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# Impact of Smoking and HPV Status on Cervical Cancer Survival in Women Living in Kentucky, 2004-2005 and 2014-2015

Brittany M. McKinley
*University of Kentucky*, brittanymckinley126@gmail.com

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Brittany M. McKinley, Student

Thomas Tucker, Committee Chair

Dr. Sarah Wackerbarth, Director of Graduate Studies

**Impact of Smoking and HPV Status on Cervical Cancer Survival in Women Living in Kentucky, 2004-2005 and 2014-2015**

**CAPSTONE PROJECT PAPER**

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By:
**Brittany M. McKinley, MD**

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Committee Members

**Thomas Tucker, PhD Chair**

**Bin Huang, DrPH**

**Krystle Kuhs, PhD**

**Jaclyn McDowell, DrPH**

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**ABSTRACT**

**BACKGROUND/ OBJECTIVE:** Cervical cancer is the fourth most commonly occurring malignancy in women worldwide, with an estimated 530,000 new cases and 270,000 new deaths each year (Small et al, 2017). While the incidence of cervical cancer has decreased by approximately 1.9% per year between 2007 and 2011, the death rate has remained stable (Bernard et al, 2014). Studies have shown that nearly all cervical cancer cases are associated with the Human Papilloma Virus (HPV). Many studies support the association of smoking with increased risk of invasive cervical cancer in women with high-risk HPV (Castle et al, 2002; Fang et al, 2018; Xi, et al, 2009). However, one study by Roura et al demonstrated the development of CIN3 irrespective of HPV serology in individuals with a history of smoking, and another study by Coker et al suggested that smoking reduced overall survival from cervical cancer (Roura et al, 2014, Coker et al, 2008). And yet, further studies have demonstrated differences in survival among cervical cancer patients with different HPV genotypes (Hallowell et al, 2018). The purpose of this study is to further explore survival differences among cervical cancer patients with specific HPV genotypes who had a history of smoking and cervical cancer patients with the same HPV genotypes who do not have a history of smoking.

**METHODS:** A total of 246 women with cervical cancer from the Kentucky Cancer Registry (KCR) were reviewed for inclusion in this study. Inclusion criteria included 18 years of age or older, a diagnosis of HPV with specific HPV genotyping, a diagnosis of cervical cancer between January 1st, 2004 and December 31st, 2005, or between January 1st, 2014 and December 31st, 2015, and smoking history information that was verified using health insurance claims data. A

final population of 198 women were included. Univariate and bivariate analyses were conducted. Survival curves were stratified by smoking status. Cox proportional hazard regression was used to assess the risk of death due to smoking in women with any HPV genotype and additionally, women with HPV 16/18.

**RESULTS:** Smokers had an increased risk of dying compared to non-smokers with HPV 16/18 (HR=1.039, [0.669, 1.614], p=0.8647). However, this difference was not statistically significant. Appalachian women with any HPV genotype had a 61.1% increased risk of dying compared to non-Appalachian women (HR=1.611, [1.054, 2.461]), which was significant (p=0.0275). Similarly, Appalachian women with HPV 16/18 had a 66.4% increased risk of dying compared to non-Appalachian women (HR=1.664, [1.060, 2.614], p=0.0270). Adenocarcinoma was also associated with a significantly increased risk of dying in the unadjusted Cox Proportional Hazards Model (HR=1.604, [1.062, 2.421], p=0.0245] in women with any HPV genotype, as well as in women with HPV 16/18 (HR=1.559, [1.006, 2.416], p=0.0471).

**CONCLUSIONS:** There were no significant differences between the survival of cervical cancer patient with any HPV genotype or with HPV 16/18 who had a history of smoking compared to those who did not have a history of smoking. However, Appalachian status and histology were important factors when considering prognosis and overall survival in women with a diagnosis of HPV and cervical cancer.

**KEYWORDS:** Cervical cancer; Kentucky Cancer Registry; Human Papillomavirus (HPV); Smoking; Appalachian status, Adenocarcinoma

## INTRODUCTION

Cervical cancer is the fourth most commonly occurring malignancy in women worldwide, with an estimated 530,000 new cases and 270,000 deaths each year (Small et al, 2017). While the incidence of cervical cancer has decreased by approximately 1.9% per year between 2007 and 2011, the death rate has remained stable (Bernard et al, 2014). However, the burden remains high in many parts of the world. Cervical cancer was the leading cause of cancer related death in women in many parts of Africa and Asia (Arbyn et al., 2019). China and India also contribute to more than one-third of the global cervical cancer burden, with an estimated 106,000 new cases and 48,000 deaths in China and 97,000 new cases and 60,000 deaths in India in 2018 (Arbyn et al., 2019). However, the highest rates of cervical cancer were noted in southern Africa, with approximately 6.5% women developing cervical cancer in Eswatini (Arbyn et al., 2019).

In the United States, cervical cancer has decreased by an estimated 54% over the past 40 years (Adegoke, et al., 2012). This decrease is partly due to the introduction of the Pap smear test in the 1940s, which allows for screening and early detection of pre-cancerous and cancerous lesions, as well as the Human Papilloma Virus (HPV) vaccine in the early 2000s (Adegoke, et al., 2012). The HPV vaccine prevents recipients from contracting certain strains of HPV, which can cause cervical cancer. Many studies demonstrated that the majority of cervical cancer cases are associated with HPV (Small et al, 2017). Despite this knowledge and the development of the vaccine, cervical cancer rates remain high. It is also important to note that Kentucky has the highest cervical cancer incidence rate and the 10th highest cervical cancer mortality rate compared to all other U.S. states (CDC USCS, 2021).

Many studies support the association of smoking with increased risk of invasive cervical cancer in women with high-risk HPV (Castle et al, 2002; Fang et al, 2018; Xi, et al, 2009). Existing literature supports the relationship between smoking and HPV infections through the direct impact on the immune system resulting in increased susceptibility and persistence of HPV infections (Schabath et al., 2012). However, one study by Roura et al demonstrated the development of CIN3 irrespective of HPV serology in individuals who had a history of smoking, and another study by Coker et al suggested that smoking reduced overall survival from cervical cancer (Roura et al, 2014, Coker et al, 2008). And yet further studies exist that have demonstrated differences in survival among cervical cancer patients with different HPV genotypes (Hallowell et al, 2018). One study by Wright et al found that patients with a diagnosis of cervical cancer who had a history of HPV 18 or 45 infection and smoking were four times more likely to die of cervical cancer than those who did not have a history of these HPV genotypes or smoking (Wright et al., 2005). The purpose of this study is to further explore survival differences among cervical cancer patients with specific HPV genotypes who had a history of smoking and cervical cancer patients with the same HPV genotypes who do not have a history of smoking.

## METHODS

### Study population

The Kentucky Cancer Registry (KCR) is an on-going, population-based central cancer registry for Kentucky that requires mandatory reporting of all cancer cases since January 1, 1991 (KCR, 2020). It is part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program and the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR), as well as a participant in the North American Association of Central Cancer Registries (NAACCR) (KCR, 2020). It is currently housed at University of Kentucky's Markey Cancer Center in Lexington, Kentucky (KCR, 2020).

For this study, a retrospective cohort was formed utilizing de-identified data from the KCR with a cervical cancer diagnosis between January 1st, 2004 and December 31st, 2005, or between January 1st, 2014 and December 31st, 2015. These cervical cancer cases were used because they were part of two separate studies that required HPV genotyping. Therefore, there are specific HPV genotypes associated with each case's record. Since there have not been any significant changes in treatment that would substantially affect the survival of patients diagnosed during these two different time periods, it was determined that these cases could be combined into a single cohort.

A total of 246 women from this combined cohort were evaluated for inclusion. These criteria included 18 years of age or older, a diagnosis of HPV, invasive cervical cancer diagnosed between January 1st, 2004 and December 31st, 2005, or between January 1st, 2014 and

December 31st, 2015, and smoking history information that was verified using claims data. Women without a diagnosis of any HPV genotype were excluded (N=23).

**Smoking status**

Smoking history information was obtained from the KCR and additional efforts were made to verify smoking history using health insurance claims data. Women were categorized by history of smoking, hereafter called "Smokers" or "Non-Smokers." Women without smoking data were excluded (N=20).

**HPV status**

Women were organized into two categories according to HPV genotype. The first category included all women with a diagnosis of any HPV genotype (N=223) and HPV 16/18 (N=176). After excluding the cases with missing data, a final study population of cervical cancer cases with any HPV genotype (N=198) and a subset of cases with HPV 16/18 (N=159) were created. This is described in greater detail below.

**Statistical Methods**

All analyses were obtained using SAS 9.4. Univariate and bivariate analyses were conducted. Bivariate comparisons were conducted using a Chi-square test. A Cox proportional hazards model was used to assess the risk of death due to cervical cancer between patients stratified by smoking and HPV genotype. The covariates of smoking history, age, race, Appalachian status, marital status, insurance, histology, first course of treatment, and stage at diagnosis, were included in the multivariate model. Survival time was calculated using the date of diagnosis and

either date of death or date of last follow up. A standard Kaplan-Meier approach was used for survival analysis. Women with any HPV genotype and HPV 16/18 were stratified by smoking history. Survival follow-up times ranged from 1 to 125 months. Significance was set at $p<0.05$.

Histology ICD codes were assessed and grouped into squamous cell carcinoma "SCC" (N=176) or "Adenocarcinoma" (N=49). No histology codes were excluded. Histology codes that were not able to be categorized into one of these two groups were placed into an "Other" category (N=21). After excluding for missingness, "SCC" (N=154), "Adenocarcinoma" (N=46), and "Other" (N=19). Only "Invasive" behavior ICD codes were reported (N=246). SEER stage at diagnosis was classified into either "Early" or "Late" stage. "Early" stage included localized cervical cancers (N= 123), and "Late" stage included regional or distant cervical cancers (N=121). There were two cases with an "Unknown" SEER stage, which were excluded from analysis. After excluding for missingness, "Early" stage (N=113) and "Late" stage (N=106). First course of treatment was reclassified into "Surgery" (N=84), "Surgery and Chemotherapy or Radiation" (N=57), "Chemotherapy and Radiation" (N=78), and "Radiation" (N=21) categories. There were no women who received chemotherapy alone. Six women who received no treatment were eliminated from analysis. After excluding for missingness, "Surgery" (N=78), "Surgery and Chemotherapy or Radiation" (N=54), "Chemotherapy and Radiation" (N=67), and "Radiation" (N=20).

Race was assessed and grouped into either "White/ Other" or "African American."
Only two woman identified as "Other" and were placed into the "White/Other" category. After excluding for missingness, "White/Other" (N=188) and African American (N=31). Marital status

was also assessed and grouped into either “Married” or “Not Married.” Those who were “Single” (N=53), “Separated” (N=3), “Divorced” (N=41), “Widowed” (N=16), and “Unmarried or Domestic Partner” (N=1) were classified as “Not Married.” After excluding for missingness, “Not married/ Unknown” (N=110) and “Married” (N=109). Finally, insurance status was assessed and placed into “Not insured/ Unknown” or “Insured.” Those who were “Not insured” (N=6), “Not insured/ Self-pay” (N=15), or “Unknown” (N=5) were placed into the “Not insured/ Unknown” group. Those with “Insurance” (N=13), “Managed Care/HMO/PPO” (N=99), “Medicaid” (N=56), “Medicare” (N=48), “Tricare/ Military/ Veteran Affairs (VA)” (N=4). After excluding for missingness, “Not insured/ Unknown” (N=24) and “Insured” (N=195).

**Potential confounders**

There are many factors that may confound the relationship between smoking, HPV, and cervical cancer survival. First, there are many known risk factors for the development of cervical cancer. One study determined that lower level of educational attainment, rural residence, limited access to healthcare, number of sexual partners, use of oral contraceptive pills (OCPs), number of sexually transmitted infections (STIs), and marital status, all contributed to cervical cancer risk (Kashyap et al., 2019). Second, smoking has been demonstrated in a number of existing studies to be more prevalent among individuals of lower socioeconomic status (Chen, 2019). Therefore, it is important to consider potential confounders, such as race, Appalachian status, insurance, and marital status.

The Institutional Review Board of the University of Kentucky approved the study protocol.

## RESULTS

Table 1 displays participant characteristics for 198 women with cervical cancer who had a diagnosis of HPV. Of these women, 80.30% were positive for HPV 16/18, while 19.70% were not positive for HPV 16/18. The majority of women identified as having a history of smoking (57.58%), while 42.42% of women did not report a history of smoking.

The average age at diagnosis for women with HPV was 47.30 (±13.79) years. The most common age at diagnosis was 40 to 49 years (33.84%), followed by 30 to 39 years (21.72%), and 50 to 59 years (18.69%). Most women identified as white/ other (86.36%) and more women lived in the non-Appalachian parts of Kentucky (68.18%). Women who were married and unmarried were equal (50.00%)1 and the majority had some form of insurance (88.38%).

Squamous cell carcinoma (SCC) was the most common cervical cancer histology in women (72.73%), followed by adenocarcinoma (19.19%), and then other types of carcinoma (8.08%). More women were determined to have an early SEER stage (54.55%) compared to late SEER stage (45.45%). The majority of women had surgery (37.37%), followed by chemotherapy with radiation (27.78%), surgery with chemotherapy or radiation (26.26%), and radiation (8.59%). The proportion of those who died were higher (61.62%) than those who were alive (38.38%) at the end of the observation period.

Table 2 displays participant characteristics for 198 women with cervical cancer who had a diagnosis of HPV and are stratified by smoking status. 114 women reported a history of smoking

and 84 women had a history of non-smoking. There was a slightly higher proportion of non-smokers who had HPV 16/18 (83.33%) compared to smokers (78.07%) (p=0.3574).

Cervical cancer in women with any HPV genotype was diagnosed at an earlier age in smokers than in non-smokers. The average age of diagnosis was 46.64 (±12.93) years in smokers and 48.20 (±14.90) years in non-smokers (p=0.4322). Of the women who reported a history of smoking, significantly more identified as white (92.11%) than African American (7.89%) (p=0.0061). There were significantly less women from Appalachia (37.72%) (p=0.0378). Significantly more women were unmarried (56.14%) (p=0.0441). There was a higher proportion of smokers with SCC (69.30%) compared to adenocarcinoma (21.93%) (p=0.4398). More women were diagnosed with early stage cervical cancer (53.51%) compared to late stage cervical cancer (46.49%) (p=0.7329). More women had surgery (36.84%) compared to other treatment modalities (p=0.9596). Finally, the majority of women were dead (63.16%) at the end of the observation period (p=0.6033).

Of the women who did not report a history of smoking, the proportion of those who were white (78.57%) was significantly greater than those who were African American (21.43%) (p=0.0061). There were significantly less women who lived in Appalachia (23.81%) as compared to non-Appalachia (76.19%) (p=0.0378). Significantly more women were married (58.33) (p=0.0441). There was a higher proportion of women with SCC (77.38%) compared to adenocarcinoma (15.48%) (p=0.4398). There were also more women with early stage cervical cancer (55.95%) compared to late stage cervical cancer (44.05%) (p=0.7329). Most women had surgery (38.10%)

as opposed to other treatment modalities (p=0.9596). Finally, the majority of women who did not have a history of smoking were dead (59.52%) at the end of the observation period (p=0.6033).

Table 3a displays the unadjusted hazards associated with smoking in women with any HPV genotype. The unadjusted hazard associated with smoking was 9.34% (HR=0.934, [0.649, 1.333]), but was not statistically significant (p=0.7127). When adjusted for age, race, insurance status, marital status, Appalachian status, histology, stage, and treatment in Table 4a, this increased slightly to 9.97% (HR= 0.997, [0.669, 1.484]). Again, this was not statistically significant (p=0.4743).

Table 3b displays the unadjusted hazards associated with smoking in women with HPV 16/18. The unadjusted hazard associated with smoking was 1.011, but was not statistically significant (p=0.9573). When adjusted for age, race, insurance status, marital status, Appalachian status, histology, stage, and treatment in Table 4b, this increased to 3.90% (HR= 1.039, [0.669, 1.614]). In other words, smokers with a diagnosis of HPV 16/18 had 3.90% times the risk of dying compared to non-smokers with a diagnosis of HPV 16/18. However, this was not significant (p=0.8647).

Women with any HPV genotype who identified as African American had an increased unadjusted hazard of 10.9% (HR=1.109 [0.633, 1.943]) when compared to white women with any HPV genotype. However, this was not significant (p=0.7186). When adjusted for possible confounders, this hazard increased to 40.2% (HR=1.402 [0.728, 2.700]). However, this was still not statistically significant (p=0.3127). Women with HPV 16/18 and identified as African

American had a reduced risk of death by 8.62% (HR=0.862 [0.432, 1.720], p=0.6735) when compared to white women with HPV 16/18. When adjusted for confounders, the risk of death increased to 13.9% (HR=1.139 [0.516, 2.516]. However, this was not statistically significant (p=0.7466). Women with any HPV genotype who identified as Appalachian had an increased hazard of 38.9% (HR=1.389 [0.947, 2.038], p=0.0931) when compared to those with any HPV genotype who are not Appalachian. When adjusted for confounders, the risk of death further increased to 61.1% (HR=1.611 [1.054, 2.461]) and became statistically significant (p=0.0275). Women with HPV 16/18 who identified as Appalachian had a significantly increased unadjusted hazard of death of 60.3% (HR=1.603 [1.054, 2.437], p=0.0275) when compared to those who have HPV 16/18 but did not identify as Appalachian. When adjusted for confounders, this hazard further increased to 66.4% (HR=1.664 [1.060, 2.614]) and remained significant (p=0.0270).

In the unadjusted model for women with any HPV genotype, those without insurance had a significantly reduced hazard of death by 5.26% compared to those with insurance (HR= 0.526 [0.295, 0.938], p=0.0296). However, when adjusted for confounders, this becomes non-significant (HR=0.608 [0.314 1.78], p=0.1406). In contrast, insurance status was not shown to be significant in the unadjusted or adjusted model for women with HPV 16/18 (HR=0.534 [0.276, 1.032], p=0.0620). The adjusted HR was 0.589 [0.274, 1.270] (p=0.1771).

Those diagnosed with adenocarcinoma were at a significantly increased risk of death compared to those with SCC. Those with adenocarcinoma and any HPV genotype had a 60.4% (HR= 1.604 [1.062, 2.421], p=0.0245) increased risk of death when compared to those with SCC and any HPV genotype. When adjusted for possible confounders, this became non-significant (HR=

1.370 [0.848, 2.213], p=0.1988). Similarly, those with HPV 16/18 and adenocarcinoma had a 55.9% (HR= 1.559 [1.006, 2.416], p=0.0471) increased risk of death when compared to those with SCC and HPV 16/18. However, when adjusted for confounders, this again became non-significant (HR=1.385 [0.832, 2.307], p=0.2106].

Women with any HPV genotype and a combined treatment of chemotherapy and radiation had a significantly reduced hazard of death (HR=0.591 [0.364, 0.960], p=0.0337) when compared to those who had any HPV genotype and underwent surgery. However, this became non-significant when controlled for possible confounders (HR=0.755 [0.406, 1.402], p=0.3731). In contrast, those with HPV 16/18 who underwent a combined treatment of chemotherapy and radiation had a non-significantly reduced unadjusted hazard (HR=0.637 [0.367, 1.104], p=0.1081] when compared to those with HPV 16/18 who underwent surgery. When adjusted for confounders, there was an increase in the adjusted HR (HR=0.886 [0.435, 1.804]), but it was not significant (p=0.7378). Surgery with chemotherapy/radiation or radiation alone did not have a significant association when compared to surgery among those with any HPV genotype or HPV 16/18.

Figure 1 displays the survival curve for 198 women with cervical cancer and a diagnosis of any HPV genotype stratified by smoking status. Overall, the survival between the two groups were not significant. Figure 2 displays the survival curve for 159 women with cervical cancer and a diagnosis of HPV 16/18 stratified by smoking status. Again, the overall-survival between the two groups was not significant.

## DISCUSSION

Although not statistically significant, women with HPV and cervical cancer who were smokers had an overall poorer prognosis. Women with HPV 16/18 who smoked had a 3.90% increased risk of death compared to women with HPV 16/18 who did not smoke. The prevalence of late stage cervical cancer in women with any HPV genotype was 46.49% in smokers compared to 44.05% in non-smokers. Only 36.84% of women with any HPV genotype who smoked were alive at follow-up, compared to 40.48% of non-smokers. Survival curves for women with any HPV genotype and HPV 16/18 were not significant.

There are many explanations for these observed differences between smokers and non-smokers. First, it has been well established that cigarette smoke contains carcinogens that cause cancer. Some studies have determined that the carcinogenic effect of smoking is related to an increase of DNA adducts, or DNA bonded to chemicals, in the cervix of smokers (Phillips et al., 1994). Other studies suggest that the carcinogenesis is due to direct mutagenic effects of tobacco smoke on cervical mucus (Holly et al., 1986). Some studies describe the general effect that smoking has on the immune system, which causes immune suppression, allowing HPV to propagate and cause cervical dysplasia and cancer (Xi et al., 2009). Yet these studies also suggest that this may be related to other confounding factors, such as sexual behavior (Xi et al., 2009).

The association between Appalachian status and decreased survival in women with HPV was significant for both women with any type of HPV and for women with HPV 16/18. Women with any HPV genotype who were residents of Appalachia at the time of diagnosis had a 61.1% increased risk of dying compared to women who were not residents of Appalachian areas of

Kentucky at diagnosis. Similarly, women with HPV 16/18 had a 66.4% increased risk of dying compared to women who were not residents of Appalachian areas of Kentucky at diagnosis. There was a higher number of smokers who resided in Appalachia (37.72%) compared to non-smokers (23.81%).

Reasons for these observed differences may correlate with the inherent complexities of living in a rural setting. Smoking rates are higher in rural areas compared to urban locations (Hutcheson et al., 2008). This is due to the intersection of intrinsic beliefs regarding the consequences of smoking and lack of self-efficacy or incentives to quit, as well as deficiency of healthcare resources in the rural setting, including access to healthcare facilities, financial resources, and limited community infrastructure and support (Hutcheson et al., 2008, Wilburn et al., 2016). There are also many physical barriers in the rural setting, including lack of transportation, limited medical personnel and specialists, and physical isolation (Wilburn et al., 2016). The study by Carney et al reported that women from rural areas were significantly less likely to be seen by a gynecologic oncologist during their course of cancer treatment, which greatly impacted overall survival (Carney et al., 2002). In contrast, those who had a comprehensive treatment team that involved a gynecologic oncologist experienced a significant survival advantage compared to the patients who did not (Carney et al., 2002).

Another explanation for the difference in survival between Appalachian and non-Appalachian women with HPV is their difference in socioeconomic status. Lower socioeconomic status may contribute to poor health literacy and understanding, which directly impacts cancer outcomes (Chan et al, 2018). Patients who have higher overall health literacy tend to be more involved in

their cancer treatment, which contributes to better outcomes than patients who have lower health literacy and are not involved in the management of their cancer (Chan et al, 2018). Other barriers may include constructs such as social norms, attitudes, and beliefs (Vanderpool et al., 2015). Many studies have demonstrated that in areas with high rates of cancer, limited access to healthcare, poverty, and fatalistic beliefs are prevalent (Befort et al., 2013; Vanderpool et al., 2015). This may contribute to individuals avoiding or delaying medical care, which may result in later diagnosis of cancer and subsequent mortality.

Another significant association found in this study was between histology of cervical cancer and overall survival. Adenocarcinoma was significantly associated with decreased survival in the unadjusted models for women with both any HPV genotype and HPV 16/18. Women with any HPV genotype had a 60.4% increased risk of dying compared to those with SCC, while those with HPV 16/18 had 55.9% increased risk of dying. Studies have shown that adenocarcinoma is associated with poorer prognosis compared to SCC (Jung et al., 2017). Similarly, other studies have demonstrated that adenocarcinoma is less likely to be diagnosed at a microinvasive stage compared to SCC, and also has a higher probability of recurrence (Bulk et al., 2003; Jung et al., 2017). However, some studies have investigated HPV 16/18 as the etiologic agent of adenocarcinoma of the cervix as opposed to cigarette smoke (Tawfik et al., 2006; Lacy et al., 2001). Further research should be conducted to explore this association.

**Limitations**

It is important to note that there are several limitations to this study. One limitation is the relatively small sample size. Only 198 women were included after excluding for missingness. A

number of variables contained “Unknown” categories which may limit this study, although the variable used for smoking history was complete. Another limitation is that this study combined cases from two different studies, one of which was conducted from 2004 to 2005, and one that was conducted from 2014 to 2015. These cases were used due to the completeness of HPV genotyping that was obtained during these studies. The first population was a random sample, while the second population was weighted for racial and ethnic minorities, including African Americans. Therefore, it is possible that there are some inherent differences between these two populations. The information regarding smoking history was also limited. This variable only reflected whether a woman reported a history of smoking, and did not include additional information, such as the amount of cigarettes smoked, length of time smoking, or whether she was a current or previous smoker. In the event that she was a previous smoker, the number of years since quitting were not reported. Thus, it is possible that there were a substantial number of women in this study who had quit smoking for many years, which would explain why smoking did not severely impact survival. Another limitation is that there were no individual-level measures of socioeconomic status, including income or educational level, which may confound the relationship between Appalachia and smoking. Finally, this study was limited to Kentucky and may not be generalizable to other geographical locations.

## Conclusions

Although a history of smoking was not significant in this study, smoking has been shown to be a significant factor contributing to poorer survival in many other studies. On the other hand, both Appalachian status and adenocarcinoma were important factors impacting prognosis and overall survival in women with a diagnosis of HPV and cervical cancer. Further studies should be

conducted with a larger population of women with HPV genotyping to better establish the relationship between smoking, HPV, and cervical cancer survival.

## Tables & Figures

**Table 1. Characteristics of Women with Cervical Cancer and a Diagnosis of HPV from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| **Characteristic** | **Participants** (N= 198) |
|---|---|
| **Tobacco Use** | |
| Non-Smoker | 84 (42.42) |
| Smoker | 114 (57.58) |
| **HPV Diagnosis** | |
| HPV 16/18 - | 39 (19.70%) |
| HPV 16/18 + | 159 (80.30%) |
| **Age at Diagnosis** (years) | 47.30 (±13.79) |
| <30 | 14 (7.07) |
| 30-39 | 43 (21.72) |
| 40-49 | 67 (33.84) |
| 50-59 | 37 (18.69) |
| 69-69 | 19 (9.60) |
| 70+ | 18 (9.09) |
| **Race** | |
| White/ Other | 171 (86.36) |
| African American | 27 (13.64) |
| **Insurance Status** | |
| Not insured/ Unknown | 23 (11.62) |
| Insured | 175 (88.38) |
| **Marital Status** | |
| Not Married/ Unknown | 99 (50.00) |
| Married | 99 (50.00) |
| **Setting** | |
| Non-Appalachian | 135 (68.18) |
| Appalachian | 63 (31.82) |
| **Histology** | |
| SCC | 144 (72.73) |
| Adenocarcinoma | 38 (19.19) |
| Other | 16 (8.08) |
| **SEER Stage** | |
| Early | 108 (54.55) |
| Late | 90 (45.45) |
| **Treatment** | |
| Surgery | 74 (37.37) |
| Surgery + Chemo/ Radiation | 52 (26.26) |
| Chemo + Radiation | 55 (27.78) |
| Radiation | 17 (8.59) |
| **Vital Status** | |
| Alive | 76 (38.38) |
| Dead | 122 (61.62) |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 198 women was analyzed

**Table 2. Characteristics of Women with Cervical Cancer and a Diagnosis of HPV by Tobacco Status from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| **Characteristic** | **Non-Smoker** (N=84) | **Smoker** (N=114) | **P-value†** |
|---|---|---|---|
| **HPV Diagnosis** | | | |
| HPV 16/18 - | 14 (16.67) | 25 (21.93) | 0.3574 |
| HPV 16/18 + | 70 (83.33) | 89 (78.07) | |
| **Age at Diagnosis** (years) | 48.20 (±14.90) | 46.64 (± 12.93) | 0.4322‡ |
| <30 | 7 (8.33) | 7 (6.14) | 0.2983 |
| 30-39 | 20 (23.81) | 23 (20.18) | |
| 40-49 | 21 (25.00) | 46 (40.35) | |
| 50-59 | 16 (19.05) | 21 (18.42) | |
| 69-69 | 10 (11.90) | 9 (7.89) | |
| 70+ | 10 (11.90) | 8 (7.02) | |
| **Race** | | | |
| White/ Other | 66 (78.57) | 105 (92.11) | **0.0061** |
| African American | 18 (21.43) | 9 (7.89) | |
| **Insurance Status** | | | |
| Not insured/ Unknown | 7 (8.33) | 16 (14.04) | 0.2159 |
| Insured | 77 (91.67) | 98 (85.96) | |
| **Marital Status** | | | |
| Not Married/ Unknown | 35 (41.67) | 64 (56.14) | **0.0441** |
| Married | 49 (58.33) | 50 (43.86) | |
| **Setting** | | | |
| Non-Appalachian | 64 (76.19) | 71 (62.28) | **0.0378** |
| Appalachian | 20 (23.81) | 43 (37.72) | |
| **Histology** | | | |
| SCC | 65 (77.38) | 79 (69.30) | 0.4398 |
| Adenocarcinoma | 13 (15.48) | 25 (21.93) | |
| Other | 6 (7.14) | 10 (8.77) | |
| **SEER Stage** | | | |
| Early | 47 (55.95) | 61 (53.51) | 0.7329 |
| Late | 37 (44.05) | 53 (46.49) | |
| **Treatment** | | | |
| Surgery | 32 (38.10) | 42 (36.84) | 0.9596 |
| Surgery + Chemo/ Radiation | 22 (26.19) | 30 (26.32) | |
| Chemo + Radiation | 22 (26.19) | 33 (28.95) | |
| Radiation | 8 (9.52) | 9 (7.89) | |
| **Vital Status** | | | |
| Alive | 34 (40.48) | 42 (36.84) | 0.6033 |
| Dead | 50 (59.52) | 72 (63.16) | |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 198 women was analyzed

† P-values were calculated using Chi-squared test

‡ P-values were calculated using Fischer's Exact test

**Table 3a. Unadjusted Cox Proportional Hazards Model for Women with Cervical Cancer and a Diagnosis of any HPV genotype (N=198) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| Characteristic | Unadjusted HR | 95% CI | P-value† |
|---|---|---|---|
| **Tobacco Use** | | | |
| Non-Smoker | REF | | |
| Smoker | 0.934 | [0.649, 1.333] | 0.7127 |
| **Age at Diagnosis** (years) | | | |
| <30 | REF | | |
| 30-39 | 1.809 | [0.913, 3.585] | 0.0894 |
| 40-49 | 0.531 | [0.273, 1.032] | 0.0620 |
| 50-59 | 0.893 | [0.429, 1.856] | 0.7615 |
| 69-69 | 0.597 | [0.254, 1.401] | 0.2363 |
| 70+ | 0.571 | [0.210, 1.554] | 0.2729 |
| **Race** | | | |
| White/ Other | REF | | |
| African American | 1.109 | [0.633, 1.943] | 0.7186 |
| **Insurance Status** | | | |
| Not insured/ Unknown | 0.526 | [0.295, 0.938] | **0.0296** |
| Insured | REF | | |
| **Marital Status** | | | |
| Not Married/ Unknown | 1.113 | [0.772, 1.606] | 0.5665 |
| Married | REF | | |
| **Setting** | | | |
| Non-Appalachian | REF | | |
| Appalachian | 1.389 | [0.947, 2.038] | 0.0931 |
| **Histology** | | | |
| SCC | REF | | |
| Adenocarcinoma | 1.604 | [1.062, 2.421] | **0.0245** |
| Other | 1.424 | [0.710, 2.853] | 0.3193 |
| **SEER Stage** | | | |
| Early | REF | | |
| Late | 0.800 | [0.537, 1.192] | 0.2722 |
| **Treatment** | | | |
| Surgery | REF | | |
| Surgery + Chemo/ Radiation | 0.851 | [0.554, 1.301] | 0.4615 |
| Chemo + Radiation | 0.591 | [0.364, 0.960] | **0.0337** |
| Radiation | 0.345 | [0.082, 1.455] | 0.1473 |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 198 women was analyzed

† P-values were calculated using Chi-squared test

**Table 3b. Unadjusted Cox Proportional Hazards Model for Women with Cervical Cancer and a Diagnosis of HPV 16 or 18 (N=159) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| Characteristic | Unadjusted HR | 95% CI | P-value† |
|---|---|---|---|
| **Tobacco Use** | | | |
| Non-Smoker | REF | | |
| Smoker | 1.011 | [0.677, 1.509] | 0.9573 |
| **Age at Diagnosis** (years) | | | |
| <30 | REF | | |
| 30-39 | 2.149 | [1.014, 4.552] | **0.0459** |
| 40-49 | 0.608 | [0.296, 1.251] | 0.1768 |
| 50-59 | 0.957 | [0.418, 2.194] | 0.9174 |
| 69-69 | 0.793 | [0.282, 2.229] | 0.6605 |
| 70+ | 0.678 | [0.240, 1.914] | 0.4633 |
| **Race** | | | |
| White/ Other | REF | | |
| African American | 0.862 | [0.432, 1.720] | 0.6735 |
| **Insurance Status** | | | |
| Not insured/ Unknown | 0.534 | [0.276, 1.032] | 0.0620 |
| Insured | REF | | |
| **Marital Status** | | | |
| Not Married/ Unknown | 0.949 | [0.631, 1.427] | 0.8011 |
| Married | REF | | |
| **Setting** | | | |
| Non-Appalachian | REF | | |
| Appalachian | 1.603 | [1.054, 2.437] | **0.0275** |
| **Histology** | | | |
| SCC | REF | | |
| Adenocarcinoma | 1.559 | [1.006, 2.416] | **0.0471** |
| Other | 1.085 | [0.435, 2.703] | 0.8611 |
| **SEER Stage** | | | |
| Early | REF | | |
| Late | 0.800 | [0.519, 1.235] | 0.3143 |
| **Treatment** | | | |
| Surgery | REF | | |
| Surgery + Chemo/ Radiation | 0.847 | [0.537, 1.335] | 0.4733 |
| Chemo + Radiation | 0.637 | [0.367, 1.104] | 0.1081 |
| Radiation | 0.360 | [0.085, 1.527] | 0.1657 |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 159 women was analyzed

† P-values were calculated using Wald Chi-squared test

**Table 4a. Adjusted Cox Proportional Hazards Model for Women with Cervical Cancer and a Diagnosis of any HPV genotype (N=198) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| Characteristic | Adjusted HR | 95% CI | P-value† |
|---|---|---|---|
| **Tobacco Use** | | | |
| Non-Smoker | REF | | |
| Smoker | 0.997 | [0.669, 1.484] | 0.9871 |
| **Age at Diagnosis** (years) | 0.975 | [0.958, 0.992] | **0.0036** |
| **Race** | | | |
| White/ Other | REF | | |
| African American | 1.402 | [0.728, 2.700] | 0.3127 |
| **Insurance Status** | | | |
| Not insured/ Unknown | 0.608 | [0.314, 1.178] | 0.1406 |
| Insured | REF | | |
| **Marital Status** | | | |
| Not Married/ Unknown | 1.121 | [0.745, 1.686] | 0.5834 |
| Married | REF | | |
| **Setting** | | | |
| Non-Appalachian | REF | | |
| Appalachian | 1.611 | [1.054, 2.461] | **0.0275** |
| **Histology** | | | |
| SCC | REF | | |
| Adenocarcinoma | 1.370 | [0.848, 2.213] | 0.1988 |
| Other | 1.205 | [0.590, 2.463] | 0.6091 |
| **SEER Stage** | | | |
| Early | REF | | |
| Late | 1.073 | [0.657, 1.754] | 0.7773 |
| **Treatment** | | | |
| Surgery | REF | | |
| Surgery + Chemo/ Radiation | 0.841 | [0.519, 1.362] | 0.4809 |
| Chemo + Radiation | 0.755 | [0.406, 1.402] | 0.3731 |
| Radiation | 0.466 | [0.097, 2.234] | 0.3396 |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 198 women was analyzed

† P-values were calculated using Chi-squared test

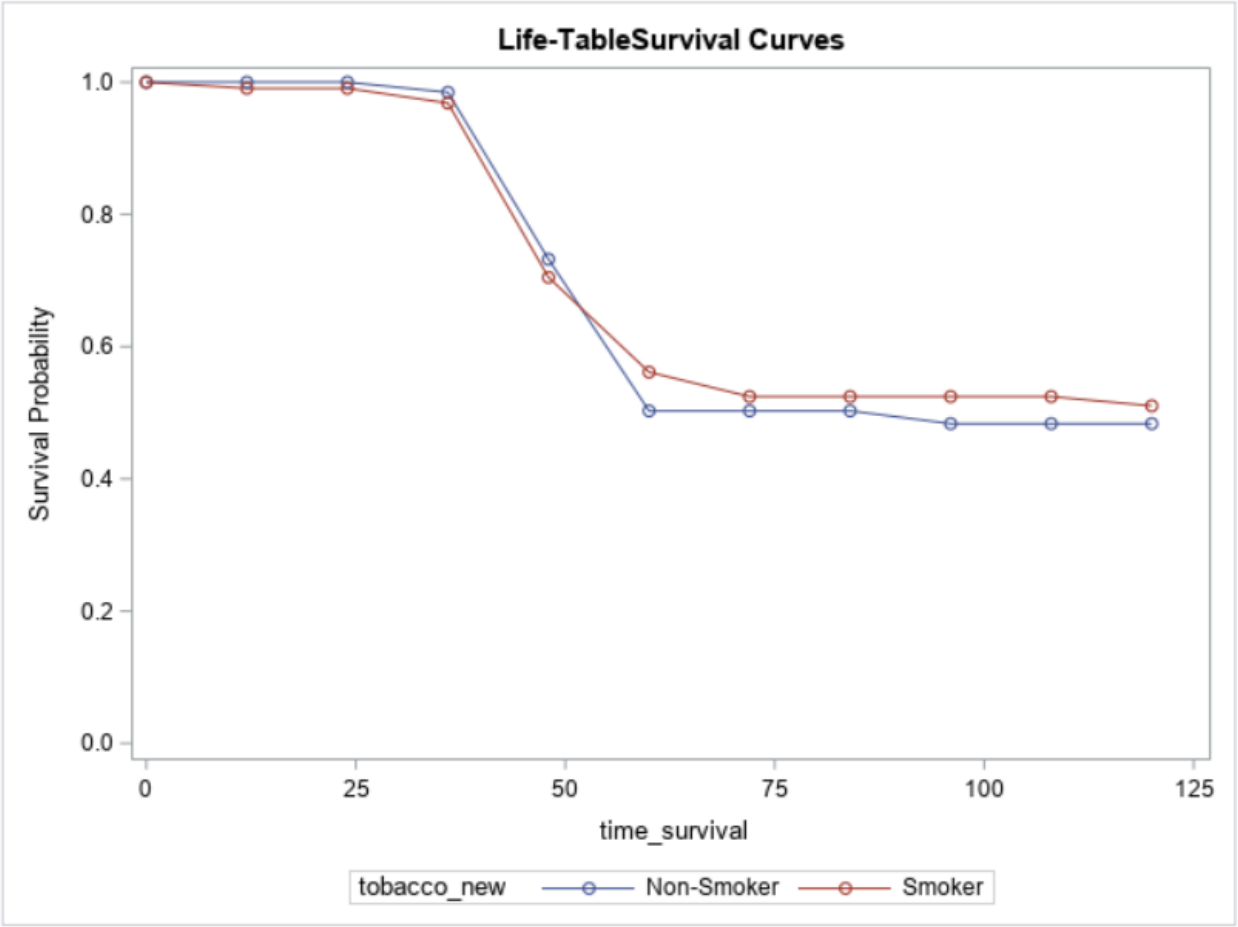
**Table 4b. Adjusted Cox Proportional Hazards Model for Participants with Cervical Cancer and a Diagnosis of HPV 16 or 18 (N=159) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015***

| Characteristic | Adjusted HR | 95% CI | P-value† |
|---|---|---|---|
| **Tobacco Use** | | | |
| Non-Smoker | REF | | |
| Smoker | 1.039 | [0.669, 1.614] | 0.8647 |
| **Age at Diagnosis** (years) | 0.976 | [0.957, 0.995] | **0.0152** |
| **Race** | | | |
| White/ Other | REF | | |
| African American | 1.139 | [0.516, 2.516] | 0.7466 |
| **Insurance Status** | | | |
| Not insured/ Unknown | 0.589 | [0.274, 1.270] | 0.1771 |
| Insured | REF | | |
| **Marital Status** | | | |
| Not Married/ Unknown | 0.960 | [0.603, 1.528] | 0.8628 |
| Married | REF | | |
| **Setting** | | | |
| Non-Appalachian | REF | | |
| Appalachian | 1.664 | [1.060, 2.614] | **0.0270** |
| **Histology** | | | |
| SCC | REF | | |
| Adenocarcinoma | 1.385 | [0.832, 2.307] | 0.2106 |
| Other | 0.902 | [0.355, 2.294] | 0.8282 |
| **SEER Stage** | | | |
| Early | REF | | |
| Late | 0.969 | [0.564, 1.665] | 0.9089 |
| **Treatment** | | | |
| Surgery | REF | | |
| Surgery + Chemo/ Radiation | 0.961 | [0.573, 1.611] | 0.8810 |
| Chemo + Radiation | 0.886 | [0.435, 1.804] | 0.7378 |
| Radiation | 0.542 | [0.106, 2.764] | 0.4616 |

*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 159 women was analyzed

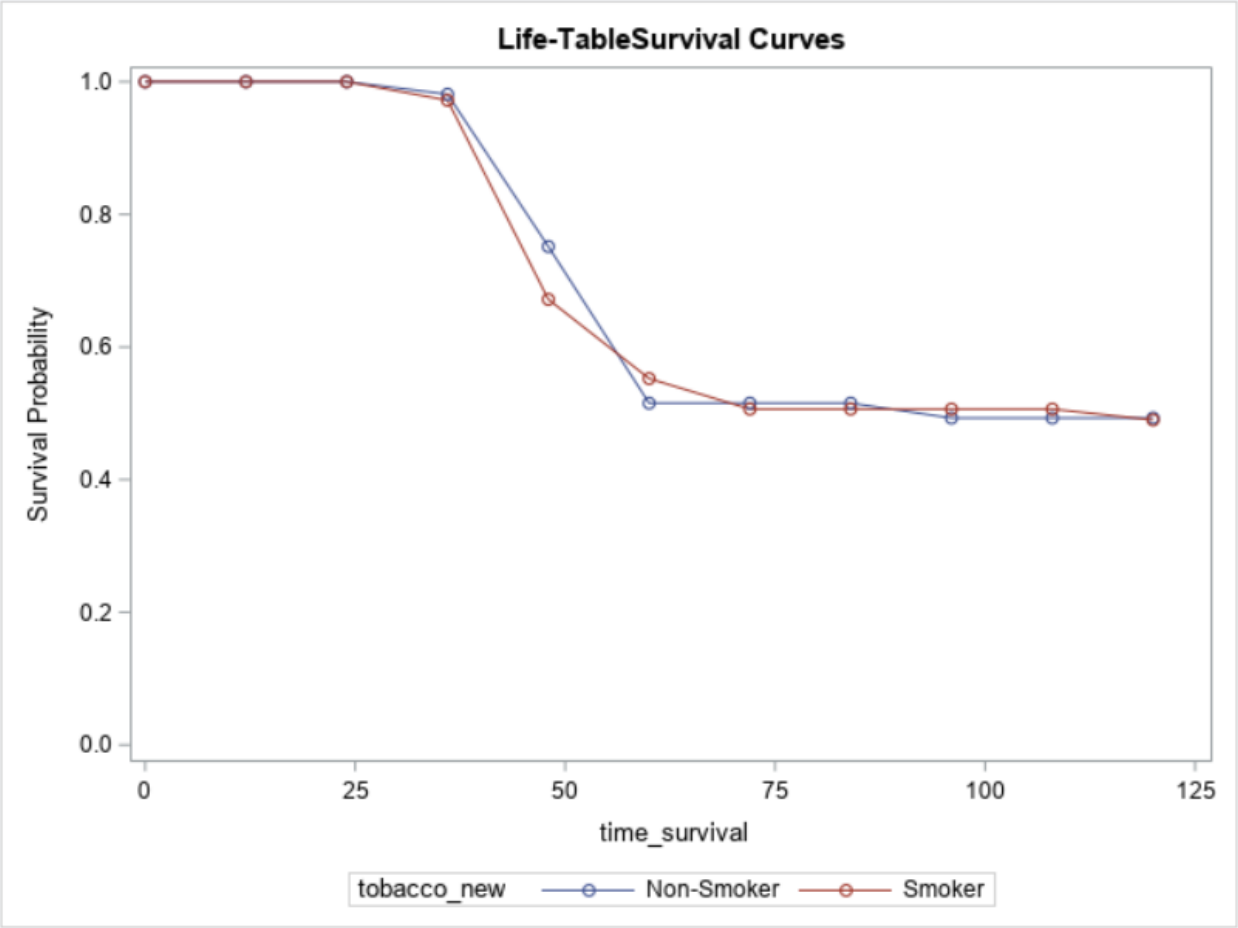
† P-values were calculated using Chi-squared test

**Figure 1. Survival Curves for Participants with Cervical Cancer and a Diagnosis of any HPV genotype (N=198) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015*†**




*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 198 women was analyzed
† Pr >Chi-Square = 0.7076 based on Log-Rank test

**Figure 2. Survival Curves for Participants with Cervical Cancer and a Diagnosis of HPV 16 or 18 (N=159) from the Kentucky Cancer Registry (KCR), 2004-2005 and 2014-2015*†**




*A total population of 246 women was obtained from KCR and evaluated for incomplete or missing data; a final population of 159 women was analyzed

† Pr >Chi-Square = 0.5553 based on Wilcoxon test

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