapy. However, that study did not present comparative data for Whites.

Published studies of regional AI/AN colorectal cancer survival among AI/AN in the U.S. regions are limited and reflect data from earlier periods. Comparison between other published results is made difficult by varying methods for calculation of survival measures. Studies use relative or absolute survival approaches, variations in study inclusion and exclusion criteria, as well as different definitions for the outcome of interest (death from all causes vs. cause-specific).

A recent comparison between relative and cause-specific survival approaches with population-based data suggests that a relative survival may reflect unnecessarily grim estimates of survival for racial minorities and that a cause-specific approach may provide more accurate estimates (Howlader et al., 2010). Despite methodological differences, our results show a similar theme of poorer survival among AI/AN people when compared to a reference White population, as well as an association between survival and variables for age and stage of diagnosis. Our study taken within the context

of other published data indicate that differences in survival between AI/AN and NHW races persist after adjustment for age, sex, and stage of diagnosis. Other biological or socioeconomic variables could be of significance in determining colorectal cancer survival among AI/AN people and should be explored.

Limitations

We acknowledge several limitations of our study. First, cause of death information coded in the cancer registry is subject to variability and biases. A study that characterized concordance between cause of death on death certificates and primary cancer site at diagnosis in three states, including Idaho, showed 86% detection of cases where colorectal cancer was the only primary cancer (German et al., 2011). An older study of agreement between cause of death coded in death certificates and hospital diagnoses of cases showed colorectal cancer death detection of 92.9% on death certificates (Percy, Stanek, & Gloeckler, 1981). A low detection percentage for colorectal cancer cause of death in the Pacific Northwest would result in the overestimation of colorectal cancer survival when using a cause-specific survival approach, such as in our study. To address potential underreporting of colorectal cancer death in our study we included any cancer cause of death to calculate survival in cases where colorectal cancer was the only primary site diagnosed in the patient's lifetime. Our broader definition for colorectal cancer death was used to try and capture potentially miscoded colorectal cancer deaths. However, our results could also be biased if accuracy of cause of death in registry sources varies between races.

Second, misclassification of AI/AN in public health data is largely unidirectional in that AI/AN are incorrectly coded as a race other than AI/AN, rather than another race being misclassified as AI/AN with misclassification percentages as high as 70% (Becker et al., 2002; Boehmer et al., 2002). The NTR source data used to improve racial ascertainment of AI/AN cases for this study represents only those patients that seek care at IHS, tribal, or urban Indian health clinics in the Pacific Northwest. During the federal fiscal year 2003, it was reported that 1.5 million AI/AN people in the United States utilized Indian Health Service (IHS) medical services. The proportion of AI/AN that utilize IHS is far lower than the 4.1 million people who identified as AI/AN alone and in combination with other races in the 2000 census (Lillie-Blanton & Roubideaux, 2005). The IHS linkage used to improve racial ascertainment in the data obtained for this study may therefore only succeed in correcting misclassification in a small proportion of potentially misclassified AI/AN cases within state cancer registries. Additionally, it is possible that other factors that influence survival may be associated with AI/AN who are misclassified. It is interesting to note that data from the aforementioned Seattle-Puget Sound Cancer Registry study indicated that AI/AN cases that were identified as AI/AN in IHS sources but non-AI/AN in SEER may experience better survival than among persons reported as AI/AN in the SEER system (Sugarman et al., 1994). The authors of that study, however, cautioned interpretation of this difference because of small case numbers.

Lastly, our study does not address further factors that affect cancer survival such as time to treatment, treatment type, and palliative care. Body Mass Index (BMI), physical activity, and nutrition are additional factors that may influence survival (Vrieling

& Kampman, 2010). Findings from the Behavioral Risk Factor Surveillance System for the period 2000 to 2006 showed that AI/AN people in the Pacific Coast region have a significantly higher prevalence of no leisure-time physical activity and obesity when compared to the overall NHW population in the United States (Steele et al., 2008).

SUMMARY AND CONCLUSION

Despite the potential limitations of this study, our data suggest that after diagnosis of colorectal cancer in the Pacific Northwest, AI/AN people have poorer survival than NHW people. Males tend to experience poorer survival than females in both races, but this difference is not statistically significant. Those diagnosed older ages have an increased risk of death compared to those diagnosed at younger ages. Stage of diagnosis has the greatest effect on risk of colorectal cancer death.

Other variables potentially associated with survival after diagnosis of colorectal cancer will need to be addressed in future studies. The Northwest Portland Area Indian Health Board performs linkages with the Northwest Tribal Registry and the three state cancer registries in the Pacific Northwest annually. Future linkages will seek to retain additional variables for analysis. Variables such as time to treatment, and treatment type should be explored with our data to see if these variables could explain the generally poorer colorectal cancer survival of AI/AN people. Future studies will also use a cause-specific approach to assess survival for other screen-detectable cancers such as prostate, cervical, and breast cancers.

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TABLE AND FIGURES

Table 1. Inclusion and exclusion criteria for the study of invasive colorectal cancer survival among American Indian and Alaska Native people in the Pacific Northwest, 1998-2007

Inclusion Criteria:	Exclusion Criteria:
1. In either the NHW or AI/AN racial groups a. NHW race includes cases coded as "White" and as "non-Hispanic" b. AI/AN race includes all NTR matched cases, plus non-matched cases coded as "AI/AN" in Race 1 or Race 2 fields 2. Coded as "Male" or "Female" 3. Resident of Oregon, Washington, or Idaho at time of diagnosis 4. Primary cancer site identified as "Colorectal" per SEER Site Recode for ICD-O-3 Definition (National Cancer Institute, 2003) 5. Diagnosed with invasive cancer (behavior code "3") between 1998-2006	1. Duration of survival can not be determined (e.g. diagnosis was found on the death certificate or at autopsy) 2. Cases not actively followed 3. Cases with unknown stage of diagnosis 4. Cases with incomplete information in any of the variables used for analysis

Table 2. Key variables for the study of invasive colorectal cancer survival among American Indian and Alaska Native people in the Pacific Northwest, 1998-2007

Variable	Definition
Age at Diagnosis	Age of the patient at diagnosis in years.
Behavior Code	Code for the behavior of the tumor being reported using ICD-O-3, used to determine cases of invasive cancer.
Cancer Site	Code for the primary site of the tumor being reported using either ICD-O-2 or ICD-O-3.
Cause of Death Recode	Cause of death aggregated to non-cancer, or cancer site as defined by SEER Cause of Death Recode 1969+ (9/17/2004) (National Cancer Institute, 2004).
Date of Diagnosis	Date of initial diagnosis by a recognized medical practitioner for the tumor being reported whether clinically or microscopically confirmed.
Date of Last Contact	Date of last contact with the patient, or date of death.
Duration	Follow up time in months. Calculated by the difference between Date of Diagnosis and Date of Last Contact variables, divided by 30.4.
CRC-Related Death	Binary variable for the event of death from colorectal cancer (CRC) or any cancer death for cases with only a primary CRC neoplasm reported. Derived from Cause of Death Recode and Sequence Number – Central variables.
Race	Code for the patient's race after post-linkage correction with NTR.
Sequence Number —– Central	Code indicates the sequence of all reportable neoplasms over the lifetime of the person.
Sex	Code for the sex of the patient.
Site 26	Primary cancers aggregated into site groups according to the SEER Site Recode for ICD-O-3 Definition (National Cancer Institute, 2003).
Spanish/Hispanic Origin	Code for identifying persons of Spanish or Hispanic origin.
Stage of Diagnosis	Stage of disease coded according to SEER Summary Staging 2000 (Young Jr, Roffers, Ries, Fritz, & Hurlbut, 2001).
State	State from patient address at diagnosis.
Vital Status	Vital status of the patient as of the date entered in Date of Last Contact.
Year of Diagnosis	Year of diagnosis by a recognized medical practitioner for the tumor being reported whether clinically or microscopically confirmed.

Table 3. Characteristics of cases included for the study of invasive colorectal cancer survival for American Indian and Alaska Native people and non-Hispanic White people in the Pacific Northwest, 1998-2006

	AI/AN	NHW	
N	453	37433	
Mean Age	64.0 (s.d. 13.1)	69.6 (s.d. 13.2)	(p<0.0001)[a]
Age at Diagnosis %			(p<0.0001)[b]
<50 years	13.0	8.1	
50-70 years	52.5	39.3	
>70 years	34.4	52.7	
Sex %			(p=0.6099)[b]
Male	53.0	51.8	
Female	47.0	48.2	
Stage of Diagnosis %[c]			(p=0.0644)[b]
Localized	33.1	37.4	
Regional	44.4	43.8	
Distant	22.5	18.8	
State of Residence %			(p<0.0001)[b]
Idaho	7.5	11.8	
Oregon	27.2	34.7	
Washington	65.3	53.5	
Year of Diagnosis %			(p=0.8837)[b]
1998	9.7	11.2	
1999	12.1	11.4	
2000	10.2	11.5	
2001	10.6	11.1	
2002	10.8	10.8	
2003	10.6	11.1	
2004	12.4	11.0	
2005	11.7	11.4	
2006	11.9	10.5	

Note: AI/AN = American Indian/Alaska Native, NHW = Non-Hispanic White

a. p-value from independent samples t-test

b. p-value from X^2 test of homogeneity.

c. *in situ* and unknown stages were excluded.

Table 4. Unadjusted Kaplan-Meier survival estimates for invasive colorectal cancer survival of American Indian and Alaska Native people compared to non-Hispanic White people in the Pacific Northwest, 1998-2007

Colorectal Cancer Survival **Unadjusted 1 year and 5 year proportions surviving**				
	AI/AN		**NHW**	
	1 Year	95% CI	1 Year	95% CI
Both Sexes	0.83	(0.78, 0.87)	0.85	(0.84, 0.86)
Male	0.84	(0.77, 0.89)	0.86	(0.85, 0.87)
Female*	0.83	(0.76, 0.84)	0.84	(0.83, 0.85)
	5 Year	95% CI	5 Year	95% CI
Both Sexes*	0.37	(0.28, 0.45)	0.50	(0.48, 0.51)
Male*	0.34	(0.23, 0.44)	0.49	(0.47, 0.51)
Female	0.40	(0.28, 0.52)	0.50	(0.49, 0.52)
**statistically significant difference between AI/AN and NHW Races*				

Table 5. Adjusted survival estimates for invasive colorectal cancer survival of American Indian and Alaska Native people compared to non-Hispanic White people in the Pacific Northwest, 1998-2007

Colorectal Cancer Survival **Adjusted 1 year and 5 year proportions surviving**				
	AI/AN		**NHW**	
	1-Year	95% CI	1-Year	95% CI
Both Sexes[a]	0.88	(0.86, 0.90)	0.91	(0.90, 0.92)
Male[b]	0.88	(0.85, 0.90)	0.91	(0.90, 0.92)
Female[b]	0.88	(0.86, 0.90)	0.91	(0.90, 0.92)
	5-Year	95% CI	5-Year	95% CI
Both Sexes[a]	0.48	(0.42, 0.54)	0.57	(0.56, 0.59)
Male[b]	0.47	(0.41, 0.54)	0.56	(0.55, 0.59)
Female[b]	0.48	(0.42, 0.54)	0.57	(0.56, 0.59)

a. Adjusted for sex, age, stage of diagnosis
b. Adjusted for age, stage of diagnosis

Table 6. Adjusted hazard ratios for colorectal cancer-related death among cases of invasive colorectal cancer in the Pacific Northwest, 1998-2007

Variable	Hazard Ratio	95% Hazard Ratio Lower Limit	95% Hazard Ratio Upper Limit
Race			
NHW*	1.00	–	–
AI/AN	1.34	1.14	1.57
Age at Diagnosis			
50 years*	1.00	–	–
55 years	1.10	1.09	1.11
60 years	1.21	1.20	1.23
65 years	1.34	1.31	1.37
70 years	1.47	1.43	1.52
75 years	1.62	1.56	1.69
80 years	1.79	1.71	1.88
Sex			
Male*	1.00	–	–
Female	0.98	0.94	1.02
Stage of Diagnosis			
Localized Stage*	1.00	–	–
Regional Stage	2.96	2.78	3.16
Distant Stage	17.57	16.49	18.73

Notes:
*Reference category

Figure 1. Kaplan-Meier plot of invasive colorectal cancer survival estimates by race for both sexes combined in the Pacific Northwest, 1998-2007

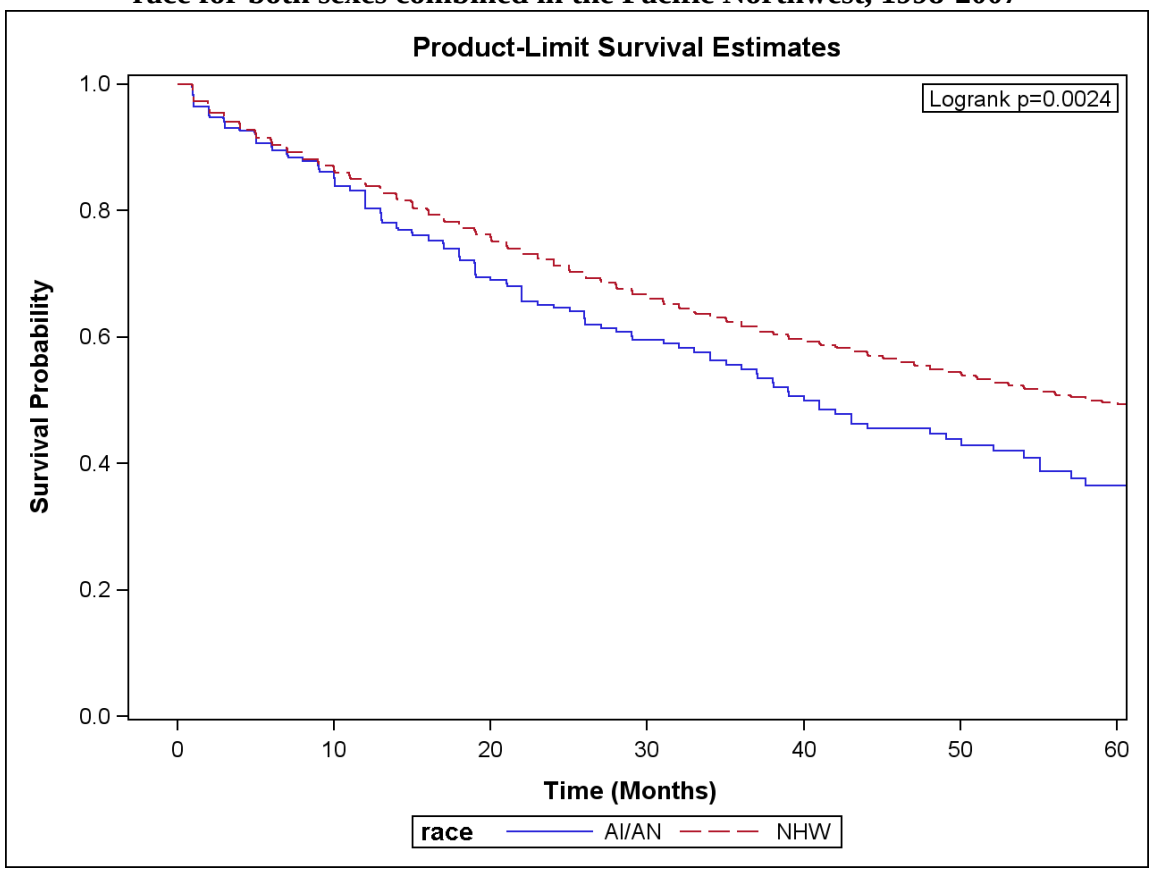

Figure 2. Kaplan-Meier plot of invasive colorectal cancer survival estimates by race for males in the Pacific Northwest by race, 1998-2007

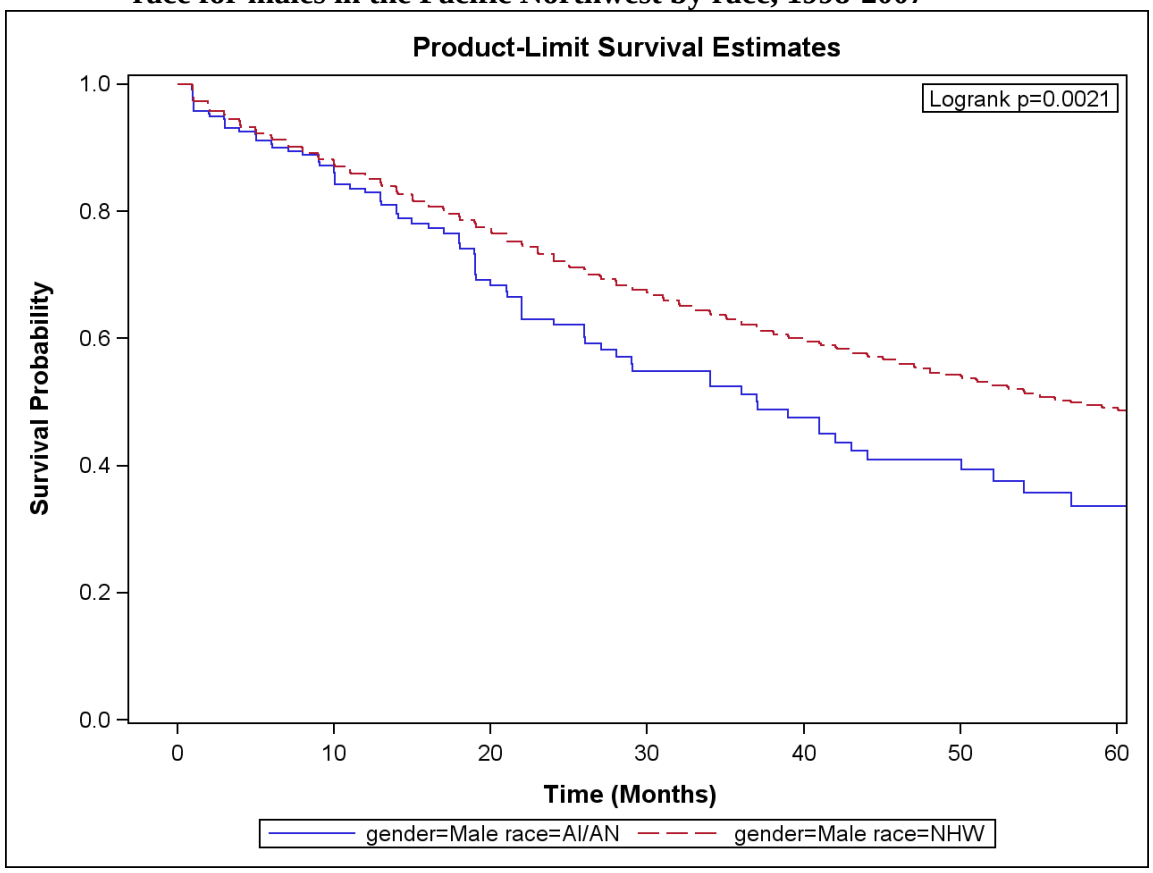

Figure 3. Kaplan-Meier plot of invasive colorectal cancer survival estimates by race for females in the Pacific Northwest, 1998-2007

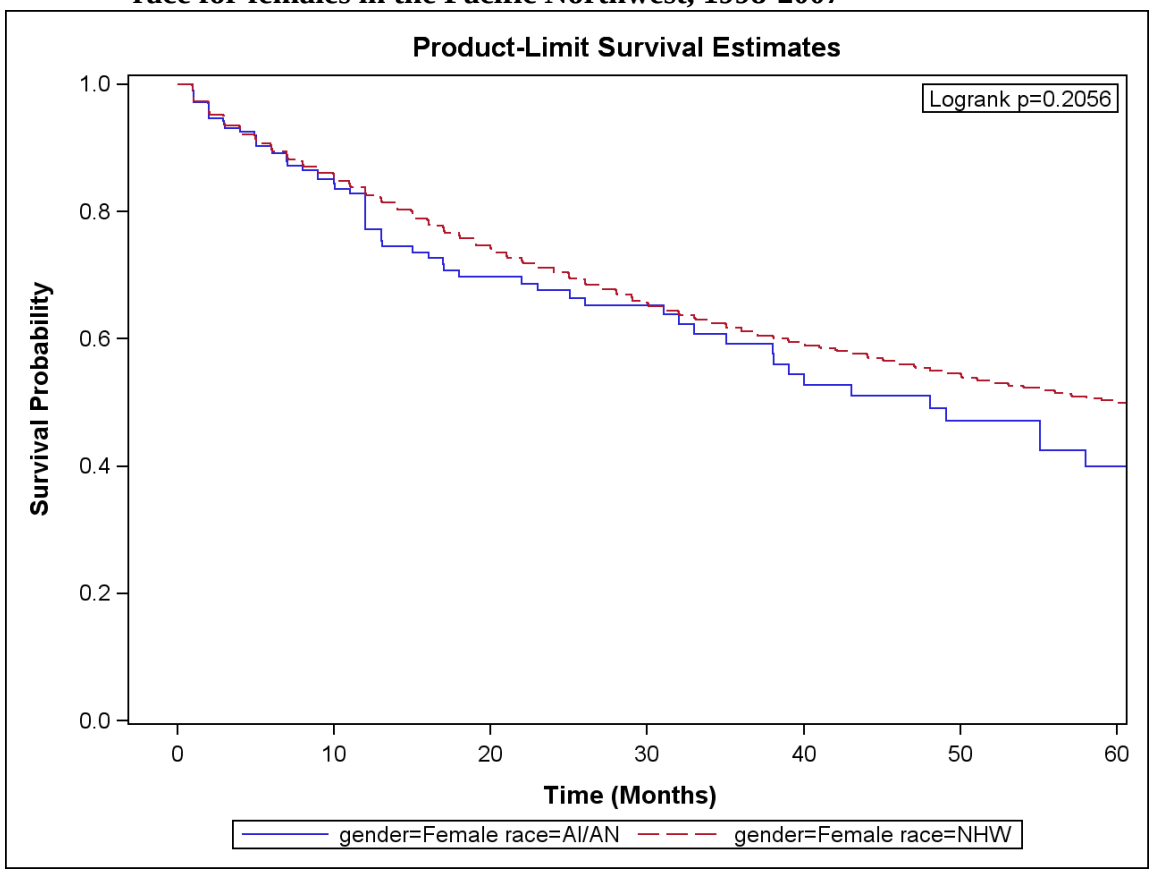

Figure 4. Plot of invasive colorectal cancer survival estimates by race for both sexes combined in the Pacific Northwest, 1998-2007 (adjusted for age at diagnosis, sex, and stage of diagnosis)

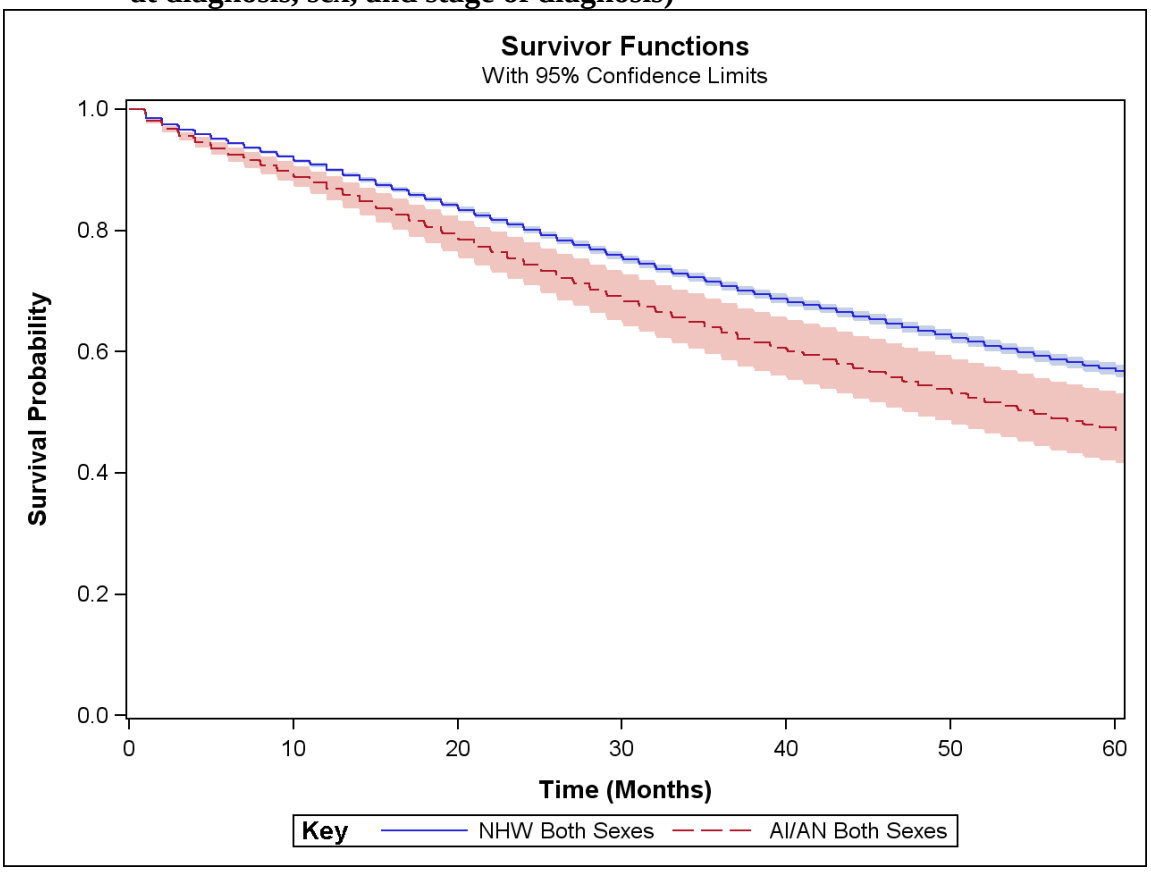

Figure 5. Plot of invasive colorectal cancer survival estimates by race for males in the Pacific Northwest, 1998-2007 (adjusted for age at diagnosis and stage of diagnosis)

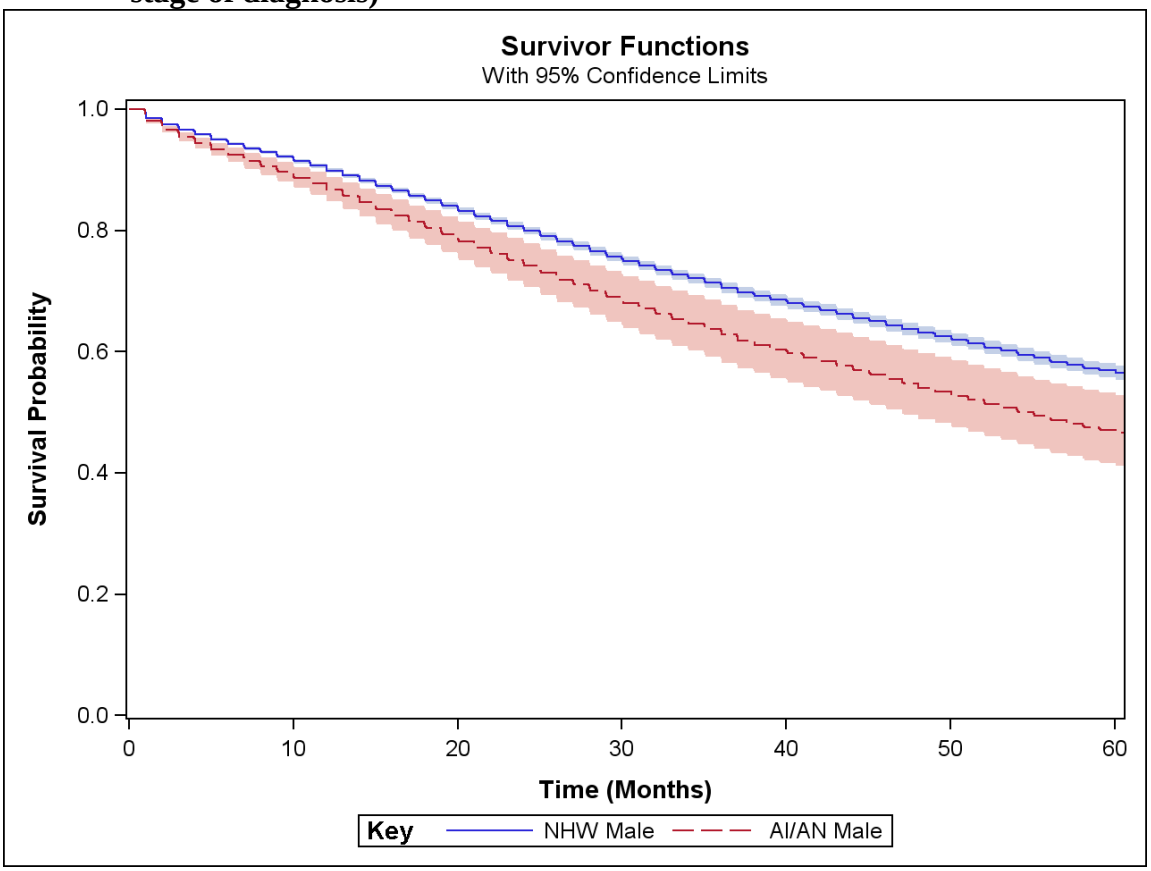

Figure 6. Plot of invasive colorectal cancer survival estimates by race for females in the Pacific Northwest, 1998-2007 (adjusted for age at diagnosis and stage of diagnosis)