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A population-based survival analysis of mesothelioma and smoking in
Appalachian and Non-Appalachian Kentucky

Capstone Project Paper

A paper submitted in partial fulfillment of the requirements
for the degree of Masters of Public Health
In the University of Kentucky College of Public Health

By Peter Van Wie
Lexington Kentucky
April 30, 2017

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Abstract

Mesothelioma is one of the most aggressive cancers in the United States and around the world, with a grim 5-year survival rate of only 8%. After diagnosis there is little that can be done to stop the progression of the disease. Smoking has been negatively associated with mesothelioma survival. This may be due to several factors including increased oxidative stress or sequestration of tobacco-related carcinogenic compounds by asbestos fibers trapped in the lung. This study investigated the association between smoking and mesothelioma survival in the Kentucky population. It examines the risk of living in the low socioeconomic region of Appalachian Kentucky. This study is a population-based study that included those diagnosed with mesothelioma as reported by the Kentucky Cancer Registry (KCR) between 1995 and 2011. The KCR is a Surveillance, Epidemiology, and End Results (SEER) organization that has maintained gold standard certification since it was founded. Stage at diagnosis was significantly associated with survival rate. Cox proportional hazard multivariable model describing mesothelioma survival from all deaths was separated by stage: early, late, and unknown. Smoking was strongly associated with late stage mesothelioma diagnosis with a HR of 1.528 ($p = 0.0057$). However there was no significant difference in survival between Appalachian and non-Appalachian residents. This study suggests that cigarette smoke exposure may decrease survival of mesothelioma.

Introduction

Mesothelioma is one of the most aggressive cancers in the United States and around the world, with a grim 5-year survival rate of only 8%. Mesothelioma has a long latency period around 30-45 years [2, 3]. After diagnosis there are few things that can be done to stop the spread of the disease. There are several treatments that have been known to slow or stop the progression of the disease after diagnosis; the standard treatments are surgery, radiation, and chemotherapy. Likewise there are a few lifestyle choices or environmental exposures that can change the progression of the disease. For example, smoking, and low socioeconomic status have been negatively associated with mesothelioma survival, while eating healthy, getting exercise, and having access to healthcare has been positively associated with mesothelioma survival [4, 5]. The 20th century has seen an increase in mesothelioma incidence [6].

Asbestos is the primary known cause of mesothelioma, though there are still cases that appear with unknown reasons [7]. Many cases of mesothelioma are related to occupational exposure. In the 1970s asbestos was banned from many household and industrial uses [8]. Though the ban is still in place, the incidence rate of the disease remains high. Asbestos is still present in many, buildings, ships, piping, automotive and household products [9, 10]. Asbestos has also been discovered in newly manufactured products imported from abroad where there are looser regulations on the use of asbestos. The continued use of asbestos makes mesothelioma an ongoing concern.

Mesothelioma is a cancer that permeates the mesothelium, which lines the lungs and chest cavity. The peritoneum may also be affected but the majority of cases affect the pleural lining of the lungs. There are three major hypotheses for the mechanism of disease reviewed by Toyokuni in 2009 [1]. The major hypotheses are oxidative stress, chromosome tangling, and the adsorption of carcinogenic agents.

There are two mechanisms linking asbestos to oxidative stress.

First, asbestos can contain iron, or possibly sequester iron that can

catalyze Fenton's reaction $H_2O_2 \rightarrow \bullet OH$. Second, when macrophages engulf asbestos, the particles can puncture the walls of the macrophages causing them to leak reactive oxygen and other digestive enzymes. For these reasons, asbestos is thought to produce reactive oxygen species (ROS) [1].

The second hypothesis, chromosome tangling, suggests that asbestos fibers facilitate the rearrangement of chromosomes during replication. Chromosome 22 is particularly noted as a hotspot for mutation in mesothelioma. Chromosomes 1, 3, 6, and 9 are also commonly mutated in mesothelioma [11]. Several studies found the tumor suppressor gene p16 on chromosome 9

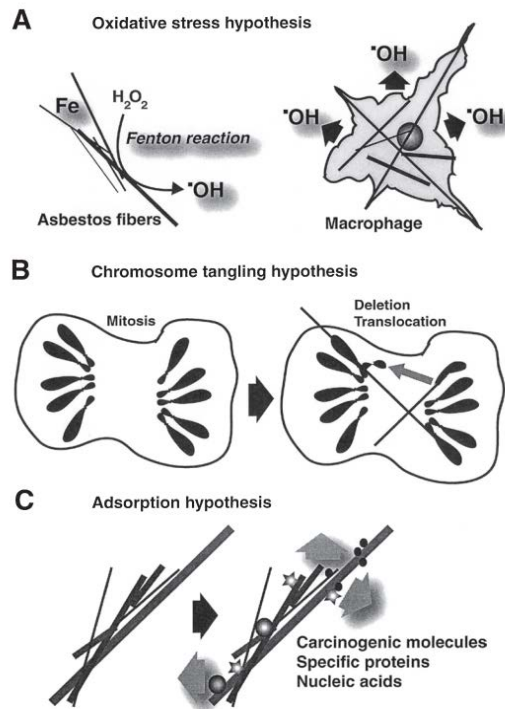


Figure 1. This figure outlines three common hypotheses for the mechanism of asbestos-induced mesothelioma [1].

(involved in cell cycle regulation by inhibiting CDKs) was absent in most mesothelioma cases. The absence of p16 is associated with worse clinical outcome [12, 13].

A third mechanism of disease commonly hypothesized is that of adsorption. Asbestos may sequester harmful chemicals for example those found in cigarettes, or may generate a film of proteins or surfactant. This can cause harm directly or may attract macrophages and neutrophils to the site, increasing inflammation and worsening prognosis [1]. There are many harmful chemicals in tobacco smoke that cause or contribute to lung inflammation and cancer. There are over 70 known carcinogens in cigarette smoke [14]. Some harmful constituents include nicotine, which has been observed to increase cell proliferation, inhibit apoptosis, and increase angiogenesis [15-17]. Acrolein, acetaldehyde, and formaldehyde are reactive aldehydes that can generate ROS contributing to oxidative stress [18]. Polyaromatic hydrocarbons can be metabolized by CYP1A1 or CYP1B1 to reactive intermediates that can cause DNA damage [19]. Carcinogenic metals like Cd, Ni, Cr, As, and Pb can also be found in cigarette smoke. These metals contribute to cancer by generation of reactive oxygen species or contributing to Fenton-like reactions [20].

Smoking has been negatively associated with mesothelioma survival [21-23]. This may be due to several factors including increased oxidative stress [24, 25] or sequestration of tobacco related carcinogenic compounds by asbestos fibers trapped in the lung [1]. This study assessed the association between smoking and mesothelioma survival in the population of Kentucky.

Socioeconomic status (SES) has been associated with cancer incidence and survival [26]. The Appalachian region of Kentucky has 38 distressed counties which rank in the worst 10% of the nation's counties [27]. A study was conducted to analyze socioeconomic status and survival of lung cancer. This study found that middle-low, middle-high, and highest SES were positively associated with survival compared with lowest SES with hazard ratios (HR) of 0.96 (95% CI 0.94-.99) 0.92 (95% CI 0.89-0.94) and 0.87 (95% CI 0.84-0.91) respectively [28]. Poor socioeconomic status has been associated with reduced mesothelioma survival [4]. For these reasons, living in Appalachian Kentucky was analyzed as a risk factor for mesothelioma survival in Kentucky.

Kentucky is the state with the highest rate of lung cancer, and is in the top ten for mesothelioma [29]. The incidence rates of mesothelioma have not returned to their former levels even after the ban on the use of asbestos. Smoking is also very common in Kentucky and is thought to increase risk for the development of mesothelioma [30]. Smoking was identified to negatively impact survival in lung cancer. One study found a hazard ratio (HR) of 1.38 (95% CI, 1.19-1.60) after adjusting for comorbidities and covariates [31]. Another study looking at lung function and survival found smoking to be negatively associated with survival with a HR of 2.29 (95% CI, 1.23-4.26) [22].

This study is a population-based study that associates smoking and abiding in Appalachian Kentucky with the survival of pleural mesothelioma patients. There have been previous studies on mesothelioma survival, but this study is different in that it focuses on the risk of smoking and the progression of

the disease in a population that is at high risk. Kentucky has the highest rate of smoking related deaths, the highest smoking rate of those in high school, and is the nation's second highest for adult smokers [32].

Material and Methods

This study is a population-based study that includes those diagnosed with mesothelioma as reported by the Kentucky Cancer Registry (KCR). The KCR is a Surveillance, Epidemiology, and End Results (SEER) organization that has maintained gold standard certification since it was founded. The KCR operates in Kentucky with its headquarters in Lexington, KY. The data was collected and de-identified by the KCR. IRB exempt status was granted for this study.

The KCR reports information gathered from medical records. The information collected was sufficient for this study. Information included: smoking status, geographical location, sex, treatment, histology, health insurance, cause of death, menopause, age, marital status, grade of tumor, stage, and race. Subjects were followed until death or considered still alive as of May 28, 2013, which was the last day of follow up in this dataset. Cases diagnosed in Kentucky from 1998-2011 were used for the study.

The variables used in this study were categorized as follows. Smoking was categorized as smoker, non-smoker, and unknown status. Location was described as Appalachian resident, non-Appalachian resident, or unknown. The Appalachian region in Kentucky is comprised of 54 counties in eastern Kentucky. The majority of counties in Appalachian Kentucky are distressed having at least double the national unemployment rate [27]. Age was analyzed as a continuous

variable. Stage indicated the metastatic progression of the cancer, and was classified as local, regional, distant, or unknown. Histology described the tissue affected as epithelial, fibrous, biphasic or unclassified mesothelioma. Healthcare variables were private insurance, Medicare, Medicaid, uninsured, or unknown. Female was used as the reference group for gender. Treatments included surgery, chemotherapy, radiation, or no treatment given by a physician. Marriage was coded as married (including common law), unmarried, or unknown. Race was not included as a variable because there were too few black cases; there were a total of 11 black cases. The final model adjusted variables include: marital status, insurance, Appalachian, site, treatment, stage, and age. These adjustments were decided beforehand to reduce variability and possible bias in comparisons.

All analyses were conducted using SAS 9.3. Kaplan-Meier curves were generated to show the survival rates and Cox regression analyses were performed for the hazard analysis. The data was analyzed unadjusted and adjusted for age, stage, treatment, site, marriage, and insurance type. The information was separated into stages as well because stage at diagnosis played an important roll in survivability. The study reports the total number of deaths after diagnosis.

Results

From the incidence demographics in table one several observations can be made. First mesothelioma appears to mostly affect white males. Smokers have a much higher percent distribution than non-smokers. Mesothelioma is normally discovered later in life, and the majority of cases are metastatic with distant colony formation. Finally, there are several common treatment options, chemotherapy being the most commonly administered. Table one provides the basic details of the study population and shows differences between Appalachian and non-Appalachian residents.

Table 1: Demographics of Appalachian and Non-Appalachian Populations

Demographics of Population at Risk	Total		Appalachian		Non-Appalachian.	
	N	%	N	%	N	%
	434	100	119	27.4	315	72.6
Age						
20-49	38	8.8	12	10.1	26	8.3
50-64	103	23.7	32	26.9	71	22.5
65-74	139	32	37	31.1	102	32.4
75+	154	35.5	38	31.9	116	36.8
Average Age	68.6 years					
Sex						
Male	322	74.2	88	74.0	234	74.3
Female	112	25.8	31	26.1	81	25.7
Race						
White/other	423	97.5	118	99.2	305	96.8
Black	11	2.5	1	0.8	10	3.2
Smoking						
Non-smoker	113	26	21	17.7	92	29.2
Smoker	258	59.5	78	65.6	180	57.1
Unknown	63	14.5	20	16.8	43	13.7
Insurance						
None	7	1.6	2	1.7	5	1.6
Private	115	26.5	27	22.7	88	27.9
Medicaid	14	3.2	7	5.9	7	2.2
Medicare	287	66.1	77	64.7	210	66.7
Unknown	11	2.5	6	5.0	5	1.6
Site						
Unspecified	262	60.4	78	65.6	184	58.4
Fibrous	34	7.8	10	8.4	24	7.6
Epithelioid	109	25.1	24	20.2	85	27.0
Biphasic	29	6.7	7	5.9	22	7.0

Stage						
Localized	73	16.8	16	13.5	57	18.1
Regional	84	19.4	23	19.3	61	19.4
Distant	197	45.4	56	47.1	141	44.8
Unknown	80	18.4	24	20.2	56	17.8
Treatment						
Surgery	109	25.1	34	28.6	75	23.8
Chemo	169	38.9	43	36.1	126	40.0
Radiation	67	15.4	17	14.3	50	15.9

Table two provides unadjusted and adjusted Cox Proportional Hazard Ratios (HR) for those who died after mesothelioma diagnosis from all causes. In this analysis smoking was significantly linked with poor survival with an adjusted HR of 1.448 (95% CI 1.14-1.84). The adjusted HR accounted for marital status, insurance, Appalachian, site, treatment, stage, and age. The crude death rate was calculated as the number of deaths by all causes divided by the number diagnosed multiplied by 100%. The next column shows the five-year survival rate post diagnosis. Other factors that played a significant role in survival were age, sex, treatment and site. Though there were differences in survival between Appalachian and non-Appalachian residents, these observations were not statistically significant.

Table 2: All Cause Unadjusted and Adjusted Survival Analysis of Mesothelioma Diagnoses from 1995 to 2011 as reported by the Kentucky Cancer Registry

	No. at Risk	No. Deaths by All Cause	Death Rate	5-Year Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All Cases	434	402	92.6%	0.871		
Age						
Continuous	434	402	92.6%	0.811	1.031 (1.02-1.04)	1.030 (1.02-1.04)
Sex						
Male	322	309	96.0%	0.864	1.680 (1.33-2.13)	1.494 (1.17-1.90)
Female	112	93	83.1%	0.658	1 (REF)	1 (REF)
Smoking						
Non-Smoking	113	102	90.3%	0.738	1 (REF)	1 (REF)
Smoking	258	243	94.2%	0.842	1.281 (1.02-1.62)	1.448 (1.14-1.84)
Unknown	63	57	90.5%	0.816	1.274 (0.92-1.76)	1.259 (0.91-1.75)
Appalachian						
Non-Appalachian	315	294	93.3%	0.817	1 (REF)	1 (REF)

Appalachian	119	108	90.8%	0.795	0.998 (0.80-1.25)	1.053 (0.84-1.32)
Treatment						
Surgery	109	91	83.5%	0.639	1 (REF)	1 (REF)
Chemo	113	104	92.0%	0.823	1.409 (1.06-1.87)	1.276 (0.96-1.70)
Radiation	28	28	100%	0.857	1.764 (1.15-2.70)	1.258 (0.80-1.98)
No Treatment	184	179	97.3%	0.899	2.282 (1.76-2.95)	1.817 (1.37-2.42)
Site						
Epithelioid	109	96	88.1%	0.729	1 (REF)	1 (REF)
Fibrous	34	33	97.1%	0.912	1.857 (1.25-2.77)	1.657 (1.10-2.49)
Biphasic	29	27	93.1%	0.947	2.279 (1.48-3.50)	2.576 (1.67-3.98)
Unspecified	262	246	93.9%	0.817	1.230 (0.97-1.56)	1.409 (1.10-1.81)
Insurance						
Private	115	95	82.6%	0.739	1 (REF)	1 (REF)
Medicaid	14	11	78.6%	0.519	1.088 (0.58-2.04)	1.331 (0.70-2.53)
Medicare	287	280	97.6%	0.863	1.800 (1.42-2.28)	0.941 (0.68-1.31)
Not Insured	7	5	71.4%	0.571	0.775 (0.31-1.91)	1.181 (0.48-2.94)
Unknown	11	11	100%	0.727	1.637 (0.88-3.06)	1.166 (0.59-2.30)
Marital Status						
Married	188	171	91.0%	0.831	1 (REF)	1 (REF)
Unmarried	95	88	92.6%	0.787	1.064 (0.82-1.38)	0.868 (0.65-1.12)
Unknown	151	143	94.7%	0.801	0.968 (0.75-1.21)	1.041 (0.81-1.34)

*Adjusted for marital status, insurance, Appalachian, site, treatment, stage, and age

It was important to stratify the data by stage because of the large impact stage at diagnosis plays in overall survival. Table 3 shows Cox Proportional Hazard multivariable models describing mesothelioma survival from all deaths separated by stages: early, late, and unknown. Smoking with a late stage mesothelioma diagnosis was negatively associated with survival with a HR of 1.528 ($p = 0.0057$). Other pronounced associations in this analysis were no treatment having an adjusted HR of 1.986 ($p < .0001$), and sites fibrous and biphasic with adjusted HRs of 2.891 ($p < .0001$) and 3.153 ($p < .0001$) respectively. However, Appalachian residency remained statistically insignificant for all stages at diagnosis.

Table 3: Adjusted Analysis by Stage at Diagnosis among those Diagnosed with Mesothelioma from 1995 to 2011 as Reported by the Kentucky Cancer Registry

	Early Stage N=73		Late Stage N=281		Unknown Stage N=80	
	All Cause Death Rate	Adjusted HRI (p value)	All Cause Death Rate	Adjusted HRI (p value)	All Cause Death Rate	Adjusted HRI (p value)
Age						
Continuous		1.032 (0.0389)		1.023 (0.0005)		1.052 (<.0001)
Sex						
Male	.964	1.799 (0.1061)	0.951	1.414 (0.0232)	0.983	1.589 (0.1806)
Female	.824	1 (REF)	0.867	1 (REF)	0.700	1 (REF)
Smoking						
Non-Smoking	0.722	1 (REF)	0.908	1 (REF)	0.895	1 (REF)
Smoking	0.932	1.001 (0.9987)	0.941	1.528 (0.0057)	0.956	1.700 (0.0880)
Unknown	1	1.109 (0.8114)	0.917	1.283 (0.2468)	0.813	1.861 (0.1235)
Appalachian						
Non-Appalachian	0.930	1 (REF)	0.946	1 (REF)	0.893	1 (REF)
Appalachian	0.938	1.072 (0.8409)	0.886	1.059 (0.6932)	0.958	0.791 (0.3994)
Treatment						
Surgery	0.778	1 (REF)	0.971	1 (REF)	0.615	1 (REF)
Chemo	1	0.901 (0.7952)	0.885	1.275 (0.1589)	0.929	1.454 (0.4607)
Radiation	1	0.454 (0.2342)	0.900	1.717 (0.0445)	1	1.128 (0.8691)
No Treatment	0.968	0.926 (0.8532)	0.971	1.986 (<.0001)	0.980	2.311 (0.0548)
Site						
Epithelioid	1	1 (REF)	0.861	1 (REF)	0.867	1 (REF)
Fibrous	1	0.221 (0.0249)	0.962	2.891 (<.0001)	1	0.582 (0.4141)
Biphasic	0.857	1.281 (0.6313)	0.947	3.153 (<.0001)	1	3.000 (0.1166)
Unspecified	0.913	0.598 (0.1562)	0.955	1.663 (0.0008)	0.915	0.952 (0.8872)
Insurance						
Private	0.750	1 (REF)	0.859	1 (REF)	0.765	1 (REF)
Medicaid	1	1.391	0.857	1.812 (0.1761)	0.600	0.955 (0.9472)
Medicare	1	1.099	0.963	0.871 (0.4855)	1	0.570 (0.2147)
Not Insured	N/A	N/A	0.750	1.193 (0.7663)	0.667	0.619 (0.6572)
Unknown	1	2.632	1	1.573 (0.4617)	1	0.657 (0.4510)
Marital Status						
Married	0.931	1 (REF)	0.922	1 (REF)	0.636	1 (REF)
Unmarried	0.943	0.496 (0.0743)	0.943	0.987 (0.9328)	0.818	0.712 (0.5946)
Unknown	0.914	0.760 (0.3439)	0.931	0.992 (0.9631)	0.983	1.722 (0.2641)

*Adjusted for marital status, insurance, Appalachian, site, treatment, stage, and age

Smokers and Non-Smokers Survival in Kentucky from 1994-2011

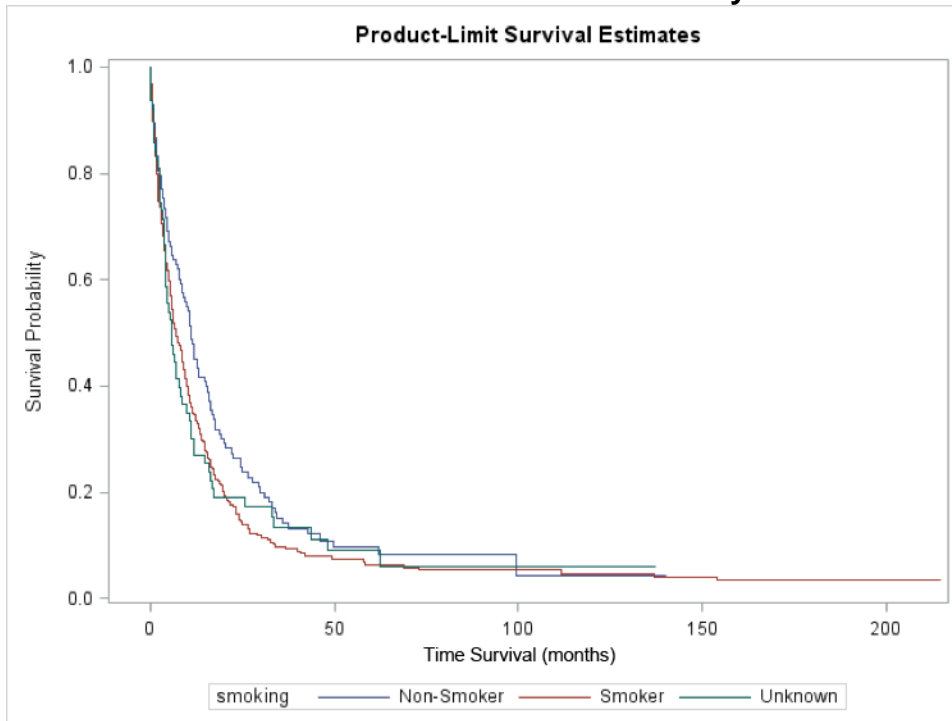


Figure 2. The survival curve for smoking illustrates that smokers had a significantly reduced survival rate compared with non-smokers. The difference is most pronounced in the first 50 months post diagnosis.

Appalachian and Non-Appalachian Survival in Kentucky from 1994-2011

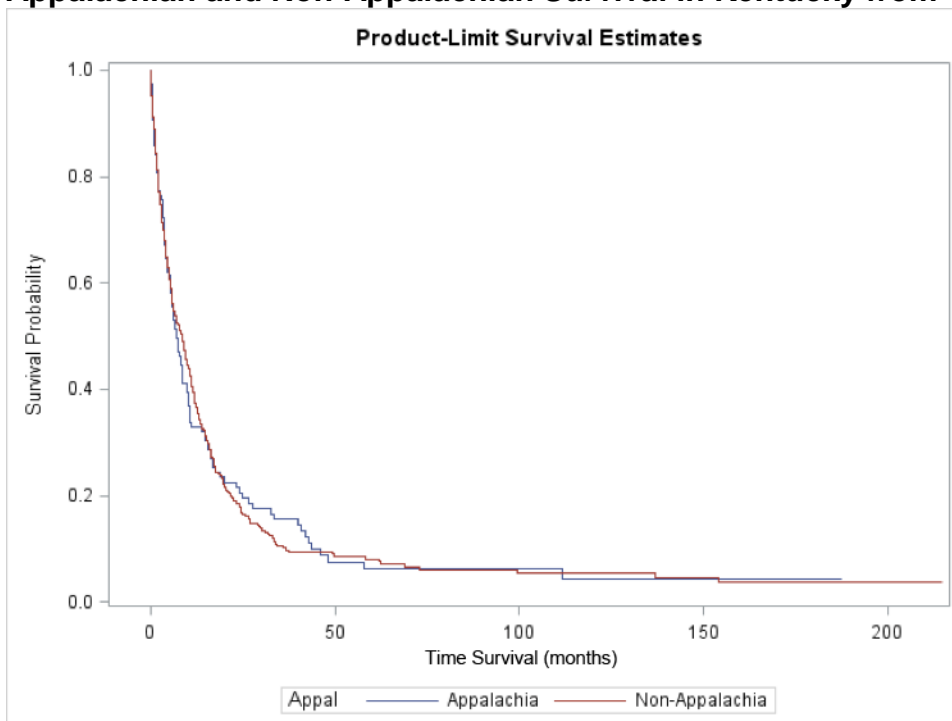


Figure 3. There was very little change between the survival curves from Appalachian and non-Appalachian Kentucky.

Discussion

Through this study smoking can be strongly associated with mesothelioma survival. Smoking status had the most dramatic effect on survival for late stage patients with a hazard ratio of 1.528 ($p = 0.0057$). The data indicate that smoking is more significantly associated with survival than many other risk factors. These findings suggest those who do not smoke will have significantly increased survival. Those in high-risk occupations may benefit greatly from smoking counseling and cessation programs prior to disease onset.

Smoking is both statistically significant and practically significant. The study found non-smokers' survival probability at 24 months is close to 40% while smokers' survival probability is close to 20%. This can be seen in the Kaplan-Meier curve in Figure 2. This survival probability gap becomes smaller as we approach the 5-year mark. Since mesothelioma is a very fast acting cancer once diagnosed, both smoking and non-smoking have very low survival probability after 5 years.

Several studies have observed similar hazard ratios when examining smoking and lung cancer. In 2003, Tammemagi et al. found a HR of 1.38 ($p > 0.001$) for smokers compared with non-smokers. Moshammer et al. in 2009 found an HR of 2.89, while Naomi et al. in 2014 found an HR of 1.39. These results support our findings that smoking decreases survival after mesothelioma diagnosis. The difference between our study and these studies is that we looked at mesothelioma specifically while these other studies reported lung cancers generally. Additionally this study is more accurate than previous studies because

it analyzes a population while previous studies reported survival ratios based on fewer cases.

Comparing Appalachian Kentucky with non-Appalachian Kentucky did not yield any significant change in survival after adjustment for smoking and other significant risk factors. The results suggest that there may be little genetic predisposition for mesothelioma survival in those who are living in Appalachian Kentucky. It indicates that socioeconomic factors in Appalachia may need to be better defined rather than analyzing at a county level. Additionally, it is important to note that there are more smokers in Appalachian Kentucky. It still may be beneficial to focus smoking cessation programs in this area to extend cancer survival.

A major strength of this study is that it is a population-based study. The data for this study represents all cancer cases from the state of Kentucky from 1995 to 2011. However, since mesothelioma is a relatively rare disease there were only 434 cases during this long time period. For example, there were only 14 cases holding Medicaid insurance, and only 28 cases received radiation. Most other variables had many cases, which increase the predictive power. Smoking status was well defined with 113 cases in non-smokers and 258 in smokers. To improve some of the lower variables like Medicaid insurance and radiation treatment, a national study may be conducted.

Some additional information on patients may provide further understanding on mesothelioma survival in the future. For example, exercise data was not included in this study. People with a history of regular exercise may

exhibit a better survival outcome for mesothelioma. It may be helpful in future studies to include a short exercise questionnaire as a part of the cancer data collection. Exercise has been shown in several studies to reduce cancer risk [33]. Additionally, a review showed exercise was correlated with improved survival, but smoking was not accounted for in that review [34]. The inclusion of exercise data may be a significant addition for mesothelioma survival studies in the future.

The second additional piece of information that may prove useful in future studies is nutritional data. People with a history consuming foods high in antioxidants may have higher survival rates. Some studies indicate nutrition plays a valuable role in cancer incidence and progression for many different cancer types. Foods high in antioxidants have been suggested to lower cancer risk while red meats, refined foods, and regular or high alcohol consumption have been shown to increase risk [35-37].

In conclusion, these data suggest that smoking is a risk factor associated with reducing mesothelioma survivability. The data collected from the Kentucky Cancer Registry is consistent with reports in the literature for smoking and lung cancer survival. Further research is needed in this area to better understand this association.

Biographical Sketch

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Van Wie, Peter

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Research Assistant

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Ahmadu Bello University , Zaria, Kaduna	OTH	05/2008	Fine Art and Pre Medicine
University of Idaho, Moscow, ID	BFA	05/2012	Fine Art and Pre Medicine
University of Kentucky, Lexington, KY	MPH	05/2018	Environmental Health
University of Kentucky, Lexington, KY	PHD	05/2018	Toxicology

A. Personal Statement

Through this training I plan to broaden my understanding of molecular pathways and human health. I plan to pursue a career path where I can apply the skills learned during this training to improve the health of the population. The techniques and skills performed during this training will equip me for studying many diseases including cancer, diabetes, obesity, and other diseases related to inflammation and oxidative stress. I plan be dedicated to my career to improving quality of life and health. This training experience will provide a strong base to build foundation for synergistic success.

B. Positions and Honors

Positions and Employment

2012 - 2013 Chemistry TA, University of Kentucky, Lexington, KY
2013 - 2014 Training Grant, NIOSH/University of Kentucky, Lexington, KY
2013 - 2014 Student Senator, University of Kentucky, Lexington, KY
2014 - 2017 Research Assistant, University of Kentucky, Lexington, KY

Other Experience and Professional Memberships

2015 - 2017 Member, Society of Toxicology

Honors

2009 Dean's List, University of Kentucky

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

OH007547, NIOSH

 Van Wie, Peter (PI)

01/01/13-05/01/14

The Southeast Center for Agricultural Health and Injury Prevention at the University of Kentucky

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