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Are There Delays in Receipt of Treatment Among Appalachian Kentucky Women With Breast Cancer

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ARE THERE DELAYS IN RECEIPT OF TREATMENT AMONG APPALACHIAN KENTUCKY WOMEN WITH BREAST CANCER?

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Abstract

Background: Women living in rural and under-resourced Appalachian Kentucky may experience delays in receiving cancer treatment yet such delays have not been systematically evaluated. In this analysis, we hypothesize that women diagnosed with breast cancer who live in Appalachian Kentucky would be more likely to have a treatment delay compared to those living in other Kentucky regions and adjusting for individual measures of socioeconomic status.

Methods: In this cohort study, women included in the Kentucky Cancer Registry with a diagnosis of an incident, primary breast cancer in the prior 12 months were interviewed by phone (n=1,245; response rate 26.9%). Cox proportional hazards regression analysis was used to estimate rates of any treatment initiation and rates of specific types of first treatment of Appalachian residence relative to non-Appalachian residence after a breast cancer diagnosis.

Results: In contrast to our hypothesis, Appalachian women received any first cancer treatment sooner than non-Appalachian women after adjusting for age and stage (adjusted hazard ratio= 1.14; p=0.04). When additionally adjusting for income and health insurance, this association was no longer statistically significant (adjusted hazard ratio=1.11; p=0.14). Among women diagnosed at an earlier stage (n=899), Appalachian residents received first treatment (primarily surgery) sooner than Non-Appalachian women (p=0.05) and among those diagnosed at a later stage (n=346), Appalachian residence received radiation sooner than non-Appalachian residents (p=0.06). There were also no statistical differences in receipt of chemotherapy or hormone therapy between Appalachian and non-Appalachians.

Conclusion: Our results indicate for the first time no disparity related to breast cancer diagnosis-treatment intervals in Appalachian Kentucky as compared with the rest of the state.

Key words: Appalachia, low socio-economic status, cancer, treatment

Introduction

The breast cancer mortality rate in the United State as a whole has decreased significantly in recent years, but this rate declined more slowly in Appalachian regions.[1] In Kentucky, the age-adjusted death rate due to female breast cancer of Appalachians was virtually the same as that of non-Appalachian residents during the period from 1995 through 2007.[2] Unfortunately, this rate has become higher in Appalachian Kentucky relative to the other regions within the state in the five recent years, and significantly higher in 2012 at respective rates of 26.4 per 100,000 (22.8 – 30.3) versus 20.4 per 100,000 (18.4 – 22.6).[2] Nevertheless, little research has explored what causes this disproportionately decreasing trend as well as the disparity related to the breast cancer mortality rate.[3] Most breast cancer death is assumed to be the result of delays in cancer detection and treatment.[4-7] Several studies indicated an association of lower socio-economic status and increased delays in breast cancer treatment.[8-11] Inherent given geographic isolation and distinguished mountain culture, Appalachian women may suffer longer delays in breast cancer treatment. However, this potential disparity has not yet been studied thoroughly because cancer survivorship data for the Appalachian region from the Surveillance, Epidemiology, and End Results (SEER) program did not become available until recent years, and information related to individual socio-economic status has not been collected from the cancer registries.[12]

To examine the disparity in treatment delays in Appalachian women, we created the Directed Acyclic Graphs (DAG) to hypothesize a mechanism by which Appalachian women may be associated with increased delays in beginning treatment for breast cancer (Figure 1). Appalachian residents are characterized by lower socio-economic status, lower income, lower educational attainments, and higher unemployment rates than residents of other regions within the state.[13,14] Such vulnerable status is likely to result in lower health insurance coverage, later cancer stage at diagnosis, and more comorbid conditions due to unfavorable health behaviors in Appalachian regions.[15] These consequences may either/both directly cause delays in cancer treatment or/and indirectly affect the delays through cancer treatment options, which are determined by stage at diagnosis and comorbid conditions.

In this report, we investigated the association between Appalachian region and delays in receipt of breast cancer treatment among women included in the Kentucky Cancer Registry and agreeing to phone surveys within 12 months of their cancer diagnosis. We hypothesized that Appalachian women with breast cancer would experience longer delays in treatment initiation as compared with non-Appalachian women, after adjusting for differences in socio-demographic characteristics and cancer stage and treatment between the two study groups. Specifically, our research questions are whether and how Appalachian women with breast cancer are associated with increased delays in receipt of cancer treatment relative to non-Appalachian women.

Methods

Study Participants

Women aged 18 to 79 who were diagnosed as an incident and primary case of cancer (excluding squamous cell skin cancer) from December 2009 to August 2014 were reported to the Kentucky Cancer Registry (KCR). After verifying pathology reports and checking with the patients' physician if the patients were approachable, eligible women were sent a letter to participate in the study, enclosed with card stamped and addressed to KCR staff. KCR staff followed up with women who did not return the card to ask if they would be willing to talk with University of Kentucky researchers about study participation. A total of 4628 women with breast cancer were identified by KCR staff as eligible based on age, incident and primary breast cancer diagnosis confirmed by biopsy, and diagnosed with in the past 12 months. Of those 4628 women, 2214 agreed to allow researchers contact (47.8%) and 1245 completed a phone interview (26.9% of all eligible and 56.2% of those consenting to researcher contact). The phone interview included questions regarding socio-demographic characteristics, lifestyle factors, and self-reported comorbidity.

Measures

The cancer treatment outcomes investigated included whether the case received treatment, if so the cancer treatment type, and the date of first treatment by type. These data were available from the Kentucky Cancer Registry and abstracted by KCR staff from case medical records. These data were used to create indicator variables describing receipt of any treatment, and specific types of treatment included as dichotomous variables for each treatment option: surgery, chemotherapy, radiation, and hormone therapy. Additionally, the date of first treatment by type was obtained and used to determine time to first treatment by type. The following time to treatment variables were created in which the date of diagnosis was used as the benchmark for time to first treatment (where time to first is calculated as date of first treatment – date of diagnosis): first treatment independent of treatment type, time to first surgery, first chemotherapy, first radiation and first hormone therapy. Time to treatment by type was also calculated and included those receiving a specific treatment yet this treatment type was not necessarily their first. Since the physicians' recommendation for treatment types is based on tumor characteristics and patient's health condition, such as chemotherapy is usually not part of first course treatment for earlier stages of cancer,[16] the cases who were recommended the treatment but had not received treatment (by type) by KCR medical abstraction (between 9 – 12 months following a diagnosis) were considered as censored for survival analyses. Lastly, because we could not determine a physicians' recommendation for treatment relative to treatment received we explored days to first treatment (and by treatment type) among those who received the specific type of treatment. The underlying assumption is that those who received treatment needed that treatment.

Living in Appalachian Kentucky was the primary exposure of interest. Data to characterize this status was available from KCR was identified based on Kentucky county of residence. Breast cancer cases were grouped as Appalachian and non-Appalachian regions for this cohort analysis.

As described in Figure 1, covariates of potential interest which may impact delays in cancer treatment included women's self-report were their (1) family's monthly income including assistance from their families (grouped into six categories: less than $1,000; $1,000 to $1,999; $2,000 to 2,999; $3,000 - $3,999; $4,000 - $4,999; and more than $5,000), (2) highest educational attainment (groups into five categories: less than high school, some high school or General Educational Development (GED), college or vocational certificates, bachelor degree, and post graduate degree), (3) current and previous smoking status (categorized as never, former and current smokers), (4) current marital status (dichotomized as married versus unmarried), and (5) health insurance coverage (grouped as uninsured including self-pay or no insurance, Medicare, Medicaid or government plans, and private insurance). Finally, to measure (6) comorbid conditions, women were asked whether a doctor had ever told them they had any of the following conditions: a) asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, b) high blood pressure or hypertension or high cholesterol, c) heart disease or a heart attack, d) hepatitis or cirrhosis, e) diabetes, metabolic syndrome or were insulin resistant, f) irritable bowel syndrome or diverticulitis or diverticulosis, g) fibromyalgia or chronic fatigue syndrome, and h) stroke or a transient ischemic attack (TIA). Response options for each condition were yes or no. Physical conditions were summed to create an ordinal variable indicating the number of conditions the woman has had (frequencies ranged from 0 to 8 conditions at cancer diagnosis). Two additional predictors of cancer survival and treatment available from KCR were (7) age at diagnosis (in years), and (8) stage at cancer diagnosis (defined as carcinoma in situ (=0), localized (=1), regional with invasion in the immediate area of the tumor site (=2), regional with cancer invasion beyond the immediate region of the tumor (=3); and distant; cancer invasion to another site (=4)).

Statistical Analysis

As described in Figure 1, socio-demographic factors may be correlated with Appalachian region. To determine these associations the Chi-square test for the proportions of categorical variables or a two-sample t- test for the means of continuous variables were calculated by Appalachian versus non-Appalachian region (Table 1). Besides, assessments of collinearity between the covariates indicated that there was no significant effect of multicollinearity as the Spearman correlation coefficients of the factors were less than 0.70, and the variance inflation factors were all less than 10, similarly (Appendix).

The primary research question evaluated was the association between Appalachian region and receipt of cancer treatment measures as a dichotomous variable, as continuous measures of time to treatment among those treated, and as time to treatment using survival analyses modeling. Three statistical methods were used to examine the effect of Appalachian residence on cancer treatment among women recently diagnosed with breast cancer. When cancer treatment was measured simply as receipt of any treatment and by specific treatment type, unadjusted and adjusted logistic regression models were used to estimate the odds of treatment among Appalachian and non-Appalachian residence (see Table 2 for results). When days to cancer treatment among those receiving treatment was used to characterize cancer treatment received, unadjusted and adjusted linear regression models were used to estimate days to treatment among those in Appalachian versus non-Appalachian regions (see Table 3 for results). And finally, when both the proportion treated and time to first treatment were used together to estimate treatment rate ratios, Cox Proportional Hazards Regression was employed for estimating rates of treatment initiation following a cancer diagnosis (see Table 4 for results). These analyses were repeated by type of cancer treatment and within stage of cancer diagnosis (dichotomized as earlier (stage 0-2) and later (stage 3-4) stage (see Table 5 for results). Kaplan Meier Curves were produced and presented in figure 2 by Appalachian versus non-Appalachian region and time to treatment by type. Finally, diagnostic tests for the final Cox model were provided in the Appendix. Cumulative sums of martingale residual plots indicated none of the covariates violated the proportional hazard assumption and functional form. In terms of influential observations that were tested by changes of beta coefficient of Appalachian variable in the model and by changes in over model likelihood, we checked information of the observations, and contrasted the uncorrected models and the models corrected for influential observations. As the information was reasonable, and the differences in uncorrected and corrected models were minor, we reported the uncorrected models for simplicity.

For each model, the following three sets of statistical adjustments to address covariates were employed (1) the crude estimates to examine the total effect of Appalachian residence on treatment outcomes, (2) adjustment for age at diagnosis, cancer stage, and other treatment types which are essential clinical factors for a consideration of treatment plans,[16,17] and (3) the final and more conservative additional adjustment of family income and health insurance. Statistical Analysis Software, SAS version 9.3 (SAS Institute; Cary North Carolina) was used for all modeling and statistical analyses.

Results

Among the 1,245 women participating in this study, 334 women lived in the Appalachian region (26.83%). Relative to women living in non-Appalachian Kentucky, those living in Appalachia (see Table 1) were more likely to be White (p=.0003), to have lower income (p<.0001), to receive less education (p<.0001), to be current smokers (p=.01), to have other than private health insurance (p<.0001), to have more comorbid conditions (p=.001) and to be diagnosed at a later stage with breast cancer (p=.007). No regional differences were noted in age at diagnosis and current marital status.

As represented in Table 2, 1,240 out of 1,245 women with breast cancer received treatment (99.6%). Similarly the majority (98.4%; 1,225/1,245) received surgery and for 92.5% surgery was the first cancer treatment. No differences by Appalachian region were noted in receipt of any treatment or receipt of surgery specifically in unadjusted or adjustment logistic regression models. The proportions of women receiving chemotherapy, radiation or hormone therapy as the first course of treatment were significantly lower in Appalachian women in comparison to these of non-Appalachian women regardless of control for age, stage and treatment types in logistic regression models. When we adjusted for these factors along with individual income and health insurance only odds ratio for receipt of radiation remained statistical significant but not for receipt of chemotherapy or hormone therapy.

The results of the analyses addressing days to treatment among those receiving treatment by Appalachian residence are provided in Table 3. Number of days between diagnosis date and first treatment date as our outcome of interest were statistically different between the Appalachian and non-Appalachian groups (the means were 19.87 versus 23.10, with a p-value for a t-test of 0.02 when adjusting for age, and stage yet when additionally (and more conservatively) adjusting for income and health insurance, regional differences were no longer significant. Briefly, women living in Appalachian Kentucky had fewer days to first treatment ($p<.05$) than did women living in Non-Appalachian Kentucky. This pattern was observed for days to first treatment, surgery, radiation, and hormone therapy when considered adjusted models. No regional differences in time to treatment were observed for chemotherapy between the two study groups.

Figure 2 illustrates the Kaplan-Meier curves for time to treatment by Appalachian region. Since p values of the Log Rank test for the time to any first treatment and time to first surgery were less than a five percent significance level, we have strong evidence to conclude that the curves are different when comparing Appalachian breast cancer women versus non-Appalachian breast cancer women, not taking into account any other covariate information. Yet we failed to reject the null hypothesis that the curves for the time to first chemotherapy or the time to first radiation or the time to hormone therapy were the same for the two groups at all points in time.

The results of the Cox proportional hazards model with and without covariate adjustments are provided in Table 4; time to median treatment probability by Appalachian region were provided as well as the hazard ratios for cancer treatment by type. The unadjusted hazard ratio for any treatment received of 1.17 [95% CI: (1.04 – 1.33)] indicates that women in Appalachian Kentucky were 17% more likely to receive any cancer treatment earlier than women living in Non-Appalachian regions. While this association remained significant when adjusting for age and stage at diagnosis (HR= 1.14; 95% CI=1.01 – 1.30), the more conservative adjustment for age, stage at diagnosis, income and health insurance resulted in a HR of 1.11 [95% CI: (0.97 – 1.28)] was no longer significant. This finding does suggest that the effect of Appalachian residence on time to any first cancer treatment may be mediated by income or insurance and not simply residence. Appalachian women appeared be more likely to receive surgery and radiation earlier than women living in Non-Appalachian regions (note differences in findings by adjustments in models).

When these analyses were repeated by stage at cancer diagnosis (Table 5) similar findings were observed for Appalachian residence being more likely to receive any and specifically surgery sooner than Non-Appalachian residents among those diagnosed at an earlier stage (0-2). No difference in treatment by Appalachian were noted among women diagnosed at later stage.

Discussion

In this cohort analysis, Appalachian women diagnosed with breast cancer tended to receive any first cancer treatment or first surgery slightly sooner than those in non-Appalachian regions. By adjusting for individual income, health insurance, other types of treatment, age and cancer stage at diagnosis the differences in rates of treatment initiation were not statistically significant. The findings did not concur with our hypothesis that women living in underserved Appalachian region might suffer delays in breast cancer treatment. Since this is the first study to explore time to first cancer treatment by type among women diagnosed with breast cancer in Appalachia compared to those living in the rest of Kentucky, we are thus not able to compare our results with others. The results might be partially explained by the higher proportion of the Appalachian women who were diagnosed and treated on the same day compared to that of non-Appalachian women (20.42% versus 16.65%, a p value for the Chi-square test of 0.12). Moreover, while the proportion of patients at stage 4 was higher in the Appalachian group compared to the non-Appalachian group, the patients at stage 4 were likely to initiate treatment sooner. By contrast, the proportion of patients at stage 0 was lower in Appalachian Kentucky, whereas the women at stage 0 were likely to start treatment later. Women with monthly income from $4,000 to $4,999, which was observed less often in Appalachian group tended to have a longer delay in cancer treatment. Yet the patients with a medium level of income, who may have underlying factors such as current employment, would take a longer time to arrange for a treatment.

Our results indicate a four-day difference in the mean or median number of days from diagnosis to any first treatment and a five-day difference in the mean or median number of days from diagnosis to first surgery between the two study groups. A recent study reported a treatment delay of more than 60 days to be associated with an increased risk of breast cancer-related death among patients at late stages.[10] We might also over adjust when controlling individual's insurance and income along with essential clinical factors that affect the treatment options. However, the findings might be good news if we can say that clinicians recognize the burden of distance of travel burden and get those from greater distance into treatment sooner.

In the Cox regression models, due to differences in treatment plans recommended for the patients we considered censors as cases who were recommended a treatment type but had not received that treatment. It is reasonable to exclude those who were not recommended for a treatment when rates of receiving specific types of treatment were estimated. For instance, 98% (54/55) of the cases at stage 0, and 60% of the cases at stage 1 were not recommended for chemotherapy, and were thus excluded in the analysis of time to first chemotherapy, whereas only 15% of the cases at stage 3 were not recommended for chemotherapy. However, analyses also suggested that Appalachian women were less likely to be recommended for a chemotherapy or radiation or hormone therapy as compared with non-Appalachian women. Without controlling for potential confounders such as cancer stage, radiation was recommended for 63% of non-

Appalachian women while it was recommended for only 54% of Appalachian women (p=.007). Hormone therapy was recommended for 73% of non-Appalachian women versus for 69% of Appalachians (p=.17). Chemotherapy was recommended for 55% of non-Appalachian women versus for 52% of Appalachians (p=.38). The results imply that our exclusion of patients who were not recommended for a specific treatment type might overshadow treatment-related disparities in the Appalachian regions. They also raise another important question for further study, whether non-clinical patient factors, including living in Appalachian regions influence doctors' recommendation for treatment plans in our study. Some previous studies suggested that patient's circumstances related to health insurance, travel difficulties or income play a role in medical oncologist decision-making for cancer treatment recommendations.[18-22]

Our study has several strengths. This is the first longitudinal study design to compare time from diagnosis to first treatment among Appalachian women diagnosed with breast cancer versus those in the rest of the state. This study also considers the effects of numerous potential predictors on diagnosis-treatment time intervals by various statistical models. In addition, missing data and recall bias are very limited in our study. There is also little to no chance of differential misclassification of outcome and exposure as the study subjects were not reporting either Appalachian status or date of treatment by type. Thus only non-differential misclassification that introduces a bias toward the null might occur.

However, our study contains some limitations. First and foremost, time to cancer treatment that was determined from date of confirmed diagnosis to date of treatment only reflects treatment delays among the women who present at health facilities for a cancer diagnosis, but does not measure the delays among those who are unable to access health services to be diagnosed. This may lead to underestimation of actual delays in cancer treatment. Comprehensive assessments of delays, including primary delays (duration between onsets of the symptoms and contacting health professionals), secondary delays (time interval of presenting at a health facility and getting a confirmed diagnosis), and these tertiary delays can be used for strengthening the results. Additional measures known to influence treatment delays, such as physician-related delays before and after diagnosis may also have been beneficial to gather and include in our regression model. Another limitation to our study is non-response bias that may be present, and questionable generalizability of the findings due to a low response rate (22.3%). However, there was no statistical difference in response rates between Appalachian women (24.6%) and non-Appalachian women (23.0%), which might mitigate the bias. Furthermore, extension of the study locations to other cancer registries in Appalachian areas to increase generalizability and further assess covariate effects such as women's educational attainment, employment, or income, may be helpful in assessing the impact of Appalachian residence on time to first cancer treatment.

In conclusion, our study contributes to the literature with regards to duration between diagnosis and treatment dates among women with breast cancer in Appalachian Kentucky in comparison to the rest within the state. While the study results did not reveal the disparity related to delays in initiating breast cancer treatment in Appalachian women as compared to non-Appalachian women in Kentucky, efforts to improve the breast cancer screening programs in order to reduce late breast cancer diagnosis for Appalachian women should continue to be.

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Biographical Sketch

Huong Luu is a medical doctor with fourteen years of professional experience, including four years clinical experience and ten years working on a range of health research studies. Currently, Huong Luu is employed as a Research Assistant for the University of Kentucky College of Public Health in Lexington, Kentucky to analyze the data on Kentucky resident drug overdose hospitalizations and emergency department visits. From 2002-2011, she served as a program officer for Vietnam field office of the Program for Appropriate Technology in Health (PATH), a United States-based international non-governmental organization with the major responsibilities for development and implementation of biomedical and public health research; and training of health care workers. Prior to her experience at PATH, Huong Luu worked as a physician at the Neonatal Care Department of Hanoi Obstetrics and Gynecology Hospital in Vietnam.

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Table 1: Demographic Profile of Women with Breast Cancer by Appalachian Residence, 2009 - 2014

Variables	All women	Appalachian	Non-Appalachian	P value (χ^2 or t test)
Age at Diagnosis	N=1,245	N=334	N=911	p= 0.12 ($t_{df=1243}$=-1.55)
Mean (SD)	56.61 (9.90)	57.33 (9.91)	56.35 (9.89)	
Race	N=1,240	N=333	N=907	p<0.0003 ($\chi^2_{df=1}$=13.19)
White	1,174 (94.68%)	328 (98.50%)	846 (93.27%)	
Non-White	66 (5.32%)	5 (1.50%)	61 (6.73%)	
Woman's Monthly Income	N=1,018	N=286	N=732	p<0.0001 ($\chi^2_{df=5}$=43.55)
<$1,000	102 (10.02%)	39 (13.64%)	63 (8.61%)	
$1,000 - $1,999	201 (19.74%)	83 (29.02%)	118 (16.12%)	
$2,000 – 2,999	151(14.83%)	48 (16.78%)	103 (14.07%)	
$3,000 - $3,999	140 (13.75%)	30 (10.49%)	110 (15.03%)	
$4,000 - $4,999	112 (11.0%)	31 (10.84%)	81 (11.07%)	
≥$5,000	312 (30.65%)	55 (19.23%)	257 (35.11%)	
Woman's Educational Attainment	N=1,244	N=334	N=910	p<0.0001 ($\chi^2_{df=4}$=54.88)
Less than High School	101 (8.12%)	52 (15.57%)	49 (5.38%)	
High School/ GED	403 (32.40%)	123 (36.83%)	280 (30.77%)	
College/Technical	224 (18.01%)	51 (15.27%)	173 (19.01%)	
Bachelor Degree	164 (13.18%)	49 (14.67%)	115 (12.64%)	
Post Graduate Degree	352 (28.30%)	59 (17.66%)	293 (32.20%)	

Variables	All women	Appalachian	Non-Appalachian	P value (χ^2 or t test)
Current Marital Status	N=1,244	N=334	N=910	p=0.55 ($\chi^2_{df=1}$=0.35)
Married	848 (68.17%)	232 (69.46%)	616 (67.69%)	
Unmarried	396 (31.83%)	102 (30.54%)	294 (32.31%)	
Woman's Smoking Status	N=1,245	N=334	N=911	p=0.01 ($\chi^2_{df=2}$=9.00)
Never smoker	707 (56.79%)	185 (55.39%)	522 (57.30%)	
Current smoker	153 (12.29%)	56 (16.77%)	97 (10.65%)	
Former smoker	385 (30.92%)	93 (27.84%)	292 (32.05%)	
Health Insurance or Plans	N=1,245	N=334	N=911	p<0.0001 ($\chi^2_{df=3}$= 32.99)
Private insurance	795 (63.86%)	174 (52.10%)	621 (68.17%)	
Medicaid/Military	97 (7.79%)	35 (10.48%)	62 (6.81%)	
Medicare	321 (25.78%)	108 (32.34%)	213 (23.38%)	
Not Insured	32 (2.57%)	17 (5.09%)	15 (1.65%)	
Number of Comorbid Conditions	N=1,241	N=333	N=908	p=0.001 ($t_{df=527}$=-3.24)
Mean (SD)	1.62 (1.24)	1.82 (1.37)	1.55 (1.19)	
Cancer Stage at Diagnosis	N=1,245	N=334	N=911	p=0.007 ($\chi^2_{df=4}$=14.09)
Stage 0	55 (4.42%)	7 (2.10%)	48 (5.27%)	
Stage 1	826 (66.35%)	227 (67.96%)	599 (65.75%)	
Stage 2	18 (1.45%)	4 (1.20%)	14 (1.54%)	
Stage 3	313 (25.14%)	80 (23.95%)	233 (25.58%)	
Stage 4	33 (2.65%)	16 (4.79%)	17 (1.87%)	

Table 2: Appalachian Residence and Type of Cancer Treatment Received among Women Diagnosed with Breast Cancer, 2009 - 2014

Variables	All women n (%)	Appalachian n (%)	Non-Appalachian n (%)	Appalachian versus Non-Appalachian		
				Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95%CI)
Received treatment						
Yes	1,240 (99.60%)	333 (99.70%)	907 (99.56%)	1.47*** (0.16 – 13.19)	1.44 (0.16 – 12.97)	1.44 (0.15 – 13.59)
No	5 (0.40%)	1 (0.30%)	4 (0.44%)			
Received surgery						
Yes	1,225 (98.39%)	326 (97.60%)	899 (98.68%)	0.54 (0.22 – 1.34)	1.07 (0.38 – 2.99)	1.004 (0.32 – 3.18)
No	20 (1.61%)	8 (2.40%)	12 (1.32%)			
First treatment was surgery						
Yes	1,151 (92.45%)	310 (92.81%)	841 (92.32%)	1.08 (0.66 - 1.74)	1.31 (0.77 – 2.23)	1.38 (0.76 – 2.52)
No	94 (7.55%)	24 (7.19%)	70 (7.68%)			
Received chemotherapy						
Yes	599 (48.11%)	145 (43.41%)	454 (49.84%)	0.77 (0.60 – 0.99)	0.68 (0.51 – 0.92)	0.66 (0.48 – 0.93)
No	646 (51.89%)	189 (56.59%)	457 (50.16%)			
First treatment was chemotherapy						
Yes	73 (5.86%)	21 (6.29%)	52 (5.71%)	1.11	0.95	0.84

Variables	All women n (%)	Appalachian n (%)	Non-Appalachian n (%)	Appalachian versus Non-Appalachian		
				Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95%CI)
No	1,172 (94.14%)	313 (93.71%)	859 (94.29%)	(0.66 – 1.87)	(0.53 – 1.72)	(0.42 – 1.70)
Received radiation						
Yes	691 (55.50%)	156 (46.71%)	535 (58.73%)	0.62 (0.48 – 0.79)	0.65 (0.50 – 0.85)	0.68 (0.50 – 0.91)
No	554 (44.50%)	178 (53.29%)	376 (41.27%)			
First treatment was radiation						
Yes	2 (0.08%)	0	2 (0.22%)	***	***	***
No	1,234 (99.12%)	334 (100%)	909 (99.78%)			
Received hormone						
Yes	805 (64.66%)	196 (58.68%)	609 (66.85%)	0.70 (0.54 – 0.91)	0.69 (0.52 – 0.92)	0.77 (0.57 – 1.04)
No	440 (35.34%)	138 (41.32%)	302 (33.15%)			
First treatment was hormone						
Yes	23 (1.85%)	6 (1.80%)	17 (1.87%)	0.96 (0.38 – 2.46)	0.65 (0.23 – 1.88)	0.78 (0.25 – 2.43)
No	1222 (98.15%)	328 (98.20%)	894 (98.13%)			

*Odds ratios (OR) for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, and other treatment received (except for specific treatment as first). 95% confidence intervals (CI) are given in parentheses.

** ORs for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, other treatment received (except for specific treatment as first), income and health insurance. 95% CIs are given in parentheses.

*******Unstable ORs due to the small number of women who received or did not received a treatment.

Table 3: Appalachian Residence and Time to First Treatment by Type among Women Receiving the Specific Treatment, 2009 – 2014

Variables	Unadjusted mean days to cancer treatment (SE)			β estimate (95% CI) for Appalachian versus Non-Appalachian		
	All women	Appalachian	Non-Appalachian	Unadjusted	Adjusted*	Adjusted**
Days to first treatment	22.23 (0.53)	19.87 (1.02)	23.10 (0.62)	-3.23 (-5.56; -0.89) p= 0.007	-2.79 (-5.13; -0.45) p= 0.02	-2.18 (-4.84; 0.49) p= 0.11
Days to first surgery	28.94 (1.05)	24.18 (1.68)	30.67 (1.29)	-6.5 (-11.14; -1.85) p= 0.01	-5.89 (-10.5;-1.29) p=0.01	-5.39 (-10.49; -0.29) p =0.04
Days to surgery where surgery is first treatment	21.88 (0.55)	19.38 (1.06)	22.80 (0.65)	-3.42 (-5.86; -0.98) p= 0.006	-3.13 (-5.60;-0.66) p= 0.01	-2.45 (-5.22; 0.33) p= 0.08
Days to first chemotherapy	62.91 (1.31)	63.69 (2.96)	62.66 (1.45)	1.03 (-5.00; 7.06) p=0.74	2.83 (-2.96; 8.62) p=0.34	3.06 (-3.46; 9.58) p=0.36
Days to chemotherapy where chemotherapy is first treatment	27.00 (1.89)	26.57 (3.22)	27.17 (2.33)	-0.60 (-8.98; 7.77) p=0.89	-3.70 (-12.55; 5.14) p=0.41	-2.02 (-13.61; 9.57) p=0.73

Variables	Unadjusted mean days to cancer treatment (SE)			β estimate (95% CI) for Appalachian versus Non-Appalachian		
	All women	Appalachian	Non-Appalachian	Unadjusted	Adjusted*	Adjusted**
Days to first radiation	137.92 (3.15)	129.30 (7.31)	140.40 (3.46)	-11.14 (-25.9; 3.62) p=0.14	-8.37 (-17.82; 1.08) p=0.08	-14.46 (-25.12; -3.8) p =0.01
Days to hormone therapy	134.84 (3.32)	124.10 (6.50)	138.30 (3.84)	-14.23 (-29.37; 0.92) p=0.07	-7.88 (-19.84; 4.09) p=0.20	-13.06 (-26.02; -0.1) p=0.048
Days to hormone therapy where hormone therapy is first treatment	19.70 (3.53)	12.33 (5.44)	22.29 (4.28)	-9.96 (-26.48; 6.56) p=0.22	8.21 (-7.98; 24.41) p=0.30	11.69 (-23.34; 46.71) p=0.45

*SE: Standard error

* Non-intercept parameter estimates (β) for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, and other treatment received (except for specific treatment as first). 95% confidence intervals (CI) are given in parentheses.

** β estimates for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, other treatment received (except for specific treatment as first), income and health insurance. 95% CIs are given in parentheses

Table 4: Survival Analyses: Appalachian Residence and First Cancer Treatment among Women with Breast Cancer, 2009 - 2014

Outcomes	Median Treatment Time* (95% CI)		HR (95% CI) for Appalachian versus Non-Appalachian		
	Appalachian	Non-Appalachian	Unadjusted	Adjusted HR**	Adjusted HR***
Time to First Treatment	16 (14 – 18) N=334	21 (20 – 22) N=911	1.17 (1.04 – 1.33) p=0.01	1.14 (1.01 – 1.30) p=0.04	1.11 (0.97 – 1.28) p=0.14
Time to first surgery	17 (15 – 20) N=334	22 (21 – 23) N=911	1.14 (1.002 – 1.29) p=0.046	1.18 (1.03 – 1.34) p=0.01	1.14 (0.99 – 1.32) p=0.08
Time to first chemotherapy	60 (52 – 65) N=155	62 (57 – 65) N=480	0.96 (0.79 – 1.15) p=0.64	0.88 (0.72 – 1.06) p=0.17	0.84 (0.68 – 1.04) p=0.12
Time to first radiation	110 (86 – 143) N=161	145 (118 – 160) N=549	1.11 (0.93 – 1.33) p=0.26	1.16 (0.97 – 1.39) p=0.11	1.33 (1.08 – 1.62) p=0.006
Time to first hormone	103.50 (82 – 136) N=206	126 (114 – 137) N=624	1.02 (0.87 – 1.20) p=0.83	0.97 (0.83 – 1.15) p=0.75	1.07 (0.89 – 1.28) p=0.50

* Time point at which 50% of patients have received first cancer treatment by Kaplan Meijer method

** Cox proportional hazards regression models: Hazard ratios (HR) for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, and other treatment received (except for specific treatment as first). 95% confidence intervals (CI) are given in parentheses.

*** Cox proportional hazards regression models: HRs estimates for receipt of cancer treatment, controlling for age at diagnosis, cancer stage, other treatment received (except for specific treatment as first), income and health insurance. 95% CIs are given in parentheses.

Table 5: Survival Analyses: Appalachian Residence and First Cancer Treatment among Women Recently Diagnosed with Breast Cancer, Stratified by Cancer Stage, 2009 - 2014

Outcomes	Median Treatment Time* (95% CI)		HR (95% CI) for Appalachian versus Non-Appalachian		
	Appalachian	Non-Appalachian	Unadjusted	Adjusted **	Adjusted ***
Among women diagnosed with earlier stage breast cancer - Stage 0 – 2 (N=899)					
Time to first treatment	17 (15 – 19) N=238	21 (20 – 23) N=661	1.25 (1.08 – 1.45) p=0.003	1.23 (1.06 – 1.43) p=0.006	1.18 (0.999 – 1.39) p=0.051
Time to first surgery	17 (15 – 20) N=238	22 (20 – 23) N=661	1.21 (1.04 – 1.40) p=0.01	1.22 (1.05 – 1.42) p=0.01	1.18 (0.997 – 1.40) p=0.055
Time to first chemotherapy	68 (60 – 78) N=81	66.5 (62 – 70) N=266	0.93 (0.72 – 1.20) p=0.57	0.87 (0.66 – 1.13) p=0.29	0.83 (0.62 – 1.12) p=0.23
Time to first radiation	85 (70 – 99) N=107	83 (75 – 95) N=381	1.10 (0.88 – 1.36) p=0.41	1.12 (0.90 – 1.39) p=0.33	1.21 (0.94 – 1.55) p=0.14
Time to first hormone	85 (70 – 108) N=148	98 (88 – 110) N=448	0.99 (0.82 – 1.20) p=0.89	1.03 (0.85 – 1.24) p=0.80	1.11 (0.90 – 1.38) p=0.33
Among women diagnosed with later stage breast cancer - Stage 3 – 4 (N=346)					
Time to first treatment	15 (12 – 21) N=96	19 (16 – 22) N=250	0.998 (0.79 – 1.27) p=0.99	0.997 (0.79 – 1.26) p=0.98	1.03 (0.78 – 1.36) p=0.85

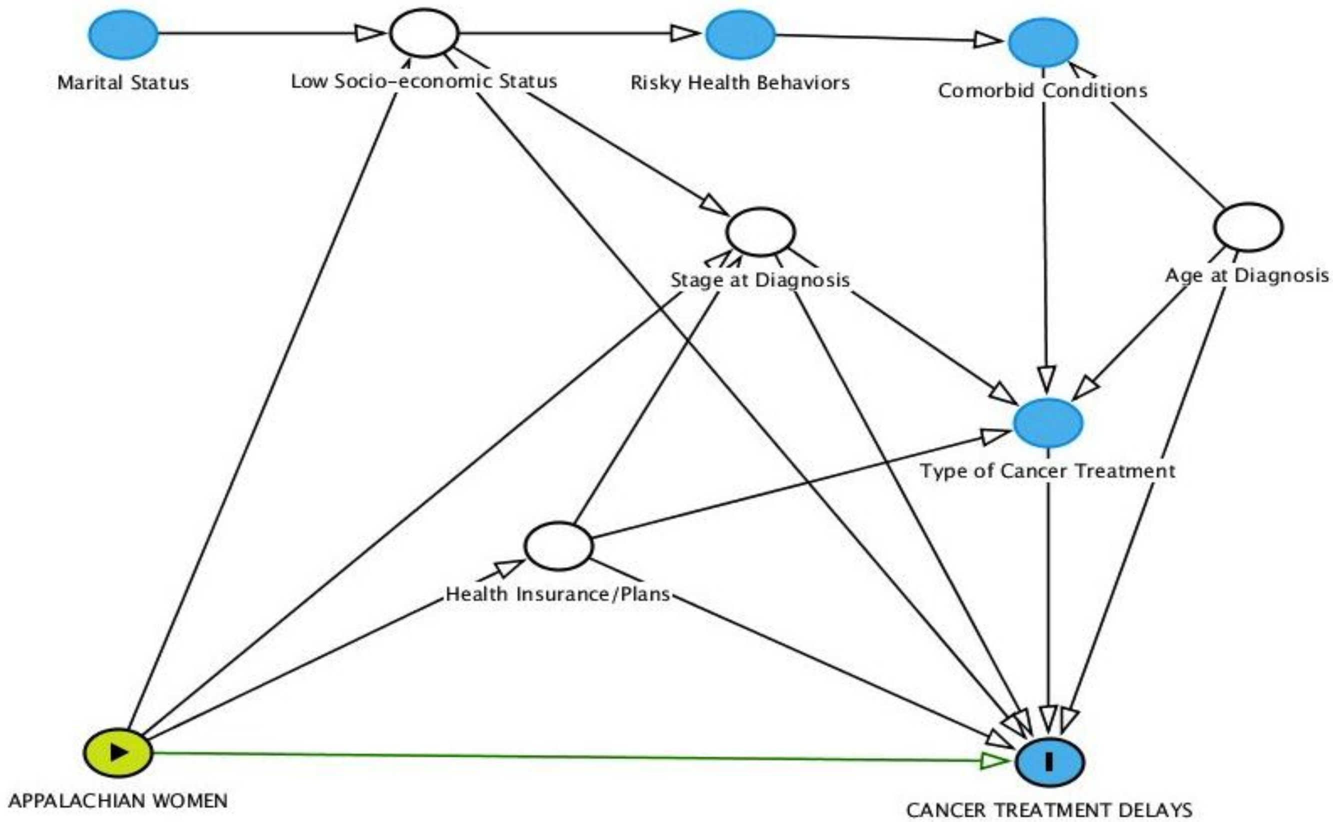
Outcomes	Median Treatment Time* (95% CI)		HR (95% CI) for Appalachian versus Non-Appalachian		
	Appalachian	Non-Appalachian	Unadjusted	Adjusted **	Adjusted ***
Time to first surgery	16.5 (14 – 24) N=96	23 (19 – 26) N=250	1.08 (0.85 – 1.37) p=0.55	1.10 (0.86 – 1.40) p=0.46	1.08 (0.81 – 1.44) p=0.60
Time to first chemotherapy	52 (46 – 61) N=74	55.5 (51 – 59) N=214	0.96 (0.73 – 1.26) p=0.78	0.93 (0.71 – 1.23) p=0.61	0.92 (0.67 – 1.25) p=0.58
Time to first radiation	188 (146 – 207) N=54	212 (203 – 220) N=168	1.15 (0.84 – 1.57) p=0.39	1.05 (0.76 – 1.44) p=0.78	1.42 (0.99 – 2.05) p=0.06
Time to first hormone	183 (128 – 209) N=58	183.5 (178 – 202) N=176	1.08 (0.80 – 1.46) p=0.62	0.89 (0.65 – 1.22) p=0.47	0.98 (0.67 – 1.43) p=0.92

* Time point at which 50% of patients have received first cancer treatment by Kaplan Meijer method

** Cox proportional hazards regression models: Hazard ratios (HR) for receipt of cancer treatment, controlling for age at diagnosis, and other treatment received (except for specific treatment as first). 95% confidence intervals (CI) are given in parentheses.

*** Cox proportional hazards regression models: HRs estimates for receipt of cancer treatment, controlling for age at diagnosis, other treatment received (except for specific treatment as first), income and health insurance. 95% CIs are given in parentheses

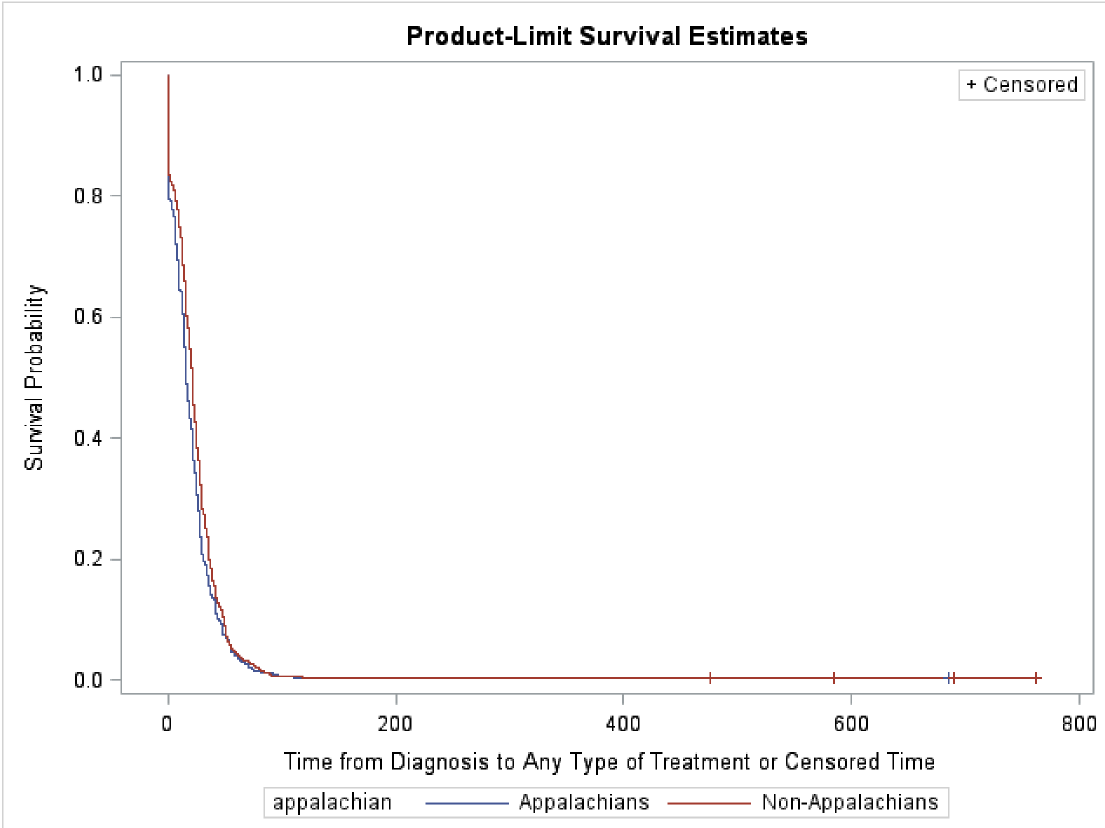
Figure 1: Directed Acyclic Graph (DAG) depicting a hypothesized mechanism for association of Appalachian women and delays in receipt of cancer treatment - Created with the online Dagitty at: http://www.dagitty.net/dags.html#



Minimal sufficient adjustment sets containing age at diagnosis for estimating the direct effect of Appalachian women on delays in receipt of cancer treatment: stage at diagnosis, socio-economic status and health insurance or plans

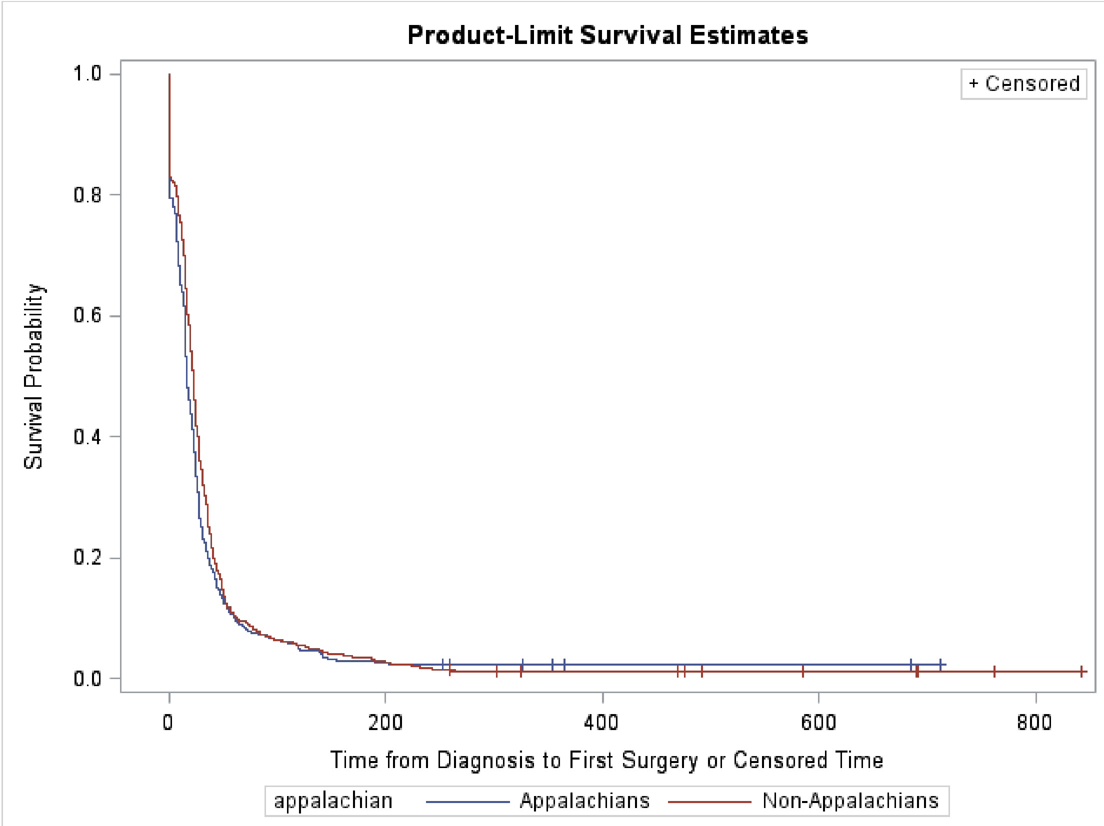
Figure 2: Kaplan Meijer Curves

Figure 2a. Time to First Breast Cancer Treatment



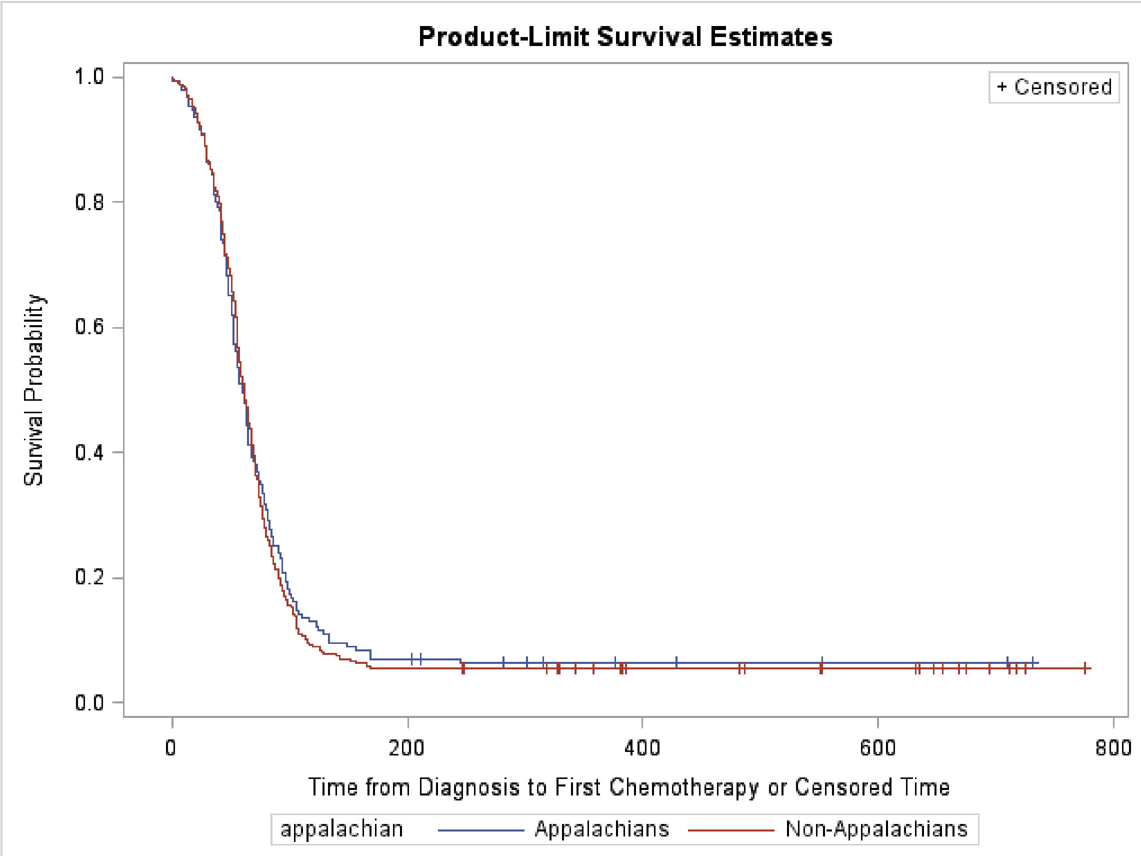
Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	6.7424	1	0.0094
Wilcoxon	11.6179	1	0.0007
-2Log(LR)	6.4775	1	0.0109

Figure 2b. Time to First Surgery



Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	4.2632	1	0.0389
Wilcoxon	11.2151	1	0.0008
-2Log(LR)	1.0371	1	0.3085

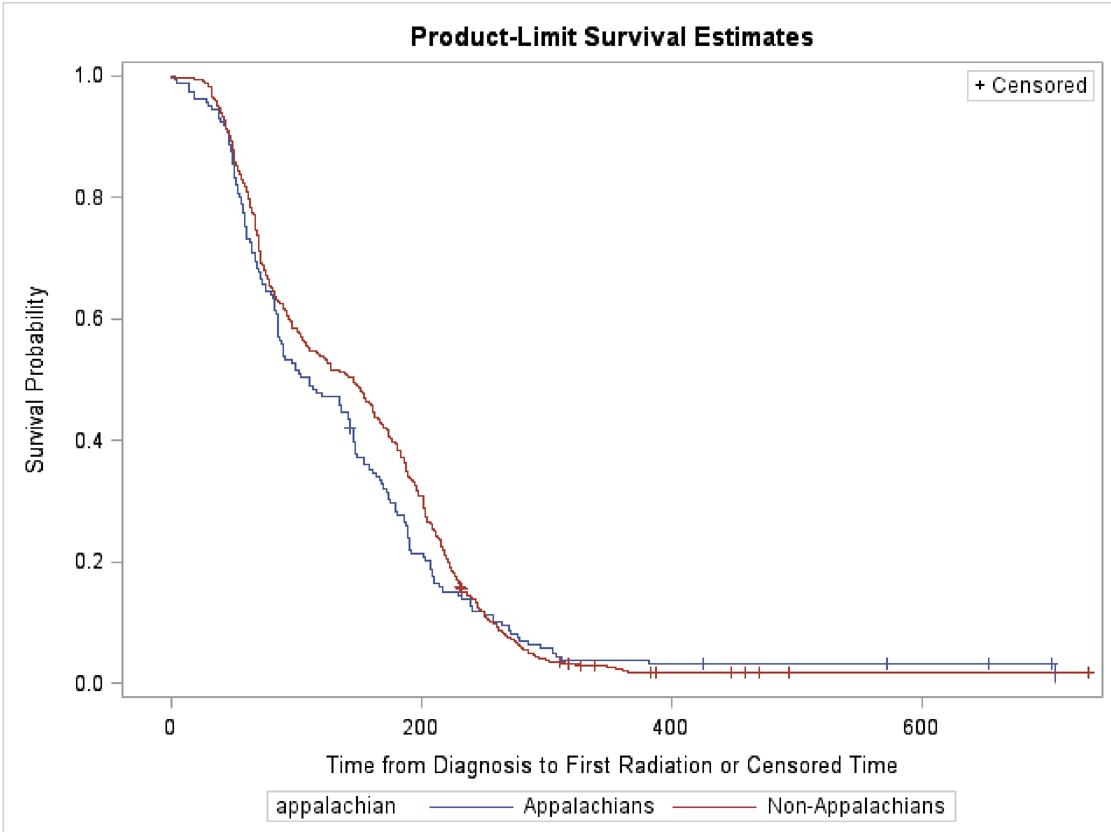
Figure 2c. Time to First Chemotherapy



Test of Equality over Strata

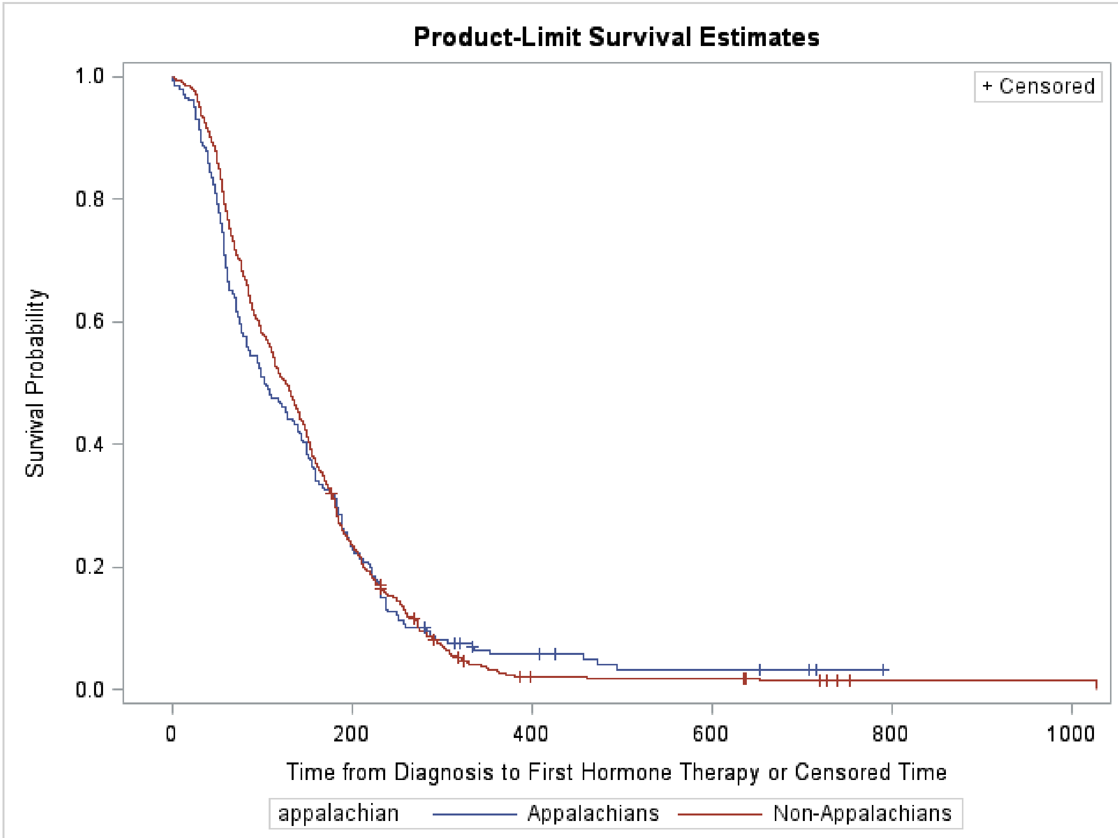
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.2283	1	0.6328
Wilcoxon	0.0068	1	0.9343
-2Log(LR)	0.0044	1	0.9473

Figure 2d. Time to First Radiation Therapy



Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.2903	1	0.256
Wilcoxon	3.6693	1	0.0554
-2Log(LR)	0.1576	1	0.6914

Figure 2e. Time to First Hormone Therapy



Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0443	1	0.8333
Wilcoxon	2.7808	1	0.0954
-2Log(LR)	0.0003	1	0.9868

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University of Kentucky Institutional Review Board Approval Number 09-0685-F1V

Appendix

Table 6: Full Cox proportional hazards regression models for time to any type of treatment

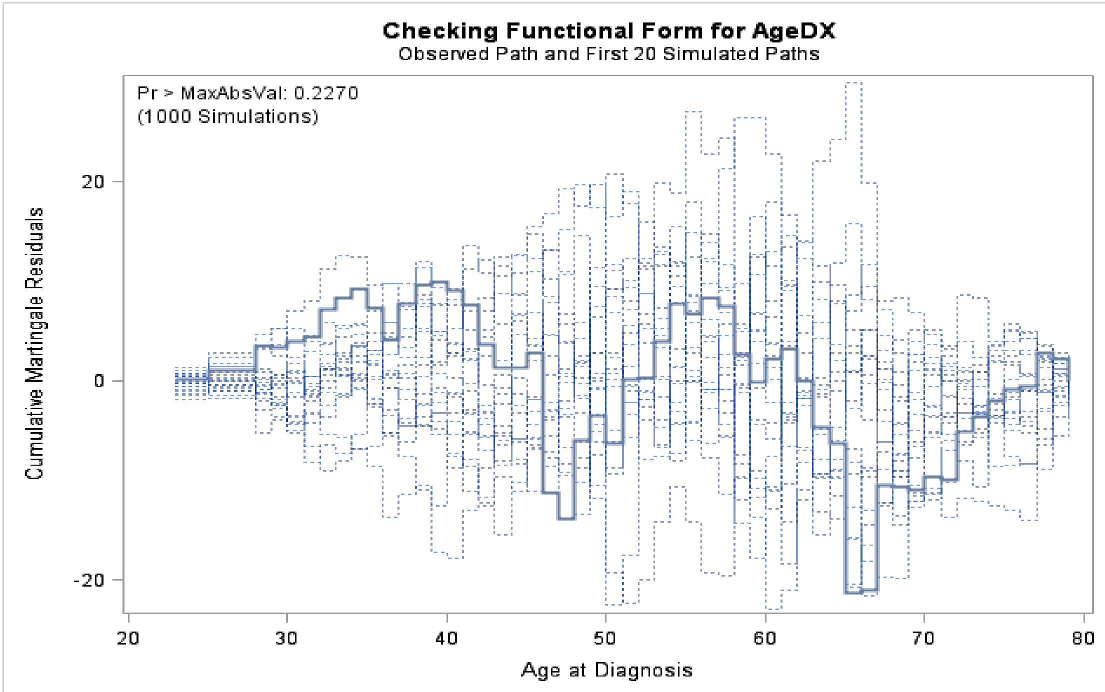
Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Appalachian Region:	p=0.01	p=0.04	p=0.14
Appalachian	1.17 (1.04 – 1.33)	1.14 (1.01 – 1.30)	1.11 (0.97 – 1.28)
Non-Appalachian	*Reference*	*Reference*	*Reference*
Age at Diagnosis:	p=0.01	p=0.02	p=0.20
	1.01 (1.002–1.01)	1.01 (1.001–1.01)	1.01 (0.99 – 1.01)
Stage at Diagnosis:	p=0.07	p=0.14	p=0.26
Stage 0	0.57 (0.37 – 0.88)	0.61 (0.39 – 0.94)	0.61 (0.37 – 1.01)
Stage 1	0.76 (0.54 – 1.08)	0.79 (0.55 – 1.12)	0.80 (0.54 – 1.18)
Stage 2 and Stage 3	0.74 (0.52 – 1.06)	0.77 (0.53 – 1.10)	0.79 (0.52 – 1.17)
Stage 4	*Reference*	*Reference*	*Reference*
Monthly Income:	p=0.04		p=0.09
<$1,000	*Reference*		*Reference*
$1,000 - $1,999	1.46 (1.15 – 1.86)		1.40 (1.09 – 1.79)
$2,000 – 2,999	1.33 (1.03 – 1.71)		1.32 (1.01 – 1.73)
$3,000 - $3,999	1.35 (1.05 – 1.75)		1.37 (1.04 – 1.80)
$4,000 - $4,999	1.14 (0.87 – 1.50)		1.13 (0.85 – 1.51)
≥$5,000	1.24 (0.99 – 1.55)		1.28 (1.00 – 1.64)
Health Insurance:	p=0.11		p=0.75
Uninsured	1.15 (0.81 – 1.64)		0.94 (0.61 – 1.45)
Medicaid	0.87 (0.70 – 1.07)		0.93 (0.73 – 1.20)
Medicare	1.12 (0.98 – 1.27)		1.07 (0.89 – 1.27)
Private insurance	*Reference*		*Reference*

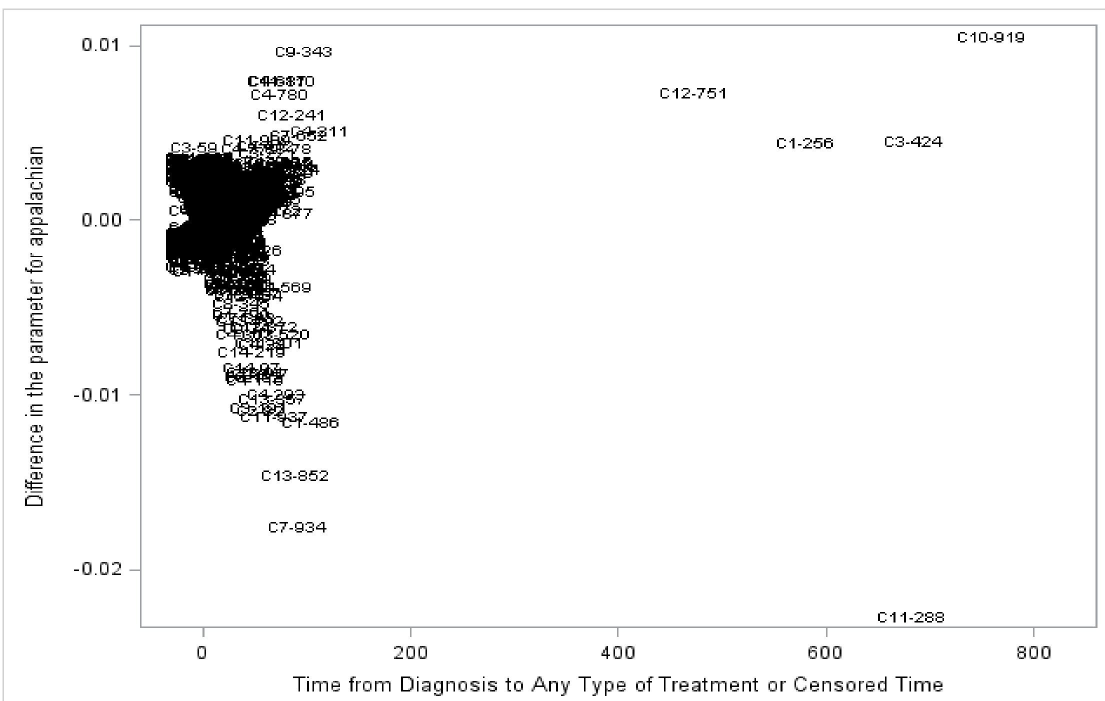
95% Confidence Interval (95% CI) of the hazards ratios are given in parentheses

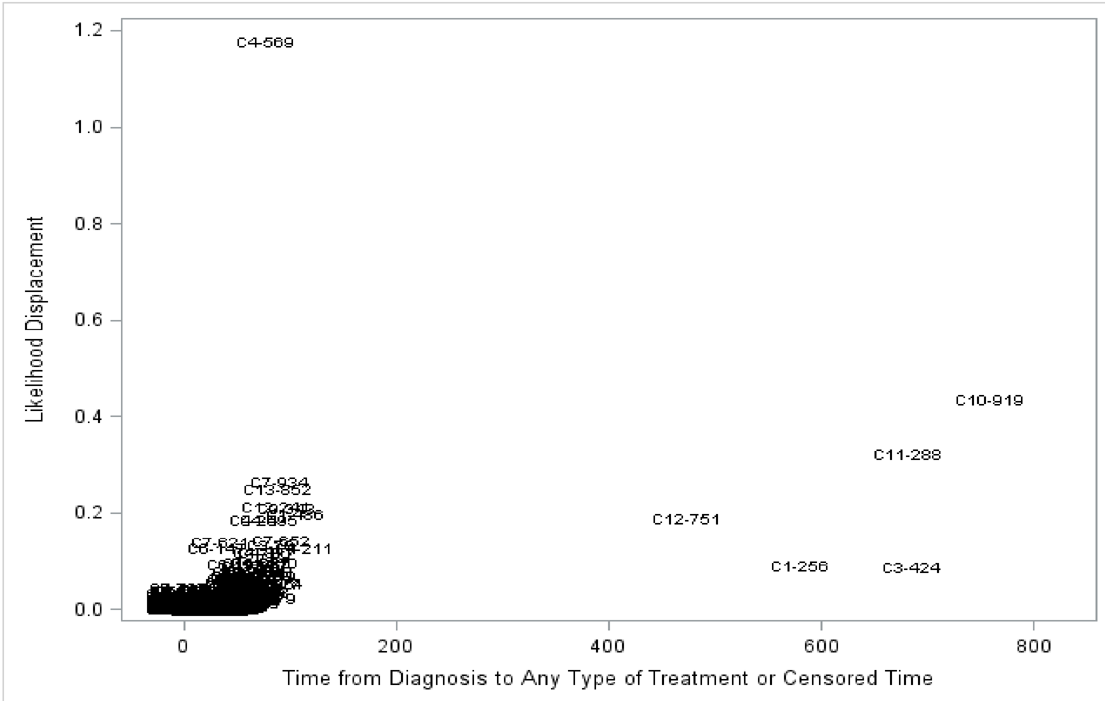
*Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis and stage at diagnosis

** Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, stage at diagnosis, family's monthly income and health insurance

Example for the Diagnostic Test







Likelihood Displacement
Time from Diagnosis to Any Type of Treatment or Censored Time
C4-569
C10-919
C11-288
C7-934
C13-852
C12-751
C1-256
C3-424

Table 7: Full Cox proportional hazards regression model for time to first surgery

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Appalachian Region:	p=0.046	p=0.01	p=0.08
Appalachian	1.14 (1.002–1.29)	1.18 (1.03 – 1.34)	1.14 (0.99 – 1.32)
Non-Appalachian	*Reference*	*Reference*	*Reference*
Age at Diagnosis:	p<0.001	p<0.0001	p=0.01
	1.02 (1.01–1.02)	1.01 (1.01 – 1.02)	1.01 (1.002–1.02)
Stage at Diagnosis:	p<0.0001	p<0.0001	p<0.0001
Stage 0	2.26 (1.40 – 3.65)	2.38 (1.46 – 3.87)	2.14 (1.25 – 3.65)
Stage 1	2.60 (1.74 – 3.90)	2.58 (1.71 – 3.87)	2.31 (1.50 – 3.55)
Stage 2 and Stage 3	2.01 (1.33 – 3.03)	2.01 (1.33 – 3.04)	1.81 (1.17 – 2.81)
Stage 4	*Reference*	*Reference*	*Reference*
Monthly Income:	p=0.17		p=0.41
<$1,000	*Reference*		*Reference*
$1,000 - $1,999	1.34 (1.05 – 1.71)		1.22 (0.95 – 1.56)
$2,000 – 2,999	1.23 (0.95 – 1.59)		1.19 (0.90 – 1.56)
$3,000 - $3,999	1.28 (0.99 – 1.66)		1.19 (0.90 – 1.57)
$4,000 - $4,999	1.09 (0.83 – 1.43)		1.02 (0.76 – 1.36)
≥$5,000	1.25 (0.99 – 1.58)		1.21 (0.94 – 1.55)
Health Insurance:	p=0.0007		p=0.09
Uninsured	1.03 (0.72 – 1.48)		1.23 (0.80 – 1.87)
Medicaid	0.79 (0.63 – 0.98)		0.80 (0.62 – 1.03)
Medicare	1.22 (1.08 – 1.40)		1.10 (0.92 – 1.32)
Private insurance	*Reference*		*Reference*
Chemotherapy:	p=0.002	p=0.54	p=0.93
Yes	0.84 (0.75 – 0.94)	0.96 (0.84 – 1.09)	0.99 (0.86 – 1.15)
No	*Reference*	*Reference*	*Reference*

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Radiation:	p=0.005	p=0.005	p=0.006
Yes	1.18 (1.05 – 1.32)	1.18 (1.05 – 1.33)	1.20 (1.05 – 1.37)
No	*Reference*	*Reference*	*Reference*
Hormone Therapy:	p=0.10	p=0.22	p=0.54
Yes	1.11 (0.98 – 1.25)	1.08 (0.95 – 1.22)	1.04 (0.91 – 1.20)
No	*Reference*	*Reference*	*Reference*

95% Confidence Interval (95% CI) of the hazards ratios are given in parentheses

*Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, other types of treatment and stage at diagnosis

** Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, stage at diagnosis, other types of treatment, family's monthly income and health insurance

Table 8: Full Cox proportional hazards regression models for time to first chemotherapy

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Appalachian Region:	p=0.64	p=0.17	p=0.12
Appalachian	0.96 (0.79 – 1.15)	0.88 (0.72 – 1.06)	0.84 (0.68 – 1.04)
Non-Appalachian	*Reference*	*Reference*	*Reference*
Age at Diagnosis:	p<0.0001	p<0.0001	p=0.0008
	0.98 (0.97 – 0.99)	0.98 (0.97 – 0.99)	0.98 (0.97–0.99)
Stage at Diagnosis:	p<0.0001	p<0.0001	p<0.0001
Stage 0	1.63 (0.22–12.15)	2.39 (0.32–17.94)	2.61 (0.34–19.94)
Stage 1	0.32 (0.21 – 0.50)	0.37 (0.24 – 0.58)	0.41 (0.25 – 0.67)
Stage 2 and Stage 3	0.47 (0.30 – 0.72)	0.54 (0.35 – 0.86)	0.64 (0.39 – 1.05)
Stage 4	*Reference*	*Reference*	*Reference*
Monthly Income:	p=0.09		p=0.007
<$1,000	*Reference*		*Reference*
$1,000 - $1,999	1.65 (1.16 – 2.33)		2.08 (1.44 – 3.01)
$2,000 – 2,999	1.47 (1.01 – 2.15)		1.58 (1.06 – 2.37)
$3,000 - $3,999	1.28 (0.88 – 1.85)		1.44 (0.97 – 2.13)
$4,000 - $4,999	1.30 (0.90 – 1.88)		1.53 (1.03 – 2.27)
≥$5,000	1.49 (1.07 – 2.06)		1.56 (1.09 – 2.25)
Health Insurance:	p=0.0009		p=0.20
Uninsured	1.02 (0.65 – 1.60)		0.80 (0.47 – 1.35)
Medicaid	0.94 (0.71 – 1.24)		0.93 (0.66 – 1.31)
Medicare	0.65 (0.53 – 0.80)		0.75 (0.57 – 0.98)
Private insurance	*Reference*		*Reference*
Surgery:	p<0.0001	p<0.0001	p=0.0008
Yes	0.20 (0.11 – 0.38)	0.27 (0.14 – 0.52)	0.30 (0.15 – 0.61)

Predictor	**Unadjusted HR (95% CI)**	**Adjusted HR* (95% CI)**	**Adjusted HR** (95% CI)**
No	*Reference*	*Reference*	*Reference*
Radiation:	p=0.15	p=0.07	p=0.32
Yes	1.13 (0.96 – 1.33)	1.17 (0.99 – 1.38)	1.10 (0.91 – 1.33)
No	*Reference*	*Reference*	*Reference*
Hormone Therapy:	p<0.0001	p<0.0001	p<0.0001
Yes	0.69 (0.59 – 0.82)	0.67 (0.56 – 0.79)	0.61 (0.50 – 0.74)
No	*Reference*	*Reference*	*Reference*

95% Confidence Interval (95% CI) of the hazards ratios are given in parentheses

*Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, other types of treatment and stage at diagnosis

** Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, stage at diagnosis, other types of treatment, family's monthly income and health insurance

Table 9: Full Cox proportional hazards regression models for time to first radiation

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Appalachian Region:	p=0.26	p=0.11	p=0.006
Appalachian	1.11 (0.93 – 1.33)	1.16 (0.97 – 1.39)	1.33 (1.08 – 1.62)
Non-Appalachian	*Reference*	*Reference*	*Reference*
Age at Diagnosis:	p=0.001	p=0.28	p=0.69
	1.01 (1.01 – 1.02)	0.99 (0.99–1.004)	0.99 (0.99–1.01)
Stage at Diagnosis:	p<0.0001	p<0.0001	p<0.0001
Stage 0	1.11 (0.57 – 2.18)	0.65 (0.33 – 1.29)	0.90 (0.44–1.88)
Stage 1	0.98 (0.57 – 1.66)	0.94 (0.55 – 1.61)	1.02 (0.59 – 1.77)
Stage 2 and Stage 3	0.41 (0.24 – 0.71)	0.55 (0.32 – 0.94)	0.60 (0.34 – 1.06)
Stage 4	*Reference*	*Reference*	*Reference*
Monthly Income:	p=0.04		p=0.17
<$1,000	*Reference*		*Reference*
$1,000 - $1,999	1.40 (0.99 – 1.98)		1.03 (0.72 – 1.48)
$2,000 – 2,999	1.71 (1.18 – 2.47)		1.10 (0.73 – 1.64)
$3,000 - $3,999	1.39 (0.97 – 2.00)		0.74 (0.50 – 1.11)
$4,000 - $4,999	1.30 (0.89 – 1.90)		0.89 (0.59 – 1.36)
≥$5,000	1.61 (1.17 – 2.22)		1.02 (0.71 – 1.47)
Health Insurance:	p=0.004		p<0.0001
Uninsured	0.97 (0.60 – 1.57)		0.86 (0.48 – 1.53)
Medicaid	0.58 (0.43 – 0.78)		0.43 (0.30 – 0.62)
Medicare	0.91 (0.76 – 1.09)		0.59 (0.46 – 0.76)
Private insurance	*Reference*		*Reference*
Surgery:	p=0.18	p=0.01	p=0.02
Yes	3.86 (0.54–27.54)	11.7 (1.63–83.91)	10.92 (1.48–80.67)
No	*Reference*	*Reference*	*Reference*

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Chemotherapy:	p<0.0001	p<0.0001	p<0.0001
Yes	0.26 (0.22 – 0.31)	0.30 (0.25 – 0.37)	0.25 (0.20 – 0.31)
No	*Reference*	*Reference*	*Reference*
Hormone Therapy:	p<0.0001	p<0.0001	p=0.003
Yes	1.55 (1.31 – 1.83)	1.48 (1.24 – 1.77)	1.34 (1.11 – 1.63)
No	*Reference*	*Reference*	*Reference*

95% Confidence Interval (95% CI) of the hazards ratios are given in parentheses

*Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, other types of treatment and stage at diagnosis

** Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, stage at diagnosis, other types of treatment, family's monthly income and health insurance

Table 10: Full Cox proportional hazards regression models for time to first hormone therapy

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Appalachian Region:	p=0.83	p=0.75	p=0.50
Appalachian	1.02 (0.87 – 1.20)	0.97 (0.83 – 1.15)	1.07 (0.89 – 1.28)
Non-Appalachian	*Reference*	*Reference*	*Reference*
Age at Diagnosis:	p<0.0001	p=0.55	p=0.16
	1.02 (1.01 – 1.03)	1.002 (0.99–1.01)	1.01 (0.997–1.02)
Stage at Diagnosis:	p<0.0001	p=0.0002	p=0.01
Stage 0	0.65 (0.37 – 1.17)	0.30 (0.17 – 0.55)	0.38 (0.19–0.75)
Stage 1	0.67 (0.44 – 1.03)	0.49 (0.31 – 0.78)	0.54 (0.32 – 0.89)
Stage 2 and Stage 3	0.38 (0.25 – 0.59)	0.42 (0.26 – 0.67)	0.46 (0.28 – 0.78)
Stage 4	*Reference*	*Reference*	*Reference*
Monthly Income:	p=0.16		p=0.01
<$1,000	*Reference*		*Reference*
$1,000 - $1,999	1.44 (1.05 – 1.98)		1.61 (1.15 – 2.25)
$2,000 – 2,999	1.54 (1.11 – 2.15)		1.24 (0.86 – 1.79)
$3,000 - $3,999	1.29 (0.93 – 1.81)		1.27 (0.88 – 1.82)
$4,000 - $4,999	1.43 (1.01 – 2.01)		1.65 (1.14 – 2.40)
≥$5,000	1.44 (1.07– 1.93)		1.59 (1.14 – 2.21)
Health Insurance:	p=0.51		p=0.0009
Uninsured	1.09 (0.65 – 1.83)		0.83 (0.45 – 1.54)
Medicaid	0.81 (0.61 – 1.08)		0.84 (0.59 – 1.19)
Medicare	0.99 (0.84 – 1.17)		0.64 (0.51 – 0.79)
Private insurance	*Reference*		*Reference*
Surgery:	p=0.001	p=0.0008	p=0.002
Yes	0.33 (0.17 – 0.64)	0.30 (0.15 – 0.61)	0.29 (0.13 – 0.62)

Predictor	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
No	*Reference*	*Reference*	*Reference*
Radiation:	p=0.86	p=0.55	p=0.59
Yes	1.01 (0.88 – 1.17)	1.05 (0.90 – 1.21)	0.96 (0.81 – 1.13)
No	*Reference*	*Reference*	*Reference*
Chemotherapy:	p<0.0001	p<0.0001	p<0.0001
Yes	0.33 (0.28 – 0.38)	0.30 (0.15 – 0.61)	0.27 (0.22 – 0.34)
No	*Reference*	*Reference*	*Reference*

95% Confidence Interval (95% CI) of the hazards ratios are given in parentheses

*Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, other types of treatment and stage at diagnosis

** Multivariate Cox Proportional Hazards Regression Model: Adjusting for age at diagnosis, stage at diagnosis, other types of treatment, family's monthly income and health insurance

Table 11: Spearman Correlation Coefficients

Variables	Appalachian Region	Education Attainment	Monthly Income	Private Insurance	Medicaid	Medicare
Appalachian Region	1	-0.18 p<.0001	-0.19 p<.0001	-0.15 p<.0001	0.06 p=0.03	0.09 p=0.001
Education Attainment	-0.18 p<.0001	1	0.49 p<.0001	0.31 p<.0001	-0.14 p<.0001	-0.22 p<.0001
Monthly Income	-0.19 p<.0001	0.49 p<.0001	1	0.41 p<.0001	-0.28 p<.0001	-0.22 p<.0001
Private insurance	-0.15 p<.0001	0.31 p<.0001	0.41 p<.0001	1	-0.39 p<.0001	-0.78 p<.0001
Medicaid	0.06 p=0.03	-0.14 p<.0001	-0.28 p<.0001	-0.39 p<.0001	1	-0.17 p<.0001
Medicare	0.09 p=0.001	-0.22 p<.0001	-0.22 p<.0001	-0.78 p<.0001	-0.17 p<.0001	1

Table 12: Variance Inflation

Dependent Variable: Number of Days between Diagnosis Date and First Treatment

Variable	DF	Parameter Estimate	Standard Error	t Value	p value|	Variance Inflation
Intercept	1	22.03	2.40	9.19	<.0001	0
Appalachian Region	1	-2.59	1.36	-1.91	0.06	1.06
Education Attainment	1	0.34	0.50	0.68	0.49	1.34
Monthly Income	1	-0.18	0.41	-0.44	0.66	1.47
Health Insurance	1	0.22	0.89	0.25	0.80	1.25