IDENTIFYING DEMOGRAPHIC, CLINICAL, AND GEOGRAPHIC FEATURES OF CERVICAL CANCER PATIENTS PRESENTING TO A MULTIDISCIPLINARY TEAM (MDT) CLINIC IN GABORONE, BOTSWANA

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This dissertation is dedicated to my parents, Harry and Geraldine Friebel, for raising me to be the person I am today. Cancer claimed both of your lives too early and I miss you every day. The experience of losing you both so young has given me the unbridled passion to pursue a career focused on fighting cancer, with the hope that fewer people will suffer the premature loss of a loved one. I will forever spend my days hoping to make you both proud.

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ABSTRACT

IDENTIFYING DEMOGRAPHIC, CLINICAL, AND GEOGRAPHIC FEATURES OF CERVICAL CANCER PATIENTS PRESENTING TO A MULTIDISCIPLINARY TEAM (MDT) CLINIC IN GABORONE, BOTSWANA

Tara Marie Friebel-Klingner

Anne Marie McCarthy

In Botswana, cervical cancer is the most common cancer and leading cause of cancer death for females. The capital, Gaborone, houses the only gynecological cancer multi-disciplinary team (MDT) clinic in the country with the expertise and facilities able to provide standard of care for cervical cancer patients. Botswana, with a 20% prevalence of human immunodeficiency virus (HIV), is experiencing increasing morbidity and mortality from HIV/AIDS-related cancers, including cervical cancer. Data, resources, and interventions are urgently needed to combat this growing burden. For this dissertation, we abstracted social, biological, clinical, and geographic characteristics of cervical cancer patients presenting for treatment to the MDT clinic. First, we used logistic regression to investigate individual patient characteristics associated with tumor stage at presentation. We found the odds of having late-stage cervical cancer at presentation decreased with previous cervical cancer screening, whereas experiencing abnormal vaginal bleeding and never being married were associated with an increased odds late-stage cervical cancer. Second, we used geo-spatial analytical methods to detect areas with high or low clustering of cervical cancer cases presenting for care in order to identify

sub-districts with disproportionate access to the MDT clinic. We identified five sub-districts with clustering, specifically highlighting sub-districts with disproportionately lower presentation rates of cervical cancer cases indicating poor access to comprehensive cervical cancer care. Furthermore, we noted individual level predictors (HIV status and presence of abnormal vaginal bleeding) among patients living in areas with disproportionate rates. Third, we used multinomial logistic regression to study the travel time from a patient's village of residence to the MDT clinic and tumor stage. We found that increased travel time was associated with later stages of cervical cancer at presentation. Additionally, women with increased travel time to the MDT clinic were more likely to be living with HIV, suggesting HIV status may also influencing referral to and receipt of cervical cancer care for women living further from the clinic in Gaborone. In conclusion, identifying individual, community, and geographic factors associated with late-stage diagnosis provides valuable insight to guide future studies, interventions, national health policy, and programs for developing strategies targeting under-served areas and high-risk women to improve the early detection of cervical cancer, decrease morbidity, and improve access to cancer treatment. These strategies will be key in controlling the emerging cervical cancer burden in Botswana.

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CHAPTER 1. Introduction

The World Health Organization estimates that there were 570,000 cervical cancer cases and 311,000 cervical cancer deaths in 2018, with more than 80% of the cervical cancer deaths worldwide occurring in low-to-middle-income countries (LMICs), predominantly in sub-Saharan Africa (SSA). In Botswana, cervical cancer is the most commonly diagnosed cancer in women and the leading cause of cancer death. In LMICs, as the chronic disease burden for diseases like cancer is accumulating, data, resources, and interventions needed to address this growing concern. It is an opportune time in LMICs to prioritize cancer care with the intent of reducing the impact of this disease.

Despite Botswana's national healthcare system and cervical cancer screening program, many cervical cancers are diagnosed at late stages (stage III or IV) and the mortality rate is high. A partnership between the University of Botswana and University of Pennsylvania (BUP), formed in 2001 to combat HIV/AIDs, has recognized the need to expand priorities to include chronic diseases and has developed an infrastructure to capture demographic, social and biological characteristics of cervical cancer patients throughout Botswana, known as the Botswana cancer cohort. Botswana has a population of approximately 2.3 million people and has government funded healthcare, ensuring affordable healthcare for all citizens. The de-centralized health care system ranges from health posts to referral hospitals. Health posts are staffed with a health education assistant, a lay counselor, a nurse and occasionally a midwife or a doctor; clinics offer mainly primary health care and outpatient services, including offering various modes of screening or testing for cervical cancer. Hospitals are three tiers: district, primary or referral hospitals. The most equipped facilities are referral hospitals, of which

there are 3 in the country. Referral hospitals are highly advanced facilities prepared to deal with specialized diseases. Two of the referral hospitals are located in the capital, Gaborone: Princess Marina Hospital (PMH) and Gaborone Private Hospital (GPH), and one is in Francistown: Nyangabgwe Referral Hospital (NRH). With two of the country's referral hospitals in the capital city of Gaborone, the first multidisciplinary tumor clinic (MDT) was formed in 2015 at PMH to provide comprehensive care for all gynecological oncology patients in Botswana. The MDT clinic coordinates comprehensive gynecological cancer care and has a highly specialized team, including the only gynecological oncologist in the country and treats patients, as appropriate, with the only radiation oncology facility located at GPH which sees and treats patients diagnosed with cervical cancer referred from health facilities around Botswana.

This dissertation research provides a rich, detailed description of individual level social and clinical characteristics as well as geographical associations of cervical cancers presenting for staging and care at the MDT clinic in Botswana. Additionally, geographic information systems (GIS) and spatial analysis, powerful epidemiologic tools for understanding variability in health patterns, were used to identify areas in need of public health interventions. This approach could particularly benefit Botswana, a country characterized by a large geographic area and a dispersed population limited to one cervical cancer treatment facility for the entire country.

The conceptual model for this work is presented in Figure 1.1. For this work we used the cohort of patients presenting to the MDT clinic for staging and care. We first investigated individual factors that differed according to tumor stage at presentation of cervical cancer. Second, we identified geography and clustering of cervical cancer

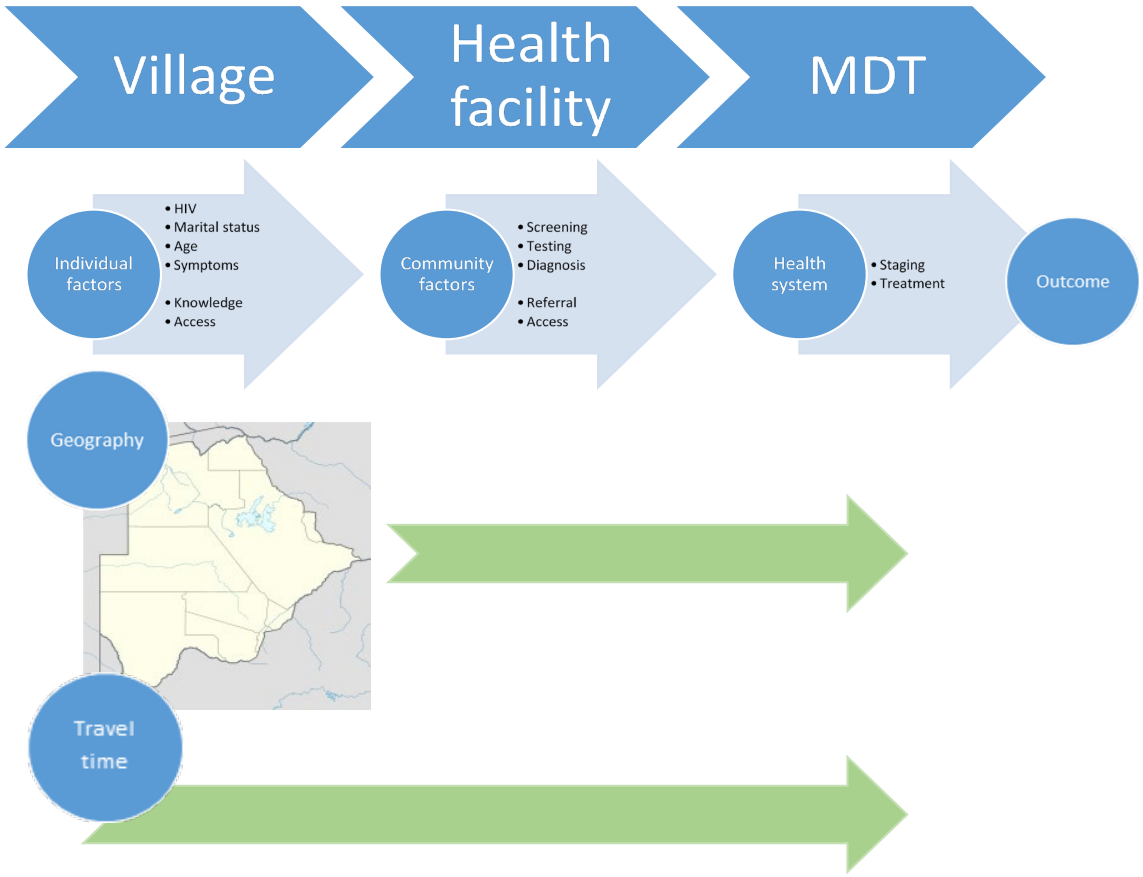
cases throughout the country using spatial statistical methods. Lastly, we determined how travel time from a patient's residence relates to stage at presentation of cervical cancer and identified factors impacting potential delays in accessing cancer care.

This research aims to highlight the growing cervical cancer burden in Botswana and learn pertinent information that will lay a foundation for future studies to confirm and characterize factors associated with the increasing burden of cervical cancer. This work will contribute to the sparse literature regarding cervical cancer in this low resource settings. We have identified important individual, community level, and health care level and geographic factors that influence late stage of cervical cancer at presentation, influencing delays and access to comprehensive cervical cancer care. These findings will guide future studies and national health programs developing strategies that target underserved areas with interventions to improve early detection of cervical cancer, to ultimately improve survival for cervical cancer patients in Botswana.

1.2. Ethics approval

All work for this dissertation was approved under the parent study, "Treatment and Outcomes of Patients Presenting with Cancer in Botswana," \ by the University of Pennsylvania as part of the Botswana-University of Pennsylvania Partnership (IRB: 820159 IRB#7 Penn) and by the Ministry of Health and Wellness of the Republic of Botswana (HPDME 13/18/1).

Figure 1. 1. Conceptual Model



CHAPTER 2. Clinical and sociodemographic factors associated with late stage cervical cancer diagnosis in Botswana

2.1. Abstract

2.1.1. Background

Cervical cancer is the leading cause of female cancer mortality in Botswana with the majority of cervical cancer patients presenting with late-stage disease. The identification of factors associated with late-stage disease could reduce the cervical cancer burden. This study aims to identify potential patient level clinical and sociodemographic factors associated with a late-stage diagnosis of cervical cancer in Botswana in order to help inform future interventions at the community and individual levels to decrease cervical cancer morbidity and mortality.

2.1.2. Methods

Women diagnosed with cervical cancer from January 2015 to March 2020 at two tertiary hospitals in Gaborone, Botswana were included. The association between late-stage (stage III or stage IV) cervical cancer at diagnosis and patient clinical and sociodemographic factors were evaluated using multivariable logistic regression. Logistic regression was done using multiple imputation with chained equations to account for missing data.

2.1.2. Results

There were 984 Women diagnosed with cervical cancer from January 2015 to March 2020 at two tertiary hospitals in Gaborone, Botswana. Four hundred forty women (44.7%) presented with late-stage cervical cancer, and 674 women (69.7%) were living with HIV. The mean age at diagnosis was 50.5 years. Women who reported undergoing cervical cancer screening had lower odds of late-stage disease at diagnosis (OR: 0.63, 95% CI: 0.47-0.84) compared to those who did not report screening. Women who had never been married had increased odds of late-stage disease at diagnosis (OR: 1.35, 95% CI: 1.02-1.86) compared to women who had been married. Women with abnormal vaginal bleeding had higher odds of late-stage disease at diagnosis (OR: 2.32, 95% CI: 1.70-3.16) compared to those without abnormal vaginal bleeding. HIV was not associated with a diagnosis of late-stage cervical cancer. Rural women who consulted a traditional healer had increased odds of late-stage disease at diagnosis compared to rural women who had never consulted a traditional healer (OR: 1.61, 95% CI: 1.02-2.55).

2.1.3. Conclusion

Increasing education and awareness among women, regardless of their HIV status, and among providers, including traditional healers, about the benefits of cervical cancer screening and about the importance of seeking prompt medical care for abnormal vaginal bleeding, while also developing support systems for unmarried women, may help reduce cervical cancer morbidity and mortality in Botswana.

2.2. Introduction

Cervical cancer affects women across the globe, with a disproportionately higher burden of morbidity and mortality in low- and middle-income countries (LMICs) (1). In 2018, more than 80% of the 311,000 cervical cancer deaths worldwide occurred in LMICs, predominantly in sub-Saharan Africa (SSA) (1). Cervical cancer is classified as a human immunodeficiency virus (HIV)-related malignancy, further contributing to the increasing cancer burden in SSA countries with a high prevalence of HIV(2). Additionally, late-stage cervical cancer at diagnosis is significantly associated with increased cervical cancer mortality, and approximately 68% of cervical cancers are diagnosed at a late stage in SSA (3). Thus, it is paramount to detect cervical cancer at an earlier, more treatable stage in order to significantly reduce cervical cancer deaths (4, 5).

Cervical cancer screening aims to prevent invasive cancer (6-10). Other clinical and sociodemographic factors have been associated with late-stage cervical cancer at diagnosis, particularly in LMICS, including abnormal vaginal bleeding (6, 7, 11, 12), age at diagnosis (9, 13-15), marital status (6, 15-18), and living in a rural area (7, 15, 16, 18, 19). In addition, the practice of traditional healers has been shown to be associated with an increase in late-stage cervical cancer at diagnosis (20) and as a barrier to cervical cancer care in low-resource settings (21).

In Botswana, an upper-middle-income country in SSA, cervical cancer is the leading cause of female cancer deaths (22, 23). However, there remains a dearth of information regarding the demographics and clinical factors that contribute to late-stage cervical

cancer at diagnosis among women from SSA. Botswana also has a high prevalence of HIV, with 25.1% of females between 15-49 years of age living with HIV in 2019(24). In recent decades, with the growing burden of HIV-related cancers (25), the Botswana Ministry of Health and Wellness (MOHW) has prioritized reducing the cervical cancer burden by adapting American Society of Clinical Oncology (ASCO) resource stratified screening strategies for its citizens, with the majority of cervical cancers being detected through loop electrosurgical excision procedure or visual inspection with acetic acid (26-29). Despite these efforts by the Botswana MOHW, approximately 50% of cervical cancers are diagnosed at a late stage (6, 30).

This study aims to identify potential clinical and sociodemographic factors associated with a late-stage diagnosis of cervical cancer in Botswana in order to help inform future interventions at the community and individual levels aimed at decreasing cervical cancer morbidity and mortality.

2.3. Methods

2.3.1. Study participants

We abstracted data from questionnaires administered during the initial consult visit and medical records for women with invasive cervical cancer who had consented to participate in research studies (30, 31) at Princess Marina Hospital (PMH) and Gaborone Private Hospital (GPH), two tertiary referral hospitals in the capital city of Gaborone, between January 2015 and March 2020 (30, 31). GPH houses the sole chemo-radiation facility in the country. Women diagnosed at either the public hospital

PMH or GPH, are treated at GPH, and their treatment is covered under the government health care system. Women were eligible for this analysis if they were over the age of 18 years, not pregnant, and diagnosed with cervical cancer. Women were excluded if they were diagnosed with cervical carcinoma in situ or if they had recurrent disease.

2.3.2. Covariates

Data collected at the time of cancer diagnosis included patient/sociodemographic and clinical factors (i.e., age, marital status, place of residence, history of cervical cancer screening, ever/never visit with a traditional doctor and/or natural healer, presence of abnormal vaginal bleeding (including post-coital bleeding/bleeding after vaginal intercourse), HIV status, and utilization of antiretroviral therapy (ART)). Additional clinical data was abstracted from medical records regarding clinical factors, such as stage, pathology, and CD4 count. Place of residence was characterized as urban or rural based on the sub-district of the participant's reported residence (32).

Cervical cancer stage at diagnosis was based on the International Federation of Gynecology and Obstetrics (FIGO) staging system (33, 34). FIGO cervical cancer stages were dichotomized as early-stage (I-II) and late-stage (III-IV).

2.3.3. Statistical Analyses

Descriptive statistics for each variable of interest were examined for the entire study sample, and by cervical cancer stage at diagnosis (early vs. late). Differences between early- and late-stage diseases were examined using Pearson's chi-squares test for

categorical variables, Fisher's exact test for small sample sizes, and Student t-tests for continuous variables. Multivariable logistic regression was used to examine potential risk factors associated with late- versus early-stage disease. Variables included in the multivariable model were determined based on purposeful selection, review of the literature, and clinical relevance. We assessed missing data, patterns, and reasons for missing data. To account for missing data, we performed multiple imputation with chained equations (MICE) for the multivariable logistic regression model, assuming data were missing at random (35-37). We also conducted complete case analyses (results not shown). We further investigated interactions between HIV status and age and HIV and screening history. We also investigated the use of traditional healers in rural and urban areas using univariate logistic regression. Additionally, because cervical cancer is an AIDS-defining malignancy, we examined clinical and sociodemographic differences between women living with HIV (WLWH) and women without HIV, and performed multivariable analyses stratified by HIV status. For the analysis of WLWH, CD4 count and ART use were included as potential risk factors. All statistical analyses were conducted using STATA 16, and p-values <0.05 were considered statistically significant.

2.4. Results

2.4.1. Patient Characteristics

Between January 2015 and March 2020, 1,007 women were diagnosed with cervical cancer. We excluded 16 women with prior cervical carcinoma in situ and seven women with recurrent disease, resulting in the inclusion of 984 women in this study. Sociodemographic and clinical characteristics are shown in Table 2.1. Four hundred

forty (44.7%) of the women included in the study were diagnosed with late-stage cervical tumors. The mean age at diagnosis was 50.5 years (range 22.4-95.2), 21.0% (n=206) lived in urban areas, 65.7% (n=646) had never been married, 57.4% (n= 539) reported previous cervical cancer screening, 69.7% (n=674) were WLWH, and 10.1% (n=95) reported ever having a visited with a traditional healer. Abnormal vaginal bleeding was reported in 73.2% (n=720) of women, and 87.3% (n=835) of the cervical cancers were squamous cell carcinoma (SCC) pathology. Women diagnosed at a late stage were less likely to report prior screening (50.8% vs. 63.2%, $p<0.001$) and were also more likely to report abnormal vaginal bleeding (82.3% vs. 66.3%, $p<0.001$).

2.4.2. Factors associated with late-stage cervical cancer at diagnosis

Table 2.2 displays factors significantly associated with late-stage cervical cancer at diagnosis in the imputed multivariable model. MICE was performed to account for missing data for the variables: stage at diagnosis (n=43), age (n=1), place of residence (n=3), marital status (n=1), screening history (n=45), HIV status (n=17), and visit with a traditional healer (n=27). Never being married (OR: 1.35, 95% CI: 1.02-1.86) and experiencing abnormal vaginal bleeding (OR: 2.32, 95% CI: 1.70-3.16) had an increased odds of late-stage cervical cancer at diagnosis, while previous cervical cancer screening was associated with decreased odds of late-stage cervical cancer at diagnosis (OR: 0.65, 95% CI: 0.49-0.85). Results from the complete case analysis were analogous to the MICE results. No significant interactions were observed between HIV status and age or between HIV status and screening history.

There were no significant associations between living in an urban residence versus living

in a rural residence and having ever visited a traditional healer and having late-stage cervical cancer at diagnosis in the multivariable model. However, in our cohort, more rural women than urban women (11% vs. 5%) had consulted with a traditional healer. Table 2.3 shows the association of presenting with late- versus early-stage cervical cancer at diagnosis when visiting a traditional healer among women living in a rural residence (OR: 1.61, 95% CI: 1.02-2.55). This increased probability was not observed among women living in an urban area when visiting a traditional healer.

2.4.3. Characteristics by HIV status

Table 2.4 shows patient characteristics by HIV status. Of the 984 cervical cancer cases, the HIV status of 967 (98.3%) women was known. Women whose HIV status was unknown (n=17) were excluded from the HIV stratified analyses. WLWH comprised 69.7% (n=674) of the study population and were significantly younger than women without HIV (45.8 years vs. 60.5 years, $p<0.001$). WLWH were also more likely to live in urban areas (24.0% vs. 14.7%, $p=0.001$), were more likely to have never been married (74.0% vs. 47.8%, $p<0.001$), and were more likely to have been screened for cervical cancer (61.8% vs. 48.4%, $p<0.001$) than women without HIV. In addition, WLWH were more likely to have SCC pathology than women without HIV (88.9% vs. 83.7%, $p=0.020$). Among the WLWH, 78.6% (n=429) had a CD4 cell count >250 cells/mm^3 at diagnosis, and 96.2% (n=640) reported being on ART.

Among the WLWH, prior cervical cancer screening showed decreased odds with late-stage disease at diagnosis (OR: 0.61, 95% CI: 0.44-0.86), and increased odds with previous abnormal bleeding symptoms (OR: 2.10, 95% CI: 1.46-3.01). Among women

without HIV, factors associated with higher odds of late-stage disease at diagnosis included increasing age (OR: 1.02, 95% CI: 1.00-1.14; p=0.041) and abnormal vaginal bleeding (OR: 3.06, 95% CI: 1.52-5.71) (Table 2.5). Results of complete case analyses by HIV status were similar to the imputed results.

2.5. Discussion

This large study of women with cervical cancer in Botswana aimed to identify potential clinical and sociodemographic factors associated with a late-stage diagnosis of cervical cancer in Botswana. Our study showed that prior cervical cancer screening was associated with decreased odds of having late-stage cervical cancer at diagnosis, whereas experiencing abnormal vaginal bleeding and having never been married were associated with an increased odds of having late-stage cervical cancer at diagnosis. Having HIV was not associated with having late-stage cervical cancer at diagnosis. Furthermore, results suggested that women living in rural areas who visited a traditional healer were more likely to be diagnosed with late-stage cervical cancer.

Screening has been shown to lead to an earlier diagnosis of cervical cancer in high-income countries with established screening programs, and screening has also been shown to be effective in low resource settings (7, 9, 38). With the growing burden of HIV-related cancers in recent decades (25), the Botswana MOHW has prioritized reducing the cervical cancer burden through implementing and supporting a national cervical cancer screening program as part of the HIV care continuum (23, 27, 28, 39, 40). A prior retrospective study by Nassali et al. (2018) reviewed 149 cervical cancer patients admitted to PMH from August 2016 to February 2017, which may include some overlap

with our study sample. In that study, Nassali et al. defined late-stage cervical cancer as FIGO stage IB2-IVB, and found an increased odds of presenting with late-stage tumors in patients not previously screened for cervical cancer. Additionally, two qualitative studies in Botswana (41, 42) have shown that lack of knowledge regarding the benefits of screening for cervical cancer can delay diagnosis. Our study provides further evidence supporting the finding that screening decreases the odds of presenting with late-stage cervical cancer at diagnosis when implemented in a low resource setting.

Early-stage asymptomatic cervical cancer can be detected through screening, but in the absence of screening, patients with cervical cancer can present with clinical symptoms including abnormal vaginal bleeding and post-coital bleeding (34). Reports of symptomatic bleeding and its association with late-stage disease at diagnosis in low resource settings have been inconsistent in the literature (6, 7, 11, 12). Studies have shown an increased risk (6), no association (7), and a decreased risk (11, 12). In Nepal, a decreased risk for having late-stage cervical cancer at diagnosis was noted if the symptoms of bleeding were reported first to the woman's husband, who might encourage his wife to seek medical care. In Morocco, the decreased association between having late-stage cervical cancer at diagnosis and having symptomatic bleeding was hypothesized to be due to understanding the severity of bleeding as a cervical cancer symptom and seeking medical care without delay. Two studies in Botswana (20, 43) showed that the perception of symptom severity was related to having advanced stage cervical cancer at diagnosis and to a having a delay in health seeking behavior. In our study, reporting gynecological bleeding symptoms, including previous abnormal vaginal bleeding and/or post-coital bleeding, was associated with a two-fold increase in the odds of presenting with late-stage cervical cancer. These results

support increasing awareness regarding abnormal vaginal bleeding and post-coital bleeding as indications of cervical cancer and emphasizing the need to seek medical care as soon as possible. In addition, these findings support screening asymptomatic women to be able to diagnose cervical cancer at an early stage.

In our study, there was no significant difference between WLWH and women without HIV with regard to their likelihood of presenting with advanced state cervical cancer. Some studies have recognized HIV as a risk factor for late-stage cervical cancer at diagnosis (16, 19), yet other studies (6, 44) have reported no association with HIV and late-stage cervical cancer at diagnosis. The role of HIV in the diagnosis of late-stage cervical cancer remains unclear and should be investigated further. When comparing WLWH and women without HIV in our cohort, the WLWH were younger, were more likely to have undergone cervical cancer screening, had more often lived in urban areas, and were more likely to be married or to have been married than women without HIV. Also, in the subgroup analyses, associations with late-stage cervical cancer at diagnosis differed between the two subgroups of WLWH versus women without HIV. Increasing age was significantly associated with late-stage cervical cancer at diagnosis in women without HIV, but not in WLWH. WLWH with a history of cervical cancer screening had lower odds of presenting with late-stage cervical cancer at diagnosis; however cervical cancer screening was not significantly associated with late-stage cervical cancer at diagnosis in women without HIV. In Botswana, cervical cancer screening programs have been implemented as part of the HIV care continuum for women, making it is plausible that women without HIV do not access screening services to the same extent as WLWH. Therefore, increasing screening services among women without HIV could reduce the prevalence of late-stage cervical cancer at diagnosis for these women.

Our study saw a decrease in late-stage cervical cancer cases among women who had been married. Similarly, a study from Nepal (11) noted that married women with symptomatic bleeding were less likely to present with a late-stage cervical cancer because husbands may encourage their wives to seek medical care. A study by Ibrahimi and Pinheiro (2017) in the United States reported that being married was an independent predictor of a more favorable prognosis of cervical cancer (45). While some studies have identified being unmarried as a risk factor for having late-stage cervical cancer at diagnosis (6, 17, 18), other studies have found no such association (15, 16). Reasons for this association are unclear. Future studies investigating differences in financial, emotional, and sociocultural marital structures and the impact on prompt cancer diagnosis are warranted. These inconsistencies could be attributed to differences among the sociocultural marital structures and support systems across countries, which need to be explored further.

Areas of residence may also impact health care. For example, living in a rural area versus living in an urban area has been investigated as a potential contributing factor for women with late-stage cervical cancer at diagnosis (7, 15, 16, 18, 19). A study in Sudan reported that an increased risk for having late-stage cervical cancer at diagnosis was associated with living in a rural setting versus living in an urban setting (15), but this result was not seen in our cohort, nor was any such association reported in other studies in Ghana (7), Florida (18), Ethiopia (19), or SSA (15). The use of traditional healers has been shown to be associated with late-stage cervical cancer at diagnosis in Botswana (20) and as a barrier to cervical cancer care in Uganda (21). In Botswana, over 95% of traditional healers live in rural areas (46), and thus women living in a rural area may be

more likely to consult with traditional healers as their first choice for healthcare. In our study, when examining only women living in a rural area, those who visited a traditional healer had a higher odds of presenting with late-stage cervical cancer. Points of intervention in rural areas could include educating traditional healers to recognize symptoms of cervical cancer in order to facilitate a referral for diagnosis and treatment.

This large study investigating late-stage cervical cancer at diagnosis in Botswana includes detailed demographic and clinical information on patients in Botswana collected over a five-year period, but it does have several potential limitations and challenges. It is important to note that, due to the cross-sectional study design, no decisive conclusions can be made about the temporality or causality among the study variables and late stage diagnosis. Patients were enrolled at PMH, a public tertiary hospital with oncology services, and at GPH, a private tertiary hospital with the only chemo-radiation oncology center in Botswana; thus, all patients who need radiotherapy should be sent to GPH. We were unable to account for patients who were not diagnosed with or treated for cervical cancer outside of these two facilities. In addition, the study collected data at the time of diagnosis and is therefore subject to recall bias, social desirability bias, and potential unmeasured confounding and missing data. Unfortunately, due to the retrospective nature of the study, we lacked important information and were unable to account for confounders including education level, knowledge and awareness of cervical cancer, and cervical cancer screening. To account for any bias due to missing data, we conducted MICE for the primary analysis (35-37). Results using MICE were similar to the complete case analysis. Although our findings represent a large proportion of cervical cancer cases in Botswana, they do not represent all cervical cancer patients in Botswana and are not generalizable to the entire country.

2.6. Conclusion

Our results highlight patient level factors associated with late-stage cervical at diagnosis and indicate potential areas for intervention to mitigate the cervical cancer burden in Botswana. Our findings show that cervical cancer screening for women in Botswana is associated with the early detection of cervical cancer, particularly in women with HIV. Future efforts to include women without HIV and women who have not been married in cervical cancer screening efforts could result in the earlier detection of cervical cancer in these groups. Future early cervical cancer detection efforts should emphasize cancer symptom awareness and early detection through cervical cancer screening, and should also include traditional healers in the cancer care continuum.

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Table 2. 1. Clinical and demographic characteristics of the study population by early- versus late-stage cervical cancer diagnosis

		Study Population		*Early Stage*		*Late Stage*		*P-value***
Variable		N	%	N	%	N	%	
		984	100	501	50.9	440	44.7	
Age category	<30	13	1.3	7	1.4	6	1.4	0.88
	≥30-40	188	19.1	98	19.6	83	18.9	
	≥40-50	369	37.5	191	38.2	159	36.1	
	≥50-60	183	18.6	98	19.6	83	18.9	
	≥60-70	148	15.1	66	13.2	70	15.9	
	≥70	82	8.3	40	8.0	39	8.9	
Residence	Rural	775	79.0	390	78.0	359	81.8	0.15
	Urban	206	21.0	110	22.0	80	18.2	
Marital status	Never married/single	646	65.7	315	63.0	307	69.8	0.08
	Married	226	23.0	124	24.8	89	20.2	
	Divorced	13	1.3	10	2.0	3	0.7	
	Widowed	98	10.0	51	10.2	41	9.3	
Previous cervical cancer screening	Never screened	400	42.6	177	36.8	205	49.2	<0.001*
	Screened	539	57.4	304	63.2	212	50.8	
Visit with a natural/ traditional healer	No	845	89.9	443	90.8	378	88.3	0.22
	Yes	95	10.1	45	9.2	50	11.7	
HIV	Negative	293	30.3	154	31.2	128	29.6	0.59
	Positive	674	69.7	340	68.8	305	70.4	
FIGO stage	I	166	17.6	166	33.1	-	-	--
	II	335	35.6	335	66.9	-	-	
	III	350	37.2	-	-	350	79.5	
	IV	90	9.6	-	-	90	20.5	
Pathology	SCC	835	87.3	422	86.1	384	89.7	0.29
	Adenocarcinoma	66	6.9	41	8.4	22	5.1	
	Invasive ductal	4	0.4	1	0.2	3	0.7	
	Other	40	4.2	20	4.1	15	3.5	
	Unknown/other	12	1.2	6	1.2	4	0.9	
Abnormal vaginal bleeding	Not reported	264	26.8	169	33.7	78	17.7	<0.001*
	Reported	720	73.2	332	66.3	362	82.3	

*p<0.05
**p-value for differences between early stage and late stage

Table 2. 2 Imputed multivariable analysis of factors associated with late-stage cervical cancer

Late Stage at Diagnosis	Adjusted Odds Ratio	95% CI	P-value
Age	1.01	1.00 -1.03	0.067
Urban vs. rural residence	0.78	0.55-1.10	0.153
Never married/single vs. married/widowed/divorced	1.35	1.02-1.86	0.044*
Cervical cancer screening vs. never screened	0.65	0.49-0.85	0.002*
Visit with a natural healer (Yes/No)	1.19	0.77-1.84	0.434
HIV seropositive vs. seronegative	1.37	0.97-1.93	0.077
Abnormal vaginal bleeding (Yes/No)	2.32	1.70-3.16	<0.001*

95% CI: 95% Confidence Interval
*p<0.05

Table 2. 3 Visit with a traditional healer in a rural setting in women with late- versus early-stage cervical cancer

	Early Stage	Late Stage	OR	95% CI	P-value
Visit with a traditional healer	35 (9%)	49 (14%)	1.61	1.02-2.55	0.043*
No visit with a traditional healer	346 (91%)	301 (86%)			

OR: Odds Ratio, 95% CI: 95% Confidence Interval
*p<0.05

Table 2. 4 Clinical and demographic characteristics of the study population by HIV status

Variable	Category	HIV Negative N	HIV Negative %	HIV Positive N	HIV Positive %	p-value
		293	30.3	674	69.7	
Age categories	<30	2	0.7	11	1.6	<0.001*
	≥30-40	23	7.9	165	24.5	
	≥40-50	44	15.1	324	48.1	
	≥50-60	60	20.5	119	17.7	
	≥60-70	98	33.6	47	7.0	
	≥70	65	22.3	8	1.2	
Residence	Rural	250	85.3	511	76.0	<0.001*
	Urban	43	14.7	161	24.0	
Marital status	Never married/single	140	47.8	498	74.0	<0.001*
	Married	91	31.1	132	19.6	
	Divorced	3	1.0	9	1.3	
	Widowed	59	20.1	34	5.1	
Previous cervical cancer screening	Never screened	143	51.6	248	38.2	<0.001*
	Screened	134	48.4	401	61.8	
Visit with a traditional healer	No	250	87.7	599	90.9	0.140
	Yes	35	12.3	60	9.1	
FIGO Stage	I	48	17.0	115	17.8	0.83
	II	106	37.6	225	34.9	
	III	100	35.5	245	38.0	
	IV	28	9.9	60	9.3	
Pathology	SCC	239	83.9	583	88.9	0.022*
	Adenocarcinoma	31	10.9	33	5.0	
	Invasive ductal	1	0.4	3	0.5	
	Other	9	3.2	30	4.6	
	Vascular invasion	0	0	1	0.2	
	Unknown	5	1.8	6	0.9	
Abnormal vaginal bleeding	Not reported	68	23.2	192	28.5	0.089
	Reported	225	76.8	482	71.5	
CD4	<250 cells/mm^3	-	-	117	21.4	--
	≥250 cells/mm^3	-	-	429	78.6	
ART**	No	-	-	25	3.8	--
	Yes	-	-	640	96.2	

*p<0.05
**ART: Anti-retroviral therapy

Table 2. 5 Imputed multivariable subgroup analyses of women living with HIV and women without HIV

Late Stage at Diagnosis	aOR	95% CI	P-value	aOR	95% CI	P-value
	WLWH n=674			Women without HIV n=293		
Age	1.01	0.99-1.02	0.480	1.02	1.00-1.04	0.041*
Urban vs. rural residence	0.79	0.54-1.16	0.234	0.88	0.43-1.81	0.730
Never married/single vs. married/widowed/divorced	1.23	0.85-1.79	0.273	1.59	0.94-2.70	0.087
Cervical cancer screening vs. never screened	0.61	0.44-0.86	0.004*	0.80	0.48-1.35	0.413
Visit with a traditional healer (Ye/No)	0.95	0.55-1.65	0.864	1.52	0.71-3.26	0.276
Abnormal vaginal bleeding (Yes/No)	2.10	1.46-3.01	<0.001*	3.06	1.52-5.71	0.001*
CD4 count <250 vs. ≥250	1.15	0.73-1.79	0.546			
Anti-retroviral treatment (Yes/No)	1.11	0.46-2.65	0.821			

aOR: adjusted odds ratio, 95% CI: 95% Confidence Interval
*p<0.05

CHAPTER 3. Evaluating the geographic distribution of cervical cancer patients referred to a multidisciplinary tumor clinic in Gaborone, Botswana

3.1. Abstract

3.1.1. Background

In Botswana, cervical cancer is the leading cause of cancer death for females. With limited resources, Botswana is challenged to ensure equitable access to advanced cancer care. The capital, Gaborone, houses the only gynecologic oncology multi-disciplinary team (MDT) and the one chemoradiation facility in the country. We aimed to identify areas where fewer women were presenting to the MDT clinic for care.

3.1.2. Methods

This cross-sectional study examined cervical cancer patients presenting to the MDT clinic between January 2015 and March 2020. Patients were geocoded to residential sub-districts to estimate age-standardized presentation rates. Global Moran's I and Anselin Local Moran's I tested the null hypothesis that presentation rates occurred randomly in Botswana. Community- and individual-level factors of patients living in sub-districts identified with higher (HH) and lower (LL) clusters of presentation rates were examined using ordinary least squares with a spatial weights matrix and multivariable logistic regression, respectively, with α level 0.05.

3.1.3. Results

We studied 990 patients aged 22-95 (mean: 50.6). Presentation rates were geographically clustered across the country (p=0.01). Five sub-districts were identified as clusters, 3 HH and 2 LL (mean presentation rate: 35.5 and 11.3, respectively). Presentation rates decreased with increased travel distance (p=0.033). Patients in LL sub-districts more often reported abnormal vaginal bleeding (aOR: 5.62, 95% CI: 1.31-24.15) compared to patients not in LL sub-districts. Patients in HH sub-districts were less likely to be living with HIV (aOR: 0.59; 95% CI: 0.38-0.90) and more likely to present with late-stage cancer (aOR: 1.78; 95%CI: 1.20-2.63) compared to patients not in HH sub-districts.

3.1.4. Conclusions

This study identified geographic clustering of cervical cancer patients presenting for care in Botswana, and highlighted sub-districts with disproportionately lower presentation rates. Identified community- and individual level-factors associated with low presentation rates can inform strategies aimed at improving equitable access to cervical cancer care.

3.2. Introduction

Cervical cancer is a preventable malignancy affecting women worldwide. Mortality from cervical cancer is disproportionately higher in low resource settings (1, 2). In 2020, there were an estimated 604,000 new cervical cancer cases and 342,000 deaths, with the vast majority of deaths occurring in low resource settings, predominantly in sub-Saharan Africa (SSA) (1-3). The majority of cervical cancer deaths in these settings can be attributed to poor access to prevention, screening, and the appropriate treatment (4-7). In Botswana, a upper-middle income country in SSA, cervical cancer is the most commonly diagnosed cancer and leading cause of cancer death for females (8). The population of approximately 2.3 million people currently has over 700,000 women over the age of 20 at risk for developing cervical cancer (9). The majority of cervical cancers are caused by Human Papilloma Viruses (HPV) (10), and co-infection of HPV and Human Immunodeficiency Virus (HIV) further increases cervical cancer risk (11, 12). With the third highest HIV prevalence in the world, cervical cancer prevention, screening, and treatment are a national priority in Botswana (13).

With limited resources, Botswana's cancer control program is challenged to ensure equitable access to advanced health care. A critical factor that affects cancer outcomes is a delay in a diagnosis which can result in the progression of a malignant tumor (14-16). Thus, delayed access to care is important when considering cancer morbidity and mortality. One aspect of access is geographic accessibility. Botswana is a sparsely populated country with only one clinic with a multi-disciplinary team (MDT) for gynecological oncology located in capital city, Gaborone. The MDT clinic includes

Botswana's only gynecological oncologist and the one chemoradiation facility in the country capable of providing standard of care, including staging and treatment, for cervical cancer patients diagnosed with locally advanced disease (17, 18).
Gaborone is located in the southeast corner of the country, over 1000 km away from the furthest residential areas. Geography, therefore, may be a particularly important barrier for accessing care (16). Geographic information systems (GIS), that enable capturing and analyzing spatial and geographic data from a wide range of sources in conjunction with one another, is an efficient and powerful methodical framework to investigate the role of geography and health in a population (19, 20). The use of GIS technology and methods is rapidly evolving. GIS can help identify areas of limited access and help direct resources/planning efforts as well as illuminate factors that contribute to the bigger picture of public health. In low resource settings these methods can contribute to the limited cancer information available (21-23). To our knowledge this is the first study to apply GIS methods to investigate the geographic distribution of cervical cancer patients presenting for care in Botswana.

The World Health Organization's projected incidence of cervical cancer in Botswana for 2020 calculated using the Botswana National Cancer Registry (8) data from 2004-2008 is 374 cases (24). Given one comprehensive MDT clinic where all women diagnosed with locally advanced cervical cancer should be referred to for treatment, we would anticipate over 300 cervical cancer cases to be referred to the MDT clinic per year. However, for the past five years the MDT clinic has averaged less than 200 cases/year (range: 96-256). We hypothesize that due to the lack of equitable access, not all women diagnosed with cervical cancer throughout Botswana are presenting for staging and treatment to the MDT clinic in Gaborone, and thus the rate of patients presenting for

treatment is not random throughout Botswana. We apply GIS to identify areas with high or low presentation rates and highlight areas where suboptimal patterns of care exist. Highlighting areas with low presentation rates and understanding community- and individual-level characteristics associated with living in areas with low presentation rates can inform strategies for more equitable distribution of resources and highlight areas in need of improved access to cancer treatment facilities.

3.3. Methods

3.3.1. Study participants

This cross-sectional study included biopsy proven cervical cancer patients referred to the MDT clinic between January 2015 and March 2020. The MDT clinic, located within Princess Marina Hospital (PMH), coordinates care for all gynecological oncology patients referred to the two tertiary hospitals in Gaborone: PMH and Gaborone Private Hospital (GPH) (18). Eligible patients were over the age of 18, not pregnant, and were not diagnosed with cervical carcinoma in situ or had recurrent disease.

3.3.2. Primary outcome measure

Our primary outcome was measuring the rate of cervical cancer patients presenting to the MDT clinic for staging and/or treatment, henceforth referred to as ‘presentation rate’. To detect areas in Botswana with disproportionately high or low presentation rates, we defined our geographic unit of analysis as administrative sub-districts in Botswana. We used an available shapefile from the USCB (9) that defined the 2nd-

order administrative boundaries for 28 sub-districts throughout the country. The USCB also defines 519 3rd order administrative divisions described as “villages and associated localities” (9). We abstracted each patient’s residential village from the questionnaire and geocoded each patient to one of USCB’s identified 519 villages (9). To calculate the presentation rates, we aggregated cervical cancer patients per village and identified the appropriate administrative sub-district for which the patient lived. The denominator for each sub-district consisted of the total female population for patients 20 years and older from January 2015 to March 2020 (9). We age-standardized the presentation rates using the overall Botswana female age distribution. Presentation rates by sub-district were visually inspected using choropleth maps for geographic variation.

3.3.3. Covariates

Sub-district-level covariates included HIV prevalence, population density, and travel distance to the MDT clinic in Gaborone. The HIV prevalence for each sub-district was obtained from the Botswana AIDS Impact Survey IV (25). Population density, an indicator of urban or rural areas, was calculated using the projected population relative to the polygon area per sub-district using projected estimates and the polygon area from the shapefile from the USCB (9). Euclidian travel distance was measured in Google maps (26) using the centroid of each sub-district to the MDT clinic in Gaborone.

Data collected from the questionnaire administered at first visit to the clinic included patient sociodemographic and clinical factors (age, marital status, residence, history of cervical cancer screening, ever/never visit with a traditional doctor and/or natural healer,

presence of abnormal vaginal bleeding (including post-coital bleeding/bleeding after vaginal intercourse), and HIV status). Additional clinical data was abstracted from medical records for cervical cancer stage at presentation based on the International Federation of Gynecology and Obstetrics (FIGO) staging system (27, 28).

3.3.4. Geographic Analysis

To assess geographic patterns of presentation rates both nationally and locally, we employed Global Moran's I and Anselin local index of spatial autocorrelation statistics, respectively (29, 30). Global Moran's I test was conducted to assess if presentation rates across the country were clustered, dispersed, or random (null hypothesis). A positive spatial autocorrelation result indicates clustering, describing sub-districts with similar presentation rates within close geographic proximity to each other. Negative spatial autocorrelation reveals dispersion, noting sub-districts with dissimilar presentation rates were closer in geographical proximity in a manner that was not random. A null result indicates presentation rates across Botswana is random.

For the geographic analysis we defined neighbors using queen's contiguity matrix (31) and conducted permutation tests with 999 simulations for significance. Using this weights matrix, the Global Moran's I test enables presentation rates of each sub-district to be correlated with the mean presentation rates of neighboring sub-districts (spatial autocorrelation), thereby accounting for spatial dependence in presentation rates between sub-districts.

Moran's I analysis does not detect local patterns of spatial association (29). To investigate local patterns of presentation rates for each sub-district, we employed the local index of spatial autocorrelation (30). This approach determines for each individual (target) sub-district if presentation rates are uniformly similar or disproportionately high or low relative to the mean presentation rates of that sub-district's neighbors, once again defined by Queen's contiguity matrix (31). Permutation tests with 999 simulations were conducted and statistically significant clusters (similar presentation rates) or outliers (dissimilar presentation rates) were identified with 95% confidence intervals. A significant result revealed one of four possible categories for each sub-district, two types of clusters or two types of outliers. A high-high (HH) cluster indicated target sub-districts with high presentation rates were surrounded by neighboring sub-districts with high presentation rates, and conversely low-low (LL) clusters identified target sub-districts with low presentation rates surrounded by neighboring sub-districts with low presentation rates. High-low (HL) or low-high (LH) outliers indicated an inverse relationship between the target sub-district presentation rates and the mean of their neighbor's presentation rates.

3.3.5. Statistical Analysis

Simple ordinary least squares (OLS) regression investigated the relationship of age-standardized presentation rates across the country with sub-district level community factors. If Moran's I identified significant autocorrelation, we accounted for non-independence of presentation rates in our multivariable OLS regression mode using a spatial weights matrix (32) to investigate associations with sub-district level variables (HIV prevalence, population density, and travel distance).

Lastly, we investigated individual-level clinical and demographic characteristics among cervical cancer cases living in a clustered (HH/LL) or outlier (HL/LH) identified sub-district compared to patients living in any other sub-district. Univariate individual level differences were assessed using student t-tests, chi-squared tests, and fishers exact tests as appropriate. Additionally, multivariable logistic regression models determined the magnitude of associations for patients living in identified LL or HH sub-districts versus patients not living in these sub-districts, while adjusting for demographic and clinical characteristics. Adjusted odds ratios and 95% confidence intervals with a cut off α value 0.05 determined significant associations. We performed geospatial analysis in ArcGIS version 10.6.1 (Esri, Redlands, CA) and open source GeoDa software (32), and conducted all Statistical analysis in STATA 16.1 (College Station, TX).

3.3.6 Alternative methods

Alternative methods using village as the unit of analysis was also explored and is described in Appendix A.

3.4. Results

One thousand nineteen cervical cancer patients presented to the MDT clinic between January 2015 and March 2020. Nineteen patients (1.8%) diagnosed with cervical carcinoma in situ and 7 (0.7%) patients with recurrent disease were excluded. Three patients (0.3%) did have village of residence, thus 990 cervical cancer patients were geocoded to one of the 28 sub-districts. Sociodemographic and clinical characteristics are shown in Table 3.1. Cervical cancer patients had a mean age of 50.6 years at time

of presentation (range: 22.4--95.2). The overall presentation rate was 27.2 per 100,000 women (IQR: 12.5-35.0) for our study period. Age-standardized presentation rates by sub-districts are visually presented in a choropleth map (Figure 3.1). Crude and age-standardized presentation rates are presented in Table 3.2.

Positive spatial autocorrelation was observed (Global Moran's I=0.249; p=0.014), identifying positive geographic clustering of cervical cancer rates across the country. Anselin local Moran's I identified specific sub-districts where presentation rates were disproportionately high or low relative to their neighbors. Of the 28 sub-districts, 5 significant clustered (17.8%) HH or LL sub-districts were identified (Figure 3.2). No outliers (HL or LH sub-districts) were found. Two sub-districts were determined as HH clusters: Kgalagadi South and Southern (rate per 100,000 women: 29.8 and 41.2, respectively). Three sub-districts were determined as LL clusters: Ngamiland West, Ngamiland East, and Ghanzi (rate per 100,000 women: 9.5, 13.8, and 10.6 respectively). Community-level factors for HH and LL sub-district clusters are shown in Table 3.3. HH sub-disricts had a mean presentation rate of 35.5 per 100,000 women and LL sub-districts had a mean presentation rate of 11.33 per 100,000 women. Population density was 8.82 per km^2 for HH sub-districts and 1.94 km^2 for LL sub-districts. For HH sub-distritcs, the mean HIV prevalance for females was from 11.45 per 100,000 women and for LL sub-districts 15.27 per 100,000 women.

Results from OLS regression showed a significant association between presentation rates across Botswana with travel distance (coefficient: -0.020, p=0.034) to Gaborone, but no association with population density or HIV prevalence. Using the spatial weights matrix, multivariable OLS found that presentation rates across Botswana increased with

decreased travel distance to Gaborone (adjusted coefficient: -0.026, p=0.033). No significant associations were found for HIV prevalence or population density (Table 3.4). Univariate individual level differences for patients living in an LL sub-district compared to not living in an LL sub-district, and differences for patients living a HH sub-district compared to not living in a HH sub-district, were assessed using student t-tests and chi-squared tests (Table 3.5). Women presenting from LL sub-districts were more commonly HIV positive (p=0.025), and more often reported abnormal vaginal bleeding (p=0.008) than women not presenting from LL sub-districts. Women presenting from HH sub-districts were older (p=0.010), more commonly HIV negative (p<0.001), and more often presented with late stage disease (p=0.009) compared to women not presenting from HH sub-districts.

Additionally, multivariable logistic regression identified individual level factors associated with patients living in sub-districts with disproportionate presentation rates. Patients living in LL sub-districts compared to patients not living in a LL sub-district more often reported experiencing abnormal vaginal bleeding (aOR: 5.88, 95% CI: 1.37-25.23) and were more likely to be HIV positive, though this did not reach statistical significance (aOR: 3.29; 95% CI: 0.97-11.17). Due to the limited number of patients presenting from LL sub-districts these results should be interpreted with caution and considered exploratory. Patients living in HH sub-districts were less likely to be living with HIV relative to those not living in HH districts (aOR: 0.46; 95% CI: 0.27-0.78) and more likely to be diagnosed with late-stage cervical cancer (aOR: 1.85; 95%CI: 1.19-2.87) compared to patients not living in a HH sub-district (Table 3.6).

3.5. Discussion

This study reveals non-random geographic patterns of patients with cervical cancer throughout Botswana presenting to the MDT clinic in Gaborone. We identified specific areas of the country with disproportionately high and low presentation rates, indicating that areas with low presentation rates may have poor access to the one comprehensive care MDT clinic in Botswana, and areas with high presentation rates have better access to the MDT clinic. Patients living in sub-districts with low presentation rates were more likely to present with abnormal vaginal bleeding, and patients living in sub-districts with high presentation rates were more likely to be HIV negative and more likely to present with late stage disease. Identifying community and individual level factors associated with access to comprehensive cervical cancer care gives national health programs insight when developing strategies that target areas and populations being underserved by health facilities. These strategies will be key in preventing and controlling the emerging cervical cancer burden in Botswana.

In the literature, GIS methods have been used to examine local and regional variation of disease and to understand equity of access to care, as significant clustering of diseases may indicate potential inequity in access (33-35). We carried out this study with the theory that geographic differences in presentation rates does not reflect the incidence or prevalence of cervical cancer, but rather differences in patients accessing and presenting for treatment. Co-infection of HIV and HPV increase risk of cervical cancer (11, 12), but our results identified no association between sub-district-level HIV prevalence and presentation rates across the country. This supports the hypothesis

that presentation rates are not likely a reflection of cervical cancer incidence or prevalence, but rather due inequity of access.

The literature has also reported that access to care is an important factor to for cancer survival, particularly in low resource settings (7, 36, 37). As reported by Penchansky and Thomas (38), access is multi-dimensional and consists of availability, accessibility, accommodation, affordability and acceptability. It could be inferred that sub-districts with high presentation rates have greater access than other sub-districts to care. One dimension of access is accessibility, or travel distance to the health center. Accounting for spatial correlation, our results found that greater/shorter travel distance to the MDT clinic in Gaborone was associated with higher/lower presentation rates. Sub-districts in the Southern region of Botswana with closer proximity to Gaborone had increased presentation rates, while sub-districts with low presentation rates were identified in the North West, further away and separated from Gaborone by the Central Kalahari Game Reserve, making travel to Gaborone much more challenging. Our study suggests that travel-distance accessibility to the MDT clinic in Gaborone presents a major barrier to care for cervical cancer patients in specific areas of the country.

Geographic accessibility is one factor impacting access to care, and a more detailed understanding of this and other barriers of access in areas with low presentation rates could inform strategies to increase the number of cervical cancer cases presenting for care. Of note, sub-districts with higher presentation rates were not geographically the closest sub-districts to Gaborone, and Gaborone itself was not an area within a high-high cluster, further signifying that additional dimensions of access besides travel-distance accessibility that are influencing access to care. For example, another barrier

of access is knowledge. Studies have shown that lack of knowledge regarding cervical cancer and cervical cancer screening as an identified barrier for cervical cancer care in Botswana, thus knowledge may differ according to geography (14, 39). Tapela et. al. demonstrated a successful strategy implemented in Botswana at the health-care level led to improved knowledge for primary care providers and reduced health system delays (40). Understanding knowledge gaps in areas with low presentation rates could potentially increase the number of cervical cancer patients presenting for care.

Previous studies in Botswana have shown that the lack of understanding of symptom severity is associated with a delay in seeking care (14, 39). Patients in sub-districts with low rates more often reported abnormal vaginal bleeding, indicating that these patients may not receiving prompt medical attention and are not being referred until later stages when they are symptomatic. It may be beneficial to assess awareness of symptoms in areas with low presentation rates as well as areas with high presentation rates, to understand if there is a difference at the provider or patient level in understanding abnormal vaginal bleeding as a symptom of cervical cancer. These findings also support previous reports to increase awareness, education, and screening for asymptomatic women in order to be able to detect cervical cancer at an earlier stage and improve outcomes (14, 39).

Our study also found that sub-districts with high presentation rates were associated with cervical cancer cases more likely to present at a late-stage. While this may seem counter intuitive, due to the lack of comprehensive screening for asymptomatic women, cases throughout the country are more likely to be diagnosed at a late-stage. Most studies have found for SSA, including Botswana, that more than half of cervical

cancer cases are diagnosed at a late-stage (5, 14, 41). We could hypothesize that for sub-districts with higher access to Gaborone, patients diagnosed at a late-stage when symptoms are present and morbidity is increased, may still be able to present to the MDT clinic for staging and treatment. However, areas with lower access may not be able to present to the MDT clinic for treatment before succumbing to their disease, and could be a reason why less late-stage cancers would be presenting from areas with lower access. While our work does not directly address this inconsistency, future work could investigate the true prevalence of cervical cancer and the influence of morbidity in areas with low presentation rates.

In Botswana, cervical cancer screening and care have been implemented as part of the HIV care continuum (42), and therefore women living with HIV are likely to have increased health visits, more contact with health providers, and increased health literacy. Sub-districts with higher presentation rates, despite having no significant difference in community level HIV prevalence, had more HIV negative women present for treatment. A previous study also speculated that access to care may be differential according to HIV status in Botswana (43). Thus, it is plausible that HIV negative women in sub-districts with lower presentation rates may be limited in terms of cervical cancer awareness, screening, and contact with health care services. Increasing health literacy and other health services among women without HIV, particularly in areas with low presentation rates, could increase the number of patients presenting for cervical cancer care.

Our study, the first to apply GIS to assess patterns of cervical cancer patients presenting for treatment in Gaborone, has limitations. It is important to note that, due to the cross-

sectional study design, no decisive conclusions can be made about the temporality or causality among the individual-level study variables. Also, those not seeking advanced medical care for symptoms of cervical cancer at the MDT clinic would not be captured in this cohort. This potential for selection bias would result in underrepresentation of cervical cancer in our dataset and could vary by geography, travel time and other factors that could have impacted our results. For example, if patients with early-stage disease were being surgically treated for cervical cancer outside of the MDT clinic in areas with low presentation rates, this could bias our results towards the null and reject our hypothesis that less patients are presenting for care from these areas. In addition, community- and individual-level factors, such as poverty, socioeconomic status, education level and employment were not accounted for. These social determinants of health, likely to be geographically dependent, also influence various aspects of access. Future work to investigate these factors could contribute to a better understanding of barriers of access in sub-districts with low presentation rates. Not accounting for these additional confounding or modifying factors could lead to a misinterpretation of our results. For example, if there is less awareness in areas further away from Gaborone, this lack of knowledge could explain the low presentation rates instead of travel-distance. Future work accounting for additional dimensions of access is important to truly understand the barriers in areas with low presentation rates.

Our results reveal areas in Botswana with low presentation rates and where women living with cervical cancer may not be presenting for appropriate cervical cancer care. Our results also hypothesize about community and individual level factors that could be limiting access to health care for areas with low presentation rates. Our results indicated travel-distance is a potential barrier to accessing cervical cancer care. We also identified

additional potential areas for intervention to mitigate the cervical cancer burden at the individual level, including increasing efforts for women without HIV to assess and improve knowledge related to cervical cancer and cervical cancer screening. Future efforts could be increased for awareness campaigns and cervical cancer screening efforts to include women without HIV. Additionally, early cervical cancer detection efforts should also emphasize cancer symptom awareness and education about the steps women should take if they experience these symptoms.

3.6. Conclusion

Botswana carries a heavy burden of cervical cancer, access to adequate treatment is essential to reduce disease and save lives. Improving equitable access to cervical cancer treatment for women living in sub-districts with lower rates of cervical cancer patients presenting for care should be prioritized to help reduce the morbidity and mortality of cervical cancer.

3.7. References

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Table 3.1. Community and individual level characteristics of sub-districts and the study population

Community level factors	N=28	
	Mean	Standard Deviation
Density per km2	290.74	644.09
Travel distance	417.80	320.71
HIV prevalence	17.82	3.89
Individual Level Factors	**N=990**	
	Mean	Range
Age	50.6	22.4-95.2
	Number	Percent
HIV Positive	680	69.9%
HIV Negative	293	30.1%
Married/widowed/divorced	339	34.2%
Never married/single	651	65.8%
Early Stage (stage I/II)	490	53.8%
Late Stage (stage III/IV)	420	46.2%
Cervical cancer screening ever	546	57.7%
Cervical cancer screening never	400	42.3%
Visit with a traditional healer (Yes)	98	10.2%
Visit with a traditional healer (No)	867	89.8%
Abnormal vaginal bleeding (Reported)	720	72.7%
Abnormal vaginal bleeding (Not reported)	270	27.3%

Figure 3. 1. Age- standardized presentation rates per sub-district referred to MDT clinic in Gaborone, Botswana

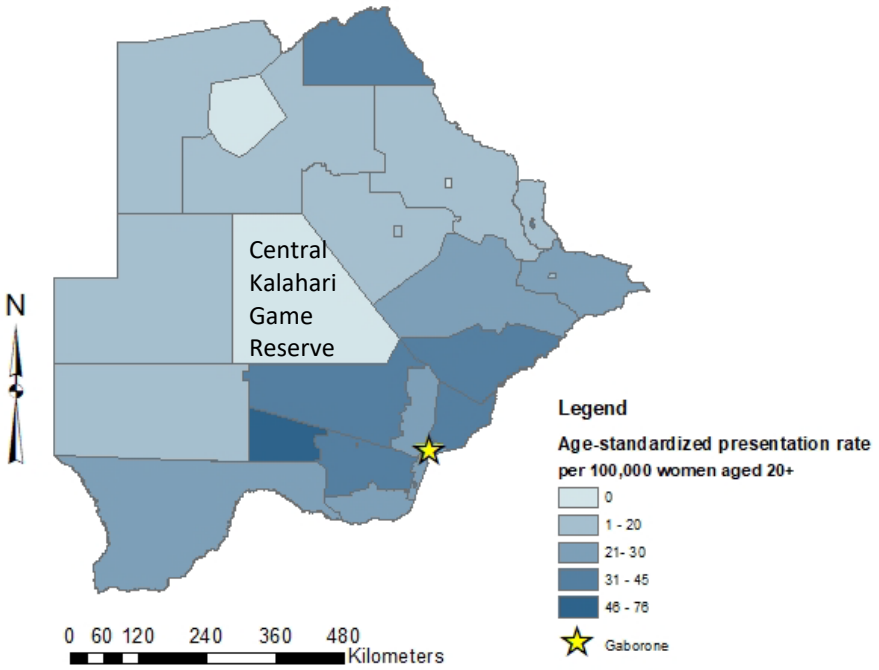

Table 3.2. Crude and age standardized presentation rates per 100,000 women

Sub-district	Total Cases	Population (age 20+)	Crude rate per 100,000	Age-standardized rate per 100,000
CENTRAL KGALAGADI GAME RESERVE	0	138	0	0
NGAMILAND DELTA	0	5,399	0	0
SOWA TOWN	0	5,204	0	0
NGAMILAND WEST	10	96,743	9.30	9.49
GHANZI	7	70,513	9.93	10.62
KGALAGADI NORTH	3	33,166	10.33	9.16
SELIBE PHIKWE	9	76,875	11.71	11.37
TUTUME	39	248,989	15.66	13.51
NGAMILAND EAST	20	154,106	12.98	13.75
NORTH EAST	19	107,059	17.75	16.07
BOTETI	15	91,761	16.35	16.48
ORAPA	2	15,783	12.67	19.56
SOUTH EAST	40	187,109	21.38	22.67
GABORONE	105	391,426	26.83	27.07
SEROWE PALAPYE	95	205,953	31.05	28.07
KWENENG EAST	142	517,133	27.46	29.42
BOBONONG	36	113,269	31.78	29.55
KGALAGADI SOUTH	16	49,078	32.6	29.76
BAROLONG	31	88,936	34.86	30.91
CHOBE	14	45,030	31.09	34.25
JWANENG	6	30,305	19.8	34.5
KWENENG WEST	28	74,313	37.68	35.37
LOBATSE	14	47,665	29.37	35.76
MAHALAPYE	75	187,537	39.99	35.94
KGATLENG	75	172,897	43.38	39.87
SOUTHERN	102	217,937	46.8	41.16
FRANCISTOWN	66	184,808	35.17	45.85
NGWAKETSE WEST	21	23,062	91.06	75.98
TOTAL	990	3,635,573	27.23	27.23

Table 3.3. Community level factors for identified HH and LL sub-districts

Community level factors	HH sub-districts	Standard Deviation	LL Sub-districts	Standard Deviation
Number of sub-districts	3	--	2	--
Number of cases	37	--	118	--
presentation rates (mean)	35.5	7.78	11.33	2.52
Population density per km^2	8.82	11.25	1.94	0.93
Travel distance	341.5	255.27	912.0	274.97
HIV prevalence	11.45	0.49	15.27	1.8

Figure 3. 2. Identified High-High and Low-Low clusters of presentation rates

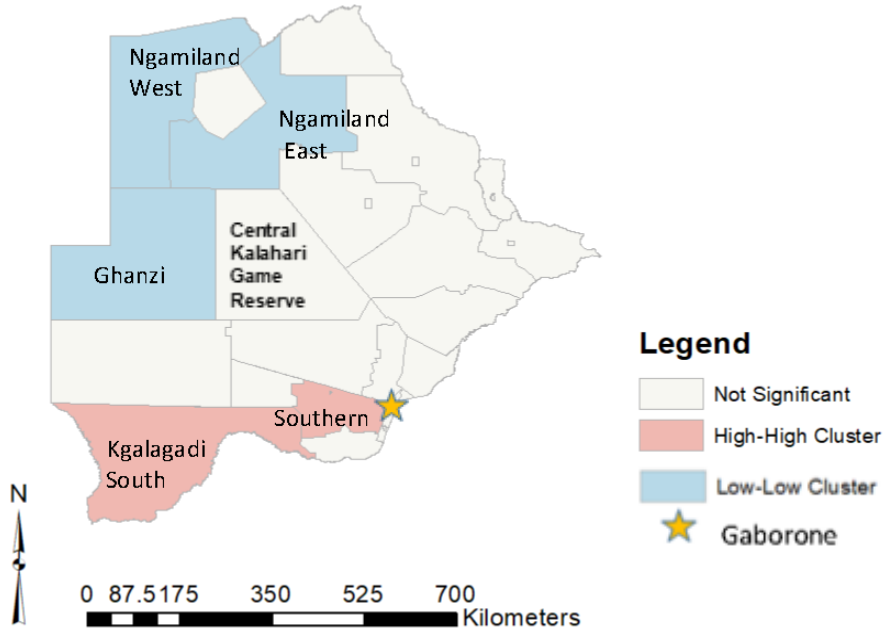

Table 3.4. Results of OLS regression with spatial weights matrix for community level factors

OLS regression	Coef	prop	aCoef*	prop
HIV	0.059	0.940	-0.084	0.912
Density	1.75	0.560	-3.044	0.406
Travel distance	-0.020	0.034	-0.026	0.033

*adjusted coefficients

Table 3. 5. Univariate analysis of Individual level factors for patients presenting from identified HH and LL sub-districts

Individual Level Factors	Patients living in an LL Sub-district	Patients not living in an LL sub-district	p-value	Patients living in an HH sub-district	Patients not living in an HH sub-district	p-value
Sample Size(n)	37	953		118	872	
Age (mean (range))	47.4 (29.0-73.5)	50.7 (22.4-95.2)	0.12	53.4 (31.0-89.4)	50.2 (22.4-95.2)	0.010
	N (%)	N (%)		N (%)	N (%)	
HIV status						
Living with HIV	32 (86.5%)	648 (69.2%)	0.025	64 (55.7%)	616 (71.8%)	<0.001
Living without HIV	5 (13.5%)	288 (30.8%)		51 (44.3%)	242 (28.2%)	
Marital Status						
Married/widowed/divorced	14 (37.8%)	325 (34.1%)	0.640	43 (36.4%)	296 (33.9%)	0.590
Never married/single	23 (62.2%)	628 (65.9%)		75 (63.6%)	576 (66.1%)	
FIGO stage at diagnosis						
Early Stage (stage I/II)	18 (52.9%)	472 (53.9%)	0.910	47 (42.3%)	443 (55.4%)	0.009
Late Stage (stage III/IV)	16 (47.1%)	404 (46.1%)		64 (57.7%)	356 (44.6%)	
Cervical cancer screening						
Ever	21 (61.8%)	525 (57.6%)	0.630	66 (59.5%)	480 (57.5%)	0.690
Never	13 (38.2%)	387 (42.4%)		45 (40.5%)	355 (42.5%)	
Visit with a traditional healer						
Ever	3 (8.3%)	95 (10.2%)	0.710	12 (10.3%)	86 (10.1%)	0.940
Never	33 (91.7%)	834 (89.9%)		104 (89.7%)	760 (89.9%)	
Abnormal vaginal bleeding						
Reported	34 (91.9%)	686 (72.0%)	0.008	89 (75.4%)	631 (72.4%)	0.48
Not reported	3 (8.1%)	267 (28.0%)		29 (24.6%)	241 (27.6%)	

Table 3.6. Multivariable regression for individual level factors associated with patients living in sub-districts with disproportionate rates

	aOR	95% CI	p-value	aOR	95% CI	p-value
	LL sub-districts			HH sub-districts		
Age	1.00	0.96-1.03	0.798	1.00	0.98-1.02	0.956
HIV (Living with vs. without)	3.29	0.97-11.17	0.057	0.46	0.27-0.78	0.004*
Never married/single vs. married/widowed/divorced	0.50	0.23-1.08	0.077	0.98	0.61-1.56	0.918
FIGO stage (stage III/IV vs. I/II)	0.95	0.46-1.99	0.898	1.85	1.19-2.87	0.006*
Cervical cancer screening (Ever vs. never screened)	1.03	0.48-2.21	0.930	1.31	0.84-2.05	0.229
Visit with a traditional healer (Ever/never)	0.88	0.26-2.98	0.832	1.24	0.73-2.12	0.906
Abnormal vaginal bleeding						
Reported vs. Not reported	5.88	1.37-25.23	0.017*	1.24	0.73-2.12	0.422

aOR: adjusted Odds ratio
95% CI: 95% Confidence Interval
*p<0.05

CHAPTER 4. Stage at cervical cancer presentation and distance to MDT clinic in Gaborone for women living with and without HIV infection in Botswana

4.1. Abstract

4.1.1. Background

Cervical cancer is the leading cause of cancer death for women in Botswana. Later stage at presentation and barriers to access are associated with increased cancer mortality in low resource settings. Reduced access to the only gynecological cancer multi-disciplinary team (MDT) clinic from a woman's residence may be associated with later stage of cervical cancer. Additionally, with a high prevalence of women living with HIV in Botswana, HIV status may also be associated with access to care.

4.1.2. Methods

We included cervical cancer cases presenting to the MDT clinic for staging and treatment between 2015 and 2020. Multinomial adjusted logistic regression was used to examine the association of stage at presentation and travel time from residence to the MDT clinic. Multivariable logistic regression was also used to evaluate the association of HIV status and travel time.

4.1.3. Results

We identified 959 cervical cancer patients. Mean age at diagnosis was 50.7 (range: 22-95). The majority of cancers were stage II (35.9%) and stage III (37.7%) at presentation, median travel time to clinic was 124 minutes, and 70.1% were living with HIV.

Increasing travel time was associated with later stage of cervical cancer at presentation. When compared to the reference group of stage I disease and a travel time within one hour to the MDT clinic, the odds of a presenting with stage II were doubled for patients traveling 3-5 hours (OR: 2.00, 95% CI 1.14-3.52) and over two-times greater for patients traveling over 5 hours (OR: 2.19, 95% CI: 1.15-4.19); the odds of stage IV was almost three times greater when traveling 3-5 hours (OR: 2.93, 95% CI 1.26-6.79) and four times greater traveling over 5 hours (OR: 4.05, 95% CI: 1.62-10.10). Logistic regression also found the odds of a patient living with HIV was increased with increasing travel time to the MDT clinic (trend test p-value=0.004).

4.1.4. Conclusions

We found that increasing travel time from residence to the MDT clinic, and living with HIV, were associated with later stage of cervical cancer at presentation. An understanding of interventions to remove distance related barriers to care may help improve early diagnosis and reduce mortality for cervical cancer patients in Botswana.

4.2. Introduction

Cervical cancer is highly preventable and treatable if detected early. In Botswana, cervical cancer is the most common cause of cancer death among women (1, 2) and is an acquired immunodeficiency syndrome (AIDS) -defining malignancy. Botswana has a high human immunodeficiency virus (HIV) prevalence: over 25% of females between 15-49 years live with HIV (3), and almost 70% of women diagnosed with invasive cervical cancer live with HIV (4, 5). Due to advances in HIV care, the population of Botswana is living longer, which has resulted in rising morbidity and mortality from AIDS related cancers including cervical cancer. The Botswana Ministry of Health and Wellness (MOHW) has partnered with the President's Emergency Plan for AIDS Relief (PEPFAR) and The Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO) to curb the cervical cancer disease burden primarily in women living with HIV (WLWH) (6, 7). The MOHW has also adapted the American Society of Clinical Oncology (ASCO) resource limited stratified screening strategies for all its citizens (8, 9). ASCO's secondary prevention for cervical cancer in limited resource settings consists of screening with HPV DNA testing for women 30 to 49 years of age every 10 years, corresponding to two to three times per lifetime (10).

Botswana has a population of approximately 2.3 million and has government funded healthcare, ensuring affordable healthcare for all citizens, including cervical cancer screening and cancer treatment (11). The de-centralized health care system ranges from health posts to referral hospitals (12). Health posts are staffed with a health education assistant, a lay counselor, a nurse and occasionally a midwife or a doctor. Clinics offer mainly primary health care and outpatient services, including offering various modes of

screening or testing for cervical cancer. Hospitals are defined by three tiers: district, primary and referral hospitals. Referral hospitals are the only facilities capable of treating specialized diseases like cancer (13). There is one referral hospital is in Francistown: Nyangabgwe Referral Hospital (NRH), and two referral hospitals located in the capital city of Gaborone: Princess Marina Hospital (PMH) and Gaborone Private Hospital (GPH). In 2015 a multidisciplinary gynecological oncology team (MDT) was formed at PMH to provide comprehensive care for all gynecological cancer patients in Botswana (14). The MDT clinic coordinates care for all cervical cancer patients referred from health facilities around Botswana and has a highly specialized team and equipment, including the only gynecological oncologist in the country and the only chemoradiotherapy facility capable of treating patients with locally invasive cancer (15-17).

With limited resources, it is a challenge for all women in Botswana to have equitable access to specialized cancer care. A critical factor that affects cancer outcomes is cancer stage. Later stage cervical cancers have higher mortality rates (5, 18). Studies in Botswana have shown that access to care can influence stage at diagnosis, as a delay in presentation can result in progression of a malignant tumor to a late stage (19-21). One aspect of access to care, accessibility, which can be measured in travel-time, has been associated with a delay in cancer presentation and subsequently late-stage outcomes (22, 23). Travel time and its impact on stage of cervical cancer patients presenting for treatment and care in Botswana has yet to be explored.

This study aimed to describe the travel burden for patients with cervical cancer presenting to the comprehensive MDT cancer clinic in Gaborone. We examine stage of cervical cancer at presentation as influenced by travel time from the patient's residence to the MDT clinic. We hypothesized that patients with a greater travel time from their residential village to the MDT clinic in Gaborone, would be more likely to present with

late-stage disease than patients with shorter travel time to the MDT clinic. We also examine HIV status among patients according to their travel time to health care facilities. We hypothesized that HIV status may influence inequity in accessing cervical cancer care, in that WLWH would be more likely to present for care from more remote villages than patients without HIV.

4.3. Methods

4.3.1. Study population

This study, describe previously, included cervical cancer patients presenting to the MDT clinic for cervical cancer staging and treatment in the capital city of Gaborone between January 2015 and March 2020(14, 24). Eligible patients were over the age of 18, not pregnant, and were not diagnosed with cervical carcinoma in situ or had recurrent disease.

4.3.2. Abstracted data

4.3.2.1. Geographic data

The residential village for each patient was abstracted from the questionnaire administered at the initial consult visit at the MDT clinic. Using the United States Census Bureau's (USCB) geographic shapefile that included 519 village polygons in Botswana (25), patients were linked to their respective village and geocoded using ARCGIS to the geographic centroid of their village. Latitude and longitude coordinates for each village

centroid were obtained from the ARCGIS geography feature(26). We also abstracted the facility patients reported being referred from and geocoded these facilities using the latitude and longitude coordinates from the Botswana health facilities list provided Maina et al. (2). PMH coordinates were used for the MDT clinic.

We also calculated rates of presentation (henceforth referred to as 'presentation rates') of cervical cancer cases for each village. We defined presentation rates for each village as the number of patients with cervical cancer presenting to the MDT clinic from each village (as the numerator) divided by the total number of women village at risk for each village abstracted from the US census average annual population projection for females 20 years and older (25) (as the denominator).

The main metric of access, geographic proximity of village of residence to the MDT clinic, was measured using travel time. In google maps (27) using the geographic coordinates of the village centroid as the starting point, we imputed the travel time in minutes to the MDT clinic at PMH in Gaborone for each patient (28). Travel time was calculated using road networks and travel routes as available in google maps.

4.3.2.2. Travel time from village to MDT clinic

Travel time to the MDT clinic in Gaborone was measured in minutes and categorized in hours. Using the mean travel time of approximately 3 hours as the midpoint, we characterized travel time into four categories: < 1 hour (11-59 minutes), 1-3 hours (60-179 minutes), 3-5 hours (180-299 minutes), 5+ hours (>300 minutes). Travel time was mapped and displayed using a choropleth map using ARCGIS (26). We additionally

measured the travel burden using 1) straight line Euclidian distance using ARCGIS (26) and 2) driving distance in kilometers from google maps (28).

4.3.2.3. Clinical Outcomes

The primary outcome of interest was stage of cervical cancer at presentation based on the International Federation of Gynecology and Obstetrics (FIGO) staging system (18, 29), and was categorized as stage I (IA, IA1, IA2, IB, IB1, IB2, IB3), stage II (IIA, IIB), stage III (IIIA, IIIB, IIIC), and stage IV (IVA, IVB). Current standard of care for patients with locally advanced cervical cancer (stages IB2 -IVA) is definitive chemoradiotherapy (18, 30).

Secondary outcome of HIV status was dichotomized to WLWH and women without HIV based on clinical abstraction of the patient's medical records at the time of the initial MDT clinic visit.

4.3.2.4. Social-demographic and clinical variables

Data were abstracted from questionnaires administered during the initial consult visit and from medical records. Data collected at the time of cancer presentation included patient sociodemographic and clinical factors (i.e., address (village), age, marital status, place of residence, history of cervical cancer screening, ever/never visit with a traditional doctor and/or natural healer, presence of abnormal vaginal bleeding (including post-coital bleeding/bleeding after vaginal intercourse), and HIV status). We also collected type of referral facility as reported in the questionnaire (health post, clinic, or hospital) (2).

Residence was characterized as urban or rural based on the village of the patient's geo-coded residence (11).

We also obtained the female HIV prevalence for each village using the estimates provided for the sub-district for each village in the Botswana AIDS Impact Survey IV((31).

4.3.3. Statistical Analysis

Descriptive statistics are presented for the entire study sample. We also examined variables of interest by travel time from village residence to the MDT clinic using Pearson's chi-squares test for categorical variables, student t-tests and ANOVA for continuous variables as appropriate. Variables of interest were determined a priori based on availability, purposeful selection, review of the literature, and clinical relevance. The explanatory variable of interest was travel time from village residence to the MDT clinic in Gaborone.

We used multinomial (polytomous) logistic regression to estimate the odds ratios for each stage of cervical cancer at presentation (stage II, III, and IV) compared with the reference stage, stage I, by travel time to MDT clinic. We ran univariate and multivariable regression models adjusted for potential confounders as previously described (24). Variables included age, marital status, history of cervical cancer screening, ever/never visit with a traditional healer, presence of abnormal vaginal bleeding, and urban versus rural residence. We also investigated the interaction of travel time with HIV status with respect to stage at presentation.

Logistic regression models, both unadjusted and adjusted for a priori selected variables: age, marital status, history of cervical cancer screening, ever/never visit with a traditional healer, urban versus rural residence, and presence of abnormal vaginal bleeding, were used to assess any association of living with HIV and different levels of access defined by travel time categories to clinical care at the MDT clinic.

All statistical analyses were conducted using STATA 16. Odds ratios (OR) and 95% confidence intervals (CIs) were reported. All tests were two-sided and p-values <0.05 were considered statistically significant.

4.3.1.5. Sensitivity Analysis

Our main analysis was a complete case analysis, but we also conducted a sensitivity analysis to account for missing data in our confounding variables. We used multiple imputation with chained equations (MICE) assuming data were missing at random (32-34) and conducted separate logistic regression models to compare each stage (stage II-IV) separately to stage I. Amounts of missingness were assessed and were mostly minimal except for health facility referred from (health post, clinic or hospital) which had over 20% missing data. Health facility was not included in the main complete case analysis, but we imputed health facility in the MICE analysis to allow us to assess any potential confounding effect of health facility.

4.4. Results

4.4.1. Patient Characteristics

Between January 2015 and March 2020, 1,019 patients presented to the MDT clinic with cervical cancer. Nineteen patients (1.8%) were diagnosed with cervical carcinoma in situ and 7 (0.7%) patients with recurrent disease were excluded. Thirty-four patients (3.3%) were missing village of residence. Sociodemographic and clinical characteristics of the 959 eligible patients are shown in Table 4.1. Almost eighteen percent (n=157) of patients presented with stage I cervical cancer, 35.9% (n=316) with stage II, 37.7% (n=332) with stage III and 8.6% (n=76) with stage IV. Locally invasive cervical cancer is defined by cancer confined to the cervix and is FIGO stage IB2 or later; 88.6% (n=832) patients had stage IB2 or later. Our sample included 70.1% (n=660) of WLWH with mean age at presentation of 50.7 years (range: 22.4-95.2). The majority of patients 65.5% (n=628) had never been married, 57.6% (n= 530) reported previous cervical cancer screening, abnormal vaginal bleeding was reported in 72.7% (n=697) of patients, 10.3% (n=96) reported ever having a visited with a traditional healer and 21.7% (n=208) lived in urban areas. Median travel time from their residence to the MDT was 124.0 minutes (IQR: 54.0-280.0) and median distance was 134.4 km (IQR: 52.8-392.9). Over half of the patients (53.8%; n=516) were referred from a clinic, 17.2% (n=165) from a health post, and 11.3% (n=108) from a hospital. Almost 18% percent (n=170) of patients did not report having been referred from a health facility.

4.4.2. Patient characteristics by travel time from village of residence to MDT clinic

Patient characteristics by travel time from village of residence to MDT clinic are presented in Table 4.2. Travel time to MDT clinic throughout Botswana is visually

presented in Figure 1. Thirty two percent of cervical cancer patients (n=309) traveled less than one hour from their village of residence to the MDT clinic, 25.5% (n=245) traveled 1-3 hours, 25.3% (n=243) traveled 3-5 hours, and 16.9% (n=162) traveled more than 5 hours. Across these groups, patients differed in stage at presentation (p=0.016), HIV status (p<0.001), age (p=0.012), urban residence (p<0.001), and type of referral facility visited (p<0.001).

4.4.3. Presentation rates by travel time from village of residence to MDT clinic

Presentation rates for cervical cancer patients (the number of patients presenting for treatment out of the number of women in the village at risk) for each travel time category are shown in Figure 4.2. Rates of cervical cancer cases presenting to the MDT clinic declined with increasing time to clinic. Rates were the highest for patients traveling 1-3 hours to the MDT clinic (39.1 per 100,000 women) and lowest for patients traveling more than five hours (17.5 per 100,000).

4.4.4. Association of travel time from village to MDT clinic and cervical cancer stage at presentation

The odds of presenting with a later stage cancer increased with travel time to MDT clinic from village of residence (Table 4.3). In the multinomial regression model, the odds of presenting with stage II versus stage I cancer were doubled (OR: 2.01, 95% CI 1.14-3.52) for patients traveling 3-5 hours and more than two-fold when traveling over five hours (OR: 2.18, 95% CI: 1.10-4.31) compared to traveling less than one hour. Also, there was a significant trend for increasing odds of stage II versus stage I with increased

travel time (p<0.001). For stage III cancers versus stage I, there were no significant associations by travel time. The odds of presenting with stage IV cancer versus stage I cancer was almost three times greater when traveling 3-5 hours (OR: 2.97, 95% CI 1.28-6.90) and increased four-fold for patients traveling over five hours (OR: 4.26, 95% CI: 1.61-11.30) compared to traveling less than one hour (trend test p<0.001). We did not find a significant interaction between travel time and HIV status with respect to stage at diagnosis (p=0.155).

4.4.5. Proportion of cervical cancer cases by HIV status presenting to the MDT clinic

The proportion of cervical cancer cases by HIV status presenting to the MDT clinic differed with increasing travel time to MDT clinic (Figure 4.3). Proportion of WLWH was the lowest for patients traveling 1-3 hours to the MDT clinic (59.8%) and highest for patients traveling more than five hours (78.6%). The average HIV female prevalence for each village using the estimates provided in the Botswana AIDS Impact Survey IV((31) was analogous across all time categories (range: 19.7-21.1).

4.4.6. Association of travel time to MDT clinic and HIV status

A significant trend was observed in the adjusted analysis showing increasing odds of living with HIV for patients with increasing travel times to the MDT clinic (p=0.002) (Table 4). Patients living over five hours away were twice as likely to be WLWH as patients traveling <1 hour (aOR: 2.03, 95% CI: 1.10-3.75).

4.4.7. Sensitivity analysis

Results for the MICE analysis for the main model were similar in magnitude and

direction to what is presented in the main analysis. For the MICE analysis including referral facility type, the results were similar and magnitude and direction, thus imputing referral facility did not alter the results.

4.5. Discussion

This study delineates the travel time for cervical cancer patients from their village of residence to the comprehensive MDT cancer clinic at PMH in Gaborone, Botswana. Approximately 50% of patients traveled over 3 hours and more than 200 km to the MDT clinic. We found that patients had an increased odds of presenting with later stage disease with increased travel time. We also found that the presentation rates differed according travel times, with the highest presentation rate for patients traveling 1-3 hours to the MDT clinic and lowest for patients traveling more than five hours. Given that we observed only very slight differences in underlying female HIV prevalence among different travel times categories supports the inference that the difference in presentation rates may not be due to biology or incidence but due to access, as patients who develop cervical cancer may not be presenting for staging and care. Travel time was also associated with a patient's HIV status. Patients with greater travel time to the MDT clinic were more likely to be living with HIV, suggesting that HIV status may increase the likelihood of presenting for cervical cancer care.

4.5.1. Association of travel time to MDT and late-stage cervical cancer

Many studies in high income countries and in LMICs have found an increased travel burden to be a risk factor for poor health outcomes, including late stage at cancer

presentation (22, 23, 35). The literature has reported access to care as an important factor for cancer survival, including in LMICs (36-38). Two studies in sub-Saharan Africa (SSA) showed that greater distance to diagnostic/treatment facility was associated with an increased odds of late-stage breast cancer (23, 35). A systematic review of over 108 studies investigating the effect of distance and health outcomes reported that most studies (77%) reported further distances having poorer health outcomes (eg, lower survival rates), a few (6%) found further distances to be associated with improved health outcomes, and some (17%) found no relationship between distance and outcomes (22), though the studies of null findings could be underestimated due to lack of reporting non-significant results. Our study found that increased travel time to the MDT clinic increased the odds of presenting with poorer outcomes defined here as later stages of cervical cancer.

Later stage at presentation is likely a result of multiple patient level and health system delays that are exacerbated at further distances. Travel time is one aspect of access to care, but multiple factors impact access. As noted by Penchansky and Thomas(39), access is multi-dimensional and consists of availability, accessibility, accommodation, affordability, and acceptability. Availability depends on adequate services and health care providers for the patient population it is servicing. Accessibility is measured in travel time and distance (as we did), but type of transportation and costs related to transportation also need to be considered. Accommodation describes the ability to see patients when they need to be seen, as well as communication between health care providers and patients. Affordability involves the financial burden as well as the individual's perception of the costs being justifiable and necessary. Acceptability takes into account attitudes, knowledge, awareness and beliefs about personal and practice

characteristics of the providers and services, as well as the providers' perception of the service as it relates to the patient(39). Living further away from comprehensive cancer care in a resource limited setting is vulnerable to all of these aspects of access.

A recent review of 15 studies in LMICs(40) reported that lack of knowledge related to cervical cancer and cervical cancer screening to be the most prevalent barrier to cervical cancer screening. Awareness and understanding of the importance and benefits for screening for cervical cancer are imperative to improve cervical cancer outcomes. Two studies in Botswana (41, 42) reported that the lack of understanding of risk factors for cervical cancer and lack of understanding the importance and benefits of cervical cancer screening were barriers to accessing cervical cancer screening. Zapka and Taplin et al (43) note in their Quality in the Continuum of Cancer Care framework 'failure to identify the need to screen and counsel' as the first potential failure during the processes of cancer care. This could be particularly true for women living further away from treatment facilities in more rural and remote areas of the country. In these areas, women and health care providers may be unaware of the need to screen for cervical cancer and may lack knowledge regarding the symptoms related to cervical cancer. These burdens for areas further away, together with the cost and feasibility of travel, are all likely contributing to barriers in access and more advanced stage disease at presentation. Future work should stress the importance of provider and patient education to address some of these barriers so that people who are at a distance are more willing to assume the cost/time of travel to a specialty care center.

4.5.2. Presentation rates of cervical cancer patients presenting to MDT

We also noted that the rate of cervical cancer patients presenting to the MDT clinic differed by travel times across the country. Areas where rates are lower could indicate that not all cervical cancer patients are presenting for appropriate care and treatment. Rates of women presenting for care were not linear in relation to travel time. Rates were the highest 1-3 hours from Gaborone. Rates were lower within a travel time of one hour and a travel time of more than five hours to the MDT clinic. These differences in rates area likely a reflection of several inadequate aspects related to access. Urban areas like Gaborone are less susceptible to distance delays, but urban areas tend to have lower socioeconomic status (SES) which has been linked to poorer health outcomes and decreased survival for cancer (44). However, with lower income populations in urban areas, the travel cost (i.e., public transportation), the burden of childcare, and lost wages due to missing work are just some of the additional factors that can contribute to the inability to access care. In densely populated urban areas there can also be low availability, particularly a disproportionate supply and demand for health services which can contribute to less patients presenting for care.

Areas beyond five hours away with low rates are also likely impacted by multilevel barriers to access including availability and accessibility to health services, as mentioned above. In Botswana, Gaborone and Francistown are considered the two main urban areas while the rest of the country is sparsely populated and largely rural. Further distances tend to be even more remote with population density of less than 1 person per km2. As described by Iyer et al (45), population density is inversely associated travel time in four SSA countries. Additionally, studies in SSA have noted more advanced disease in rural patients compared to urban patients (46, 47). In Botswana, remote, rural areas over 5 hours away from Gaborone may have less cervical cancer awareness

campaigns, less cancer related services, and fewer providers capable of providing care for cancer patients. These burdens, together with the cost and feasibility of travel, all contribute to fewer patients presenting for care and delays in access contributing to more late-stage disease at presentation.

4.5.3. Travel time and HIV status

Our results also show that the proportion of patients living with HIV increased with increasing distance from the MDT clinic. Given that the prevalence of WLWH was quite similar by travel time categories(31), we wouldn't expect that risk factors for HPV/HIV infection to differ drastically across locations, and therefore we do not expect the differences in rates to be driven by underlying risk differences or difference in incidence. Instead, our results may give us insight into the influence HIV status may have when presenting for care. In the wake of the HIV epidemic, several steps have been taken to prioritize cervical cancer prevention, particularly in WLWH, who are 4-6 times more likely to develop cervical cancer than women without HIV (48). Collaborating with the President's Emergency Plan for AIDS Relief (PEPFAR) (19), the MOHW established national cervical cancer prevention services (17). Understanding that these programs have been initiated targeting high-risk WLWH, women without HIV may have different experiences with cervical cancer screening. These differences could include individual level factors such as awareness of the benefits or the availability of cervical cancer screening, as well as health system level effects, where providers recognize cervical cancer screening as beneficial for high risk WLWH but not in women without HIV. Additionally, over 80% of people living with HIV in Botswana are on anti-retroviral therapy as appropriate (31), and thus have regular contact with healthcare providers and

facilities. This increased interaction could provide WLWH with more educational resources and more opportunities to test or screen for cervical cancer than women without HIV (49). Thus, women without HIV likely have decreased awareness, knowledge, resources, and opportunities regarding cervical cancer and cancer screening and may not be referred to diagnostic/treatment facilities in Gaborone to the same extent as WLWH. This phenomenon was also hypothesized in a previous study in Botswana investigating delays in cancer care (49). Thus, without appropriate awareness and knowledge, women and health care providers may fail to identify the need to screen and treat all women at risk for cervical cancer. This could be particularly challenging for patients without HIV and living further away from treatment facilities, and a hypothesis supported by our findings of less patients without HIV from further distances presenting to the MDT clinic.

4.5.4. Strengths and weaknesses

This study investigating later stage of cervical cancer at presentation to an MDT clinic in Botswana includes almost one thousand cervical cancer patients, but it does have several potential limitations and challenges. Due to the cross-sectional study design, no conclusions can be made about causality of the study variables on late stage at presentation. Here we are using travel-time to generate hypothesis aimed at understanding geographic differences in late-stage diagnosis. Caniglia et al (50) described methodological challenges when using distance to care as an exposure for health outcomes and identified selection bias as an influencing factor affecting the relationship. While our study is vulnerable to selection bias, the degree of selection bias in our study cannot be accurately quantified due to the lack of a reliable population

based cancer registry indicating the known incidence and/or prevalence of cervical cancer (1). While we were unable to account for patients who did not present to the MDT clinic, our results do give us valuable insight into differences between those presenting and not presenting for treatment, specifically selection bias by travel time and HIV status. There is also the possibility of selection bias by disease stage, as some cervical cancers, particularly stages earlier than locally advanced disease (stage< IB2), may be treated with surgical procedures outside of Gaborone or even outside of Botswana and not get referred for further treatment. For example, cervical cancer patients living closer to Francistown may present to the tertiary hospital NRH. Early-stage patients presenting to NRH may be treated with surgery and/or chemotherapy, and thus our results would have an underrepresentation of cervical cancers in this area. Additionally, if a radiotherapy facility is not needed for treatment with curable intent for patients with stage IV disease, these patients may also not be referred to Gaborone. However, all patients with locally advanced invasive disease (stage IB2-IVA) should be referred to MDT for appropriate standard of care treatment with radiotherapy. Of note, our sample did include 65 patients from Francistown, 12.3% presenting with earlier than stage IB2 disease. This is consistent with the overall presenting rate earlier than stage IB2 in our sample (11.4%). Our results showed that the proportion of cancers with stages less than locally advanced disease did not significantly differ across the travel time categories, suggesting that our findings are unlikely to be fully explained by selection bias. Though selection bias is a potential issue in estimating associations of exposures with cervical cancer outcomes in this study, identifying potential selection bias in this study is an important finding in itself, as it can help identify women that are not being “selected” or presenting for the appropriate cervical cancer treatment in Botswana.

To account for bias in our study due to missing data, we conducted MICE for sensitivity analysis (32-34). Results using MICE were similar to the complete case analysis. In addition, the study collected data at the time of presentation and is therefore subject to recall bias, social desirability bias, and potential unmeasured confounding. Caniglia et al (50) also described unmeasured confounding as a potential bias for studies investigating distance to care. Unfortunately, due to the retrospective nature of the study, we lacked important information and were unable to account for confounders including socioeconomic status, education level, knowledge, and awareness of cervical cancer and cervical cancer screening, although we were able to account urban and rural status which could be a proxy for some of these factors. Lastly, it is possible that there is some degree of misclassification of the travel time designation due to the centroid of the village being used and not a specific address. However, we don't expect this as a major source of bias as choosing the centroid of the village is a more systematic way to determine a location than any random point in the village and we would not expect this bias to be differential in any way.

As mentioned, this study examined only on metric of access, travel time, it will be important for future studies to investigate additional aspects of access. Untangling differences in awareness, knowledge, screening, and health systems factors along the cervical cancer care continuum will offer insight into areas where future interventions would be most effective and beneficial.

4.5.4. Conclusion

Increasing travel time is associated with later stage cervical cancer at presentation to the MDT clinic for treatment. Additionally, the proportion of WLWH also increases with increasing travel time to the MDT clinic, suggesting that HIV status may be influencing inequity in presenting for cervical cancer care. This study highlights the importance of investigating barriers to accessing advanced cancer care and identifying modifiable factors that influence inequitable access to appropriate treatment to improve cervical cancer outcomes for all women in Botswana.

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Table 4.1. Characteristics of the study population

CHARACTERISTICS	CATEGORIES	TOTAL
TOTAL		N=959
STAGE OF CERVICAL CANCER	I	157 (17.8%)
	II	316 (35.9%)
	III	332 (37.7%)
	IV	76 (8.6%)
LOCALLY ADVANCED CERVICAL CANCER	< Stage IB2	107 (11.4%)
	≥ Stage IB2	832 (88.6%)
HIV STATUS	Women without HIV	282 (29.9%)
	WLWH*	660 (70.1%)
AGE IN YEARS	mean (range)	50.7 (22.4-95.2)
YEAR PRESENTED AT MDT	2015	95 (9.9%)
	2016	169 (17.6%)
	2017	240 (25.0%)
	2018	199 (22.3%)
	2019	218 (22.0%)
	2020	42 (4.4%)
MARITAL STATUS	Ever married	331 (34.5%)
	Never married	628 (65.5%)
EVER CERVICAL CANCER SCREENING/TESTING	Never	390 (42.4%)
	Ever	530 (57.6%)
REPORT OF ABNORMAL VAGINAL BLEEDING	Not reported	262 (27.3%)
	Reported	697 (72.7%)
EVER VISIT WITH A TRADITIONAL HEALER	Never	839 (89.7%)
	Ever	96 (10.3%)
URBAN/RURAL RESIDENCE	Rural	750 (78.3%)
	Urban	208 (21.7%)
TRAVEL TIME TO MDT IN MINUTES	median (IQR)	124.0 (54.1-280.0)
TRAVEL DISTANCE TO MDT IN KILOMETERS	median (IQR)	2.4 (65.4-443.8)
REFERRAL FACILITY	Clinic	516 (53.8%)
	Health Post	165 (17.2%)
	Hospital	108 (11.3%)
	Unknown	170 (17.7%)

*WLWH: women living with HIV

Figure 4. 1. Distribution of travel time from the MDT clinic in Gaborone

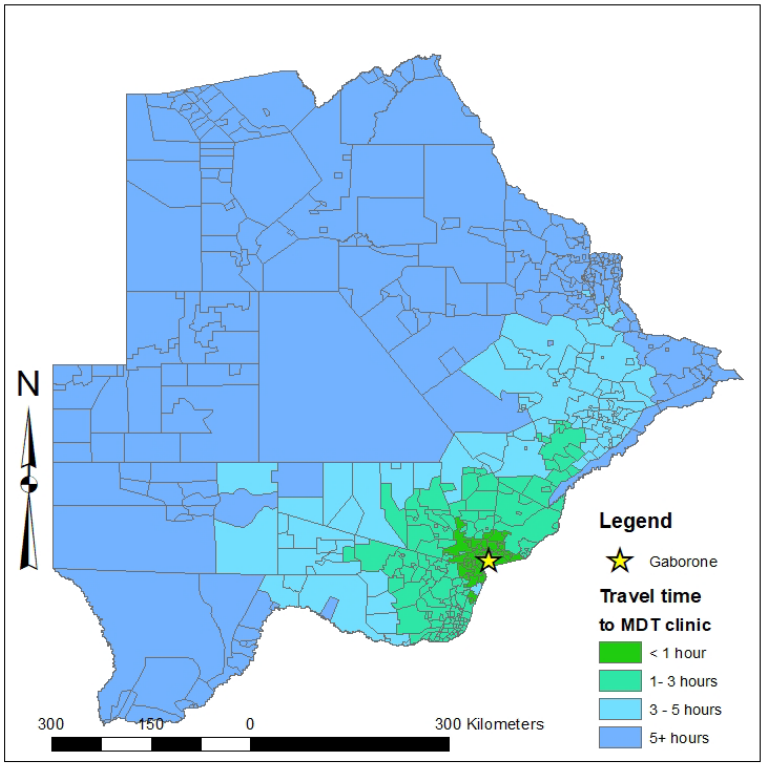


Table 4.2. Characteristics of the study population by travel time

		< 1 HOUR	1-3 HOURS	3-5 HOURS	5+ HOURS	p-value
TOTAL		N=309	N=245	N=243	N=162	
STAGE OF CERVICAL CANCER	I	60 (21.3%)	48 (20.8%)	31 (14.4%)	18 (11.8%)	0.016
	II	96 (34.0%)	71 (30.7%)	88 (40.7%)	61 (40.1%)	
	III	111 (39.4%)	93 (40.3%)	72 (33.3%)	56 (36.8%)	
	IV	15 (5.3%)	19 (8.2%)	25 (11.6%)	17 (11.2%)	
LOCALLY ADVANCED CERVICAL CANCER	< Stage IB2	35 (11.6%)	36 (17.9%)	21 (8.9%)	15 (9.4%)	0.170
	≥ Stage IB2	267 (88.4%)	206 (85.1%)	214 (91.1%)	145 (90.6%)	
HIV STATUS	Women without HIV	84 (27.9%)	97 (40.2%)	67 (27.8%)	34 (21.4%)	<0.001
	WLWH*	217 (72.1%)	144 (59.8%)	174 (72.2%)	125 (78.6%)	
AGE IN YEARS	mean (range)	50.0 (27.5-84.4)	52.9 (27.7-86.8)	49.8 (22.4-95.2)	50.2 (22.6-81.2)	0.020
MARITAL STATUS	Ever married	106 (34.3%)	84 (34.3%)	85 (35.0%)	56 (34.6%)	1.00
	Never married	203 (65.7%)	161 (65.7%)	158 (65.0%)	106 (65.4%)	
CERVICAL CANCER SCREENING/TESTING	Never	131 (43.7%)	103 (43.6%)	96 (41.6%)	60 (39.2%)	0.79
	Ever	169 (56.3%)	133 (56.4%)	135 (58.4%)	93 (60.8%)	
ABNORMAL VAGINAL BLEEDING	Not reported	84 (27.2%)	72 (29.4%)	65 (26.7%)	41 (25.3%)	0.83
	Reported	225 (72.8%)	173 (70.6%)	178 (73.3%)	121 (74.7%)	
VISIT WITH A TRADITIONAL HEALER	Never	273 (89.5%)	208 (86.7%)	209 (90.5%)	149 (93.7%)	0.15
	Ever	32 (10.5%)	32 (13.3%)	22 (9.5%)	10 (6.3%)	
URBAN/RURAL RESIDENCE	Rural	190 (61.7%)	235 (95.9%)	164 (67.5%)	161 (99.4%)	<0.001
	Urban	118 (38.3%)	10 (4.1%)	79 (32.5%)	1 (0.6%)	
TRAVEL TIME TO MDT IN MINUTES	median (IQR)	39.1 (11.9-54.1)	98.3 (87.0-124.9)	252.6 (219.1-298.7)	389.7 (348.2-560.8)	<0.001
TRAVEL DISTANCE TO MDT IN KILOMETERS	median (IQR)	35.6 (8.2-52.8)	106.4 (90.5-151.1)	375.5 (296.5-439.7)	532.3 (485.8-842.8)	<0.001
REFERRAL FACILITY	Clinic	176 (57.0%)	134 (54.7%)	148 (60.9%)	58 (35.8%)	<0.001
	Health Post	43 (13.9%)	45 (18.4%)	35 (14.4%)	42 (25.9%)	
	Hospital	41 (13.3%)	18 (7.3%)	24 (9.9%)	25 (15.4%)	
	Unknown	49 (15.9%)	48 (19.6%)	36 (14.8%)	37 (22.8%)	

Figure 4. 2. Cervical cancer rates per 100,000 among women age 20+ presenting to the MDT clinic

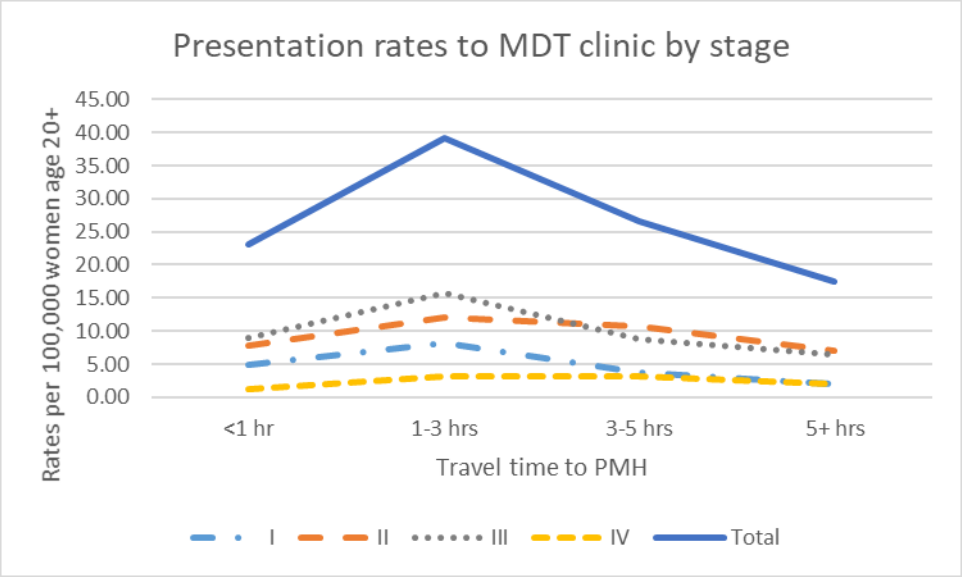


Table 4. 3. Multinomial logistic regression for travel time and stage at presentation

	cOR*	95% CI	p-value	cOR**	95% CI	p-value
	unadjusted			adjusted		
STAGE I	ref			ref		
STAGE II						
<1 HR	ref			ref		
1-3 HRS	0.92	0.57-1.51	0.752	0.93	0.54-1.62	0.805
3-5 HRS	1.77	1.05-2.99	0.031	2.00.	1.14-3.52	0.015
5+ HRS	2.12	1.14-3.92	0.017	2.18	1.10-4.31	0.025
	test for trend		0.002	test for trend		0.002
STAGE III						
<1 HR	ref			ref		
1-3 HRS	1.05	0.66-1.67	0.847	1.07	0.62-1.86	0.804
3-5 HRS	1.26	0.74-2.12	0.396	1.51	0.84-2.71	0.165
5+ HRS	1.68	0.91-3.12	0.099	1.72	0.86-3.46	0.127
	test for trend		0.076	test for trend		0.056
STAGE IV						
<1 HR	ref			ref		
1-3 HRS	1.58	0.73-3.44	0.246	1.33	0.55-3.25	0.528
3-5 HRS	3.23	1.49-6.99	0.003	2.97	1.28-6.90	0.011
5+ HRS	3.78	1.58-9.03	0.003	4.26	1.61-11.30	0.004
	test for trend		<0.001	test for trend		<0.001
	Test of interaction with HIV		0.075	Test of interaction with HIV		0.155

* conditional odds ratio

** conditional odds ratios, adjusted for HIV status, age, marital status, report of abnormal vaginal bleeding, report of ever screen, visit with a natural healer, urban vs. rural residence

Figure 4. 3. Proportion of cervical cancer cases by HIV status across travel times

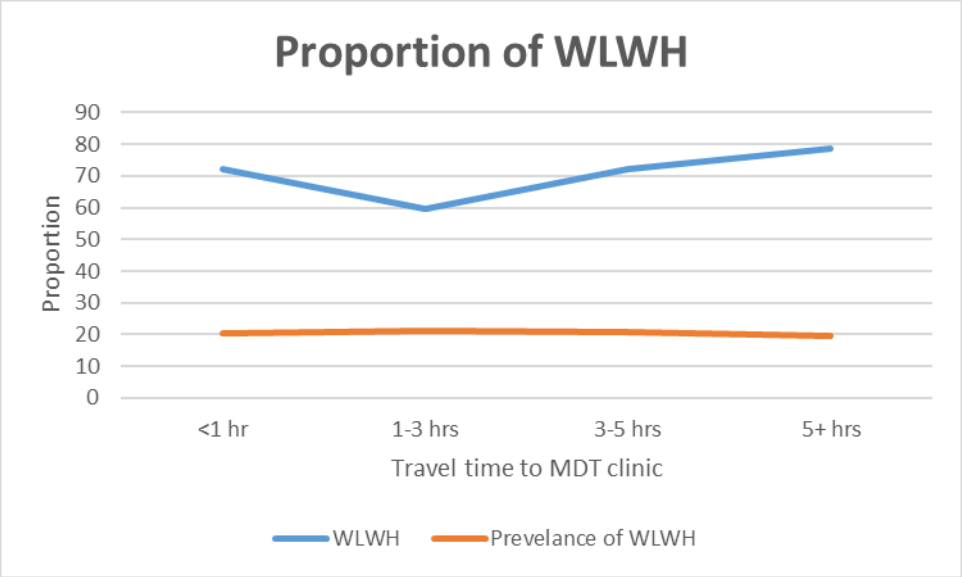


Table 4. 4. Logistic regression for travel time and HIV status

Travel time	HIV negative	HIV positive	p-value	aOR*	95% CI	p-value
	N=282	N=660				
<1 HR	84 (29.8%)	217 (32.9%)	<0.001	ref		
1-3 HRS	97 (34.4%)	144 (21.8%)		0.64	0.39-1.04	0.073
3-5 HRS	67 (23.8%)	174 (26.4%)		1.33	0.80-2.23	0.271
5+ HRS	34 (12.1%)	125 (18.9%)		2.03	1.10-3.75	0.024
				test for trend		0.002

* adjusted for stage at diagnosis, age, marital status, report of abnormal vaginal bleeding, report of ever screen, visit with a natural healer

Chapter 5. Summary and future directions

5.1. Summary

In summary, this dissertation titled: “Identifying demographic, clinical, and geographic features of cervical cancer patients presenting to a multidisciplinary tumor (MDT) clinic in Gaborone, Botswana”, offers insight and epidemiologic data that can be used to guide future interventions and research to maximize the impact of implementing programs and policies aimed at reducing the growing cervical cancer burden in Botswana.

Our first study examining demographic and clinical factors associated with late-stage disease at presentation to the MDT clinic shows that prior cervical cancer screening is associated with decreased odds of having late-stage cervical cancer at diagnosis, whereas experiencing abnormal vaginal bleeding and having never been married are associated with an increased odds of having late-stage cervical cancer at diagnosis. Additionally, rural women who consulted a traditional healer have increased odds of late-stage disease at diagnosis compared to rural women who have never consulted a traditional healer.

We also found that living with HIV was not associated with having late-stage cervical cancer at diagnosis, but when comparing WLWH and women without HIV in our cohort, the WLWH were younger, were more likely to have undergone cervical cancer screening, more often lived in urban areas, and were more likely to be married or to have been married than women without HIV. Additionally, associations with late-stage

cervical cancer at diagnosis differed between WLWH versus women without HIV. Increasing age is significantly associated with late-stage cervical cancer at diagnosis in women without HIV, but not in WLWH. WLWH with a history of cervical cancer screening have lower odds of presenting with late-stage cervical cancer at diagnosis; however cervical cancer screening is not significantly associated with late-stage cervical cancer at diagnosis in women without HIV.

Our second study reveals non-random geographic patterns of patients with cervical cancer throughout Botswana presenting to the MDT clinic in Gaborone. We identify specific areas of the country with disproportionately high and low presentation rates, indicating that areas with low presentation rates may have poor access to the one comprehensive care MDT clinic in Botswana, and areas with high presentation rates may have better access to the MDT clinic. Patients living in sub-districts with low presentation rates are more likely to present with abnormal vaginal bleeding, and patients living in sub-districts with high presentation rates are more likely to be HIV negative and more likely to present with late stage disease.

Our results also generate novel hypothesis regarding community and individual level factors that could be limiting access to health care for areas with low presentation rates, such as travel-distance as a potential barrier to accessing cervical cancer care. We also identify additional potential areas for interventions to mitigate the cervical cancer burden at the individual level, including increasing efforts for women without HIV to assess and improve knowledge related to cervical cancer and cervical cancer screening. Future efforts should increase awareness campaigns and cervical cancer screening efforts to include women without HIV. Additionally, early cervical cancer detection efforts should

also emphasize cancer symptom awareness and education about the steps women should take if they experience these symptoms.

Our third study delineates the travel time for cervical cancer patients traveling from their village of residence to the comprehensive MDT cancer clinic at PMH in Gaborone. The average travel time was almost 3 hours and more than 200 km to the MDT clinic. We note that patients have an increased odds of presenting with later stage disease with increasing travel time to the MDT clinic. We also find that the rates of patients presenting to the MDT clinic differ according travel times, with the highest presentation rate for patients traveling 1-3 hours to the MDT clinic and lowest for patients traveling more than five hours, thus our results indicate that not all women who develop cervical cancer are presenting equally for staging and care. We also show that an association with travel time and a patient's HIV status. Patients with greater travel time to the MDT clinic are more likely to be living with HIV, suggesting that HIV status may increase the likelihood of presentation for cervical cancer care for women living at further distances.

In conclusion, increasing education and awareness among women, both women living with and without HIV, and among providers, including traditional healers, about the benefits of cervical cancer screening and about the importance of seeking prompt medical care for abnormal vaginal bleeding, while also developing support systems for unmarried women, may help reduce cervical cancer morbidity and mortality in Botswana. Moreover, focusing future interventions on education, screening, and referral infrastructure for cervical cancer in areas of Botswana where fewer women are presenting for cervical cancer care, may increase the impact of programs and decrease the cervical cancer burden. Lastly, identifying the need to investigate barriers to

accessing advanced cancer care including the travel burden, cervical cancer awareness, knowledge, and resources to ensure equitable access to appropriate treatment for all women in Botswana, both WLWH and without, is needed to improve cervical cancer outcomes. Our study shows cervical cancer as a burden in Botswana, and highlights important risk factors, barriers to access, and areas for improved intervention. Importantly, reliable resources, such as an up-to-date population based cancer registry, are also needed to capture the true epidemiology of cervical cancer and for the future, to be able to truly understand quantify the morbidity and mortality of cervical cancer so as to understand and measure the impact of future interventions aimed at alleviating the cancer burden.

5.2. Future directions

Botswana carries a heavy burden of cervical cancer, access to adequate treatment is essential to reduce disease and save lives. Improving equitable access to cervical cancer treatment for women living in sub-districts with lower rates of cervical cancer patients presenting for care should be prioritized to help reduce the morbidity and mortality of cervical cancer. Future efforts to include women without HIV and women who have not been married in cervical cancer screening efforts could result in the earlier detection of cervical cancer in these groups. Future early cervical cancer detection efforts should emphasize cancer symptom awareness and early detection through cervical cancer screening, and should also include traditional healers in the cancer care continuum.

Identifying community and individual level factors associated with access to comprehensive cervical cancer care gives national health programs insight when developing strategies that target areas and populations being underserved by health facilities. These strategies will be key in preventing and controlling the emerging cervical cancer burden in Botswana. Our results highlight patient level factors associated with late-stage cervical at diagnosis and indicate potential areas for intervention to mitigate the cervical cancer burden in Botswana. Our findings show that cervical cancer screening for women in Botswana is associated with the early detection of cervical cancer, particularly in women with HIV. Future efforts to include women without HIV and women who have not been married in cervical cancer screening efforts could result in the earlier detection of cervical cancer in these groups. Future early cervical cancer detection efforts should emphasize cancer symptom

awareness and early detection through cervical cancer screening, and should also include traditional healers in the cancer care continuum.

Next steps for this work could include working with the appropriate stakeholders (MOHW, UICC, etc) to prioritize resources to ensure more accurate estimates of cervical cancer rates for the Botswana national cancer registry. This work highlights important differences among women with and without HIV for cervical cancer screening, and that not all women, specifically women without HIV, may not be presenting for cervical cancer treatment because of the overall focus on implementing screening and testing for high-risk WLWH. Currently, the health system may fail to recognize the need to educate, screen and treat lower-risk women for cervical cancer and future work should focus on including lower-risk women in cervical cancer prevention and screening efforts.

Next steps for a research study would be to identify additional barriers for access to treatment. One could use a mixed methods study to identify health facilities in 2-3 different areas throughout Botswana (ex: one in Botswana, one 3 hours away and one 5 hours away) and investigate knowledge and understanding (availability and acceptability) regarding cervical cancer and screening for patients and health care providers, and evaluate structural and health systems to determine where interventions make the most impact with a focus on ensuring equitable access to care for WLWH and without.

APPENDIX

A.1. Alternative methods for Chapter 3

A.1.1. Study participants and covariates

Study participants, patient demographic and clinical factors were all the same as that main analysis. However, for more granular data, the GIS unit of analysis included 519 villages as defined by administrative boundaries for Botswana (8). Community level variables for sub-districts included HIV prevalence, population density, and travel distance to Gaborone were still based on sub-district of analysis as noted in 3.3.2.

A.1.2. Covariates

A.1.3. Geocoding Methods

To detect areas in Botswana with disproportionately high or low rates of cervical cancer patients presenting for treatment, we defined our geographic unit of analysis as village of residence in Botswana. We used an available shapefile from the USCB (8) to define the administrative boundaries for 519 villages throughout the country. We abstracted each patient's residential village from the questionnaire and geocoded each patient to one of USCB's identified 519 villages (8). We aggregated cervical cancer patients per village. The denominator for each sub-district consisted of the total female population projection for patients 20 years and older from January 2015 to March 2020(8). We then calculated

the age-standardized cervical cancer rates per 100,000 women for each sub-village. Rates by village were visually inspected using choropleth maps for geographic variation.

A.1.4. Geographic Analysis

To statistically assess geographic correlation of cervical cancer patients both globally and locally, we employed the Global Moran's I and the Anselin local index of spatial autocorrelation statistics, respectively (29, 30). We conducted a Global Moran's I test to assess if cervical cancer rates across the country were clustered, dispersed, or random. The null hypothesis assumed that cervical cancer distribution was random across Botswana. The cervical cancer rates of each village were correlated with the mean rate of neighboring sub-districts. We defined neighbors using queen's contiguity matrix (31) and conducted permutation tests with 999 simulations for significance. A significant Moran's I test indicated a non-random geographic distribution and therefore spatial autocorrelation would exist. A positive spatial autocorrelation result indicated clustering, describing sub-districts with similar rates within close geographic proximity to each other. Negative spatial autocorrelation revealed dispersion, noting sub-districts with dissimilar rates were closer in geographical proximity in a manner that was not random.

Moran's I analysis is limited in that it does not detect local patterns of spatial association (29). To investigate local patterns of cervical cancer referral rates for each village we employed the local index of spatial autocorrelation (30). This tool determined for each individual (target) village if cervical cancer rates were uniformly similar or disproportionately high or low relative the mean rate of that village's neighbors, once

again defined by Queen's contiguity matrix (31). Permutation tests with 999 simulations were conducted and statistically significant clusters (similar rates) or outliers (dissimilar rates) were identified with 95% confidence intervals. A significant result revealed one of four possible categories for each village, two types of clusters or two types of outliers. A high-high (HH) cluster indicated target villages with high rates were surrounded by neighboring villages with high rates, and conversely low-low (LL) clusters identified target villages with low rates surrounded by neighboring villages with low rates. High-low (HL) or low-high (LH) outliers indicated an inverse relationship between the target village rates and the mean of their neighbor's rates.

A.1.5. Statistical Analysis

Simple ordinary least squares (OLS) regression investigated the relationship of age-standardized rates across the country with village level community factors. If Moran's I identified any form of autocorrelation, we accounted for non-independence of rates in our multivariable OLS regression mode using a spatial weights matrix(32) to investigate associations with village level variables (HIV prevalence, population density, and travel distance).

Lastly, we aimed to identify individual level characteristics that were associated with patients living in an identified HH or LL villages. We investigated clinical and demographic characteristics of cervical cancer patients living in an identified LL village compared to patients not living in a LL village and also for patients living in an identified HH village compared to patients not living in a HH village. Univariate individual level

differences were assessed using student t-tests and chi-squared tests. Additionally, multivariable logistic regression models determined the magnitude of associations for patients living in identified LL or HH villages versus patients not living in these villages, while adjusting for multiple demographic and clinical characteristics. Adjusted odds ratios and 95% confidence intervals with a cut off off-value 0.05 determined significant associations. We performed geospatial analysis in ArcGIS version 10.6.1 (Esri, Redlands, CA), and Geo-da, and conducted all Statistical analysis in STATA 16.1.

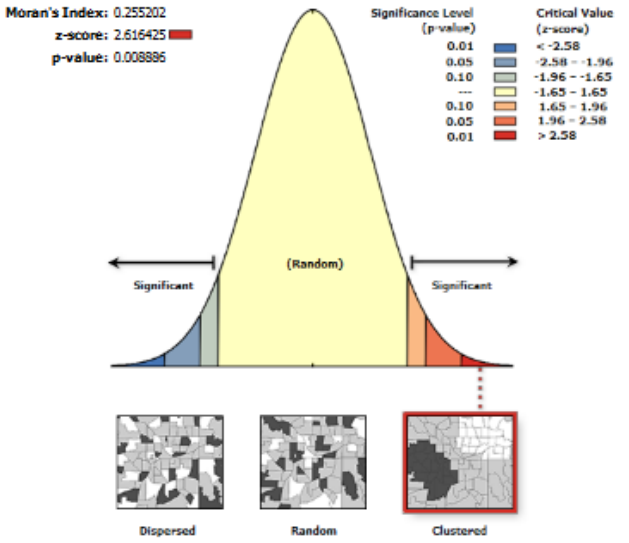
A.2. Results

We manually matched 1006 of 1033 (97.5%) cervical cancer cases to villages identified in the USCB database. Village match reviewed by Botswana Team. 1006 women included in the analysis, observed rate was generated for each village. Underlying population for women ≥20 years was per year was approximately 698,905, with an observed rate of 14.4 per 10,000 women over the study period. Globocan estimated 374 incident cervical cancer cases in 2020, using the same underlying population, this gave an expected rate of 30.2 per 10,000 women, giving an overall rate ratio of 47.7%.

We identified a non-random, clustered distribution of CC rates across the 519 villages in Botswana as indicted by Global Moran's I (p=0.010, Figure A.1), the LISA statistic showed HH, HL, LL, and LH clusters (Figures A.2). Figure A.3 visually depicts the distribution of cervical cancer rates throughout Botswana by village.

Figure A. 1. Moran's I results for clustering of cervical cancer rates throughout Botswana by village

Spatial Autocorrelation Report



Given the z-score of 2.61642531287, there is a less than 1% likelihood that this clustered pattern could be the result of random chance.

Global Moran's I Summary

Moran's Index:	0.255202
Expected Index:	-0.002398
Variance:	0.009693
z-score:	2.616425
p-value:	0.008886

Dataset Information

Input Feature Class:	Projected_Bots
Input Field:	OBS_EXP_RISK_3.30.2021.CSV.LOG_ES
Conceptualization:	INVERSE_DISTANCE
Distance Method:	EUCLIDEAN
Row Standardization:	False
Distance Threshold:	90754.6868 Meters
Weights Matrix File:	None
Selection Set:	False

Figure A. 2. Local Index of Spatial Autocorrelation by Village

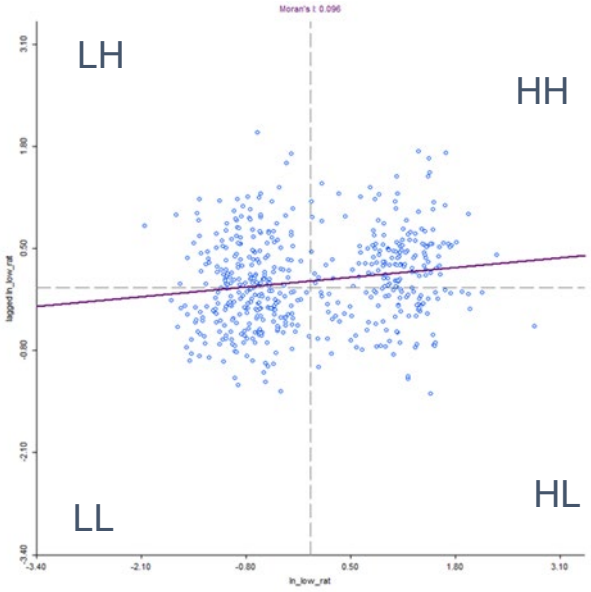


Figure A. 3.Distribution of cervical cancer rates throughout Botswana by village