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UTERINE CORPUS MALIGNANCIES IN APPALACHIA KENTUCKY: INCIDENCE, SURVIVAL AND RELATED HEALTH DISPARITIES

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UTERINE CORPUS MALIGNANCIES IN APPALACHIA KENTUCKY:

INCIDENCE, SURVIVAL AND RELATED HEALTH DISPARITIES

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
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By

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ABSTRACT OF THESIS

UTERINE CORPUS MALIGNANCIES IN APPALACHIA KENTUCKY: INCIDENCE, SURVIVAL AND RELATED HEALTH DISPARITIES

Uterine cancer is the nation's most common gynecologic malignancy but is understudied in the geographically and socioeconomically diverse state of Kentucky (KY). This study assessed the frequency, distribution, and survival of uterine corpus malignancies in KY, and specifically the differences between Appalachia (AP) and non-Appalachia (NAP).

This study utilizes SEER and Kentucky Cancer Registries to study uterine corpus malignancy between January 1, 2000 and December 31, 2014. The analysis looks at incidence between diagnoses in AP and NAP. Evaluation criteria includes: tumor histology (Type I, Type II, sarcoma, and mixed uterine malignancy), age, race, smoking status, stage at diagnosis, insurance status, and county of residence at diagnosis.

KEYWORDS: Uterine Cancer, Appalachia, Kentucky

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CHAPTER 1. INTRODUCTION

1.1 Background

According to 2018 Surveillance Epidemiology and End Results (SEER) data, the state of Kentucky (KY) has the highest incidence and the highest death rate for female cancers in the United States (U.S.).1 Kentucky's cancer woes are a result of a constellation of enduring social, economic, and healthcare access inequities. Eastern KY is in the heart of Central Appalachia, an area that is mountainous, mostly rural, and one of the nation's most economically disadvantaged regions. It is also a population that is almost exclusively non-Hispanic white (95%).2 The high cancer burden in Appalachia has been repeatedly linked to widespread poverty and related societal mores, including: tobacco abuse, obesity and associated metabolic syndromes, lower levels of education, unemployment, and limited access to healthcare.3-5 Many of these factors are known to influence the development of corpus uterine cancers.

Cancer of the uterine corpus is the most common malignancy of the female reproductive system and the fourth most common cancer in U.S. women. Over the past decade, the incidence of uterine cancer in the U.S. has steadily increased, creating a growing gap between the number of new corpus cancers versus new female malignancies.1,6 From 2008 to 2018, the magnitude of the incidence gap in KY was twice the national trend, with a 46% increase in corpus cancers compared to a 12% increase in new female cancers.1,6 The geographic distribution of these cancers is an important part in explaining the elevated incidence in KY. Before we can overcome the disparities affecting uterine cancer in Kentucky's different geographic regions, we must first understand the chief contributing factors.

1.2 Objectives

The principle objective of this retrospective cohort study is to utilize SEER and the Kentucky Cancer Registry to compare the frequency, distribution, and disease survival of uterine corpus malignancies in the U.S. and Kentucky, and examine the differences between Appalachian and non-Appalachian KY regions. Secondary study objectives include an analysis of factors that influence the outcome of uterine corpus malignancies, including histology, stage, age, race, cigarette smoking, insurance status, and geographic area of residence.

CHAPTER 2. METHODS

2.1 Data Collection Approval

The University of Kentucky Institutional Review Board approved an expedited protocol for this cohort study. All U.S. population incidence data were obtained from SEER registries, while Kentucky data were collected through the Kentucky Cancer Registry (KCR). All Kentucky acute care hospitals, freestanding treatment centers, non-hospital pathology laboratories and physician offices are mandated to report cancer cases to KCR. Data from KCR is included in the National Cancer Institute's SEER program and the Cancer in North America publication. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in reporting the results of this study.[7]

2.2 Eligibility Criteria

Women are eligible for this study if they are age 20 years or older, have a pathologic diagnosis of a uterine corpus malignancy, and are diagnosed in either the SEER and/or KCR between January 1, 2000 and December 31, 2014. Abstracted KCR data includes Appalachia region, tumor histology, age, race, smoking status, stage at diagnosis, insurance status, and county of residence at time of diagnosis. Cases were excluded for the following reasons: failure to meet age criteria, incomplete data abstraction with diagnosis from death certificate only, non-invasive disease, malignant neoplasm not otherwise specified, uncommon histology, or non-uterine malignancy.

2.3 Definition of Variables

Uterine corpus malignancies are categorized into 4 groups according to tumor histology: Type I, Type II, sarcoma, and mixed uterine malignancy. Type I uterine cancer is defined as low-grade (grade 1 or 2), endometrioid, diploid, and hormone-receptor

positive. Type II uterine cancer is defined as high-grade endometrioid, non-endometrioid (serous, clear cell, undifferentiated), aneuploid, TP53-mutated, and hormone-receptor negative.[8] Uterine sarcoma includes both homologous and heterologous mesenchymal tumors of the uterus.[9,10] Mixed uterine malignancies include both carcinomatous and sarcomatous components, and are alternatively named carcinosarcoma or malignant mixed Mullerian tumor (MMMT).[10-12]

Uterine corpus malignancy diagnoses in Appalachian KY counties (AP) were compared to uterine corpus malignancy diagnoses in non-Appalachian KY counties (NAP). In 1965, the Congress of the Commonwealth of Kentucky designated 54 of KY's 120 counties as Appalachia. The economic growth and development of these counties is overseen by the Appalachian Regional Commission.[4] Demographic data, type of uterine malignancy, and AP and NAP region are analyzed. Further county-specific analysis is performed to screen for clustering of cases in specific geographic regions.

2.4 Statistical Analysis

Age-adjusted cancer incidence is calculated for SEER, KY, AP, and NAP standardized by the U.S. 2000 population. Rate ratio test is used to decide the statistical significance of cancer incidence rates between SEER (excluding KY) and KY, AP and NAP.[13] Descriptive analyses for demographics and clinical factors and bivariate analyses by AP and NAP are performed. Chi-square tests are used to examine the association between Appalachian status and histology types and other covariates. Kaplan-Meier plot and Log-Rank test survival analyses are conducted to examine characteristics of histology and Appalachian status. Cox regression analysis is performed to identify which

demographics and clinical factors are associated with survival while controlling for other factors. All analyses are performed by SAS Statistical software version 9.4 (SAS Institute, Inc., Cary, NC). US cancer survival information is calculated based on SEER*Stat 8.3.5 (https://seer.cancer.gov/seerstat/). All statistical tests are two-sided with a 0.05 level of statistical significance.

CHAPTER 3. RESULTS

3.1 Overview

Between the years of 2000 to 2014, we identified 165,713 uterine corpus malignancies in SEER, and 8,948 in the KCR. The overall age–adjusted incidence rates are similar for US and KY populations; however, types and distribution differ. Compared to the US population, the incidence in KY is higher for Type I, but lower for Type II, sarcoma, and mixed malignancies (Table 3.1). For Kentucky women, the age-adjusted incidence of corpus cancers is significantly higher in AP compared to NAP counties (37.8 vs. 31.5; $P < .0001$, Table 3.2). Type I malignancies were 6-7 fold more common than Type II, which had the second highest incidence. Specifically, AP has a higher incidence of Type I ($P < .0001$) and mixed malignancy ($P = .04$), while Type II and sarcoma are of similar incidence in AP and NAP counties (Table 2). A comparison of demographics by type of uterine malignancy is summarized in Table 3.3. Type I (79.3%) is the most common uterine corpus malignancy, followed by Type II (12.6%), mixed (4.2%), and sarcoma (3.9%). The mean age is significantly lower for sarcoma and Type I compared to Type II and mixed malignancies ($P < .0001$). A summary of all uterine cancer demographics by KY region is shown in Table 3.4. In addition to a higher age-adjusted incidence of Type I and mixed malignancy, AP compared to NAP counties have a younger age at diagnosis, larger NHW population, and fewer smokers. In addition, the AP cohort has more uninsured and Medicaid recipients, while NAP has a higher percentage of privately insured.

3.2 Incidence

The overall age–adjusted incidence rate for uterine corpus cancer diagnosed from 2000-2014 is the same for KY and US populations at 33.49 and 33.29 per 100,000, respectively (P = .51). Compared to uterine malignancies in the US, KY has a higher incidence of Type I (P = .03), but a lower incidence of Type II (P = .003), sarcoma (P = .0063), and mixed uterine malignancies (P < .001). In KY, the age-adjusted incidence rate per 100,000 women is as follows: Type I, 26.44; Type II, 4.15; sarcoma, 1.36; and mixed, 1.35. Nearly one third of all KY uterine malignancies are diagnosed in women from AP counties (2,899 of 8,948). The age-adjusted incidence of uterine corpus malignancies in AP is significantly higher compared to NAP (37.76 vs. 31.53), a consequence of more Type I (P < .0001) and mixed malignancies (P = .04). In addition, the incidence of Type I and Type II cancers in Kentucky has continued to rise each of the last five years.

3.3 Survival

The overall survival for uterine corpus malignancy is similar for US and KY populations (Figure 1, P = .2415), and there is no difference when evaluated by specific histology. In both populations, survival is better for Type I and worse for Type II, sarcoma and mixed malignancy.

On Kaplan-Meier analysis, KY women with Type I uterine cancer have the highest probability of survival, while mixed tumors have the lowest (Figure 2, P < .0001). These survival outcomes persist even when controlled for smoking status and race, and are similar in both AP and NAP counties (X^2 = 303, p<0.0001; X^2 = 680, P <

.0001, respectively). Whether comparing all corpus malignancy as one group or as individual types, there is no survival difference between AP and NAP counties ($P = .47$).

On Cox regression analysis (Table 3.5), the hazard ratio for death (HR) is lowest for Type I (HR 0.655; 95% CI 0.547-0.783) and Type II cancers (HR 0.652; 95% CI 0.538-0.791) compared to mixed malignancies (HR 0.926; 95% CI 0.764-1.21) and sarcoma (reference). This finding is independent of geographic region. Women from AP have similar survival compared to NAP (HR 0.896; 95% CI 0.795-1.009). Younger (20-50 years) and middle aged (51-64 years) women have a significantly lower HR than women 65 years and older ($P < .001$). Nonsmokers have better overall survival than smokers, regardless of AP versus NAP region. Increasing grade and stage are associated with lower survival ($P < .001$). In AP, women with Medicaid (HR 1.67; 95% CI 1.14-2.44) and Medicare (HR 1.54; 95% 1.05-2.26) insurance have an increased risk of death.

3.4 Age

The mean age at diagnosis for Type I uterine corpus malignancies is younger in AP versus NAP counties (59.4 vs. 60.7 years, $P < .0001$); likewise, women with mixed uterine tumors are diagnosed at a younger age in AP counties (65.4 vs. 68.4, $P = .02$). There are no observed differences in mean age at diagnosis for Type II or sarcoma malignancies. Over half of the Type II cancers are diagnosed in women over the age of 65, and this is consistent in both AP and NAP regions. Women diagnosed with uterine sarcomas are evenly distributed between age groups in both regions. On Cox regression analysis, young age at diagnosis is an independent predictor of better survival for age 20-

50 years (HR 0.29; 95% CI 0.25-0.35) and 51-64 years (HR 0.56; 95% CI 0.50-0.63) compared to over 65 years (Table 3.5)

3.5 Race

Each histology has a significantly higher proportion of Non-Hispanic Whites (NHW) compared to Non-Hispanic Blacks (NHB) ($P < .0001$). In AP counties, the percentage of NHW women by histology is as follows: 99% Type I, 98% Type II, 97% mixed, and 97% sarcoma. In NAP counties, NHB women are diagnosed with 5%, 13%, 16%, and 16% Type I, Type II, mixed, and sarcoma, respectively. Overall, NHW have a higher probability of survival compared to NHB or other race ($X^2 = 64$, $P < .0001$). NHW smokers and non-smokers both have higher overall survival compared to NHB ($X^2 = 38$, $P < .0001$; $X^2 = 14$, $P = .003$, respectively). On Kaplan-Meier survival estimate, NHB have significantly worse survival than NHW (Figure 3.3, $P < .0001$); however, after controlling for individual factors on Cox regression analysis, race is not a significant independent variable for the entirety of KY (Table 3.5), or in AP and NAP regions ($P = .24$).

3.6 Smoking

For the overall study population, 55% are nonsmokers, 24% are smokers, and the smoking status is unknown for 21%. Smokers with a uterine corpus malignancy have inferior survival compared to nonsmokers or those with unknown smoking status ($X^2 = 34$, $P < .0001$). There are fewer smokers in AP compared to NAP counties (Table 3.4, $P = .002$). For women diagnosed with uterine corpus cancers, the AP cohort is less likely to smoke for Type I ($P = .005$) and Type II ($P = .083$) cancers, though the later didn't reach

statistical significance. There are no significant smoking associations between regions for mixed malignancies. Interpretation of the sarcoma group is confounded by a relative large number of unknown results compared to other histology groups. Smoking is associated with a worse survival on Cox multivariate regression analysis (HR 1.2; 95% CI 1.10-1.31. Table 3.5).

3.7 Insurance

Insurance coverage for women with uterine corpus malignancy differs across all four histologic types. Women from AP compared to NAP counties with Type I and Type II cancers are more likely to be uninsured or receive Medicaid assistance, while more women from NAP counties are privately insured ($P < .001$, $P = .003$, respectively). There are a similar percentage of uninsured cases for mixed tumors and sarcoma. Mixed cancers in NAP are more likely to have private insurance or Medicare compared to AP cases who receive Medicaid ($P = .017$). For uterine sarcoma, over 50% of NAP have private insurance, while the highest percentage in AP is Medicare (41.3%). Similar to the trend seen for all corpus malignancies, AP sarcomas have at least twice the number of Medicaid recipients compared to NAP counties (15.2% v 7.5%). On Cox regression analysis (Table 3.5), private insurance in KY is an independent predictor of better survival compared to no insurance (HR 0.57; 95% CI 0.47-0.69). More specifically, Medicaid or Medicare is associated with worse survival in AP, while private insurance is an independent predictor of better survival in NAP (HR 0.48; 95% CI 0.38-0.60).

3.8 Stage

Information regarding stage is challenging to interpret because of changing treatment trends over the last decade. Since it doesn't appear to alter survival, many low risk Type I uterine cancers do not undergo formal staging lymphadenectomy. Overall, stage I and II combined were of similar percentage between AP and NAP regions. The stage at diagnosis for sarcomas was unknown for the majority of cases; therefore, a reliable comparison cannot be made. There is a high number of unknown stages for mixed uterine malignancies as well; however, the percentage of advanced stage diagnoses in AP is double the rate recorded for NAP ($P = .019$).

3.9 Incidence by County

For Type I uterine cancer, the highest incidence is seen in 3 NAP compared to 7 AP counties (33.37 to 45.28 cases per 100,000 people, Figure 3.4). In addition, 9 other AP counties are identified in the second highest incidence group compared to 3 NAP counties. Similarly, for Type II histology 2 NAP counties and 10 AP counties have the highest incidence (7.92-12.79 per 100,000). For mixed and sarcoma, the highest incidence counties are more evenly distributed between AP and NAP counties. For mixed malignancies, there are 2 NAP and 3 AP counties (3.78-6.78 cases per 100,000), and for sarcoma there is 1 NAP and 2 AP counties (4.87-9.64 per 100,000).

Table 3.1 Age-Adjusted Cancer Incidence for Uterine malignancy, U.S. vs Kentucky, 2000-2014

	N	Age-adjusted Rate*	Lower 95% CI	Upper 95% CI	*P*-Value
All- US	165,713	33.49	33.33	33.66	.5063
All- KY	8,948	33.29	32.59	33.99	
Type 1- US	127,257	25.69	25.55	25.83	.0274
Type 1- KY	7,100	26.44	25.82	27.07	
Type 2- US	22,463	4.53	4.47	4.59	.0027
Type 2- KY	1,127	4.15	3.90	4.40	
Sarcoma- US	7,538	1.57	1.54	1.61	.0063
Sarcoma- KY	347	1.36	1.22	1.51	
Mixed- US	8,455	1.70	1.67	1.74	< .0001
Mixed - KY	374	1.35	1.21	1.49	

Comparison between SEER (U.S.) and KCR (KY), 2000-2014.

*Age-adjusted Rate is per 100,000.

Rate-ratio test for statistical comparison.

Table 3.2 Age-Adjusted Cancer Incidence for Uterine Malignancy in Kentucky, Non-Appalachia vs Appalachia, 2000-1014 (N=8,948)

	N	**Age-adjusted Rate***	**Lower 95% CI**	**Upper 95% CI**	***P*-Value**
All- KY					< .0001
NAP	6049	31.53	30.73	32.34	
AP	2899	37.76	36.37	39.18	
Type 1					< .0001
NAP	4764	24.86	24.16	25.59	
AP	2336	30.41	29.17	31.69	
Type 2					.1212
NAP	781	4.02	3.74	4.32	
AP	346	4.46	4.00	4.96	
Sarcoma					.5836
NAP	255	1.39	1.22	1.57	
AP	92	1.30	1.04	1.60	
Mixed Tumor					.0452
NAP	249	1.25	1.10	1.42	
AP	125	1.58	1.32	1.89	

*Age-adjusted Rate is per 100,000. NAP- Non-Appalachia KY, AP- Appalachia KY.

Chi square test for statistical comparison.

Table 3.3 Comparison of Demographics by Type of Uterine Malignancy in Kentucky, 2000-2014 (N=8,948).

	Type I		**Type II**		**Sarcoma**		**Mixed**		***P*-Value**
	N	%	N	%	N	%	N	%	
Total	7100	79.35%	1127	12.59%	347	3.88%	374	4.18%	
Age									<.0001
Mean	60.38±12.59		65.23±12.69		56.73±14.07		67.38±11.45		
20-50	1406	19.80%	138	12.24%	125	36.02%	24	6.42%	
51-64	3170	44.65%	397	35.23%	119	34.29%	129	34.49%	
65+	2524	35.55%	592	52.53%	103	29.68%	221	59.09%	
Race									<.0001
White	6771	95.37%	1010	89.62%	302	87.03%	329	87.97%	
Black	269	3.79%	110	9.76%	43	12.39%	43	11.50%	
Other	31	0.44%	5	0.44%	1	0.29%	1	0.27%	
Unknown	29	0.41%	2	0.18%	1	0.29%	1	0.27%	
Hispanic									.4807
Non-Hispanic	6913	97.37%	1105	98.05%	340	97.98%	366	97.86%	
Hispanic	32	0.45%	60	5.32%	2	0.58%	3	0.80%	
Unknown	155	2.18%	16	1.42%	5	1.44%	5	1.34%	
Marital									<.0001
Never married	950	13.38%	137	12.16%	49	14.12%	43	11.50%	
Ever Married	3759	52.94%	518	45.96%	181	52.16%	172	45.99%	
Divorced or Widowed	1704	24.00%	384	34.07%	87	25.07%	125	33.42%	

Table 3.3 (continued)

Unknown	687	9.68%	88	7.81%	30	8.65%	34	9.09%	
Smoke									.0017
Non-Smoker	3982	56.08%	592	52.53%	168	48.41%	199	53.21%	
Smoker	1637	23.06%	284	25.20%	110	31.70%	103	27.54%	
Unknown	1481	20.86%	251	22.27%	69	19.88%	72	19.25%	
Insurance									<.0001
Not Insured	335	4.72%	46	4.08%	21	6.05%	20	5.35%	
Private Insured	3177	44.75%	399	35.40%	170	48.99%	99	26.47%	
Medicare	2707	38.13%	560	49.69%	111	31.99%	214	57.22%	
Medicaid	538	7.58%	80	7.10%	33	9.51%	32	8.56%	
Other Public	71	1.00%	7	0.62%	3	0.86%	2	0.53%	
Unknown	272	3.83%	35	3.11%	9	2.59%	7	1.87%	
Stage									<.0001
In situ	6	0.08%			1	0.29%			
Stage I	5311	74.80%	541	48.00%	11	3.17%	60	16.04%	
Stage II	425	5.99%	106	9.41%	3	0.86%	16	4.28%	
Stage III	503	7.08%	237	21.03%	1	0.29%	37	9.89%	
Stage IV	251	3.54%	153	13.58%	3	0.86%	48	12.83%	
Unknown	604	8.51%	90	7.99%	328	94.52%	213	56.95%	

Chi square test for statistical comparison.

Table 3.4 Comparison of Demographics by Region for Uterine Malignancy in Kentucky, 2000-2014 (N=8,948).

	Total		**NAP**		**AP**		***P*-Value**
	N	%	N	%	N	%	
Total	**8948**	**100.00%**	**6049**	**67.60%**	**2899**	**32.40%**	
Age							.0023
20-50	1693	18.92%	1108	18.32%	585	20.18%	
51-64	3815	42.64%	2543	42.04%	1272	43.88%	
65+	3440	38.44%	2398	39.64%	1042	35.94%	
Mean	61.14±12.81		61.56±12.86		60.25±12.67		.3549
Race							< .0001
White	8412	94.01%	5555	91.83%	2857	98.55%	
Black	465	5.20%	434	7.17%	31	1.07%	
Other	38	0.42%	36	0.60%	2	0.07%	
Unknown	33	0.37%	24	0.40%	9	0.31%	
Hispanic							.0139
Non-Hispanic	8724	97.50%	5890	97.37%	2834	97.76%	
Hispanic	43	0.48%	38	0.63%	5	0.17%	
Unknown	181	2.02%	121	2.00%	60	2.07%	
Marital							< .0001
Never married	1179	13.18%	876	14.48%	303	10.45%	
Ever Married	4630	51.74%	3073	50.80%	1557	53.71%	
Divorced/Widowed	2300	25.70%	1586	26.22%	714	24.63%	
Unknown	839	9.38%	514	8.50%	325	11.21%	

Table 3.4 (continued)

Smoke							.002
Non-Smoker	4941	55.22%	3287	54.34%	1654	57.05%	
Smoker	2134	23.85%	1509	24.95%	625	21.56%	
Unknown	1873	20.93%	1253	20.71%	620	21.39%	
Insurance							< .0001
Not Insured	422	4.72%	256	4.23%	166	5.73%	
Private Insured	3845	42.97%	2814	46.52%	1031	35.56%	
Medicare	3592	40.14%	2403	39.73%	1189	41.01%	
Medicaid	683	7.63%	309	5.11%	374	12.90%	
Other Public	83	0.93%	59	0.98%	24	0.83%	
Unknown	323	3.61%	208	3.44%	115	3.97%	
Stage							< .0001
In situ	7	0.08%	3	0.05%	4	0.14%	
Stage I	5923	66.19%	4026	66.56%	1897	65.44%	
Stage II	550	6.15%	341	5.64%	209	7.21%	
Stage III	778	8.69%	556	9.19%	222	7.66%	
Stage IV	455	5.08%	318	5.26%	137	4.73%	
N/A	558	6.24%	407	6.73%	151	5.21%	
Unknown	677	7.57%	398	6.58%	279	9.62%	
Histology							.0466
Type I	7100	79.35%	4764	78.76%	2336	80.58%	
Type II	1127	12.59%	781	12.91%	346	11.94%	
Sarcoma	347	3.88%	255	4.22%	92	3.17%	
Mixed	374	4.18%	249	4.12%	125	4.31%	

NAP- Non-Appalachia KY, AP- Appalachia KY.

Chi square test for statistical comparison.

Table 3.5 Cox Regression Survival Analysis, Kentucky. 2000-2014.

	HR	95% CI		P-Value
Histology				< .001
Type I	0.655	0.547	0.783	
Type II	0.652	0.538	0.791	
Mixed	0.926	0.764	1.121	
Sarcoma	ref			
Age				< .001
20-50	0.294	0.249	0.348	
51-64	0.564	0.501	0.634	
65+	ref			
Race				.2435
Black	1.080	0.936	1.254	
Other	0.852	0.424	1.711	
Unknown	0.186	0.026	1.322	
White				
Region				.0687
Appalachia	0.896	0.795	1.0090	
Non-Appalachia	ref			
Cigarette Smoking				< .001
Smoker	1.201	1.100	1.310	
Unknown	1.125	1.027	1.232	
Non-Smoker	ref			
Insurance				< .001
Medicaid	1.063	0.852	1.326	
Medicare	0.016	0.827	1.247	
Other Public	0.685	0.412	1.139	
Private Insured	0.568	0.469	0.689	
Unknown	0.846	0.655	1.092	

Table 3.5 (continued)

Not Insured	ref			
Stage				< .001
In situ	0.449	0.063	3.197	
Stage II	1.669	1.440	1.934	
Stage III	2.645	2.356	2.969	
Stage IV	7.457	6.586	8.444	
Unknown	2.236	1.989	2.513	
Stage I	ref			
Grade				< .001
Unknown	2.096	1.839	2.388	
2	1.168	1.049	1.301	
3	1.887	1.677	2.123	
Undifferentiated	2.211	1.910	2.560	
1	ref			
High School Education				.0002
High	0.781	0.665	0.916	
Low	0.788	0.697	0.890	
Moderate	0.885	0.772	1.015	
Very Low	ref			

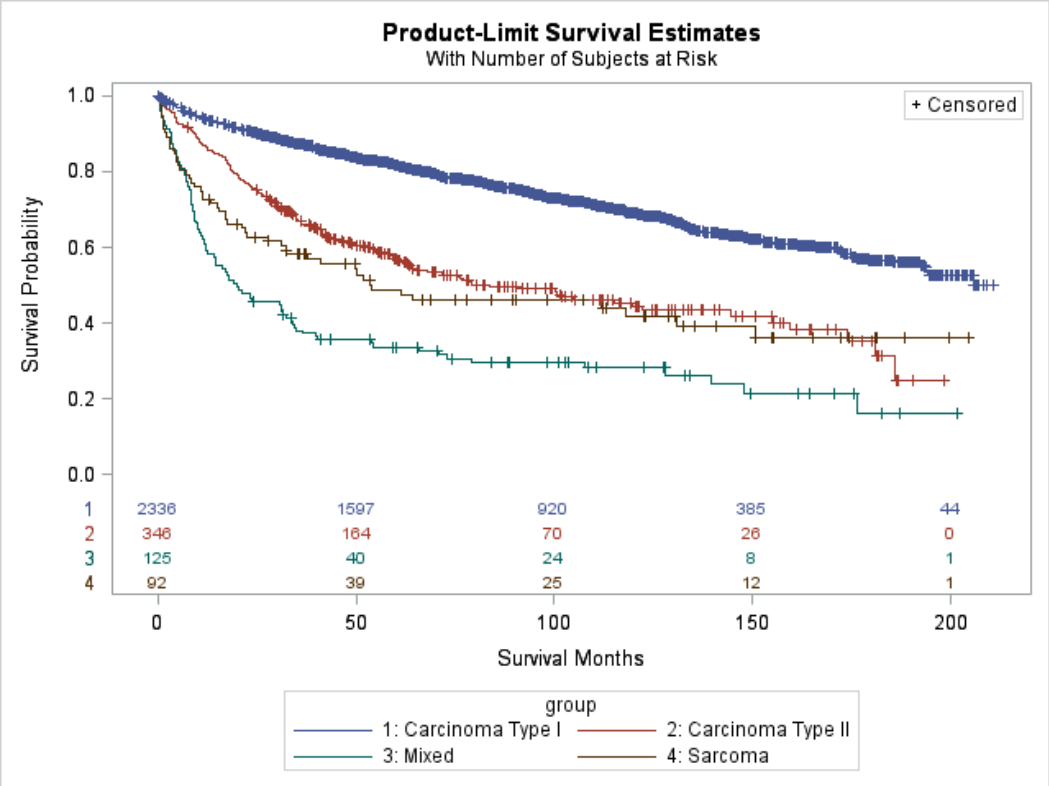

Figure 3.1 Kaplan-Meier Survival Estimate from SEER data comparing the U.S. to Kentucky 2000-2014 (p=0.2415)

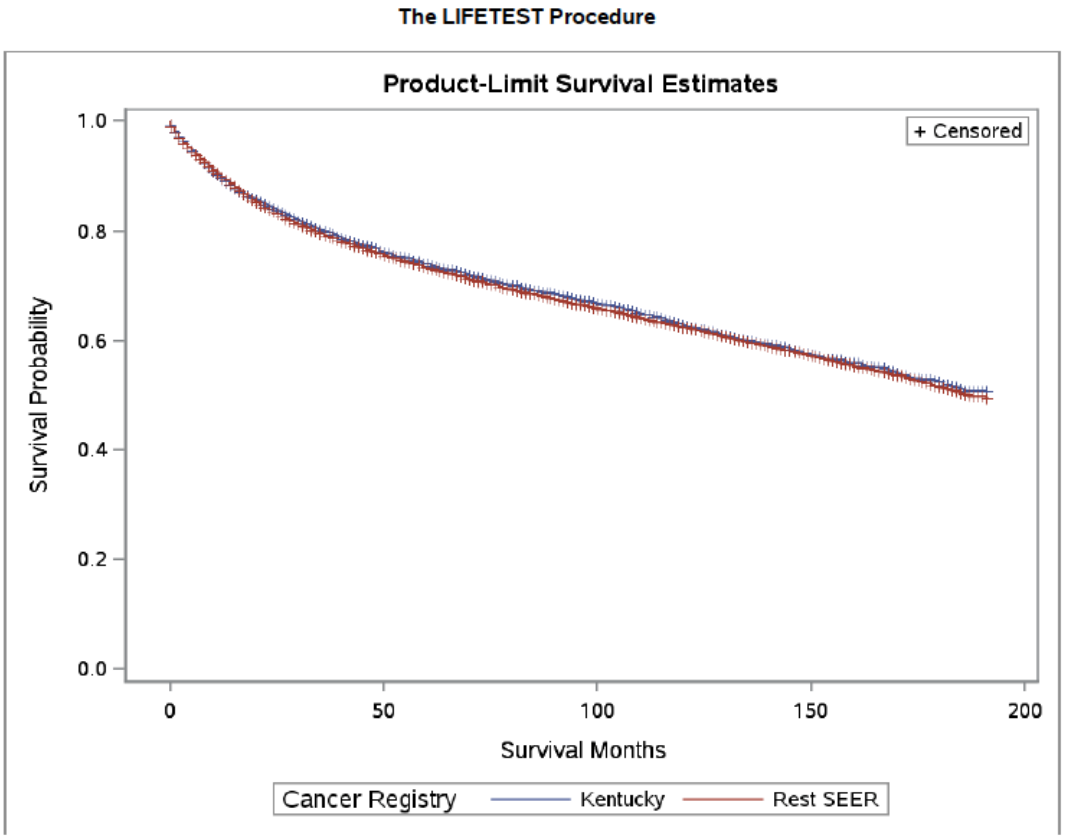

Figure 3.2 Kaplan-Meier Survival Estimate by Type of Uterine Malignancy for Kentucky, 2000-2014 ($p<0.0001$)

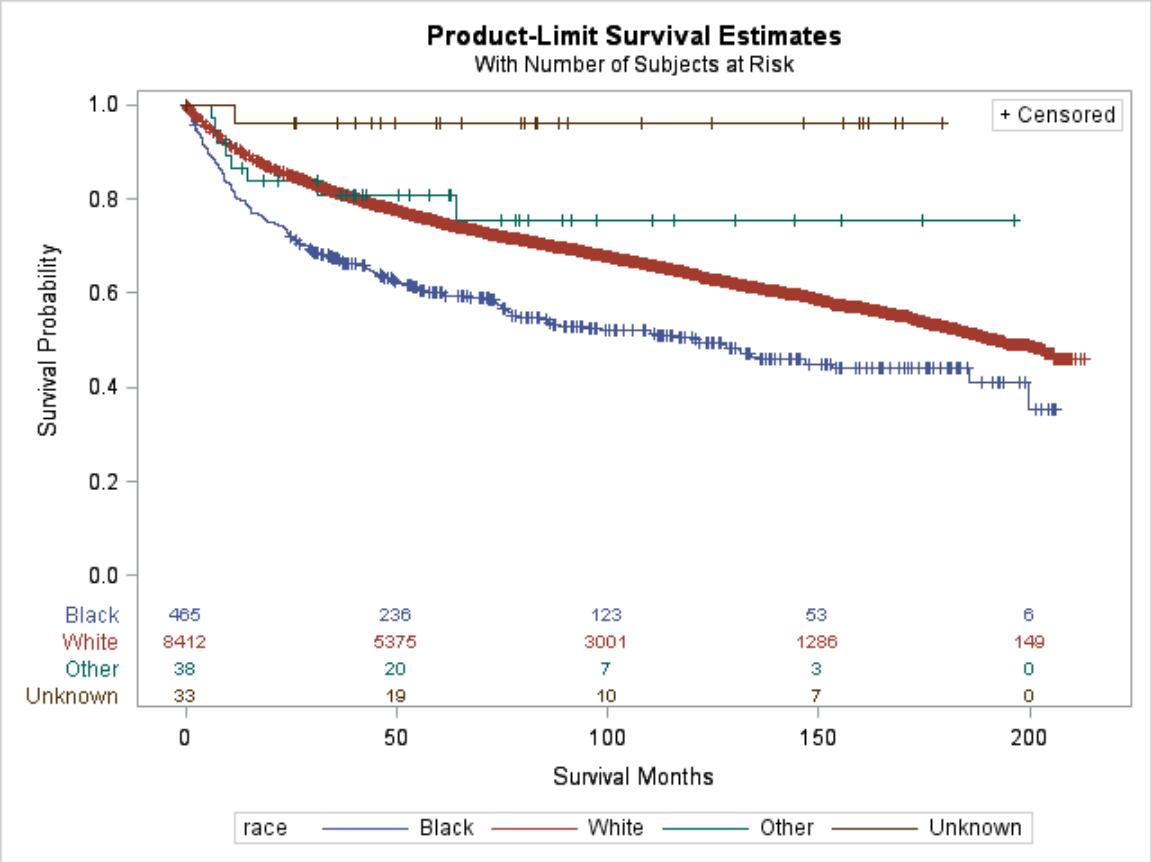

Figure 3.3 Kaplan-Meier Survival Estimate by Race for Kentucky, 2000-2014 ($p<0.0001$).

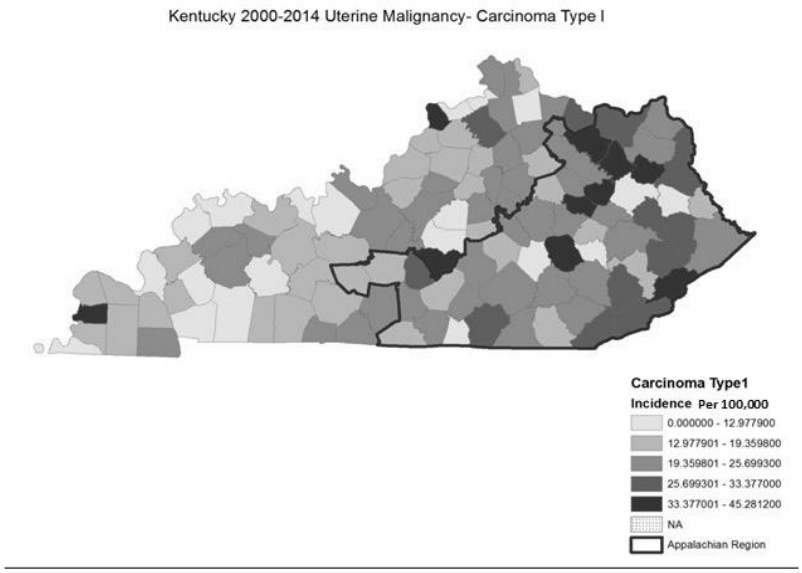

Figure 3.4 Incidence of Type I Uterine Malignancy by Kentucky Region, 2000-2014.

CHAPTER 4. DISCUSSION

Kentucky leads the nation in female cancer incidence and mortality. Similar to US trends, the incidence of uterine malignancy in KY is steadily increasing; however, it varies significantly based on geographic region and cancer type. Uterine corpus cancers in AP compared to NAP KY are different in cause and consequence. There are several relevant socioeconomic factors, including: age, obesity, cigarette smoking, race, insurance, and perhaps hereditary syndromes. Further characterizing these factors and understanding how they influence the cause and outcome of corpus cancers is important, particularly in Appalachia KY where the cancer burden is disproportionately high.

4.1 Commentary on Results

Compared to the rest of the nation, Type I uterine cancers are significantly more common in KY while other types of corpus cancers are less common. Our findings also show that Type I cancer in KY is more commonly a disease of younger, non-smoking, non-Hispanic white (NHW) women. Appalachia has a much higher incidence of corpus malignancies than NAP KY, and the numbers are particularly disproportionate given the population distribution in the state. While AP counties are home to 26.4% of Kentucky's population, 32.4% of the uterine cancers come from this geographic region.[2] In addition to Type I cancers, the age-adjusted incidence of mixed uterine malignancies is higher and the mean age at diagnosis is lower in AP compared to NAP counties. Although more cancer in younger women is an alarming trend, we did observe that younger women have improved survival regardless of geographic location.

Cancer outcomes are not always inferior for those living in socioeconomically disadvantaged regions like AP.[14] Although the incidence of uterine cancers was higher in AP versus NAP counties, cancer-specific survival did not differ based on geographic location. This may reflect a balance of influences on survival, for instance: more cancers in AP but younger age at diagnosis, or fewer cancers in NAP but more cigarette smokers. For this investigation, the most likely explanation is the high percentage of Type I cancers relative to other types of uterine malignancy. Not only do Type I cancers make up 79% of the study population, they also have the highest survival, followed in order by Type II, sarcoma, and mixed malignancies.

The prevalence of cigarette smokers in Kentucky remains the highest in the nation.[1] Nearly 1 in 4 Kentucky residents smokes cigarettes (26%), contributing to the high number of lung, head and neck, and other smoking-attributable cancers.[5] But for Type I uterine corpus cancers, cigarette smoking appears to be protective, possibly through an increase in progesterone receptor expression.[15] A recent meta-analysis confirmed an inverse relationship between current and past cigarette smoking and the risk of endometrial cancer (RR=0.81; OR=0.72), especially in postmenopausal women.[16] In this investigation, we observed that there are fewer cigarette smokers in AP than in NAP KY; though causation cannot be inferred, this may influence the higher incidence of Type I cancers in this geographic region.

Uterine malignancy has historically been a disease of older women, but this is no longer the case. Findings from this investigation show that women from AP KY are being diagnosed with Type I and mixed uterine tumors at younger age. A recent pooled analysis of 24 studies found the mean age at diagnosis for Type I uterine corpus cancers is 61.9

years.[17] In KY, women are being diagnosed with Type I uterine corpus cancers at a younger age, especially in AP compared to NAP counties (59.4 vs. 60.7 years, respectively; $P < .0001$). Interestingly, this trend is counter to the general KY population which is actually older in AP counties. The 2011-2015 American Community Survey reports a mean age in AP compared to NAP of 40.8 and 38.1 years, respectively.[2] The same trend toward younger age at diagnosis is observed for mixed tumors in AP versus NAP KY (65.4 vs. 68.4 years, respectively; $P = .02$). In AP counties, 67% of Type I cancers are diagnosed in the age groups from 20-50 and 51-64 years compared to 63% for NAP KY, and a surprisingly high percentage of mixed tumors are identified in AP versus NAP counties in women under the age of 50 years (11% vs. 4%, respectively). At least for estrogen-dependent uterine cancers, the obesity epidemic may be a contributing factor, as a linear decrease in age at diagnosis has been correlated with an increasing body mass index (BMI) over time.[18]

Prolonged estrogen exposure is an established risk factor for uterine corpus cancer, and is related to a number of factors, including: obesity, nulliparity, late menarche, early menopause, and exogenous estrogen or tamoxifen.[17,19-22] When all Appalachian states are considered, KY has the highest prevalence of obesity (35.2%), and the seventh highest obesity rate in the U.S.[3,23] Even NAP KY has a higher prevalence of obesity than the national average of (31.2% vs 27.4%, respectively).[23] Previous population-based reports have linked obesity to the high rate of uterine corpus cancers in AP KY.[24] An association between estrogen excess and mixed tumors may also be relevant, since they are now thought to arise from genetic mutations of a pure carcinoma cell line.[9,12,25]

Mixed uterine malignancy, also known as carcinosarcoma or malignant mixed Mullerian tumor (MMMT), is now believed to be a high-grade carcinoma that arises from a monoclonal cell which can dedifferentiate into a sarcomatous component.[9,11,12,26,27] Unlike Type I corpus cancers, mixed tumors are typically diagnosed in the seventh decade, and are disproportionately seen in NHB women and in women exposed to tamoxifen and pelvic radiation. Like Type I corpus cancers, a national trend of decreasing age at diagnosis has also been reported for mixed uterine tumors, with previous mean age of diagnosis in the early seventies compared to current mean age of 68.2.[28] Compared to other uterine corpus cancers, patient outcomes are considerably worse for this high-grade malignancy, though reportedly similar for black and white women provided they receive comparable treatment.[29] Over the last two decades, national trends demonstrate a dramatic decrease in NHW from 86% to 60%, and a concomitant increase in NHB from 12% to 20%.[27] In Kentucky, the racial distribution in AP is overwhelmingly NHW, so it is an unexpected finding that more mixed tumors were diagnosed in AP than NAP.

Historically, the AP population has been non-migratory. Over the last decade, there has been a net AP emigration of only 1.3%, compared to a net immigration into NAP of 3.3%.[2] The population stability of the AP region makes it an intriguing target for the study of hereditary and environmental exposure. Previous evaluations of cancer inheritance patterns in AP contributed to the discovery of Lynch syndrome. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome (HNPCC), can includes uterine, as well as gastrointestinal, ovarian, hepatobiliary, and upper urinary tract cancers. This inherited germline mutation has alterations in several mismatch repair genes that result in microsatellite instability which predisposes to early

onset cancers. These HNPCC germline cancers are often diagnosed at a younger age compared to similar cancers from somatic mutation. Given the increased incidence in AP of Type I cancers and a shift toward younger age at diagnosis, it is conceivable that genetic factors have contributed to our findings. In addition, there are reports suggesting mixed uterine malignancies may also be associated with Lynch syndrome, specifically in carriers of the MSH 2 and MLH 1 mutation.[30,31] There is a well-known founder population in AP KY with the MSH 2 mutation.[32] More comprehensive genetic testing of women in this region may provide further insight into the association between Type I cancers, mixed malignancies, and hereditary syndromes.

Disparities in uterine cancer incidence and outcomes in Kentucky, and specifically in AP, are not necessarily a consequence of racial disparity. As background, AP is known to have a high cancer prevalence and is predominantly NHW. The measured death rates in KY are equivalent for NHB and NHW (Death Rate Ratio = 1.01; 95% CI 0.93-1.10).[1] For this investigation, Kaplan-Meier analysis shows inferior survival for NHB compared to NHW women overall; however, a multivariate Cox regression survival analysis shows that race does not independently impact survival (HR 1.08; CI 0.94-1.2, p=0.24. Table 5). What is evident in KY is that NHW women are three times more likely to be diagnosed with Type I uterine cancer than any other race. The general population in AP KY is 95% NHW contrasted with 82.1% for NAP counties, which may explain why 98.8% of Type I uterine cancers in AP counties are diagnosed in NHW women. In KY, non-Hispanic black women are more likely to be diagnosed with aggressive uterine cell types, namely Type II, sarcoma and mixed malignancies. This is consistent with national trends, as the U.S. incidence of uterine sarcoma for NHB women is nearly twice that of

NHW women.[24,33,34] We observed that the percentage of NHB women diagnosed with sarcoma or mixed tumors throughout the state is double the percent of NHB in the KY study population. Given the underrepresentation of NHB women in the statewide population, it is not surprising that the age-adjusted cancer incidence for uterine sarcoma and mixed malignancies is lower in Kentucky that the United States (Table 1).

It has been previously reported that cancer patients with Medicaid or no insurance compared to those privately insured present with more advanced disease, are less likely to receive National Comprehensive Cancer Network®-compliant cancer care (including surgery, chemotherapy, and radiation), and experience worse outcomes.[35] We observe a higher percentage of uninsured or Medicaid in AP versus NAP counties. Overall, women in KY with a uterine malignancy and private insurance have better survival than those with no insurance, mostly from a significant contribution in NAP KY. Conversely, Medicaid and Medicare are independently associated with worse outcomes in AP KY.

4.2 Limitations

The limitations to this investigation are inherent to any observational registry study. As a retrospective study, Appalachian status was only measured at the time of cancer diagnosis which may not reflect the whole residential history of patients. Central pathology review is also not possible, and standard treatment or histologic interpretation may have changed over the study period affecting observed outcomes. In addition, KCR does not collect weight or BMI data for cancer patients so we are unable to validate previous studies that demonstrated a relationship between obesity and endometrial cancer in Kentucky.[20,23] Lastly, while the identified correlations are significant, a causal

relationship cannot be determined because of the retrospective study design. The strengths of this investigation include the large study population identified using SEER and KCR databases, and the novel and robust comparison of AP and NAP regions that includes several variables relevant to disease incidence and survival.

4.3 Conclusion

Kentucky is split into 2 distinct geographic regions, Appalachia and non-Appalachia. AP KY has a higher age-adjusted incidence of Type I and mixed uterine corpus cancers compared to NAP KY, and these cancers are being identified at a significantly younger age. In addition to obesity which has previously been reported, we identify several predisposing and inter-related socioeconomic factors that may influence uterine corpus cancers, including cigarette smoking, type of insurance, and possible hereditary syndromes (HNPCC). AP and NAP cohorts have a similar survival comparable to survival at the national level. While Type I corpus cancer is the most prevalent malignancy in KY, it is also associated with the best clinical outcomes. As the cost of testing decreases, a comprehensive population-based genetic study of Appalachia would help determine the impact of hereditary syndromes on the observed increased incidence and younger age at diagnosis for both Type I and mixed uterine corpus malignancies.

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