2021

COLORECTAL CANCER DIFFERENCES IN STAGING AND SURVIVAL: APPALACHIAN AND NON-APPALCHIAN KENTUCKIANS

Ripley Lucas
University of Kentucky, rhlu223@uky.edu

STUDENT AGREEMENT:

I represent that my capstone and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's capstone including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Ripley Lucas, Student

Thomas Tucker, PhD, Committee Chair

Sarah Wackerbarth, PhD, Director of Graduate Studies

COLORECTAL CANCER DIFFERENCES IN STAGING AND SURVIVAL: APPALACHIAN AND NON-APPALCHIAN KENTUCKIANS

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the requirements for the degree of

Master of Public Health

in the

University of Kentucky College of Public Health

By

RIPLEY LUCAS

Lexington, Kentucky

XXXX XX, XXXX

Committee Members

Thomas Tucker, PhD Chair

Jaclyn McDowell, DrPH

Steven Browning, PhD

Table of Contents

Abstract

Colorectal cancer is the third most commonly diagnosed cancer in the United States. Historically, the Appalachian region of Kentucky has experienced disparities in colorectal cancer screening and survival as compared to both the non-Appalachian region of the state and the United States. The aim of this paper is to investigate the differences in cancer staging and survival after diagnosis in Appalachian and non-Appalachian Kentuckians. The present time period of study is a retrospective, population-based cohort with data taken from the Kentucky Cancer Registry. Binomial logistic regression and Cox proportional hazards models were used to estimate unadjusted and adjusted odds ratios and hazard ratios, respectively. Of colorectal cancer cases, 61% of Appalachian (n=1875) and 58.8% of non-Appalachian (n=3843) cases were late stage. There were 749 colorectal cancer related deaths among Appalachians and 1527 deaths among non-Appalachians. A multivariable binomial logistic regression model found the odds of late-stage cancer diagnosis were 1.08 (95% CI: 0.99-1.18) times higher for Appalachians. A multivariable Cox proportional hazards model found the hazards of cancer related mortality were 1.03 (95% CI: 0.94-1.13) times higher for Appalachians. Both adjusted models produced insignificant associations between Appalachian residence and the outcomes of interest. Further investigation is needed to fully understand the factors that influence cancer disparity in Appalachia.

1. Introduction

1.1. Background

Despite declines in both incidence and mortality in past decades, colorectal cancer is the third most commonly diagnosed cancer in both men and women in the United States (Siegel et al., 2017). Higher rates of diagnoses are in part due to nationwide efforts to increase colorectal

cancer screenings, although improvements have varied by state. Kentucky has had the highest increase in colorectal cancer screening rates among all states, with a 53% increase between 1999 and 2016 (Kentucky Cancer Consortium Colon Cancer Committee, 2018). As colorectal cancer screening rates have increased in Kentucky, colorectal cancer incidence and mortality have decreased by 23% and 30%, respectively (Kentucky Cancer Consortium Colon Cancer Committee, 2018). Increased screening, as well as improvements to treatment and historical improvements to colorectal cancer risk factors, are associated with decreases in colorectal cancer incidence and mortality (Siegel et al., 2017).

Disparities in colorectal cancer staging and survival have been identified in those with lower socioeconomic status both domestically (Clegg et al., 2002) and abroad (Kweon et al., 2017) (Booth et al., 2010). This association has been seen in other cancer sites as well, including but not limited to lung, prostate, breast, and cervical cancers (Booth et al., 2010) (Lantz et al., 2006). Colorectal cancer disparity in Kentucky begins at the point of screening, as those with less than a high school education and those with a household income of less than $25,000 are at a greater risk of not having been screened when compared to their more educated and higher income counterparts (Kentucky Department for Public Health & The Centers for Disease Control and Prevention, 2018).

The Appalachian region of the United States faces many health disparities (Arnold, 2017); notably, cancer is among the highest contributors to excess morbidity and mortality in the area (Appalachian Regional Commission, 2017). In Appalachia, the leading cause of death is cancer, as opposed to the rest of the United States where it is heart disease (Arnold, 2017). The cancer disparity in Appalachia has been present historically, as it has been shown that between 1969 and 2011, cancer incidence rates were 36% higher in rural Appalachian Kentucky counties

than in non-Appalachia urban areas nationwide (Cavallo, 2017) (Arnold, 2017). This difference in incidence was underscored by an increase of 182.2 to 195.2 cases per 100,000 during the same specified time frame (Cavallo, 2017). Appalachians experience a disparity in colorectal cancer survival as well; as after age-adjustment, Appalachians have a mortality rate of 20.6 compared to a non-Appalachian rate of 16.9 per 100,000 (Kentucky Cancer Consortium, 2019). Furthermore, the 3- and 5-year rates for cancer survival are lower for Appalachians when compared to non-Appalachians; 57% and 50% of cancer patients survive at least 3 and 5 years, respectively, in Appalachia, while 65% and 58% of cancer patients survive at least 3 and 5 years urban, non-Appalachian areas (Cavallo, 2017).

Colorectal cancer screening efforts in Kentucky have increased over recent years, but not as rapidly as in the non-Appalachian area of the state (Kentucky Department for Public Health, 2017). The present literature suggests that potential reasons for lower cancer screening rates in Appalachian Kentucky include a lack of access to healthcare, limited financial resources, and lower education levels (Schoenberg et al., 2012a). There is a continued need to identify potential associations between the population at risk and colorectal cancer staging and survival (Schoenberg et al., 2012a).

1.2. Setting

Appalachia is a distinct geographic region of the eastern United States, comprised of 420 counties across 13 states (Appalachian Regional Commission, 2018). Of Kentucky's 54 Appalachian-designated counties, 38 counties have been identified by the Appalachian Regional Commission as financially distressed and 13 others are considered at-risk (Appalachian Regional Commission, 2018). Kentucky has the highest rate of poverty among Appalachian states, where nearly a quarter of Appalachians (25.4%) are considered impoverished, compared to 18.9% of

those in non-Appalachian counties (Fahe, 2019). Unemployment, however, is not a primary contributor to this disparity, but rather that those employed make significantly less than the average American ($30,308 vs. $46, 049, respectively) (Fahe, 2019). These earnings are potentially associated with the level of educational attainment in the region, as 77% of adults over 25 in Appalachian Kentucky counties have graduated high school, compared to the state average of 90% and the national average of 85% (National Center for Education Statistics, 2018).

Current qualitative research suggests that individuals in the Appalachian region of Kentucky also tend to hold attitudes toward healthcare that may serve as a barrier to colorectal cancer screenings and treatment (Schoenberg et al., 2012a). Appalachians report lack of awareness of and access to screening and cancer resources, embarrassment and concern about screening practices, and a lack of trust towards the medical establishment (Schoenberg et al., 2012a). Appalachians also report a lack of knowledge of family histories, as cancer is viewed as a stigmatized condition and therefore there is a reluctance to share information on diagnoses (Schoenberg et al., 2012a). These attitudes are cited as factors that contribute to the stagnation in screening rates in the area.

1.3. Cancer Staging and Survival

Colorectal cancer staging begins at 0 (*in situ*), the earliest, and then ranges from stage I (1) to stage IV (4) (American Cancer Society, 2020). The American Joint Committee on Cancer defines the colorectal cancer stages as follows: stage I is cancer that has grown through the muscularis mucosa into the submucosa, potentially grown into the muscularis propria, and has not spread to nearby lymph nodes or distant sites; stage II is cancer that has grown into, though, or past the outermost layers of the colon or rectum, potentially attached to a nearby organ, and

has not spread to nearby lymph nodes or distant sites; stage III cancer is cancer that has grown into, though, or past the outermost layers of the colon or rectum, potentially attached to a nearby organ, has spread to nearby lymph nodes or the tissue surrounding them, and has not spread to distant sites; stage IV cancer is that has may or may not have grown through the colon or rectum, may or may not have spread to nearby lymph nodes, and has spread to a distant organ or to distant parts of the peritoneum. For the purpose of this study, SEER summary staging guidelines will be followed. Early-stage will correspond with stage I cancers (localized) and late-stage will correspond with stage II-IV cancers (regional and distant).

Late-stage cancer diagnosis is a strong predictor for fewer years of survival after diagnosis, both in the United States and internationally (Clegg et al., 2002) (Ortiz-Ortiz et al., 2016). When diagnosed at an early stage, treatment for colorectal cancer is significantly more effective and often less aggressive than when diagnosed at a late state, increasing the patient's likelihood of survival (Andrew et al., 2018). Because of this, there is a present need to further identify characteristics of patients that may put them at a higher risk of a late-stage colorectal cancer diagnosis.

A variety of factors are associated with stage at diagnosis, including those regarding the patient's biological or genetic risk factors, their sociodemographic characteristics, or specific information related to their medical treatment and access to care. Evidence suggests that cancer specific characteristics, such as tumor grade and lymph node involvement, are associated with increased cancer stage progression, increasing the likelihood that the cancer will be diagnosed at a later stage (Bal et al., 2012). Race is a significant demographic characteristic associated with cancer stage at diagnosis in the United States, but there is strong evidence that a portion of this association is due to factors such as lower income and educational attainment that have been

historically associated with minority populations in the U.S. (Lantz et al., 2006). Higher household income and education level has been shown to be associated with earlier stages of cancer diagnosis and lower rates of cancer related mortality (Tomic et al., 2018). Socioeconomic status may also explain disparities between timeliness of care, as it has been observed that patients who experience delays between symptom onset and diagnosis or enter the healthcare system through the emergency room rather than through a primary care provider have a higher risk of late-stage diagnosis (Ortiz-Ortiz et al., 2016). Access to care is a multifaceted issued. Spatial access to care has been associated with cancer survival as well, as patients who are farther from treatment centers are at an increased risk of cancer related mortality (Cramb et al., 2012). Financial access to care in the United States is often determined by insurance type, and it has been seen that patients without an insurance provider are at a significantly greater risk of late-stage cancer diagnosis and poorer cancer related outcomes (Fayanju et al., 2013).

Socioeconomic status influences many of the potential risk factors associated with late-stage diagnosis of colorectal cancer. Further research is needed to better identify individuals who may be at risk through their relationship between SES and additional risk factors; improved understanding of these relationships will better help clinicians target screening interventions and inform decisions in medical care.

1.4. Study Objective

Current literature suggests that there is a clear relationship between lower socioeconomic status (SES) and worse cancer outcomes, particularly years of survival after diagnosis (Booth et al., 2010). Later stage diagnoses in those with lower SES may potentially be a contributor to higher cancer mortality among this population (Byers et al., 2008). Differences in survival between those of lower SES and those of higher SES have been observed across genders, age

groups, and races and ethnicities (Thomson et al., 2001) (Lantz et al., 2006). The Appalachian region of Kentucky is characterized by lower than average household income, lower levels of educational attainment, less accessible healthcare systems, and cultural attitudes associated with lower colorectal cancer screening uptake (Schoenberg et al., 2012a). Because of the multitude of risk factors facing this population, the purpose of this paper is to investigate the differences in cancer staging and survival after diagnosis in Appalachian and non-Appalachian Kentuckians.

1.5. Research Hypothesis

The current study aims to investigate the relationship between Appalachian residence in Kentucky with respect to colorectal cancer staging and survival. The study will investigate two hypotheses:

Hypothesis 1: The stage at which colorectal cancer is diagnosed will be later for residents who live in an Appalachian designated Kentucky county when compared to non-Appalachian residents.

Hypothesis 2: Years lived after colorectal cancer diagnosis will be fewer for residents who live in an Appalachian designated Kentucky county when compared to non-Appalachian residents.

2. Methods

2.1. Data Source

2.1.1. Kentucky Cancer Registry

The present study is a retrospective, population-based cohort with data taken from the Kentucky Cancer Registry (KCR). Mandatory case reporting to the KCR began January 1, 1991 after legislation was passed by the State General Assembly to establish the KCR as the state's population based central cancer registry (Kentucky Cancer Registry, 2020). KCR actively

monitors for cancer cases, collects follow-up information after diagnosis, and links to state and national vital record keeping agencies (Kentucky Cancer Registry, 2020). The KCR has been a part of the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program for over two decades (est. 2000), has participated in the Center for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR), and has consistently received the highest rating for completeness, accuracy, and timeliness from the North American Association of Central Cancer Registries.

2.1.2. Study Cohort

The cohort selected for the present study included all primary colorectal cancer cases aged 18 years or older diagnosed in Kentucky between January 1st, 2012 and December 31st, 2017. Inclusion criteria limited the study cohort to cases that were invasive (stage I-IV), alive at time of diagnosis, and were first and only primary cases. Exclusion criteria excluded those with *in situ* or stage 0 cancer, those who were diagnosed through an autopsy or death record, or those who had previous or subsequent cancer diagnoses. The initial sample supplied by KCR comprised of 10,044 complete cases. Participants were excluded due to unknown race (n=71) and unknown cancer stage (n=363) The final sample included 9,610 participants. 1851 participants were excluded from survival-specific analyses due to unrelated cause of death, resulting in a sample size of 7,829.

2.2. Variables Included in Analysis

The variables listed below were used in the following analyses. Descriptions of variables and variable manipulation is provided.

- Sex – The variable used for sex is categorical; patients were identified as either male or female. Transgender individuals were assigned to the sex they were assigned at birth to account for potential biological associations.
- Race – The variable used for race is categorical; patients were grouped as White/Other and Black.
- Age – The variable used for age group is continuous; this variable represents the patient's age at time of diagnosis.
- Age group - The variable used for age group is categorical; patients were grouped as less than 50 years aged, between 50 and 69 years aged, or above 70 years aged.
- Year of Diagnosis – The variable used for year of diagnosis is categorical; diagnosis years range between 2012 and 2017.
- Appalachian Status - The variable used for race is categorical; patients were identified as either from an Appalachian or non-Appalachian Kentucky county at the time of diagnosis.
- Primary payer – The variable used for primary payer is categorical; patients were grouped by either having had a type of private insurance, Medicaid, Medicare, no insurance, and unknown insurance type.
- Stage at diagnosis – The variable used for stage at diagnosis is categorical; patients were grouped as early-stage (localized) or late-stage (regional or distant). Stage is determined by the 2000 SEER Summary Staging Guide.
- Marital status - The variable used for marital status is categorical; patients were grouped at time of diagnosis as married/partnered or single (including those who were separated, divorced, or widowed).

- Survival interval – The variable used for survival interval is continuous; this variable represents the months from diagnosis to either last contact or death.
- Survival status – The variable used for survival status is categorical; patients were grouped as either alive, dead due to the primary colorectal cancer tumor, or dead due to reasons unknown or unrelated to the primary colorectal cancer tumor.

2.3. Statistical Analysis

Sociodemographic, diagnostic, and survival factors were examined to investigate the associations between Appalachian status and colorectal cancer stage at diagnosis and survival. Exploratory data analysis and descriptive statistics of categorical variables consisted of counts and percentages generated for both the overall sample and the sample stratified by the primary exposure of interest, Appalachian status. The significance of categorical variable associations between the stratified results was assessed by preforming Pearson's chi-squared test (χ^2). Significance testing for continuous variables was assessed by preforming independent samples t-test. All p-values calculated were two-sided with a 0.05 significance level.

Univariate and multivariable binomial logistic regression models were used to identify differences in association between exposure groups through the use of odds ratios and 95% confidence intervals. The variables found to be independently associated with the outcome of a late-stage colorectal cancer diagnosis were racial group, primary insurance payer, and partner status. Clinical and academic evidence also supports the inclusion of age in the model (Kweon et al., 2017) (Cramb et al., 2012). The final logistic regression model estimated the odds of late-stage colorectal cancer diagnosis for Appalachian Kentuckians, adjusting for racial group, primary insurance payer, partner status, and age in years.

Univariate and multivariate Cox proportional-hazards models were used to identify differences in survival after colorectal cancer diagnosis between exposure groups through the use of hazards ratios and 95% confidence intervals. The variables found to be independently associated with the outcome of survival were stage at diagnosis, sex, age, primary payer, and marital status. Backward selection with a significance level of 0.05 supported this decision. The final Cox proportional hazards model estimated the hazard of colorectal cancer survival for Appalachian Kentuckians, adjusting for diagnosis, sex, age, primary payer, and marital status.

Estimated correlation matrices were generated for logistic regression and proportional-hazards models to identify potential multicollinearity between variables. No collinearity within either model was found.

Kaplan-Meier curves were generated for Appalachian status and stage of diagnosis to visualize survival trends from time of diagnosis to last follow-up or confirmed death.

All analyses were performed using SAS statistical software (SAS Institute, Inc., Cary, NC, USA).

3. Results

As seen in Table 1, between 2012 and 2017, a total of 9,610 primary cases of invasive colorectal cancer were diagnosed in alive individuals in the state of Kentucky. Of those diagnosed, 59.50% were considered late-stage at time of diagnosis. The sample was primarily non-Appalachian (68.01%), non-Black (93.26%), married (55.10%) and above 50 years of age (86.25%), with the average age being 63.94 years old. There were fairly even proportions of males and females (52.59% vs. 47.41% respectively). Colorectal cancer diagnoses were consistent over the 5-year study time frame. The majority of individuals primary payer at time of treatment, or insurance type, was Medicare (51.07%), followed by private insurance (29.20%),

Medicaid (10.65%), an unknown insurance type (6.08%) and uninsured (2.61%). Using data from the most recent contact or notification of death, it was found that much of the sample was alive (57.05%), with 23.69% of the sample having died from the cancer or complications caused by the cancer identified at time of diagnosis.

Table 1. Basic characteristics of total sample (n = 9,610)

	n	(%)
Total	9610	100.00
Stage at diagnosis		
Early	3892	40.50
Late	5718	59.50
Appalachian Status		
Non-Appalachian	6536	68.01
Appalachian	3074	31.99
Sex		
Male	5091	52.59
Female	4590	47.41
Race		
White/Other	8962	93.26
Black	648	6.74
Age in years		
(mean, SD)	63.94	13.85
Age Group		
<50	1321	13.75
50-69	4891	50.89
>70	3395	35.36
Year of Diagnosis		
2012	1577	16.41
2013	1578	16.42
2014	1625	16.91
2015	1608	16.73
2016	1605	16.70
2017	1617	16.83
Primary Payer		
Private	2819	29.20
Uninsured	251	2.61
Medicaid	1030	10.65
Medicare	4939	51.07
Unknown	584	6.08
Marital Status		
Married/Partnered	5295	55.10

Single	4077	42.42
Unknown	238	2.48
Vital Status		
Alive	5482	57.05
Dead (cancer related)	2276	23.69
Dead (cancer unrelated)	1851	19.26

When the total sample was stratified by Appalachian (n=6536) and non-Appalachian (n=3074) residence in Table 2, significant differences were found among select sociodemographic characteristics. Appalachian individuals were more often diagnosed at a later stage of colorectal cancer (p-value=0.041), with 61.00% of diagnoses in Appalachians being late-stage as compared to 58.80% of non-Appalachian diagnoses. Individuals diagnosed with colorectal cancer from Appalachia were less racially diverse than their non-Appalachian counterparts (p-value=<0.0001), with 1.30% cases being Black versus 9.03% of cases, respectively. There was a statistically significant, although clinically insignificant, difference in the average age at diagnosis (p-value=<0.0001), with the average age of Appalachians being 63.62, compared to 64.22 years of age in non-Appalachians. While clinical or practical significance is unlikely, there were statistically significant differences in calendar year of diagnoses between residence groups (p-value=0.024). Non-Appalachian cases had a fairly even distribution of diagnoses per year between 2012 and 2017, while Appalachian cases peaked in 2014 (571 cases) and have been slightly declining thereafter (502 cases in 2017). Primary payer at time of diagnosis differed between groups as well (p-value=<0.0001), with a higher proportion of Appalachian cases utilizing Medicare (54.81%) and Medicaid (13.21%) than non-Appalachians (49.79% and 9.55% respectively). The increased utilization of public insurance is countered by a decreased utilization of private insurance, with 21.80% of Appalachians utilizing a private insurance provider, 10% less than their non-Appalachian counterparts (32.68%).

Appalachians were also married significantly more often (p-value = 0.017) than non-Appalachians (56.25% and 54.59%, respectively).

Variables found to have statistically insignificant differences between exposure group were sex (p-value=0.083), age group (p-value=0.082), and vital status (p-value=0.287).

Table 2. Basic characteristics stratified by Appalachian Status (n=9,681)

	Non-Appalachian (n=6536)		Appalachian (n=3074)		
	n	(%)	n	(%)	p-value
Stage at diagnosis					
Early	2693	41.20	1199	39.00	**0.041**
Late	3843	58.80	1875	61.00	
Sex					
Male	3393	51.91	1654	53.81	0.083
Female	3143	48.09	1420	46.19	
Race					
White/Other	5928	90.70	3034	98.70	**<0.0001**
Black	608	9.03	40	1.30	
Age in years					
(mean, SD)	64.22	13.95	63.62	13.55	**<0.0001**
Age Group					
<50	888	13.59	433	14.09	0.082
50-69	3288	50.31	1603	52.15	
>70	2360	36.11	1038	33.77	
Year of Diagnosis					
2012	1106	16.92	471	15.32	**0.024**
2013	1093	16.72	485	15.78	
2014	1053	16.13	571	18.58	
2015	1084	16.59	524	17.05	
2016	1084	16.59	521	16.95	
2017	1115	17.06	502	16.33	
Primary Payer					
Private	2136	32.68	670	21.80	**<0.0001**
Uninsured	171	2.62	80	2.60	
Medicaid	624	9.55	406	13.21	
Medicare	3254	49.79	1685	54.81	
Unknown	351	5.37	233	7.58	
Marital Status					
Married/ Partnered	3566	54.59	1729	56.25	**0.017**

Single	2823	43.19	1254	40.79	
Unknown	147	2.25	91	2.96	
Vital Status					
Alive	3762	55.97	1720	55.97	0.287
Dead (cancer related)	1527	24.37	749	24.37	
Dead (cancer unrelated)	1247	19.66	604	19.66	

p-value for chi-square test

Table 3 summarizes univariate logistic regression estimates for sociodemographic characteristics of the sample. Univariate logistic regression estimated that the odds of having a late-stage colorectal cancer diagnosis were 1.01 (95% CI: 1.00-1.20) times higher for those of Appalachian residence compared to those of non-Appalachian residence. This model estimates a statistically insignificant association between Appalachian residence and late-stage colorectal cancer diagnosis. Significant associations between late-stage cancer diagnosis and other variables of interest were found.

Primary payer method was found to be both significantly and insignificantly associated with the outcome of interest. Cases that were uninsured (OR: 1.73, 95% CI: 1.31-2.29) or used Medicaid (OR: 1.22, 95% CI: 1.06-1.42) had a higher odds of late-stage colorectal cancer diagnosis than those with private insurance (reference group); however, cases whose primary payer was unknown (OR: 0.81, 95% CI: 0.68-0.97) had significantly decreased odds of late-stage colorectal cancer diagnosis when compared to those who had private insurance. Medicare utilization was insignificantly associated with stage of diagnosis (OR: 1.01, 95% CI: 0.998-1.20).

It was found that the odds of having a late-stage colorectal cancer diagnosis were 1.15 (95% CI: 1.05-1.25) times higher for those who were single than those who were married at time

of diagnosis. Those of unknown marital status had insignificantly decreased odds of late-stage colorectal cancer diagnosis that those who were married at time of diagnosis (OR: 0.86, 95% CI: 0.67-1.12).

Variables found to have statistically insignificant associations with the outcome of interest were sex (p-value=0.105), race (p-value=0.146), and age (p-value=0.929).

Table 3. Univariate logistic regression odds ratios (n = 9,681)

	Late-stage diagnosis	
	OR (95% CI)	p-value
Appalachian Status		
Non-Appalachian	1 (reference)	
Appalachian	1.10 (1.00-1.20)	**0.041**
Sex		
Male	1 (reference)	
Female	0.94 (0.86-1.01)	0.105
Race		
White/Other	1 (reference)	
Black	0.89 (0.76-1.04)	0.146
Age		
By year	1.000 (0.997-1.003)	0.929
Primary Payer		
Private	1 (reference)	
Uninsured	1.73 (1.31-2.29)	**<0.001**
Medicaid	1.22 (1.06-1.42)	**0.007**
Medicare	1.10 (1.00-1.20)	0.056
Unknown	0.95 (0.79-1.14)	0.577
Marital Status		
Married/Partnered	1 (reference)	
Single	1.15 (1.05-1.25)	**0.001**
Unknown	0.86 (0.67-1.12)	0.273

OR: odds ratio, 95% CI: 95% confidence interval
p-value for Wald chi-square

Table 4 summarizes multivariable logistic regression estimates for key sociodemographic characteristics of the sample. multivariable logistic regression estimated that the odds of having a late-stage colorectal cancer diagnosis were 1.08 (95% CI: 0.99-1.18) higher for those of

Appalachian residence compared to those of non-Appalachian residence, after adjusting for sex, marital status, marital status, racial group, and age in years. Therefore, this model estimates a statistically insignificant association between Appalachian residence and late-stage colorectal cancer diagnosis after adjustment. Significant associations between late-stage cancer diagnosis and other variables of interest were also found within the adjusted model.

After adjustment, the two primary payer methods that were previously significant remain so. Uninsured individuals (OR: 1.67, 95% CI: 1.26-2.22) and those who utilize Medicaid (OR: 1.17, 95% CI: 1.01-1.36) remain significantly associated with greater odds of late-stage colorectal cancer diagnosis when compared to those with private insurance. The significance of the relationship between those with Medicare (p-value=0.199) or those with unknown insurance status (p-value=0.547) with the outcome of interest remains absent after adjustment.

It was estimated that the odds of late-stage colorectal cancer diagnosis were 0.92 (95% CI: 0.84-0.99) times lower for cases that were female compared to cases that were male, after adjustment for the previously mentioned variables.

Of those who were single and whose marital status was unknown, only the association between single individuals and the outcome remained significant. After adjustment, the odds of late-stage colorectal cancer diagnosis were 1.15 (95% CI: 1.05-1.25) times higher for those who were single than those who were married. Unknown marital status was statistically insignificant (p-value=0.24) after adjustment.

Additional variables found to have statistically insignificant associations with the outcome of interest after inclusion in the adjusted logistic regression model were race (p-value=0.100) and age in years (p-value=0.666).

Table 4. Multivariate logistic regression odds ratios– adjusting for sex, marital status, primary payer, racial group, and age (n = 9,681)

	Late-stage diagnosis	
	OR (95% CI)	p-value
Appalachian Status		
Non-Appalachian	1 (reference)	
Appalachian	1.08 (0.99-1.18)	0.104
Sex		
Male	1 (reference)	
Female	0.92 (0.84-0.99)	**0.0362**
Race		
White/Other	1 (reference)	
Black	0.87 (0.74-1.03)	0.100
Age		
By year	0.999 (0.995-1.003)	0.666
Primary Payer		
Private	1 (reference)	
Uninsured	1.67 (1.26-2.22)	**<0.001**
Medicaid	1.17 (1.01-1.36)	**0.037**
Medicare	1.08 (0.96-1.22)	0.199
Unknown	0.95 (0.79-1.13)	0.547
Marital Status		
Married/Partnered	1 (reference)	
Single	1.15 (1.05-1.25)	**0.002**
Unknown	0.85 (0.66-1.11)	0.243

OR: odds ratio, 95% CI: 95% confidence interval
p-value for Wald chi-square

Table 5 summarizes univariate Cox proportional hazards estimates for diagnostic and sociodemographic characteristics of the sample. Univariate Cox proportional hazards estimated that the hazards of colorectal cancer related mortality were 1.06 (95% CI: 0.97-1.16) times higher for those of Appalachian residence compared to those of non-Appalachian residence. This model estimates a statistically insignificant association between Appalachian residence and colorectal cancer related mortality. However, significant associations between colorectal cancer related mortality and other variables of interest were found.

Stage at diagnosis was estimated to have an increased hazard of colorectal cancer related mortality among variables investigated. It was estimated that the hazard of colorectal cancer related mortality was 9.9 (95% CI: 8.53-11.49) times higher for those with a late-stage colorectal cancer diagnosis compared to those diagnosed at an early stage.

Age in years was also significantly associated with the outcome, as it was estimated that with each year of age, the hazard of colorectal cancer related mortality was 1.029 (95% CI: 1.025-1.032) times higher than the last.

As was seen with the previous univariate model in Table 3, each primary payer was significantly associated with the outcome, however in this model all types of payer method were associated with an increased hazard. Cases that were uninsured (HR: 2.26, 95% CI: 1.80-2.84), used Medicaid (HR: 1.49, 95% CI: 1.28-1.73), used Medicare (HR: 1.93, 95% CI: 1.75-2.15), or whose insurance status was unknown (HR: 1.40, 95% CI: 1.16-1.69) had a higher hazard of colorectal cancer related mortality than those with private insurance.

Marital status showed significant associations regarding single and unknown individuals. It was estimated that that the hazard of colorectal cancer related mortality were 1.56 (95% CI:1.43-1.69) times higher for those who were single at time of diagnosis than those who were married and 1.51 (95% CI:1.17-1.94) times higher for those of unknown marital status.

Additional variables found to be insignificantly associated with colorectal cancer related mortality include sex (p-value=0.517) and race (p-value=0.828).

Table 5. Univariate Cox proportional hazard ratios (n=7,759)

	Cancer related mortality	
	HR (95% CI)	p-value
Stage at diagnosis		
Early	1 (reference)	
Late	9.90 (8.53-11.49)	**<0.0001**
Appalachian Status		
Non-Appalachian	1 (reference)	
Appalachian	1.06 (0.97-1.16)	0.183
Sex		
Male	1 (reference)	
Female	0.97 (0.90-1.06)	0.517
Race		
White/Other	1 (reference)	
Black	1.02 (0.87-1.20)	0.828
Age		
By year	1.029 (1.025-1.032)	**<0.0001**
Primary Payer		
Private	1 (reference)	
Uninsured	2.27 (1.80-2.85)	**<0.0001**
Medicaid	1.49 (1.28-1.73)	**<0.0001**
Medicare	1.93 (1.75-2.14)	**<0.0001**
Unknown	1.40 (1.16-1.69)	**0.001**
Marital Status		
Married/Partnered	1 (reference)	
Single	1.56 (1.43-1.69)	**<0.0001**
Unknown	1.51 (1.17-1.94)	**0.001**

HR: hazard ratio, 95% CI: 95% confidence interval
p-value for Wald chi-square

Further investigation into univariate associations between primary variables of interest, specifically Appalachian residence and cancer stage at diagnosis, prompted the use of Kaplan-Meier curves to visualize survival from time of diagnosis to most recent follow up. Figure 1 and figure 2 show survival estimates for Appalachian residence and stage at diagnosis, respectively. Figure 1 finds a statistically insignificant (p-value=0.1808) relationship between Appalachian residence and survival over time. However, there does appear to be the beginnings of a divergence between the two populations near the 95th month of follow up, where a noticeable

drop in survival probability is seen. Figure 2 finds a statistically significant (<0.0001) difference between early- and late-stage individuals and survival over time. The difference between populations is clear throughout the full follow up period and is most noticeable within the first twenty months.

Figure 1. Kaplan-Meier Curve – survival estimate for Appalachian and non-Appalachian

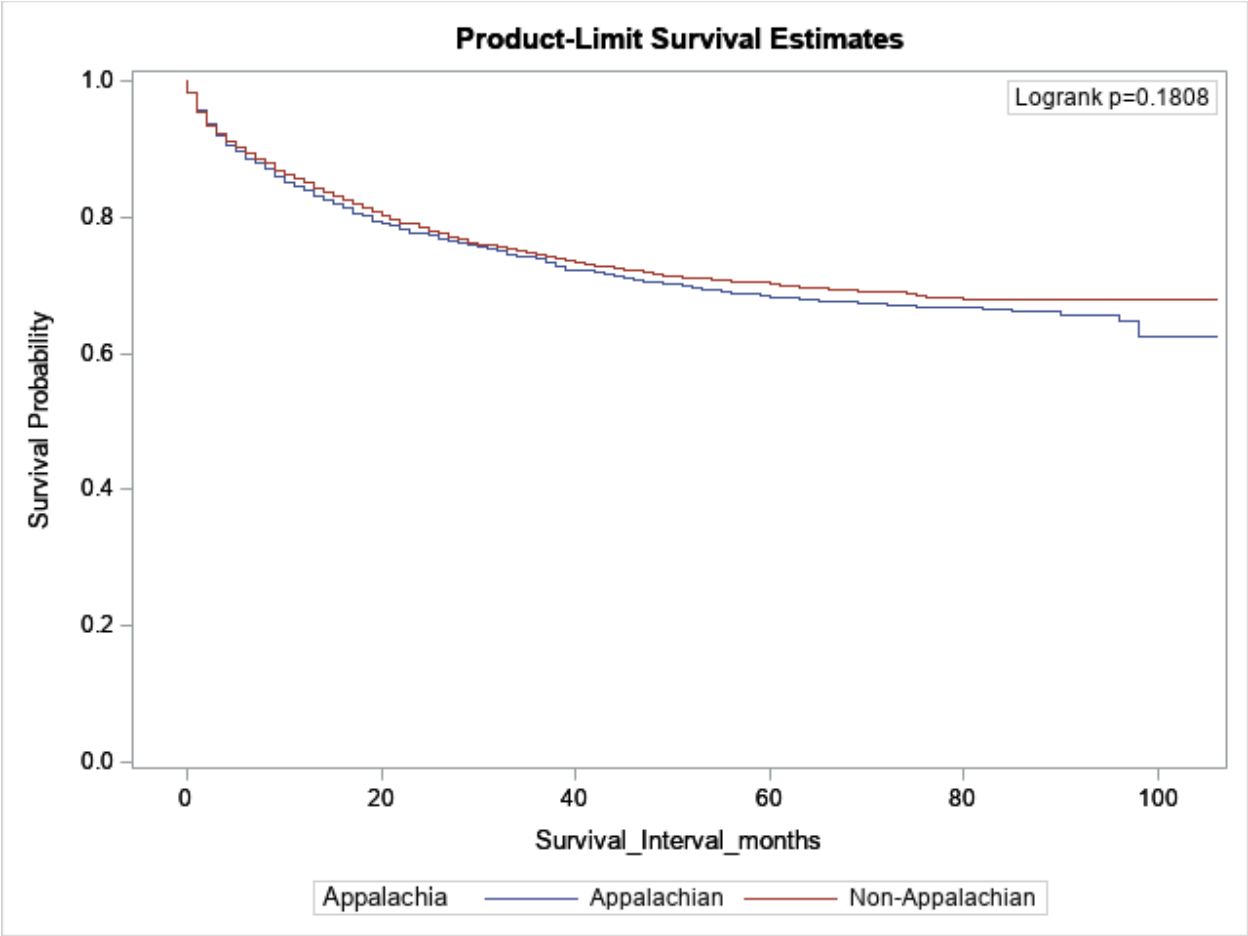

Figure 2. Kaplan-Meier Curve – survival estimate for early- and late-stage cancer diagnoses

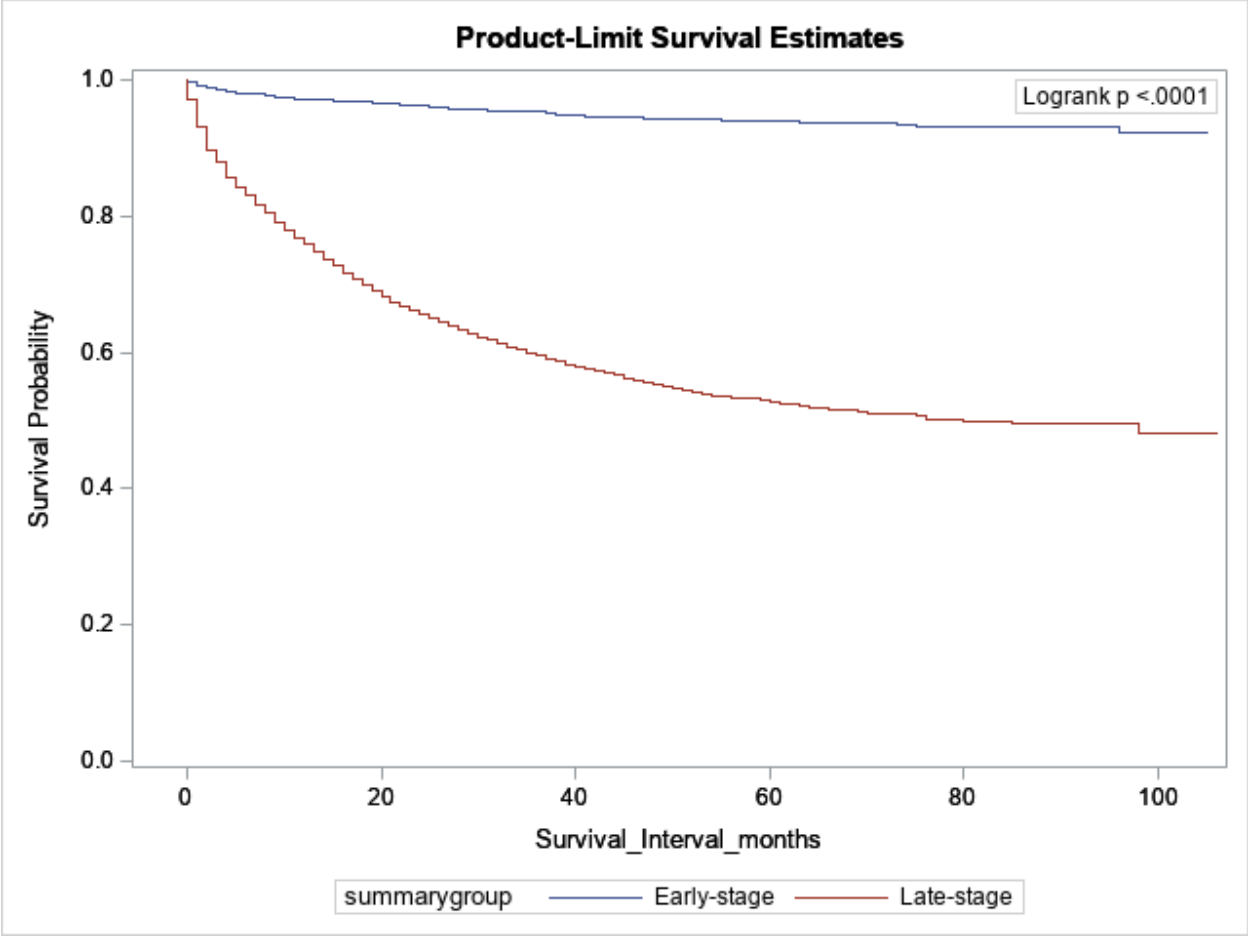

Table 6 summarizes multivariate Cox proportional hazards estimates for diagnostic and sociodemographic characteristics of the sample. Multivariate Cox proportional hazards estimated that the hazards of colorectal cancer related mortality were 1.03 (95% CI: 0.95-1.13) times higher for those of Appalachian residence compared to those of non-Appalachian residence, after adjusting for stage at diagnosis, sex, age, primary payer, and marital status. This model estimates a statistically insignificant association between Appalachian residence and colorectal cancer

related mortality. However, significant associations between colorectal cancer related mortality and other variables of interest were found.

Stage at diagnosis was again estimated to have the highest increased hazard of colorectal cancer related mortality among variables investigated. It was estimated that the hazard of colorectal cancer related mortality was 9.92 (95% CI: 8.55-11.52) times higher for those with a late-stage colorectal cancer diagnosis compared to those diagnosed at an early stage after adjustment.

Sex became statistically significant when included in the adjusted model. It was estimated that the hazards of colorectal cancer related mortality were 0.89 (95% CI: 0.82-0.97) times lesser for those who were female than those who were male.

Age in years was also significantly associated with the outcome, nearly unchanged from the univariate model, as it was estimated that with each year of age the hazard of colorectal cancer related mortality was 1.03 (95% CI: 1.03-1.04) times higher than the last after adjustment.

After adjustment, primary payer remained significantly associated with the outcome, however in this model three of the four types of payer method were associated with an increase in hazards. Cases that were uninsured (HR: 1.83, 95% CI: 1.45-2.30), used Medicaid (HR: 1.34, 95% CI: 1.14-1.56), or whose insurance status was unknown (HR: 1.40, 95% CI: 1.15-1.69) had a higher hazards of colorectal cancer related mortality than those with private insurance. However, after adjustment the relationship between those with Medicare and colorectal cancer related mortality became statistically insignificant (HR: 1.01, 95% CI: 0.97-1.24).

Marital status showed significant associations regarding both single individuals and individuals of unknown marital status within this model. It was estimated that that the hazard of

colorectal cancer related mortality was 1.40 (95% CI:1.29-1.53) times higher for those who were single at time of diagnosis than those who were married. The association between unknown marital status and colorectal cancer related mortality, after inclusion in the adjusted model, were also found to be statistically significant (HR: 1.56, 95% CI: 1.21-2.01).

Appalachian residence and Medicare utilization were found to be the only insignificant variables within the adjusted Cox proportional hazards model with respect to colorectal cancer related mortality.

Table 6. Multivariable Cox proportional hazard ratios – adjusting for stage at diagnosis, sex, age, primary payer, and marital status (n=7,829)

	Cancer related mortality	
	HR (95% CI)	p-value
Stage at diagnosis		
Early	1 (reference)	
Late	9.92 (8.55-11.52)	**<0.0001**
Appalachian Status		
Non-Appalachian	1 (reference)	
Appalachian	1.03 (0.94-1.13)	0.484
Sex		
Male	1 (reference)	
Female	0.88 (0.82-0.97)	**0.006**
Age		
By year	1.03 (1.03-1.04)	**<0.0001**
Primary Payer		
Private	1 (reference)	
Uninsured	1.83 (1.45-2.30)	**<0.0001**
Medicaid	1.34 (1.14-1.56)	**<0.001**
Medicare	1.10 (0.97-1.24)	0.155
Unknown	1.40 (1.15-1.69)	**0.001**
Marital Status		
Married/Partnered	1 (reference)	
Single	1.40 (1.29-1.53)	**<0.0001**
Unknown	1.56 (1.21-2.01)	**0.001**

HR: hazard ratio, 95% CI: 95% confidence interval
p-value for Wald chi-square

4. Discussion

Late-stage cancer diagnosis is a strong predictor of poor survival probability, however, sociodemographic characteristics at the individual level have been previously found to be associated with late-stage diagnoses (Ortiz-Ortiz et al., 2016) (Tomic et al., 2018). The Appalachian portion of Kentucky is a distinct region of the state, characterized by low socioeconomic status, a lack of access to care, and historically high presence of health behaviors associated with poor health outcomes (Schoenberg et al., 2012a) (Arnold, 2017). Because of this, the objective of this study was to investigate the relationship between Appalachian residence and colorectal cancer stage at diagnosis and survival. The present study additionally explored the relationships between key sociodemographic characteristics available from individual medical record/cancer registry data and the outcomes previously mentioned.

Descriptive summaries provided found significant differences between Appalachian and non-Appalachian residents with respect to stage at diagnosis, race, age, year diagnosed, and primary payer. These findings are consistent with the current literature regarding sociodemographic differences within this population (Fleming et al., 2011) (Schoenberg et al., 2012b). General summaries stratified by Appalachian residence also showed many sociodemographic characteristics to be heterogenous within the population. Of note, Appalachian residents in Kentucky are in large majority white and primary utilize publicly provided forms of insurance. While this may imply there are significantly less persons of color within the Appalachian community, it does not negate the disparity highlighted by previous literature between white and black individuals in Appalachia regarding cancer outcomes (Antwi et al., 2013). Differences with respect to insurance group may be explained through a higher proportion of the Appalachian population qualifying for Medicaid eligibility, with household income at under

138% of the Federal Poverty Guidelines (Kentucky Cabinet for Health and Family Services, 2017).

An initial univariate model found significant associations between Appalachian residence and late-stage colorectal cancer diagnosis; however, after adjusting for historically and significantly associated confounding variables, the relationship became insignificant. These findings suggest that despite proportional differences between Appalachian and non-Appalachian individuals regarding stage at time of diagnosis, the relationship can be partially explained by sociodemographic characteristics such as age, insurance status, and martial status. For decades, it has been well supported that increases in age are associated with increases in colorectal cancer incidence and mortality (Cooper et al., 1995). Differences in insurance provider have also shown associations with stage at diagnosis, with specific emphasis on uninsured populations past literature (Greenbaum et al., 2012). While the present study found that uninsured individuals had the highest odds of late-stage colorectal cancer diagnosis within the adjusted model, the proportion of uninsured individuals in Appalachian and non-Appalachian counties is comparable (2.59% vs. 2.63%, respectively). This could imply some generalizability between populations regarding late-stage diagnosis risk. Marital status has also been found to be associated with late-stage colorectal cancer diagnosis within SEER registries, with married individuals presenting the higher proportions of early-stage diagnoses (Li et al., 2015).

Univariate hazards models initially displayed an insignificant relationship (p-value=0.183) between Appalachian residence and colorectal cancer related mortality. The statistical significance of the relationship diminished further (p-value=0.484) after the multivariable model adjusted for stage at diagnosis, sex, age, primary payer, and marital status. Each variable included in the adjusted model, except Appalachian status, showed a significant relationship with

cancer related survival. The Appalachian region of Kentucky has historically had significantly higher rates of colorectal cancer related mortality than other regions of the state and country (Blackley et al., 2012). The present study did not find significant associations between Appalachian residence and colorectal cancer survival; therefore, this could imply that the associations seen between Appalachian status and colorectal cancer mortality are significantly explained by the characteristics presently explored, or by characteristics outside the scope of the present study.

Findings from this study indicate a greater need to explore other factors associated with stage at diagnosis in Appalachian individuals as it is clearly the most significant contributor to increased cancer related mortality (HR: 9.92, CI: 8.55-11.52). Additional research should further investigate individual and community level characteristics that may be associated with colorectal cancer screening utilization among Appalachian and non-Appalachian individuals, as previous research suggests a strong relationship between screening utilization, earlier stage of diagnosis, and improved cancer related survival (Fleming et al., 2011).

4.1. Public health impact

By the end of 2021, the American Cancer Society projects 149,500 new colorectal cancer cases and 52,980 deaths within the US (American Cancer Society, 2021). While the mortality rate has dropped over past decades, colorectal cancer mortality in those younger than 55 has increased by 1% each year between 2008 and 2017 (American Cancer Society, 2021). Because of this and other trends previously explored regarding staging and survival, it is imperative that research and resources are directed toward underserved areas of the country that could be most impacted. The present study provides affirmation of preexisting literature and acts to generate hypotheses for future research. Reproducibility is necessary within all contexts of research, and

the present study was able to find similar results to past research and confirm findings found in other comparable populations. The present study's findings differed at times from published literature as well, and further investigation into these differences should be considered.

4.2. Strengths and Limitations

The greatest strength of this study is its use of population-based, individual case level data for all analyses. Because of this, the present study can be confident all primary colorectal cancer cases, alive at time of diagnosis, were identified within the study population. However, analyses are limited to Appalachian counties in Kentucky and is therefore not applicable to other Appalachian areas. Of the initial 10,044 cases, 363 were excluded due to missing cancer stage information and 1,851 of the remaining cases were excluded from survival analyses due to unrelated causes of death, potentially limiting the strength of claims made regarding the present study's results. An additional potential limitation could be the rational used to group individuals within categorical variables, such as race being operationalized as White/other and Black. While this has the potential to impact findings, the decision to do so is supported by previous literature and is analytically necessary due to extremely small minority populations within Appalachia. An additional positive of the present study is that it also investigated sociodemographic characteristics outside of Appalachian residence and could control for them during analyses.

4.3. Conclusions

In conclusion, significant associations between late-stage colorectal cancer diagnosis and Appalachian residence are seen within the study population, even when adjusting for multiple sociodemographic characteristics historically and statistically associated with the exposure and outcome of interest. A significant association between Appalachian residence and colorectal cancer related survival could not be found within the study population and follow up time frame

with or without adjusting for stage at diagnosis and related sociodemographic characteristics. Further research is necessary to explore the associations, and lack thereof, between Appalachians and colorectal cancer outcomes.

References

American Cancer Society. (2020, June 29). *Colorectal Cancer Stages*. Early Detection, Diagnosis, and Staging . https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/staged.html

Andrew, A. S., Parker, S., Anderson, J. C., Rees, J. R., Robinson, C., Riddle, B., & Butterly, L. F. (2018). Risk Factors for Diagnosis of Colorectal Cancer at a Late Stage: a Population-Based Study. *Journal of General Internal Medicine*, *33*(12), 2100–2105. https://doi.org/10.1007/s11606-018-4648-7

Antwi, S., Tucker, T. C., Coker, A. L., & Fleming, S. T. (2013). Racial Disparities in Survival After Diagnosis of Prostate Cancer in Kentucky, 2001-2010. *American Journal of Men's Health*, *7*(4), 306–316. https://doi.org/10.1177/1557988312473774

Appalachian Regional Commission. (2017, August 24). *Appalachian Region Endures Dramatic Health Challenges Compared with Nation, New Research Shows - Appalachian Regional Commission*. https://www.arc.gov/news/appalachian-region-endures-dramatic-health-challenges-compared-with-nation-new-research-shows/

Appalachian Regional Commission. (2018). *About the Appalachian Region*. Appalachian Region. https://www.arc.gov/about-the-appalachian-region/

Arnold, C. (2017). Appalachia's Cancer Problem. In *Journal of the National Cancer Institute* (Vol. 109, Issue 3). NLM (Medline). https://doi.org/10.1093/jnci/djx045

Bal, W., Jarzab, M., Stobiecka, E., Zebracka, J., Mianowska, M., Oczko-Wojciechowska, M., Rusinek, D., Tyszkiewicz, T., Nowara, E., Jarzab, B., & Tarnawski, R. (2012). Clinical and biologic factors associated with time to progression in patients treated by first-line palliative FOLFOX chemotherapy in metastatic colorectal cancer. *Journal of Clinical Oncology*, *30*(15_suppl), e14159–e14159. https://doi.org/10.1200/jco.2012.30.15_suppl.e14159

Booth, C. M., Li, G., Zhang-Salomons, J., & Mackillop, W. J. (2010). The impact of socioeconomic status on stage of cancer at diagnosis and survival: A population-based study in Ontario, Canada. *Cancer*, *116*(17), 4160–4167. https://doi.org/10.1002/cncr.25427

Byers, T. E., Wolf, H. J., Bauer, K. R., Bolick-Aldrich, S., Chen, V. W., Finch, J. L., Fulton, J. P., Schymura, M. J., Shen, T., Van Heest, S., & Yin, X. (2008). The impact of socioeconomic status on survival after cancer in the United States. *Cancer*, *113*(3), 582–591. https://doi.org/10.1002/cncr.23567

Cavallo, J. (2017). *Stemming the Growing Cancer Crisis in Rural Appalachia*. American Society of Clinical Oncology. https://ascopost.com/issues/september-25-2017/stemming-the-growing-cancer-crisis-in-rural-appalachia/

Clegg, L. X., Li, F. P., Hankey, B. F., Chu, K., & Edwards, B. K. (2002). Cancer survival among US whites and minorities: A SEER (Surveillance, Epidemiology, and End Results) Program population-based study. *Archives of Internal Medicine*, *162*(17), 1985–1993. https://doi.org/10.1001/archinte.162.17.1985

Cooper, G. S., Yuan, Z., Landefeld, C. S., Johanson, J. F., & Rimtn, A. A. (1995). A national population-based study of incidence of colorectal cancer and age. Implications for screening

in older Americans. *Cancer*, *75*(3), 775–781. https://doi.org/10.1002/1097-0142(19950201)75:3<775::AID-CNCR2820750305>3.0.CO;2-D

Cramb, S. M., Mengersen, K. L., Turrell, G., & Baade, P. D. (2012). Spatial inequalities in colorectal and breast cancer survival: Premature deaths and associated factors. *Health & Place*, *18*(6), 1412–1421. https://doi.org/10.1016/j.healthplace.2012.07.006

Fahe. (2019). *Poverty in Appalachia*. https://fahe.org/appalachian-poverty/

Fayanju, O. M., Jeffe, D. B., Elmore, L., Ksiazek, D. N., & Margenthaler, J. A. (2013). Patient and process factors associated with late-stage breast cancer diagnosis in safety-net patients: A pilot prospective study. *Annals of Surgical Oncology*, *20*(3), 723–732. https://doi.org/10.1245/s10434-012-2558-1

Fleming, S. T., Schoenberg, N. E., Tarasenko, Y. N., & Pearce, K. A. (2011). Prevalence of colorectal cancer screening among a multimorbid rural appalachian population. *Southern Medical Journal*, *104*(12), 811–818. https://doi.org/10.1097/SMJ.0b013e31823a8879

Greenbaum, A., Singhal, V., Cosgrove, J. M., & Farkas, D. T. (2012). The effect of insurance status on the stage of colorectal cancer at diagnosis. *Journal of Clinical Oncology*, *30*(4_suppl), 420–420. https://doi.org/10.1200/jco.2012.30.4_suppl.420

Kelz, R. R., Gimotty, P. A., Polsky, D., Norman, S., Fraker, D., & DeMichele, A. (2004). Morbidity and mortality of colorectal carcinoma surgery differs by insurance status. *Cancer*, *101*(10), 2187–2194. https://doi.org/10.1002/cncr.20624

Kentucky Cabinet for Health and Family Services. (2017). *Medicaid Enrollment*. Eligibility Policy Branch. https://chfs.ky.gov/agencies/dms/dpo/epb/Pages/enroll.aspx

Kentucky Cancer Consortium. (2019). *Cancer Action Plan*. https://www.kycancerc.org/wp-content/uploads/sites/14/2019/08/KCC Action Plan 2019_revised_July26_2019.pdf

Kentucky Cancer Consortium Colon Cancer Committee. (2018). *Colorectal Cancer in Kentucky*. http://www.kycancerc.org

Kentucky Cancer Registry. (2020, March 3). *History of Cancer Reporting in Kentucky*. About the Kentucky Cancer Registry. https://www.kcr.uky.edu/about.php

Kentucky Department for Public Health. (2017). *State Health Assessment Report, 2017 Update*. http://chfs.ky.gov/NR/rdonlyres/490FEA8C-0C46-47F8-8CE5-CDAF970E1190/0/The2017KentuckyStateHealthAssessmentUpdate31517.pdf

Kentucky Department for Public Health, & The Centers for Disease Control and Prevention. (2018). *Kentucky Behavioral Risk Factor Survey (KyBRFS) 2018 Annual Report*. http://chfs.ky.gov/brfss

Kweon, S. S., Kim, M. G., Kang, M. R., Shin, M. H., & Choi, J. S. (2017). Difference of stage at cancer diagnosis by socioeconomic status for four target cancers of the National Cancer Screening Program in Korea: Results from the Gwangju and Jeonnam cancer registries. *Journal of Epidemiology*, *27*(7), 299–304. https://doi.org/10.1016/j.je.2016.07.004

Lantz, P. M., Mujahid, M., Schwartz, K., Janz, N. K., Fagerlin, A., Salem, B., Liu, L., Deapen,

D., & Katz, S. J. (2006). The Influence of Race, Ethnicity, and Individual Socioeconomic Factors on Breast Cancer Stage at Diagnosis. *American Journal of Public Health*, *96*(12), 2173–2178. https://doi.org/10.2105/AJPH.2005.072132

Li, Q., Gan, L., Liang, L., Li, X., & Cai, S. (2015). The influence of marital status on stage at diagnosis and survival of patients with colorectal cancer. *Oncotarget*, *6*(9), 7339–7347. https://doi.org/10.18632/oncotarget.3129

National Center for Education Statistics. (2018). High School Graduation Rates. In *Fast Facts*. https://nces.ed.gov/fastfacts/display.asp?id=805

Ortiz-Ortiz, K. J., Ríos-Motta, R., Marín-Centeno, H., Cruz-Correa, M., & Ortiz, A. P. (2016). Factors associated with late stage at diagnosis among Puerto Rico's government health plan colorectal cancer patients: A cross-sectional study. *BMC Health Services Research*, *16*(1), 1–10. https://doi.org/10.1186/s12913-016-1590-4

Schoenberg, N. E., Howell, B. M., & Fields, N. (2012a). Community strategies to address cancer disparities in Appalachian Kentucky. In *Family and Community Health* (Vol. 35, Issue 1, pp. 31–43). NIH Public Access. https://doi.org/10.1097/FCH.0b013e3182385d2c

Schoenberg, N. E., Howell, B. M., & Fields, N. (2012b). Community strategies to address cancer disparities in Appalachian Kentucky. In *Family and Community Health* (Vol. 35, Issue 1, pp. 31–43). https://doi.org/10.1097/FCH.0b013e3182385d2c

Siegel, R. L., Miller, K. D., Fedewa, S. A., Ahnen, D. J., Meester, R. G. S., Barzi, A., & Jemal, A. (2017). Colorectal cancer statistics, 2017. *CA: A Cancer Journal for Clinicians*, *67*(3), 177–193. https://doi.org/10.3322/caac.21395

Thomson, C. S., Hole, D. J., Twelves, C. J., Brewster, D. H., & Black, R. J. (2001). Prognostic factors in women with breast cancer: Distribution by socioeconomic status and effect on differences in survival. *Journal of Epidemiology and Community Health*, *55*(5), 308–315. https://doi.org/10.1136/jech.55.5.308

Tomic, K., Ventimiglia, E., Robinson, D., Häggström, C., Lambe, M., & Stattin, P. (2018). Socioeconomic status and diagnosis, treatment, and mortality in men with prostate cancer. Nationwide population-based study. *International Journal of Cancer*, *142*(12), 2478–2484. https://doi.org/10.1002/ijc.31272