5-12-2019

Disparities in Prostate Cancer Survival in Appalachian Kentucky: A Population-Based Study

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Rural and Remote Health

rrh.org.au
James Cook University ISSN 1445-6354

ORIGINAL RESEARCH

Disparities in prostate cancer survival in Appalachian Kentucky: a population-based study

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PUBLISHED

12 May 2019 Volume 19 Issue 2

HISTORY

RECEIVED: 2 July 2018

REVISED: 18 December 2018

ACCEPTED: 13 February 2019

CITATION

Myint ZW, O'Neal R, Chen Q, Huang B, Vanderpool R, Wang P. Disparities in prostate cancer survival in Appalachian Kentucky: a population-based study. Rural and Remote Health 2019; 19: 4989. https://doi.org/10.22605/RRH4989

ETHICS APPROVAL: The study was approved by local IRB at University of Kentucky. The approval number is 17-0533-P1G.

ABSTRACT:

Introduction: Prostate cancer (PC) is the most common male cancer in the USA. When comparing the incidence and mortality rates of PC, the Surveillance Epidemiology and End Results data of 2005–2014 show that Appalachian Kentucky had a lower incidence (113/100 000 v 137/100 000) but a higher mortality rate (23.8% v 21.8%) when compared to non-Appalachian Kentucky. The aim of this study was to further characterize the survival disparities of PC between Appalachian and non-Appalachian Kentucky.

Methods: All stages of PC patients diagnosed between 2007 and 2011 were collected through the Kentucky Cancer Registry. Baseline characteristics and survival outcomes were compared between Appalachian Kentucky and non-Appalachian Kentucky, using Pearson χ^2 and Cox regression analyses in this population-based analysis.

Results: Of 12 871 patients studied, 3482 (26.8%) were from Appalachian Kentucky whereas 8489 (73.2%) were from non-Appalachian Kentucky. Caucasians predominated in both groups. Most Appalachian Kentucky patients were aged 65–74 years. Appalachian Kentucky patients had a higher Gleason score, higher prostate specific antigen (PSA), more aggressive histologic grade, more distant disease, higher comorbidity score, lower education, and higher poverty compared to patients from non-Appalachian Kentucky. There was a 5-year survival difference between Appalachian Kentucky and non-Appalachian Kentucky in unadjusted analysis ($p<0.001$) that disappeared after adjusting with Cox regression analysis ($p=0.4$). However, worsened survival was still seen with higher Gleason score, higher PSA, distant stage disease, higher Charlson comorbidity index, and very low high school education ($p<0.001$).

Conclusion: In this population-based analysis, this study shows a significant difference in PC survival between Appalachian and non-Appalachian Kentucky. The difference was not related to geographic location, but rather to high comorbidity score, high poverty rate, and low education. Additional research is needed to understand the healthcare restraints for Appalachian Kentucky.

Keywords:

prostate cancer, Appalachian Kentucky, Kentucky Cancer Registry, non-Appalachian Kentucky, survival disparities, USA.

FULL ARTICLE:

Introduction

Cancer continues to be one of the top five leading causes of death globally, and specifically ranks second as the leading cause of mortality in the USA[1]. In particular, individuals living in non-metropolitan (rural) regions of the USA have higher cancer mortality rates than persons living in metropolitan (urban) regions even though nationwide cancer mortality rates are 20% lower[2]. Yao et al found that cancer mortality rates were 36% higher in rural Appalachian Kentucky compared to West Virginia, the only state wholly designated as Appalachian[3].

As of July 2016, approximately 25.6 million or 8% of the US population live in the 13-state Appalachian region of the USA[4]. Of those individuals residing in Appalachia, 16 million live in metropolitan areas compared to 7 million who live in non-metropolitan areas. The Appalachian region is divided into five subregions: Northern, North Central, Central, South Central, and Southern[4]. The region follows the spine of the Appalachian Mountains, from New York to Mississippi, and comprises 420 counties in 13 states. The 54 primarily rural counties designated as Appalachian in the state of Kentucky are considered part of Central Appalachia[4].

Over 1.1 million people live in Appalachian Kentucky and 3.2 million live in non-Appalachian Kentucky[4]. As of July 2016, Caucasians were the predominant racial group in both Appalachian (94.7%) and non-Appalachian (81.5%) Kentucky. Individuals residing in non-Appalachian Kentucky are more likely to have higher levels of education than their Appalachian counterparts. For example, approximately 26% of non-Appalachians versus 14.3% of Appalachians have a bachelor's degree. From 2012 to 2016, the median per capita income for Appalachian Kentucky residents was $19,212 and 11% of the population were below 50% of the federal poverty level; this is in comparison to a median per capita income of $26,835 in non-Appalachia, and only 7% of residents below 50% of the poverty level[4].

Cancer incidence varies among the different regions of Appalachia. For example, Wingo et al investigated the cancer incidence in Appalachia from 2001 to 2003 and found that the incidence of prostate cancer (PC) was higher in Northern Appalachia compared to Central Appalachia and that this difference was related to socioeconomic conditions[5]. In contrast to these findings, a study by Wilson et al from 2004 to 2011 showed that Southern Appalachia had a higher incidence of PC than Northern or Central Appalachia[6]. The authors hypothesized that the findings might be related to the demographics of the population: approximately 30% of the Appalachian African American population lived in the Southern region compared to 15% in Central Appalachia and 17% in the Northern region[6]. Antwi et al. demonstrated that PC-specific mortality was significant in the Appalachian region compared to the non-Appalachian area of the USA[7].

Despite being the most commonly diagnosed malignancy in men in the USA[1], and differing findings from across the Appalachian region, PC in Appalachian Kentucky has not been well studied. Therefore, the purpose of this study was to conduct a population-based survival analysis of PC focused on comparisons between Appalachian Kentucky and non-Appalachian Kentucky.

Methods

Data sources

This retrospective population-based study extracted records of all PC patients residing in Kentucky from the Kentucky Cancer Registry (KCR) from 2007 to 2011. The KCR is a population-based registry, awarded the highest level of certification by the North American Association of Central Cancer Registries for objective evaluation of completeness, accuracy, and timeliness every year since 1997 and is also part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. The KCR also links its database to 2011 health administrative claims for additional comorbidity and treatment information. The linked data includes claims from Medicare, Medicaid, and private insurance companies (eg Humana, Blue Cross), thereby providing a more complete review of treatment procedures, medical comorbidities, and insurance-related variables across all age groups.

Study population and variables

The study included all PC patients residing in Kentucky between 2007 and 2011 and included in the linked KCR data. To limit biases, only first primary cancer cases with a minimum age of 20 years were included. To minimize selection bias, cases extracted through death certificate and autopsy cases were excluded. A total of 12 971 out of 14 680 PC cases met selection criteria and were used for data analysis. If a patient had treatment-related claims, such as radiation, chemotherapy, and hormone treatment, captured 1 month prior to their cancer diagnosis up to 1 year after diagnosis, this claims information was used to augment KCR treatment data.

Prostate-specific antigen (PSA) level at diagnosis was defined based on the patient's laboratory value and recategorized as 1–10, 10–20 or >20. Gleason score at diagnosis was grouped as <6, 6–8, >8–10 and unknown. The Charlson comorbidity index (CCI) was calculated based on the KCR-linked claims data and represented the 1–12-month time period prior to cancer diagnosis[8]. The CCI variable was categorized as 0, 1, 2 and ≥3; it was treated as unknown if a case did not have 12 months of continuous insurance coverage prior to the cancer diagnosis.

Urban/rural status was based on the US Department of Agriculture's 2003 Urban–Rural Continuum Codes, with 1–3 defined as 'urban' and 4–9 as 'rural'[9]. The county-level Appalachian status was based on definitions from the Appalachia Regional Commission[10]. Percentage below poverty was defined based on quantiles of census tract level, with less than 6.51% as 'low', >6.51–12.31% as 'moderate', >12.31–20.17% as 'high', and >20.17 as 'very high'. Ascertainment of a high school education was also defined based on quantiles of census tract level, with less than 66.12% as 'very low', >66.12–75.54% as 'low', >75.54–85.38% as 'moderate', and >85.38% as 'high'. Other study demographic and clinical variables included age at diagnosis, year at diagnosis, race, smoking history, insurance status, survival status, stage at diagnosis, number of lymph nodes examined, tumor size, tumor histology, and treatment type.

Statistical analysis

Descriptive analysis of demographic and clinical factors was performed. Bivariate analyses with χ^2 tests were performed to examine the association between Appalachian status and other covariates. Kaplan–Meier plots and log-rank tests were conducted for survival analysis. Stepwise Cox regression analyses were performed to estimate the effect of Appalachian status and other clinical and demographic variables for both observed survival and cause-specific survival. All analyses were performed using Statistical Analysis Software v9.4 (SAS Institute, Inc., http://www.sas.com). All statistical tests were two-sided with $p<0.05$ used to identify statistical significance.

Ethics approval

The study was approved by the Institutional Review Board at the University of Kentucky (17-0533-P1G).

Results

A total of 12 971 individuals diagnosed with PC between January 2007 and December 2011 were identified. As presented in Table 1, 73.2% of these cases were from non-Appalachian Kentucky counties and 26.8% were from Appalachian counties. The most common age group in non-Appalachia was 50–64 years and in Appalachia 65–74 years. Caucasian was the predominant race in both geographic regions. Compared to their non-Appalachian Kentucky counterparts, more PC patients in Appalachia were uninsured (1.8%), lived in rural areas (87.8%), were rated with an ascertainment of 'very low' high school education (65.9%), and associated with 'very high' poverty (68%) (Table 2). Clinically, PC patients from Appalachia were more likely to present with a Gleason score of 8–10 (16.8%) and with a PSA level >20 (12.3%), be diagnosed with stage 4 disease (6.9%), have poorly differentiated histology (53.5%), and have a CCI>3 (5.4%) compared to non-Appalachian patients. Appalachian PC patients had higher rates of no treatment, radiation therapy only, hormone treatment only, and combined radiation/hormone treatment.

In an unadjusted survival analysis, there was a 5-year overall survival difference between Appalachian Kentucky and non-Appalachian Kentucky PC cases ($p<0.001$) (Fig1). After controlling for demographic and clinical variables in a Cox regression model, no survival difference was seen between Appalachian Kentucky and non-Appalachian Kentucky PC cases ($p=0.4$) (Table 2). However, statistical significance in survival was observed among other variables such as age at diagnosis, insurance, smoking status, Gleason score, PSA, CCI, treatment, and education (Table 2).

Despite a 5-year lower incidence of PC in Appalachia as compared to non-Appalachian Kentucky, Kentucky, and the USA, the authors observed a significantly higher 5-year PC mortality rate in Appalachian Kentucky compared to non-Appalachian Kentucky as well as the USA as a whole (Table 3).

Table 1: Demographic and cancer attributes for patients diagnosed with prostate cancer in Kentucky from 2007 to 2011: comparison between Appalachian and non-Appalachian Kentucky

Variable	Non-Appalachian Kentucky (*n*=9489, 73.2%)		Appalachian Kentucky (*n*=3482, 26.8%)		*p*-value†
	n	%	*n*	%	
Age at diagnosis (years)					<0.001
20–49	308	3.2	82	2.4	
50–64	4111	43.3	1330	38.2	
65–74	3386	35.7	1374	39.5	
≥75	1684	17.7	696	20.0	
Race					<0.001
White and other	8298	87.4	3368	96.7	
Black	976	10.3	70	2.0	
Unknown	189	2.0	40	1.1	
Insurance type					<0.001
Uninsured	136	1.4	61	1.8	
Private	3807	40.1	959	27.5	
Medicare	4150	43.7	1919	55.1	
Medicaid	126	1.3	99	2.8	
Other public	373	3.9	112	3.2	
Unknown	897	9.5	332	9.5	
Rural–urban status					<0.001
Rural	2521	26.6	3056	87.8	
Urban	6968	73.4	426	12.2	
High school education ascertainment					<0.001
Very low	950	10.0	2295	65.9	
Low	2499	26.3	764	21.9	
Moderate	2912	30.7	333	9.6	
High	3128	33.0	90	2.6	
% below poverty					<0.001
Low	3189	33.6	68	2.0	
Moderate	3015	31.8	224	6.4	
High	2260	23.8	995	28.6	
Very high	1025	10.8	2195	63.0	
Smoking status					0.007
No	2350	24.8	770	22.1	
Yes	3565	37.6	1345	38.6	
Unknown	3574	37.7	1367	39.3	
Charlson comorbidity index					<0.001
0	5439	57.3	1886	54.2	
1	1291	13.6	628	18.0	
2	446	4.7	221	6.3	
≥3	343	3.6	189	5.4	
Unknown	1970	20.8	558	16.0	
Gleason score					<0.001
6	3791	40.0	1218	35.0	
7	3457	36.4	1302	37.4	
8–10	1296	13.7	584	16.8	
Unknown	945	10.0	378	10.9	
Prostate-specific antigen					<0.001
1–10	5850	61.7	2097	60.2	
>10–20	925	9.7	474	13.6	
>20	880	9.3	427	12.3	
Unknown	1834	19.3	484	13.9	
Stage group					0.002
Stage I	3	0.0	5	0.1	
Stage II	7506	79.1	2732	78.5	
Stage III	824	8.7	284	8.2	
Stage IV	515	5.4	241	6.9	
Unknown	641	6.8	220	6.3	
Nodes examined					<0.001
0	7058	74.4	2662	76.5	
1–11	1734	18.3	575	16.5	
≥12	173	1.8	96	2.8	
Unknown	524	5.5	149	4.3	
Grade					<0.001
Well differentiated	66	0.7	52	1.5	
Moderately differentiated	4210	44.4	1368	39.3	
Poorly differentiated	4764	50.2	1862	53.5	
Undifferentiated	27	0.3	17	0.5	
Unknown	422	4.4	183	5.3	
Size					<0.001
<5 cm	1209	12.7	350	10.1	
5-10 cm	48	0.5	23	0.7	
>10 cm	71	0.7	14	0.4	
Not available	8161	86.0	3095	88.9	
Treatment type					<0.001
No therapy	1388	14.6	532	15.3	
Surgery only	4044	42.6	1184	34.0	
Radiation only	1539	16.2	661	19.0	
Hormone only	590	6.2	264	7.6	
Radiation/hormone	1234	13.0	605	17.4	
Other treatments only	254	2.7	84	2.4	
Combination therapy	440	4.6	152	4.4	

† Based on χ^2 tests.

Table 2: Estimates of Appalachian status and other covariates in a Cox-regression model

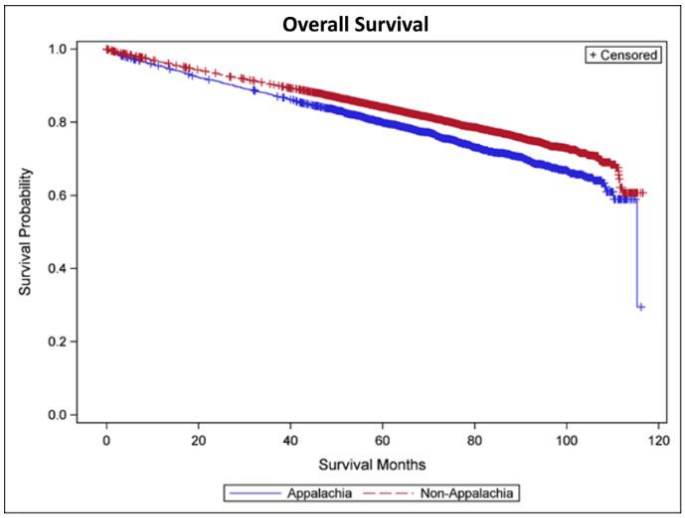
Variable†	Hazard ratio	95% confidence interval	*p*-value
Age at diagnosis (years)			<0.001
20–49	Ref		
50–64	1.89	1.24–2.87	
65–74	2.46	1.61–3.75	
≥75	5.02	3.29–7.68	
Race			0.004
White	Ref		
Black	0.96	0.83–1.10	
Other	0.61	0.23–1.64	
Unknown	0.21	0.09–0.50	
Insurance type			<0.001
Private	Ref		
Medicaid	1.71	1.34–2.19	
Medicare	1.32	1.16–1.50	
Uninsured	2.15	1.61–2.89	
Other public	1.48	1.17–1.86	
Unknown	1.41	1.20–1.66	
Smoking status			<0.001
No	Ref		
Yes	1.40	1.26–1.56	
Unknown	1.10	0.98–1.23	
Appalachian status			0.387
Non-Appalachian	Ref		
Appalachian	0.96	0.87–1.06	
Gleason score			<0.001
6	Ref		
7	1.12	1.00–1.24	
8–10	1.93	1.72–2.18	
Unknown	1.66	1.47–1.89	
Prostate-specific antigen			<0.001
1–10	Ref		
>10–20	1.37	1.21–1.54	
>20	1.64	1.45–1.84	
Unknown	1.51	1.36–1.69	
Charlson comorbidity index			<0.001
0	Ref		
1	1.59	1.44–1.75	
2	2.02	1.77–2.30	
≥3	3.10	2.73–3.51	
Unknown	0.97	0.83–1.08	
Treatment group			<0.001
Surgery only	Ref		
No therapy	2.16	1.88–2.48	
Hormone only	2.16	1.86–2.51	
Radiation only	1.25	1.08–1.44	
Other treatments only	1.56	1.19–2.04	
Radiation/hormone	1.34	1.17–1.54	
Combination therapy	2.17	1.84–2.55	
High school education ascertainment			0.001
High	Ref		
Low	1.25	1.12–1.40	
Moderate	1.18	1.05–1.32	
Very low	1.27	1.11–1.45	

† Only variables of interests and significant variables were included using the backward selection approach.
Ref, reference value.

Table 3: Age-adjusted incidence and mortality rates of prostate cancer in Appalachian Kentucky, non-Appalachian Kentucky and USA, 2010–2014

Measure	USA		Kentucky		Appalachian Kentucky		Non-Appalachian Kentucky	
	Rate/%	95%CI	Rate/%	95%CI	Rate/%	95%CI	Rate/%	95%CI
Incidence rate per 100 000†	136.7	136.4–137.1	125.4	123.9–126.9	113.0	110.7–116.0	130.5	128.7–132.3
Mortality rate per 100 000	21.8	21.7–21.9	22.3	21.5–23.0	23.1	21.2–24.5	21.6	20.8–22.5
Observed 5-year survival†	85.0%	84.9–85.2%	82.2%	81.6–82.7%	79.6%	78.5–80.7%	83.1%	82.5–83.7%
Cause-specific 5-year survival†	94.0%	93.9–94.0%	93.1%	92.8–93.5%	92.0%	91.2–92.7%	93.5%	93.1–93.9%

† Calculated based on Surveillance, Epidemiology and End Results 18 data.
CI, confidence interval.



† Only three cases had survival information greater than 115 months in the Appalachian group. One patient died at month 115, which led to a pronounced drop at the end of the curve.

Figure 1: Kaplan–Meier plots by Appalachian status.†

Discussion

PC is the most common malignancy among men in the USA. Interestingly, when comparing the PC incidence and mortality rates using SEER data from 2005 to 2014, findings suggest that Appalachian Kentucky had a lower incidence but a higher mortality rate compared to non-Appalachian Kentucky and the USA. This population-based study based on PC data from the KCR from 2007 to 2011 showed that men in Appalachian Kentucky have a significantly higher mortality rate of PC compared to their counterparts in non-Appalachian Kentucky. This disparity in PC mortality may be primarily attributed to lower socioeconomic status, lower levels of education, increased risk behaviors and presence of comorbidities, and fewer available health resources in rural Appalachian Kentucky[11]. However, the disparity can't be explained by geography alone. Interestingly, Appalachian PC patients were also more likely to present with advanced clinical cases, including higher Gleason scores, higher PSA values, stage 4 disease, and poorly differentiated tumor histology, which may have impacted overall survival.

Uninsured patients had worse outcomes compared to individuals covered by Medicaid, and Medicaid patients fared worse compare to men covered by Medicare. Uninsured and low-income PC patients with Medicaid may have inadequate access to primary, secondary, and tertiary-related health care services and experience variations in treatments[12,13]. Additionally, these PC patients may face other barriers to care such as limited transportation and financial distress related to their diagnosis. PC patients who did not finish high school had an increased risk of dying compared to those who had a bachelor's degree or more. Blackley et al suggested that education and income status are associated with higher cancer mortality and suggested that improving education levels could result in decreased cancer mortality rate in Appalachia[14].

As expected, this study demonstrates that men aged over 75 years, those with higher Gleason scores and PSA values, smokers, and those with a higher number of comorbidities experienced lower survival as all these factors are associated with poorer overall health and negative cancer-related outcomes.

In order to improve PC outcomes in Appalachian Kentucky, more research and educational programming are needed at multiple levels, including the patient and their family. Schoenberg et al conducted a community survey to address cancer disparities in Appalachian Kentucky and identified three challenges: (1) inadequate awareness of the need for cancer prevention and screening, (2) insufficient access to services across the cancer continuum and (3) concern for lack of privacy[15]. Barriers related to the lack of privacy comprise personal attitudes such as fear or discomfort, personal (negative) beliefs about cancer, and misperceptions about health care and limited patient-centered communication[15]. Coyne et al conducted a study that explored cultural norms in rural Appalachia about health and concluded that rural Appalachian residents have a sense of place, strong family ties, and a strong spiritual belief[16]. Increased awareness of family cancer history, adopting a healthy lifestyle, securing social and familial support, and engaging in informed and shared decision making between PC patients and providers – along with alleviating fear and correcting misperceptions – can empower men to take control of their health.

Not only should there be efforts to educate Appalachian Kentuckians at the individual patient and family levels, but interventions are also needed to train and empower healthcare systems, clinicians, and support teams to deliver quality PC care. For example, the University of Kentucky Markey Cancer Center (MCC) is the only National Cancer Institute-designated cancer center in Kentucky[17]. MCC provides high quality clinical and psychosocial cancer care, along with the opportunity for patients to participate in clinical trials. The MCC also supports an Affiliate Network, a collaborative of 26 community hospitals across Kentucky[18], including Appalachia, focused on increasing access to oncology education, training, clinical trials, and screening services,

all with the mission of providing evidence-based, quality cancer care close to home.

Improvements in PC screening could contribute to improvements in PC survival in Appalachian Kentucky as this population is more likely to have more advanced disease at the time of diagnosis. Similarly, improvements in access to insurance, primary care providers, urology and oncology providers, and supportive care services are needed in the region. More research is also needed to understand the advanced clinical presentation of PC in Appalachia, including related behavioral, environmental, genetic, and cultural factors.

A limitation to the current study is its design as a retrospective population-based data analysis; in addition, the data is dependent on accurate coding in the KCR database. For example, data for some of the variables such as race, smoking status, PSA level and Gleason score are missing. Despite these limitations, this study presents a novel and comprehensive population-based analysis of PC survival disparities between Appalachian and non-Appalachian Kentucky and contributes to a related gap in the literature.

Conclusion

In this population-based analysis, there was a significant difference in PC survival between men from Appalachian Kentucky and that of men from non-Appalachian Kentucky. This study supports the concept that patients from Appalachia generally present with later stage, more aggressive disease. This is likely most impacted by the differences in socioeconomic and educational backgrounds of the Appalachian and non-Appalachian population that may delay diagnosis and care. Long-term efforts to improve cancer care in this population must focus on barriers to early diagnosis and treatment. Improvements in socioeconomic status and education levels, which are independent predictors of poor outcomes in this population, must be achieved in order to see a decrease in PC mortality rates in Appalachian Kentucky.

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