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Association between Patient-reported HIV and Cervical Cancer Screening Utilization and Outcomes in Nigeria

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Abstract

Of the half million new cases of invasive cervical cancer (ICC) reported globally each year, over 80% occur in Low-and Middle Income Countries (LMICs)[1]. Nigeria is one of these countries with a huge burden of ICC incidence and mortality.[2] As reported in the Global Burden of Cancer 2013, cervical cancer is ranked the 2nd most common in incidence and mortality among all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health care service intervention known to significantly reduce the incidence and mortality from invasive cervical cancer, particularly in developed countries where organized CCS programs are available. [4-10] However, such organized CCS programs are currently lacking in Nigeria and in most other LMICs. Therefore, the opportunity for such screening intervention likely depends on several factors ranging from systems-level factors such as availability of screening and health systems support to overcome barriers to access services, provider-level factors such as offering screening recommendations, and patient-level factors related to health beliefs and ability to complete a screening intention. Indeed, the literature on cancer screening suggests that screening is a process of care consisting of several steps and interfaces between patients, providers, and health care organizations.[11] In this context, screening rates are largely driven by strategies that promote interface across organizational boundaries, recruit patients and promote referrals, facilitate appointment scheduling, and promote continuous patient care and engagement.[11]

Cervical cancer screening services in Nigeria has been largely opportunistic, and dependent on either recommendation or referral from a provider or the individual woman's decision to go for screening if aware of such services.[12] In such opportunistic screening setting, we currently do not understand the sociodemographic characteristics associated with cervical

cancer screening utilization and outcomes. Our overarching hypothesis was that patient-reported HIV was significantly associated with cervical cancer screening utilization in an opportunistic cervical cancer screening service in Nigeria. The scientific premise for this is evidence that ICC is entirely attributable to the persistent infection of a sexually transmissible virus, the high-risk human papillomavirus (HPV),[13] and its persistence is facilitated by HIV-mediated cellular immune compromise leading to increased risk of cervical dysplasia and ICC.[14-18]

This retrospective analysis utilized the de-identified records of women who received cervical cancer screening services offered in an opportunistic screening program through the "Operation Stop" cervical cancer unit of the Jos University Teaching Hospital, Jos, Nigeria over a 10-year period (2006-2016). We adapted the constructs of the Health Belief Model (HBM)[19] and the system-model of clinical preventive care[20] to understand three interrelated but distinct aims in this dissertation: 1. Understand the association between patient-reported HIV and the likelihood of provider referral for a cervical cancer screening; 2. Understand the association between patient-reported HIV and the age at which women have their first cervical cancer screening; and 3. Understand the predictors of abnormal cervical cytology outcome at the time of first cervical screening, and also to understand the hazard of an abnormal cervical cytology outcome at subsequent follow up pap in women with a prior normal pap cytology.

The findings of this dissertation contribute to the knowledge and understanding of health care service factors that could guide implementation of cervical cancer screening and prevention in settings with opportunistic screening services. Specifically, this study provides evidence that women who report being infected with HIV are significantly more likely to receive a provider referral for cervical cancer screening compared to women who are HIV uninfected (aOR=2.35; 95% CI: 1.95, 2.82). This study provide for the first time in Nigeria, evidence that women initiate cervical cancer screening at relatively older age (median age: 37 years; IQR: 30-45 years) compared to the recommended age by screening guidelines in developed countries.[21-23] We also

found that women who were HIV infected had their first cervical cancer screening at a significantly younger age than HIV uninfected women (the mean age at first screening for HIV infected women was 35.0 ± 7.4 years, compared to 38.2 ± 10.2 years for HIV uninfected (p-value=0.001). We also found a positive correlation between the median age at first cervical cancer screening and the severity of underlying precancerous cervical abnormalities. In other words, women who screened at an older age were more likely to have underlying severe dysplasia than women who screened at a younger age. Patient-reported HIV was not significantly associated with mild (aOR=1.04; 95% CI: 0.80, 1.36) or severe (aOR=1.26; 95% CI: 0.83, 1.92) cervical dysplasia. We found that women with other sociodemographic characteristics, such as age at first cervical cancer screening ≥35 years were significantly more likely to have an underlying mild (aOR=2.56; 95% CI: 2.23, 2.95) or severe (aOR=3.57; 95% CI: 2.74, 4.64) cervical dysplasia. Similarly, women who were ≥35 years had a significant hazard of developing an abnormal cytology outcome at follow up (aHR=1.63; 95% CI: 1.11, 2.41).

Finally, our analysis showed that women who completed 7-12 years (aOR=3.07; 95% CI: 2.69, 3.51) or more (aOR=1.43; 95% CI: 1.27, 1.62) of formal education were significantly more likely to have their first cervical cancer screening before age 35. Women with this educational attainment were also significantly less likely to have an underlying precancerous cervical lesion at first screening compared to women of less formal education (aOR=0.65; 95% CI: 0.48, 0.88, and aOR=0.75; 95% CI: 0.58, 0.98, respectively for 7-12 years and >12 years of completed education).

These findings are important and a clarion call for policy makers and women's care advocates such as the Society of Gynecology and Obstetrics of Nigeria (SOGON) to develop or adopt guidelines that will facilitate early initiation of cervical cancer screening in Nigeria. The effect of education in women seen in these analyses supports the importance of the society to view and invest in women education as a social and public health intervention in Nigeria. In our subsequent

project we plan to obtain qualitative data on barriers and facilitators to CCS implementation in Nigeria, and with our current findings we might have sufficient evidence to inform the design of effective health services interventions to improve CCS and outcomes in Nigeria and similar settings in Africa.

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Dedication

This dissertation work is dedicated to the memory of those women who died prematurely from invasive cervical cancer due to lack of access to screening and treatment services.

I also dedicate this work to my beloved wife, Joy, and daughter, Judy Musa who accompanied me from Nigeria to share with me the extreme Chicago cold weather, and to our beloved son, Jeremy Robert Musa, who by providence joined our family during the spring of 2015.

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Chapter 1: Introduction

Although invasive cervical cancer (ICC) has a well-known natural history with treatable precancerous abnormalities detectable through screening, it is a significant public health burden in Low-and Middle-Income Countries (LMICs). Of the half million new cases of ICC reported globally each year, over 80% occur in LMICs[1]. Nigeria is one of these countries with a high burden of CC incidence and mortality.[2] The Global Burden of Cancer 2013 ranked cervical cancer the 2nd most common in incidence and mortality for all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health care service intervention for reducing ICC incidence and mortality. The precancerous abnormalities detectable at screening range from minor atypical cells, low-grade epithelial cell abnormalities to severe or high-grade epithelial cell abnormalities that could progress to invasive cervical cancer if not detected and treated. The reporting of these epithelial cell abnormalities detected through screening by the Papanicolou smear test (pap test) and cytologic interpretation is guided by the Bethesda system.[4] The benefits of CCS are evident from data in developed countries, where organized CCS programs have led to a substantial decline in ICC incidence and mortality.[5-11] One important CCS intervention is the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), a Centers for Disease Control and Prevention (CDC) initiative targeting low-income, under-insured and medically underserved women in the US.[9] This program has led to significant decrease in incidence and mortality from cervical cancer with a substantial gain in quality adjusted life-years in the target population.[9] Specifically, among 1.8 million women screened in 1991-2007, the NBCCEDP added 10,369 life-years (LYs) gained compared to No Program intervention, and 101,509 LYs gained compared to No Screening. Also, the NBCCEDP prevented 325 women from dying of cervical cancer relative to No Program, and 3,829 relative to No Screening.[9]

In Nigeria and other LMICs where organized CCS programs are lacking, the opportunity to have a screening test likely depends on multi-level factors such as: 1. Organizational or systems-level factors (availability of screening and system support to overcome barriers to accessing services). The literature on cancer screening suggests that cancer screening is a process of care consisting of several steps and interfaces between patients, providers, and health care organizations.[12] In this context, screening rates are largely driven by strategies that limit the number of interfaces across organizational boundaries: recruiting patients, promoting referrals and facilitating appointment scheduling, and promoting continuous patient care.[12] The organizational capability of the health care system to address these boundaries could explain the relatively higher CCS rates of 83% in the US[13], compared to Nigeria and similar LMICs in sub-Saharan Africa that have lower CCS rates, ranging between 6-8%.[14,15] 2. Patient-related factors (risk perception for ICC, illiteracy, and lack of awareness of CCS, or where to go for such screening.[15-18]) Other patient-related factors such as cost of screening, health insurance coverage, education, perception of screening benefits and ability to overcome barriers to accessing services are significant contributors. Indeed the effect of health insurance coverage on cervical cancer screening suggests that women with public health insurance are less likely to have screening compared to women with private insurance, and that women with no insurance are significantly less likely to have screening compared to women with any type of health insurance.[19] Sadly, the only health insurance system currently available in Nigeria is a public health insurance system that does not provide coverage for cancer screening or treatment; women who go for screening or cancer treatment incur heavy out-of-pocket expenses.[20,21] This cost-related factor could be a barrier to cervical cancer screening utilization in this setting, particularly if family income is not sufficient for other competing needs. 3. Provider-related factors include behavior towards screening counseling and providing a screening referral during the course of routine clinical care to eligible women. Also, recent literature has supported the

effectiveness of a provider recommendation for screening on cervical cancer screening participation.[22,23]

The framework for improving the quality of cancer care provides a plausible explanation of how failures at various levels in care processes could affect the delivery of critical preventive care services for cancer.[24] These include failure in the organization of care that enable patients and providers to conduct risk assessment or give screening counseling to women at risk; failure to detect precancerous abnormalities and offer appropriate treatment; and failure in other processes of care for improving ICC outcomes.[24] For instance, failure of providers to initiate CCS recommendation to eligible women during opportunistic clinical care visits could lead to women missing the critical opportunity to have a screening test even when seen in health facilities offering such services. Closely related to provider factors is the evidence in HIV-infected populations, which suggests that women's awareness that HIV infection increases the risk of ICC and having a strong provider-patient relationship were significant facilitators for CCS utilization.[25] This evidence further justifies the need for understanding the contributions of provider and patient-related factors in CCS utilization, particularly in settings where screening is largely opportunistic. Additionally, interventions such as physician recommendation for screening, and strategies that help physicians and patients to make screening decisions, have shown a significant impact on CCS rates.[12,26-28]

In Nigeria, there is currently no organized cancer screening for any specific cancer, and most of the screening activity for either breast or cervical cancer is largely dependent on provider-initiated counseling and screening. The HIV care and treatment program in Nigeria has been well-supported by the US Presidential Emergency Plan for AIDS Relief (PEPFAR) program for over a decade, and efforts at integrating cervical cancer screening as part of care for HIV infected women are underway.[29,30] One of the existing gaps in our knowledge on cervical cancer screening utilization is the relationship between patient-reported HIV infection and provider behavior in

providing a cervical cancer screening referral during the care process. This understanding is particularly relevant in settings where cervical cancer screening is largely opportunistic and there is a lack of national screening program subsidized by federal funds. The findings of this dissertation project may help to guide implementation of health systems strategies that could improve utilization of this critical cancer prevention service in women at risk for ICC.

The scientific premise for this understanding is related to the evidence that ICC is entirely attributable to the persistent infection of a sexually transmissible virus, the high-risk human papillomavirus (HPV).[31] Indeed, the persistence of HPV is influenced by HIV-mediated cellular immune compromise, and women infected with HIV have increased risk of cervical dysplasia and ICC.[32-36] Also, previous studies have shown a strong association between sexually transmissible infections (STIs) and HIV infection.[37] It is also noteworthy that HPV vaccination for primary prevention of cervical cancer is currently not included in the Nigeria National Program on Immunization (NPI). This makes early detection and treatment of precancerous cervical abnormalities through screening an important public health service option for women at risk of cervical cancer. Since HPV and HIV have a synergistic effect on development of cervical cancer, it is expected that women with HIV infection are likely to be self-aware of this risk, and also their providers are more likely to be aware of this association with cervical cancer and offer CCS referral. These high-risk women are therefore more likely to utilize cervical cancer screening services compared to HIV uninfected women. We therefore, hypothesize that patient-reported HIV is significantly associated with cervical cancer screening utilization in an opportunistic cervical cancer screening service in Nigeria.

This retrospective analysis utilized the cervical cancer screening data at the “Operation Stop Cervical Cancer” screening program of the Jos University Teaching Hospital, Jos to achieve 3 closely related, but distinct, aims that may contribute to the cervical cancer screening and

prevention literature, particularly in settings were such screening are opportunistic. These aims are:

1. To examine the association between patient-reported HIV and the likelihood of provider referral for a cervical cancer screening. *We hypothesized that women with reported HIV infection are significantly more likely to receive a CCS referral by a provider compared to women who are HIV negative.* The findings and contributions of this aim are summarized in chapter 3 of this dissertation.

2. To examine the association between patient-reported HIV and the age at which women have their first cervical cancer screening. *We hypothesized that the median age at first CCS is lower in women with reported HIV than in women who are HIV negative.* The findings and contributions of this aim are summarized in chapter 4 of this dissertation.

3. To ascertain predictors of an abnormal cervical cytology outcome at the time of first cervical screening and assess the hazard of an abnormal cervical cytology outcome at subsequent follow up pap in women with a prior normal pap cytology. *We hypothesized that the likelihood of an abnormal cytology outcome will be significantly higher in women who were HIV infected at first CCS compared to those who were HIV uninfected. T*he findings and contributions of this aim are summarized in chapter 5 of this dissertation.

Literature Review

The Burden of Cervical Cancer Globally and in Nigeria

In absolute numbers, 485,000 new cases of cervical cancer and 236,000 deaths occurred in 2013, ranking among the top 10 cancers in incidence and mortality globally.[3] This cancer caused 6.9 million disability adjusted life-years (DALYs), with 85% occurring in developed countries and 15% in developing countries.[3] Also, the American Cancer Society and the Globocan 2015 reported that cervical cancer is the second commonest cancer contributing

24% of new cases and 22% of deaths from all cancers among the female population in the West African region.[38] Worldwide, it is estimated that 1 in 70 women will develop cervical cancer between birth and age 79.[3] In Western sub-Saharan Africa overall, the age-standardized incidence rate of cervical cancer is 30.2 per 100,000 population per year and the age-standardized death rate 22.3 per 100,000 population per year.[3] Among women in Nigeria cervical cancer represents the most common cancer diagnosis (24%) and cancer-related cause of death (22%), with 9,659 deaths per year.[3,38] The public health problem of this cancer is significant enough that in Nigeria it is second only to liver cancer in terms of incidence and cancer-related mortality[3], with a mortality rate of 22.9 deaths per 100,000 people per year. Despite being largely preventable with highly effective vaccines against the causative virus and early detection and treatment of precancerous abnormalities through screening, premature mortality due to cervical cancer contributes to great economic loss, deep suffering and social isolation.[6,39] The high burden of cervical cancer in sub-Saharan Africa is attributable to weak public health policy and systems to support primary prevention with vaccine and the lack of organized screening programs that enables early detection and treatment of precancerous abnormalities.[40]

HIV, HPV and Risk of Cervical Cancer

One of the reasons for the growing burden for cervical cancer in Nigeria is the lack of a national program support for HPV vaccination in the absence of organized cervical cancer screening programs and aggravated by health services factors such as health insurance coverage for CCS. Additionally, CCS services are limited to the few tertiary health care facilities with specialist cytopathologist and screening services in such facilities are largely dependent on either recommendation by a provider or when a woman decides to go for screening if aware of availability of such services. These multiple health services related factors could be contributory to the high incidence and mortality due to cervical cancer in one of Africa's most populous

nations.[2,40] Furthermore, this situation is worsened by a high prevalence of human immunodeficiency virus (HIV) infection among women of reproductive age, with Nigeria ranked second in the world in HIV burden.[41,42] Also, epidemiologic evidence has shown that infection with high-risk human papillomavirus (HPV) is a necessary factor in the causal pathway for cervical carcinogenesis.[43] Indeed, the recent report on the global burden of cancers attributable to infection further affirms the link between cervical cancer and infection by high-risk human papillomavirus.[31] Furthermore, the synergistic role of HIV-mediated immune suppression has been shown to increase the prevalence of precancerous lesions of the cervix and the hazard of progression from precancerous to invasive cervical cancer stages among HIV infected women.[44-48]

Age at first Cervical Cancer Screening and Risk of Cervical Cancer

The optimal age to initiate CCS has been a subject of debate and controversies, and recommendations vary with guidelines. For instance, the US Preventive Service Task Force (USPSTF) recommends initiation of CCS as early as age 21[49,50], while other guidelines have expressed concerns about the benefit and risk of screening, detection and treatment of abnormal cervical lesions with Pap cytology earlier than age 25.[51] In Nigeria, CCS is largely opportunistic, and we presently do not know the median age at which women initiate CCS either by self-referral or the recommendation of a provider to a CCS facility. Also, of significance to this study is the finding that development of invasive cervical cancer occurs at a lower median age of 35 years in HIV positive women compared to a median age of 40 years in women who are HIV negative. [52] Additionally, among women less than 35 years old, being HIV positive confers a 4-fold higher risk of having invasive cervical cancer (ICC) compared to being HIV negative.[52] Therefore, understanding the age at first cervical cancer screening in our women population will provide significant programmatic data for improving quality of screening services in our communities. Also, the risk of developing ICC increases with increasing age in women who are

HIV negative and women whose HIV serostatus is unknown, but this risk peaks at age 35 with no significant change with increasing age in HIV positive women.[52] Although there have been previous reports that the median age at first cervical cancer screening was higher in HIV seropositive women compared to HIV seronegative women utilizing a large cervical cancer screening program[53], the data on age at first screening described above highlights the critical role of understanding how to improve screening, detection and treatment of precancerous cervical lesions at an early age, particularly in high-risk women who are HIV infected.

Late Stage at Cervical Cancer Diagnosis and Survival in sub-Saharan Africa

In addition to the lack of organized cervical cancer screening services and poor access to cervical cancer screening services, most women with cervical cancer often present at advanced clinical stages with subsequent high death rates and poor survival.[54-57] Apart from the problems of delayed diagnosis of this cancer, the treatment facilities for women with invasive cervical cancer are inadequate in Nigeria, justifying the need to invest in cervical cancer prevention through vaccination against the causative agents, the high-risk human papillomavirus, and through screening, early detection and treatment efforts.[58] Recent survival data from Jos Nigeria showed a high death rate of 79.8 per 100 person-years, and poor survival attributable to late stages at diagnosis with limited treatment infrastructure for invasive cervical cancer patients.[59] This makes cervical cancer screening and the understanding of novel health services interventions that could improve access and utilization of available screening services a highly significant priority research endeavor for Nigeria and its population.

Rationale for Improving Health Services for Cervical Cancer Screening and Outcome in Nigeria

Indeed, cervical cancer screening has resulted in significant reduction in morbidity and mortality, mainly because of organized screening programs offering opportunities for early detection and treatment of premalignant conditions of the cervix. One of these health services interventions is the widespread access, acceptability and affordability of screening services

through the National Breast and Cervical Cancer Early Detection Program to uninsured and underinsured low-income women. [5-11] To expand access to these screening interventions in different countries around the world, the World Health Organization (WHO) in 2013 issued resource setting-specific guidelines for cervical cancer screening including special considerations for women who are HIV infected.[5] In most settings strategies to improve screening utilization have focused either on opportunistic screening requested by a physician or an individual, or organized cervical cancer screening in which a defined population is contacted and invited to screen at regular intervals.[38] In this regard, provider recommendation for screening has been shown to increase utilization and cervical cancer screening rates.[60,61] The role of provider recommendation in screening utilization is further supported by findings in a population-based study in Nigeria that showed that lack of awareness of cervical cancer and screening services were barriers to screening by women at risk of cervical cancer.[62] Studies have also shown evidence that organizational processes that promotes patient recruitment and referral, appointment scheduling, and continuous patient care have a substantial effect on increasing cancer screening rates.[12]

Therefore, this project provides information and significant contributions to the literature on how patient-reported HIV and other sociodemographic factors are associated with utilization of cervical cancer screening in an opportunistic cervical cancer screening service in Nigeria. These findings are important for policy makers and women's health advocates to design and implement health services interventions such as resource-specific cervical cancer screening guidelines that could improve utilization of screening services.

Innovation

This retrospective cross-sectional secondary analysis is innovative because:

1. Cervical cancer screening has been ongoing at the OSCC unit for over a decade with available operational health services data, but no prior analyses of such these data have been done to understand factors associated with screening utilization in such opportunistic screening settings in Nigeria.
2. We have a unique screening data set covering patient demographics, HIV and STI variables, and cervical cancer screening cytology outcome variables reported according to the 2001 Bethesda system of Pap cytology reporting.[4] Utilizing such de-identified data to understand health services, patient-related factors and the outcome of cervical cancer screening outcomes in such opportunistic screening settings is innovative.

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Chapter 2: Methodologic considerations and Baseline Characteristics of Study Sample

This chapter provides a description of the overall research design, the conceptual framework for studying the 3 aims, key study variables, data source and study sample derivation. The chapter also provides a brief description of the statistical analysis and summary results of the baseline socio-demographic characteristics of the study sample. The specific methods and results for each of the study aims have been described in the respective chapters.

Study Design and Methods

Overall research design

This was a retrospective cross-sectional secondary analysis of data on women who received cervical cancer screening offered at the “Operation Stop Cervical Cancer” (OSCC) unit of the Jos University Teaching Hospital (JUTH) in Jos, Nigeria. Aim 1 of this project tests the hypothesis that women with reported HIV infection are more likely to receive a CCS referral by a provider than women who are HIV negative. Aim 2 assessed the median age at first CCS in women with reported HIV infection in comparison to the median age of women who are HIV negative. Finally, aim 3 assessed the relationship between the age at first screening and the likelihood of having an abnormal cervical cancer screening outcome after controlling for patient-reported HIV and other socio-demographic factors.

Conceptual framework

The overall goal of this study is to understand factors related to cervical cancer screening utilization in an opportunistic screening setting and the predictors of an abnormal cervical cytology screening outcome. The OSCC unit has no formal system of inviting or recalling eligible women

for cervical cancer screening. Therefore, women either initiate the process of having the test by coming to the unit ("self-referral") or by recommendation for screening by a health care provider to eligible women ("provider-referral"). The Health Belief Model (HBM)[1] in Fig. 2.1 and the systems model of clinical preventive care[3] in Fig. 2.2 offer explanations on the provider's role ("Cues-to-action") in utilization of cervical cancer preventive services. These two models also explain the behavior of individual patients in taking and completing a screening behavioral action (perception of susceptibility, perception of seriousness of condition, perception of benefits of screening and ability to overcome barriers in the screening pathway- "self-efficacy"). We adapted the constructs of the HBM as illustrated in the conceptual framework in Fig. 2.3 for the 3 aims of this project. The systems model of clinical preventive care recognizes the critical influence of physician-patient interaction and how situational and environmental factors in the health care system (cues-to-action) promotes preventive behavior towards cancer care.[3]

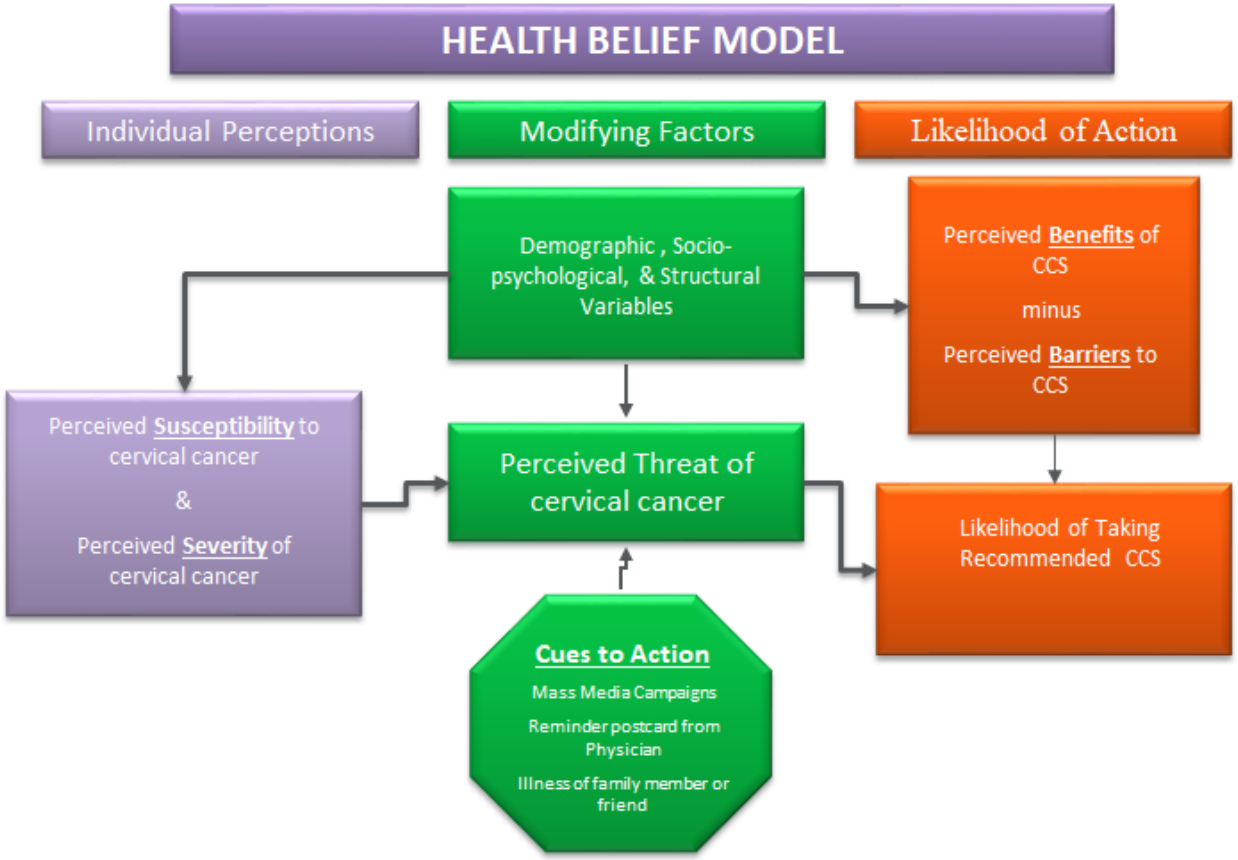

Fig. 2.1. The Health Belief Model[1] (Adapted from Rosenstock, 1974)

The HBM was first described in the 1950s by a psychologist working in the US Public Health Service and has become one of the most widely used conceptual frameworks of health behavior.[1] The framework is based on the theory that people are afraid of getting serious illnesses, and that health-related behaviors are influenced by an individual's level of fear, based on severity of threat perceived and the expected benefit of taking appropriate health behavioral action to avoid having the disease.[1,4]

Specifically, we adapted the following constructs of the HBM model to understand the 3 research questions in our secondary data analysis for this project:

1. “Perceived susceptibility”: this construct helps our understanding of how patient-reported HIV and other risk factors could influence patients’ decisions to seek cervical cancer screening at an earlier age or prompt a provider to initiate risk counseling and offer a referral note to have a cervical cancer screening
2. “Cue-to-Action”: this construct further helps explain how provider-patient interaction will lead to making a screening referral based on identified risk factors for cervical cancer during clinical care visits
3. “Perceived benefit”: this construct is related to how patient-reported risk factors and demographic variables could predict the likelihood of detection of an abnormal cervical cytology outcome whose treatment will result in effective prevention of this serious disease in the population.

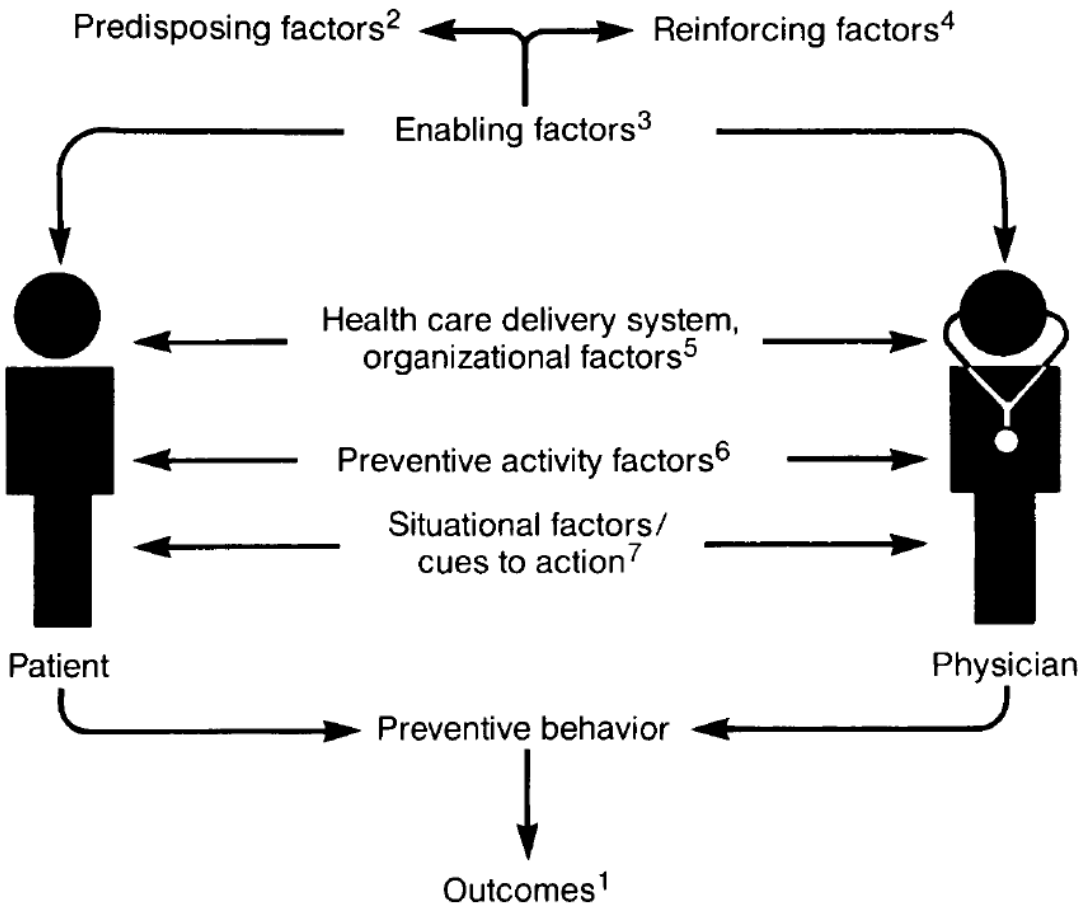

Fig. 2. 2. A Systems Model of Clinical Preventive Care: An Analysis of Factors Influencing Patient and Physician. In: Judith M.E. Walsh, *Health Educ Behav,* 1992.[3] (1**. Outcomes** are defined as decreased disease incidence, decreased morbidity, and decreased mortality. 2. **Predisposing factors** related to the motivation to perform a particular health behavior. Patient predisposing factors include demographics; beliefs (health beliefs); attitudes; expectations; motivation (internal locus of control); self-efficacy; health value orientation. Physician predisposing factors include demographics; gender; ethnicity; language concordance; beliefs; attitudes; prior clinical experiences; and personal health preferences. 3. **Enabling factors** include education; health knowledge; skills; income; logistical factors; and physiologic factors. Physician enabling factors include training; technical expertise; knowledge; logistical factors; and availability of materials. 4. **Reinforcing factors** are those that support or reward the behavior. Patient reinforcing factors include social support/approval and inherent reinforcement value of the preventive activity. Physician reinforcing factors include patient satisfaction; support/approval of peers; and case finding. 5. **Health care delivery system/organizational factors** include access to care; availability of technology and personnel; organizational priorities; structure of the office practice; reimbursement; and coordination with community resources. 6. **Preventive activity factors** are features of the preventive activity itself and include costs; risks; efficacy; and effectiveness. 7. **Situational factors/cues to action** are triggers to health behavior and include internal cues, such as symptoms and external cues such as physician reminders.

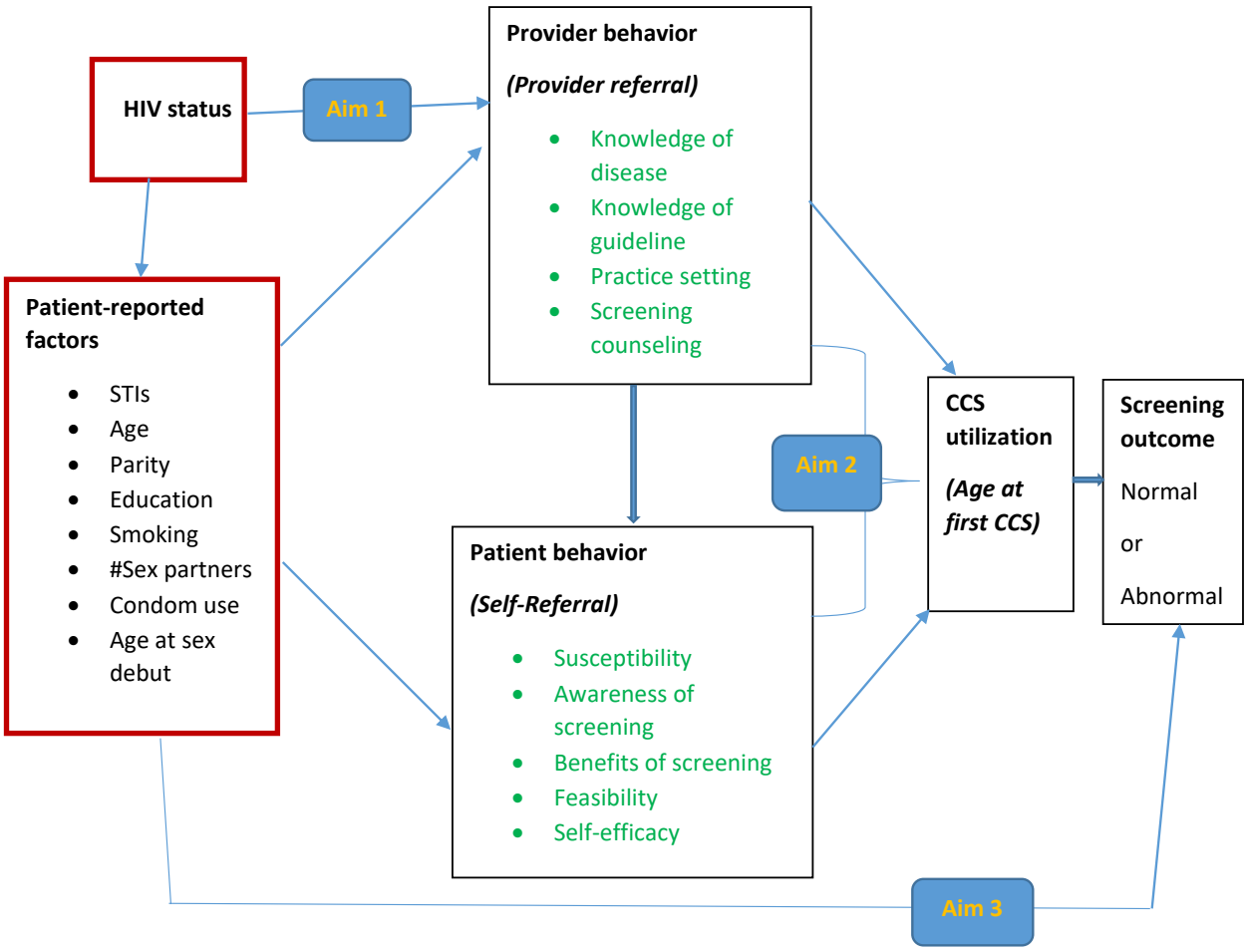

Fig.2.3. Conceptual framework for understanding patient-reported HIV and other socio-demographic variables on cervical cancer screening utilization and cytology outcomes in an opportunistic screening unit, Jos Nigeria***. Adapted constructs of the Health Belief Model***[1,4]*** Aim 1 assessed patient reported-HIV and the likelihood of provider referral for CCS. Aim 2 assessed the relationship between patient-reported HIV and the age at first CCS; while Aim 3 assessed patient-reported HIV and predictors of abnormal cervical cancer screening abnormality. **Note: Green colored text are possible explanatory variables not measured and were not included in this analysis**

Description of study setting and Data sources

The Jos University Teaching Hospital (JUTH) is a federal academic medical center located in northern Nigeria. JUTH provides inpatient and outpatient care services and is an affiliate of the faculty of medical sciences, University of Jos. JUTH is one of the top federal government Universities in Nigeria involved in training of medical students and is accredited by both the National Postgraduate Medical College of Nigeria and the West African Postgraduate Medical College for residency training of graduate medical doctors in various specialties. JUTH serves as a referral center for five states within Nigeria's north-central geopolitical zone. The clinical departments under the faculty of medical sciences at the University of Jos are located within JUTH, where faculty members are engaged in clinical care services, research and teaching of undergraduate medical students, training of resident doctors and allied health professionals. JUTH has 182 specialist doctors in various medical sub-specialties. There are 26 clinical and 13 non-clinical departments and units. JUTH is also an epicenter for diagnosis, treatment and care of HIV-infected adults and children in Nigeria, offering care to over 24,000 patients to date.

The Operation Stop Cervical Cancer (OSCC) unit commenced cervical cancer screening and treatment in 2006 with funding from Exxon Mobil, Texas, USA, through the African Organization for Research and Training in Cancer (AORTIC). This project started in two regional federal academic medical centers (JUTH and the University College Hospital, Ibadan in northern and south-western Nigeria, respectively). The project became institutionalized in the two regional hospitals, which have taken ownership and providing CCS services and maintaining an electronic database and backup paper records of all the women utilizing services. The data utilized in this analysis are limited to women who utilized CCS at the OSCC unit in JUTH to date. The JUTH CCS unit is located in the gynecology outpatient department of the hospital and is about 8 miles away from the adult HIV care and treatment facility supported

by PEPFAR. The screening is provided by trained nurse/midwives with supervising gynecologists who have received training in cervical cancer screening, colposcopy and treatment by cryotherapy and loop electrosurgical excision procedures (LEEP).

This study utilized de-identified patient data in the operational database of the OSCC in JUTH for this cross-sectional secondary analysis of the 3 study aims. Since the inception of the OSCC unit, women receiving services are administered a patient demographic and risk factor questionnaire prior to collection of the Pap smear sample. Each participant is given a unique medical record number, and all subsequent records including the cytopathology reports are entered in the operational database on FileMaker Pro version 8.0.[5] We utilized the sociodemographic, risk factors and cervical cancer screening cytology outcome variables in this dissertation project. The database has important variables ranging from age at first screening, socio-demographic variables, source of referrals, patient reported HIV status, presence of STIs, age at first sexual debut, smoking history, reported life-time number of sexual partners, years of completed education, use of contraceptives and other risk factors. The cervical Pap cytology screening outcomes were reported according to the Bethesda 2001 cytology reporting system.[2] The de-identified data in the database covering a period of 10 years (2006 to 2016) was accessed after obtaining institutional and IRB approvals for the secondary analysis in this dissertation. The Northwestern IRB (NUeIRB) offered a non-human subject research determination for this secondary analysis.

Data source and Derivation of Study Sample

The study utilized de-identified records of women who received cervical cancer screening services offered in an opportunistic screening program through the OSCC unit of the Jos University Teaching Hospital.

We accessed 17,016 patient records covering a period of the inception of the screening program in 2006 to 31st December 2016. After removing 2,928 multiple follow up entries, our final eligible sample of 14,088 women with records of first cervical cancer screening was used for analyses for aims 1, 2 and 3.

We also performed a retrospective cohort analysis for a subset of the primary sample of 14,088 women to understand factors associated with hazard of developing an abnormal cytology outcome in the population (secondary aim 3). For this retrospective cohort analysis, we derived a subset of 1,599 women who had normal cervical cytology at first screening and had at least one follow up cytology screening not less than 6 months after the initial screening report. We calculated the follow-up time from first cervical cancer screening to last follow-up screening or development of an abnormal cytology reported as the time variable for this analysis. The details of sample derivation for this dissertation have been summarized in Fig. 2.4 below.

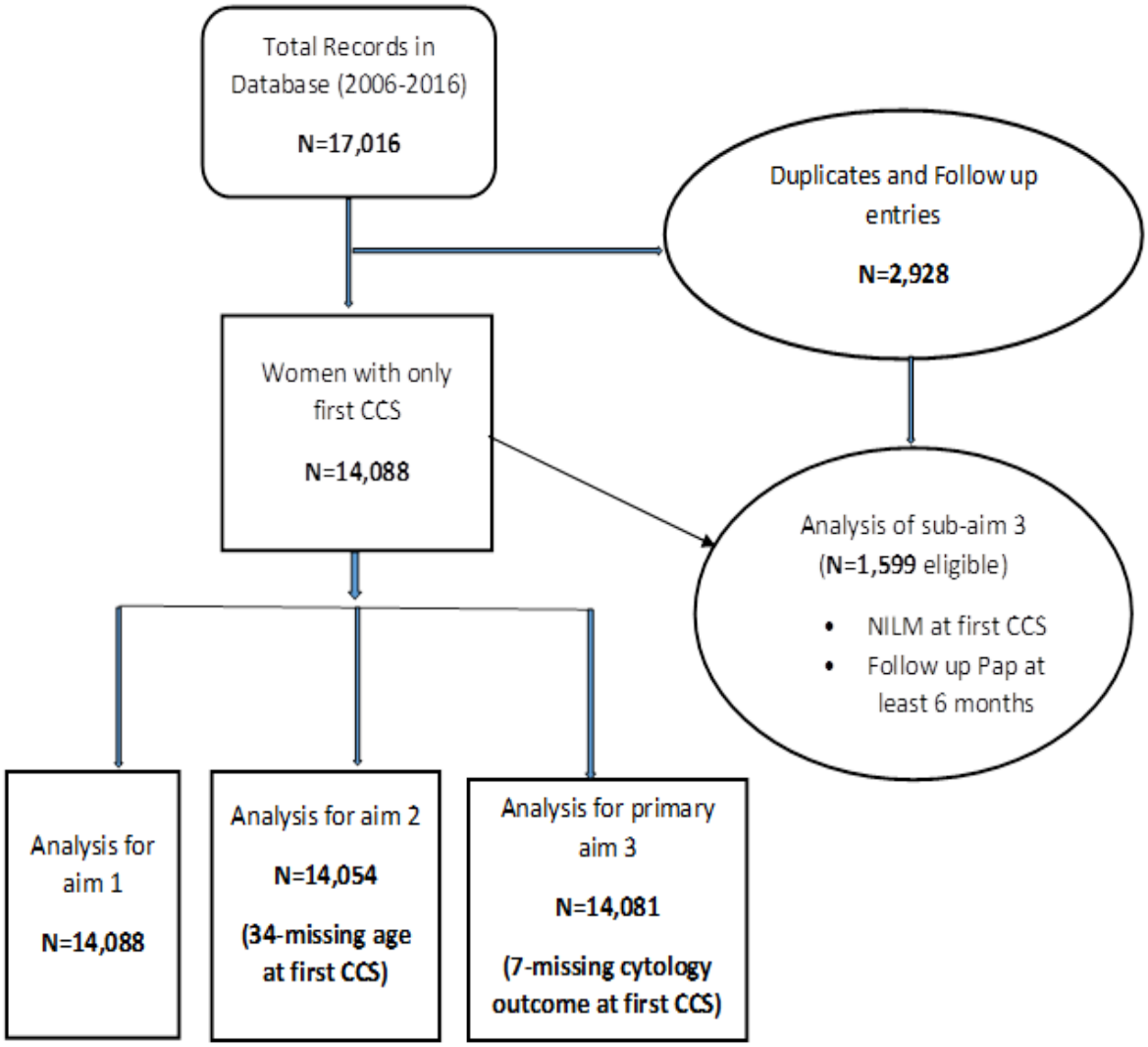

Fig. 2. 4. Study sample derivation for study aims 1, 2 and 3. Note: the subset for sub-aim 3 was derived from the primary sample of women with normal cervical cytology outcome at first CCS (NILM) and had at least one follow up cytology outcome (N=1,599)

Description of Key Study Variables

There are several variables captured in the OSCC screening database and we utilized only the key variables relevant to the analysis of the 3 aims for this dissertation project. The dependent and independent variables differ by aims, and table 2.1 below provides definitions of the key outcome and predictor variables for each aim. We have also provided some more detail information on each of the variables presented in the database derived for this dissertation. Some of the rationale for the covariates included in our analyses for each aim have been briefly described under each aim in the statistical analyses section of each aim in the respective chapters of this dissertation.

Table 2.1. ***Study population and key variables for each study aim***

Analytic sample	Key predictor variables	Primary outcome variable	Study Aim
First documented screening records of all women who have received CCS	Main independent variable: HIV status. Other covariates are: STIs, History of vaginal infection, parity, age at first CCS, age at first coitus, number of life-time sex partners, years of education completed, smoking history (yes or no), use of condoms, alcohol consumption	Provider-referral for CCS (yes or no)	1
First documented screening records of all women who have received CCS	Main independent variable: HIV status. Other covariate are: STIs, History of vaginal infection, parity, age at first coitus, number of life-time sex partners, years of education completed, smoking history (yes or no), use of condoms, alcohol consumption	Age at first CCS	2
First documented screening records of all women who have received CCS (primary aim 3)	Main independent variable: HIV status. Other covariates are: STIs, History of vaginal infection, parity, age at first CCS, age at first coitus, number of life-time sex partners, years of education completed, smoking history (yes or no), use of condoms, alcohol consumption	Abnormal screening cytology category	3 (primary aim)
First documented screening records of all women who screened with a normal cytology outcome and have documented follow up screening reports	Main independent variable: HIV status. Other covariates to control include- Age at first CCS, STIs, parity, age at first coitus, number of life-time sex partners, smoking history (yes or no), use of condoms, alcohol consumption	Time-to-detection of cervical abnormality	3 (sub-aim)

Box 1. The operational definition of independent variables and the primary outcome variables

Age at first cervical cancer screening: This is the reported age in years at the time of first cervical cancer screening.
Age at first sexual intercourse: This is the reported age in years at which a woman had first penetrative intercourse.
Total number of life time sexual partners: This is the reported number of total life time sexual partners at the time of first cervical cancer screening.
HIV status: This is the reported HIV status of the woman at the time of first cervical cancer screening. This variable is captured as either "HIV infected", "HIV uninfected", or "HIV unknown".
History of vaginal infection: This is the reported history of vaginal infection. This variable is captured as "yes", "no", or "unknown".
Ever diagnosed with a sexually transmissible infection (STI): This is the reported history of ever receiving a diagnosis of an STI from a health care provider. This variable is captured as "yes" or "no" or "unknown". Those who responded "yes" were asked to specify the type of STI diagnosis e.g.genital warts, syphyllis, gonorrhea, etc
Use of condoms: This is the reported use of condoms during sex. This variable is captured as "yes", "no", or "unknown". There was no specification on frequency, or consistency of use of condoms.
History of smoking: This is the reported history of ever smoking up to 100 cigarettes or more. This variable is captured as "yes", "no", or "unknown".
History of alcohol consumption: This is the reported history of alcohol consumption. This variable is captured as either "yes", "no", or "unknown". It did not specify the quantity of alcohol used.
Education years completed: This is the reported total number of years of formal education completed.
Parity: This is the reported total number of deliveries that a woman has had irrespective of whether those children were alive or not at the time of first cervical cancer screening.
Annual household income. This is the reported total estimate of household income in the family. This estimate was provided in Nigerian naira and converted to USD for international comparison at the 2016 exchange rate of 200 naira to 1 USD (0.005).
Source of referral: This is the reported source of referral at first CCS. This variable is either "yes" for provider-referral or "no" for self-referral.
Cytology outcome: This is the cytopathological report of the first cervical cancer screening. The cytopathological interpretation and reporting was as described by the 2001 Bethesda system of reporting.[2] The details of this classification is provided in Box 2 in Chapter 5 of this dissertation.

Statistical analysis

We used Excel 2013 to code our data variables and kept a codebook in a Microsoft 2013 word document for future reference during analysis. The final Excel database was imported to STATA version 14.1, College Station, Texas, USA for subsequent statistical analysis. We performed descriptive analysis of the baseline demographic characteristics of the study population and obtained estimates of the proportions and the corresponding 95% confidence intervals for categorical variables. We also estimated the mean/median and the corresponding standard deviation (SD) or interquartile range (IQR), where applicable, for continuous variables. Relevant distributional plots of the study sample were also obtained to assess the normality of the sample, particularly the age at first cervical cancer screening for women with HIV infection compared to women who were HIV uninfected. We also compared the baseline socio-demographic characteristics of women who were HIV infected and women who were HIV uninfected in the study sample. Categorical variables were compared using Pearson's chi-square test, while continuous variables were compared using the Student's t-test for differences in means. For all statistical tests, we estimated the 95% confidence intervals for the outcome and the level of significance was set at < 0.05.

General descriptive statistics of the study sample

During the 10-year study period (2006 to 2016), there were 17,016 records of women who received cervical cancer screening service at the OSCC. Because this cross-sectional secondary analysis focuses on data records of women at first cervical cancer screening, women with multiple follow-up visits totaling 2,928 were excluded. Therefore, our final study sample of 14,088 women was utilized for analyses of the 3 aims of this dissertation (Fig.2.4). The median age at first CCS in the sample population was 37 years (IQR, 30-45) and a mean of 38.1 years

± 10.1. More than third (37.3%) of the women, initiated CCS between ages 31 and 40, and 87.4% had first CCS between ages 21 and 50 years. A total of 703 out of 14,088 women reported their HIV status as infected, giving a patient-reported HIV prevalence of 5.0% (95% CI: 4.6, 5.4). The descriptive statistics for other socio-demographic characteristic of the study sample have been summarized in table 2.2. Also, the baseline socio-demographic characteristic of the women with reported HIV infection compared to women not HIV infected is summarized in table 2.3. Figs. 2.5 to Fig.2.7 showed the distributional plots of the sample assessing normality of age distribution at first CCS. Fig.2.8 showed the pie chart distribution of age groups at first CCS. All the Tables of results and Graphs referenced in this chapter and in chapters 3, 4, and 5 of this dissertation are in chapter 7 (Tables, Figures and Graphs).

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Chapter 3. The Association between Patient-reported HIV Status and Provider-referral for Screening in an Opportunistic Cervical Cancer Screening Setting in Jos, Nigeria

Abstract

Background

Cervical cancer screening is an important health service intervention for prevention of morbidity and mortality from invasive cervical cancer. The role of provider-referral is critical in utilization of this services particularly in settings where screening is largely opportunistic. We sought to understand how patient-reported HIV status is associated with provider-referral in an opportunistic screening setting.

Methods

We utilized a database of women who had received cervical cancer screening at the OSCC in Jos, Northern Nigeria covering a period of 10 years (2006-2016). We used the de-identified records of women who had their first CCS to analyze the association of patient-reported HIV and likelihood of provider-referral at first CCS. We performed descriptive statistics with relevant test of association using t-test for continuous variables and chi square test or Fisher exact test where applicable for categorical variables. We also used a bivariable and multivariable logistic regression models to estimate the independent association of patient-reported HIV on provider

referral. All statistical tests were performed using STATA version 14.1, College Station, Texas, USA. Level of statistical significance was set at 0.05.

Results

During the 10-year period, 14,088 women had their first CCS. The HIV prevalence in the population was 5.0%; 95% CI: 4.6, 5.4 (703/14,088). The median age of women who were screened for CC was 37 years (IQR; 30-45). Women who were HIV infected received more referrals from providers compared to women who were HIV uninfected (68.7% versus 49.2%). Similarly, we found an independent effect of patient-reported HIV infection on the likelihood for provider-referral in the study population (aOR=2.35; 95% CI: 1.95, 2.82).

Conclusion

Our analysis supports the design of health systems that facilitates providers' engagement and provision of necessary counseling for CCS in the course of routine clinical care. The practice of offering referrals for CCS to women at high risk of cervical cancer, such as HIV infected women should be supported.

Introduction

Of the half million new cases of invasive cervical cancer (ICC) reported globally each year, over 80% occur in Low-and Middle Income Countries (LMICs)[1]. Nigeria is one of these countries with a huge burden of ICC incidence and mortality.[2] The Global Burden of Cancer 2013 ranked cervical cancer the 2nd most common in incidence and mortality among all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health care service intervention for reducing ICC incidence and mortality and its benefits are evident from data in developed

countries, where organized CCS programs have resulted to a substantial declined in ICC incidence and mortality. [4-10] However, in Nigeria and other LMICs where organized CCS programs are lacking, the opportunity to have a screening test likely depends on several factors ranging from availability of screening, offering screening recommendations by providers, to health system support to overcome barriers to accessing services. The literature on cancer screening suggest that it is a process of care, consisting of several steps and interfaces between patients, providers, and health care organizations.[11] In this context, screening rates are largely driven by strategies that limit the number of interfaces across organizational boundaries; recruiting patients, promoting referrals, and facilitate appointment scheduling; and promote continuous patient care.[11] The organizational capability of the health care system to address these boundaries could explain the relatively higher CCS rates of 83% in the US[12], in comparison to Nigeria and similar LMICs in sub-Saharan Africa with much lower CCS rates, ranging between 6-8%.[13,14]

Indeed, we have an established body of literature on the effectiveness of provider recommendation for screening on cervical cancer screening participation.[11,15-18] Also, we have evidence in HIV (Human Immune deficiency Virus) infected populations, suggesting that women's awareness that HIV infection increases the risk of ICC and having a strong provider-patient relationship were significant facilitators for CCS utilization.[19]

Provider-patient discussions about cervical cancer screening and offering referrals for such screening are critical because there is a high burden of HIV in Nigeria and also a high burden of HIV-associated precancerous abnormalities of the cervix and invasive cervical cancer in HIV infected population.[20-22] We, however, do not understand the relationship between patient-reported HIV infection and provider behavior in providing a cervical cancer screening referral during the care process particularly in settings where cervical cancer screening is

largely opportunistic. In brief, opportunistic screening is dependent on a woman or her healthcare provider taking the initiative to do a pap test.[23] Indeed, strategies to improve early detection of cervical cancer through screening have focused either on opportunistic screening requested by a provider or an individual, or organized cervical cancer screening in which a defined population is contacted and invited to screen at regular scheduled intervals.[24] We therefore hypothesize that in opportunistic screening settings, women with HIV infection are more likely to receive a provider-referral for cervical cancer screening compared to women who are HIV uninfected.

Methods

Study design and setting

We performed a retrospective cross-sectional secondary analysis of data on a sample of women who had received a cervical cancer screening at the “Operation Stop” cervical cancer (OSCC) unit in Jos, Nigeria over a 10-year time period (2006-2016). The OSCC unit commenced cervical cancer screening and treatment in 2006 with funding from Exxon Mobil, Texas, USA, through the African Organization for Research and Training in Cancer (AORTIC). This project offered opportunistic cervical cancer screening services to eligible women in Jos, neighboring towns, and states in northern Nigeria. Also, the project has maintained an up-to-date electronic database and backup paper records of women utilizing the service. This database has records of patient demographic and risk factor variables that are obtained from eligible women at the first screening visit prior to cervical sample collection for Pap smear test. Each participant is given a unique medical record number, and all subsequent records including the cytopathology reports are entered into an operational database on FileMaker Pro version 8.0.[25]

Study sample

This study utilized de-identified patient data in the OSCC electronic database. After obtaining relevant IRB approvals for this study, we accessed the sociodemographic, risk factors and cervical cancer screening cytology outcome variables for this analysis. Our source database included all women who had received cervical cancer screening with cytology report documented in the database. We excluded follow-up entries and utilized only the records at the first cervical cancer screening. The detailed description of the study sample derivation is illustrated in Fig. 2.4.

Key independent and primary outcome variables

The electronic database has important variables ranging from age at first screening, socio-demographic variables, source of referrals, patient-reported HIV status, presence of STIs, age at first sexual debut, smoking history, alcohol consumption, reported lifetime number of sexual partners, parity, years of completed education, use of contraceptives and other risk factors. The cervical pap cytology screening outcomes were reported according to the Bethesda 2001 cytology reporting system.[26] The summary of the key independent and dependent variables have been described in Table 1. The primary outcome variable for this aim was source of referral. This variable is captured as binary: “yes” for provider-referral and “no” for self-referral. The main independent variable was HIV status. The operational definition of the variables has been described in Box 1 in chapter 2 of this dissertation.

Statistical Analysis

Descriptive statistics: We performed summary statistics on continuous and categorical variables of the study sample and obtained means, medians and proportions for the independent variables and outcome. We also compared the baseline characteristics of the sample with the primary outcome. Since the principal exposure variable in this analysis was

patient-reported HIV, we estimated the proportion of women who received a provider referral for CCS by patient-reported HIV status. We then performed a Pearson's chi square test of the association between reported HIV status and provider-referral for CCS.

Bivariable and multivariable logistic regression model: To understand the independent effect of HIV status on the likelihood of receiving a provider referral for a CCS, we evaluated the unadjusted association between HIV status and provider referral using logistic regression to get an unadjusted OR and 95% CI. A multivariable logistic regression analysis was performed to assess the independent effect of HIV status on provider referral for CCS adjusting for other characteristics. The adjusted OR and 95% Cis were computed from the final model.

In the first step, we created a new binary variable "HIV status" from patient reported HIV to either "HIV infected" as "1" and "HIV not infected" as "0". Women who did not know their HIV status were treated as "missing". Similarly, we created indicator (dummy) variables from age at first screening, parity, number of lifetime sexual partners, education groups, age at first sexual intercourse, reported history of vaginal infection and ever diagnosed with an STI. We also created a binary variable "referral group" with "provider-referral" as "1" and "self-referral" as "0". The significant predictor variables associated with receiving a provider referral in the bivariable logistic regression analyses were included in a multivariable logistic regression model to estimate the independent effect of patient reported HIV infection on the likelihood of receiving provider referral in the study sample. Our final predictive model was selected using the backward selection method, and the model fitness was assessed by the Hosmer-Lemeshow goodness-of-fit test. A p-value greater than 0.05 is considered a good model-fit.[27] We also considered the magnitude of change in the likelihood ratio chi square for each model before selecting the final model that best fits our data.

Results

During the 10-year study period (2006 to 2016), there were 17,016 records of women who received cervical cancer screening services (Pap test) at the OSCC. Since this cross-sectional secondary analysis focuses on data records of women at first cervical cancer screening, women with multiple follow-up visits were excluded for this analysis (see Fig. 2.4 for details of sample derivation).

Therefore, a final study sample of 14,088 women was utilized in this analysis. The median age at first CCS in the sample population was 37 years (IQR, 30-45) and a mean of 38.1 years ± 10.1. A total of 703 out of 14,088 women reported their HIV status as infected leading to patient-reported HIV prevalence of 5.0% (95% CI: 4.6, 5.4). The proportion of women who received provider referral was 50.1 % (95% CI: 49.2, 50.5), while women who received CCS by self-referral was 49.9% (95% CI: 49.1, 50.8). When we compared the proportion of women who received a provider referral by patient reported HIV status, we found that 68.7% (95%CI: 65.3, 72.1) of women with HIV received a provider referral compared to 49.2% (95% CI: 48.4, 50.1) of women who were HIV uninfected. The student's t-test of the difference in this proportion was statistically significant; p-value <0.001. Also, the unadjusted odds ratio for receiving a provider referral if HIV infected was 2.27 (95% CI: 1.92, 2.68) compared to being HIV uninfected. The unadjusted odds ratio for receiving a provider referral for other patient-reported socio-demographic and risk factors have been summarized in table 3.2. In the final model, adjusting for smoking, age at first coitus < 22 years, age at first CCS ≥ 35 years, parity ≥ 5, history of condom use for sex, and 7-12 years of completed education, women with who reported HIV infected were 2.35 times more likely to receive a provider referral for their first CCS compared to women who were HIV uninfected (aOR=2.35; 95% CI: 1.95, 2.82, p=0.001). Other socio-demographic factors that were independently associated with provider-referral for

first cervical cancer screening were age ≥ 35 years (aOR=1.25, 95% CI: 1.15, 1.35), parity ≥ 5 (aOR=1.18, 95% CI: 1.09, 1.28), age at first sex ≤ 22 years (aOR=1.27; 95% CI: 1.16, 1.39), smoking history (aOR=3.20; 95% CI: 1.67, 6.12) and use of condoms (aOR=1.47; 95% CI: 1.28, 1.70). We also found that women who reported completing 7-12 years (grade 7 to high-school) of education were less likely to receive a provider-referral than women with less than 7 years (equivalent to grade 6 or less) of completed education (aOR=0.77; 95% CI: 0.71, 0.84). These results have been summarized in Tables 3.1 and 3.2 in chapter 7 (supplementary material) of this dissertation.

Discussion

The principal findings in this analysis showed that women who reported being HIV infected were more than 2 times more likely to be referred by a provider at the time of first cervical cancer screening compared to women who were HIV uninfected (aOR=2.35; 95% CI: 1.95, 2.82). We also found that women who had completed 7-12 years of education were less likely to received provider-referral compared to women of less than 7 years of completed education (aOR=0.77; 95% CI: 0.71, 0.84). Other socio-demographic factors that were significantly associated with provider-referral for first cervical cancer screening were age ≥ 35 years, parity ≥ 5, age at first sex ≤ 22 years, smoking history, and use of condoms.

This cross-sectional secondary analysis with findings that patient-reported HIV was significantly associated with provider-referral at first cervical cancer screening is particularly important since several studies have found that HIV infected women are at greater risk of developing precancer and invasive cervical cancer. Because of this risk, studies have demonstrated the critical role of health care providers in linking HIV infected women to important reproductive health services including cervical cancer screening in areas with a high HIV

burden.[28] The finding that patient-reported HIV was associated with provider-referral in our study population is not surprising giving that the OSCC is located in one of the tertiary health institutions supported by Presidential Emergency Plan for AIDS Relief (PEPFAR) and one of the largest facilities that offers HIV care and treatment in West Africa. It is possible that providers offering HIV care to these women are aware of both the risk of cervical cancer in these women and the availability of screening services in the facility, thereby offering referral to such high-risk population. Indeed, prior reports on the role of medical care providers facilitating cervical cancer screening for HIV infected women receiving care in the same facility with a gynecologic care provider has been documented in a U.S. HIV population,[29] and it has been recommended that HIV care be integrated with gynecologic care, and educating clinicians to recommend cervical cancer screening to these women could significantly improve adherence and utilization of cervical cancer screening.[30,31]

Although, the prevalence of smoking is reportedly very low (0.6%) in our study population, these women were more likely to have received a provider-referral for their first cervical cancer screening. This could be related to provider's knowledge that smoking is a risk factor for cervical cancer[32-36] thereby initiating counselling and offering screening referrals for such high-risk women. Other demographic factors such as age and parity have been documented in previous studies as epidemiologic risk factors for cervical precancer and progression to invasive cancer.[37] These demographic factors were also found to be significantly associated with a higher likelihood for receiving a provider-referral at the time of first cervical cancer screening in our study population.

The finding that more educated women were less likely to receive provider-referral for first cervical cancer screening is interesting. This possibly implies that more educated women were more likely to be aware of cervical cancer screening and more likely to self-refer themselves for cervical cancer screening compared to the less educated. This explanation has some plausibility

given the findings of recent systematic review of qualitative studies on the barriers to utilization of Pap screening in sub-Saharan Africa.[38] The systematic review reported client factors such as lack of knowledge and awareness about Pap smear among the barriers for low utilization of Pap screening.[38] Also related to provider-referral, the study found that provider barriers such as failure to inform or encourage women to screen were important provider factors contributing to low Pap utilization in sub-Saharan Africa.[38] A related systematic review also recommended improvement in cervical health education, addressing cultural beliefs and practices, spousal support, provider attitude and addressing the problems of cost and physical access to cervical cancer screening services as interventions to improve screening utilization in sub-Saharan Africa.[39]

Our findings suggest that women with known potential risk factors for cervical cancer such as HIV infection, multiparity, and smoking were more likely to be referred for screening by providers. This is an important finding for opportunistic cervical cancer screening, and implementation of screening guidelines in such settings should encourage providers to assess potential risk factors in women accessing routine clinical care and those with such reported risk factors should be given screening referrals and encouraged to receive cervical cancer screening. Studies have also identified that interventions that increased discussions between providers and women, educating women on the benefits of screening, and allaying their fears on possible screening outcomes are significantly associated with participation in screening.[40]

The strength of our study findings is related to the relatively large sample size of our study population spanning a decade of cervical cancer screening services offered in an opportunistic setting in a cosmopolitan Nigerian city that also offers care to a large population of HIV infected adults in West Africa. To the best of our knowledge this is the first secondary analysis of CCS data in Nigeria focusing on understanding the contributions of providers in utilizing cervical cancer screening. We feel that our findings could be generalized to other settings in West Africa with

ongoing HIV care and availability of opportunistic cervical cancer services. We however, recognize and acknowledge the limitations of self-reported risk factors in this analysis. It is possible that some women may have concealed some information that could affect the internal validity of our estimates.

Our future research will aim at elucidating provider and patient perspectives on the facilitators and barriers to cervical cancer screening in an opportunistic screening setting using qualitative research methodology. For instance, it will be appropriate to understand the perspectives of providers on implementation of cervical cancer screening guidelines in Nigeria and the factors that could enhance adherence to such guidelines in various practice settings. It is also important to understand patient perspectives on the acceptability of male providers performing pelvic examinations and alternative screening methods such as self-sampling for HPV testing in various cultural settings in Nigeria. Despite the limitations identified in this secondary data analysis, healthcare providers in Nigeria should be encouraged and supported to make cervical cancer screening recommendations during routine clinical care to eligible women who have not had a cervical cancer screening. This is particularly important in the current Nigerian setting where HPV vaccination is not supported and the opportunity for screening is largely dependent on provider-initiated counseling and screening either by the provider or through referral to facilities offering a screening service.

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Chapter 4: The Association between Patient-reported HIV Status and Age at First Cervical Cancer Screening in Jos, Nigeria

Abstract

Background

Although cervical cancer screening (CCS) provides opportunities for early detection and treatment of premalignant precursors of the cervix, the optimal recommended age for initiating screening is an ongoing debate and varies with guidelines. The age at first screening is not known in Nigeria, and we sought to estimate the age at which women have first CCS and whether this differs by HIV infection status in an opportunistic screening setting.

Methods

We utilized a database of women who had received cervical cancer screening at the OSCC in Jos, Nigeria covering a period of 10 years (2006-2016). The de-identified records of women who had their first CCS was used to analyze the association between patient-reported HIV status and the mean age at first CCS. We performed descriptive statistics with relevant tests of association using a t-test for continuous variables and a chi-square or Fisher exact test where applicable for categorical variables. We also used bivariable and multivariable logistic regression models to estimate the independent effect of patient-reported HIV on the likelihood of having first CCS before age 35 years. All statistical tests were performed using STATA version 14.1, College Station, Texas, USA. Level of statistical significance was set at 0.05.

Results

During the study period 14,054 out of the 14,088 (99.8%) women in the study sample reported their age at first screening. The median age at first CCS was 37 years (IQR; 30-45). The proportion of women who screened at <35 years was significantly higher in women who were HIV infected (51.5%) than women who were HIV uninfected (40.2%). The mean age at first screening was 35.0 ± 7.4 years for HIV infected women compared to 38.2 ± 10.2 years for HIV uninfected women (p-value=0.001). In the multivariable logistic regression model adjusting for the effect of education years completed, history of vaginal infection, use of condoms and history of smoking, patient-reported HIV status was not significantly associated with first CCS at age <35 (adjusted OR= 1.18; 95% CI: 0.99 - 1.41). We found that women who completed at least 7-12 years of education were 1.27 to 3.51 times more likely to have first CCS at <35 years compared to women with less education.

Conclusion

The median age at first CCS is relatively late compared to the recommended age for initiating CCS by most guidelines from developed settings. Though HIV infected women on the average initiate CCS at relatively younger age compared to the HIV uninfected women, education is a significant factor for early initiation of CCS in our setting.

Introduction

Although invasive cervical cancer (ICC) has a well-known natural history with treatable precancerous abnormalities detectable through screening, it is a significant public health burden in Low-and Middle-Income Countries (LMICs). Of the half million new cases of ICC reported

globally each year, over 80% occur in LMICs[1]. Nigeria is one of these countries bearing a huge burden of CC incidence and mortality.[2] The Global Burden of Cancer 2013 ranked cervical cancer the 2nd most common in incidence and mortality for all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health care intervention for reducing ICC incidence and mortality. The benefits of CCS are evident from data in developed countries, where organized CCS programs have led to a substantial decline in ICC incidence and mortality. [4-10] In Nigeria the high prevalence of HIV and the lack of organized CCS programs could be significant contributing factors to the high burden on invasive cervical cancer. In such settings where organized CCS programs are lacking, the opportunity to have a screening test likely depends on several factors including the availability of a screening service and system support to overcome barriers to accessing such services; patient-related factors such as risk perception for ICC, illiteracy, and lack of awareness of CCS, or where to go for such screening.[11-14] Other patient-related factors such as cost of screening, health insurance coverage, education, perception of screening benefits and ability to overcome barriers to accessing services are significant contributors.[12,15] Sadly, the current Nigerian Health Insurance System does not provide health coverage for cancer screening or treatment, and women who go for screening or cancer treatment incur heavy out-of-pocket expenses.[16,17] This cost-related factor could be a barrier to cervical cancer screening utilization in such settings, particularly if family income is not sufficient for other competing needs. Also, provider-related factors such as behavior towards screening counseling and providing a screening referral during the course of routine clinical care to eligible women have been shown to be effective in increasing CCS utilization.[18,19]

The framework for improving the quality of cancer care provides a plausible explanation of how failures at various levels in the care processes could affect the delivery of critical preventive care services for cancer. [20] These include failure in the organization of care that enable patients

and providers to conduct risk assessment to provide screening counseling to women at risk; failure to detect precancerous abnormalities and offer appropriate treatment, or failure in other processes of care for improving ICC outcomes.[20] For instance, failure of providers to initiate CCS recommendation to eligible women population during opportunistic clinical care visits could lead to women missing the critical opportunity to have a screening test even when seen in health facilities offering such services. Closely related to provider factors is the evidence in HIV (Human Immune deficiency Virus) infected populations, suggesting that women's awareness that HIV infection increases the risk of ICC and having a strong provider-patient relationship were significant facilitators for CCS utilization.[21]

Previous studies have shown that development of invasive cervical cancer occurs at a lower median age of 35 years in HIV positive women compared to a median age of 40 years in women who are HIV negative. [22]. Also, among women less than age 35, being HIV positive confers a 4-fold higher risk of having ICC compared to being HIV negative.[22] In a large cervical cancer screening program in Zambia, data on age at screening showed that the median age at first cervical cancer screening was unexpectedly higher in HIV seropositive women compared to HIV seronegative women.[23] In Nigeria, the age at which women initiate CCS is not known; we therefore hypothesized that the median age at first CCS is lower in women with reported HIV compared to the median age of women who are HIV negative in an opportunistic cervical cancer screening service in Nigeria.

Methods

Study design and setting

We performed a retrospective cross-sectional analysis of data on a sample of women who had received a cervical cancer screening at the "Operation Stop" cervical cancer (OSCC)

unit in, Jos, Nigeria over a 10-year time period (2006-2016). The OSCC unit commenced cervical cancer screening and treatment in 2006 with funding from Exxon Mobil, Texas, USA, through the African Organization for Research and Training in Cancer (AORTIC). This project offered opportunistic cervical cancer screening services to eligible women in Jos, neighboring towns, and states in northern Nigeria. Also, the project has maintained an up-to-date electronic database and backup paper records of all women utilizing the service. This database has records of patient demographic and risk factor variables that are obtained from eligible women at the first screening visit prior to cervical sample collection for Pap smear test. Each participant is given a unique medical record number, and all subsequent records including the cytopathology reports are entered into an operational database on FileMaker Pro version 8.0.[24]

Study sample

This study utilized de-identified patient data in the OSCC electronic database. After obtaining relevant IRB approvals for this study, we accessed the sociodemographic, risk factors and cervical cancer screening cytology outcome variables for this analysis. Our source database included all women who had received cervical cancer screening with cytology report documented in the database. We excluded follow-up entries, and utilized only the records at the first cervical cancer screening. The detailed description of the study sample derivation is illustrated in Fig. 2.4.

Key independent and primary outcome variables

The electronic database has important variables ranging from age at first screening, socio-demographic variables, source of referrals, patient-reported HIV status, presence of STIs, age at first sexual debut, smoking history, alcohol consumption, reported lifetime number of sexual partners, parity, years of completed education, use of contraceptives and other risk factors. The cervical Pap cytology screening outcomes were reported according to the Bethesda 2001 cytology reporting system.[25] The key independent and dependent variables have been

described in Table 1 of chapter 2 of this dissertation. The primary outcome variable for this aim is age at first cervical cancer screening. This variable is continuous and is recorded as the age in years of the woman at the time of first cervical cancer screening. The primary independent variable is patient-reported HIV status documented at the time of first cervical cancer screening. The operational definition of other independent variables has been described in Box 1 in chapter 2 of this dissertation.

Statistical Analysis

Descriptive statistics: We performed summary statistics on continuous and categorical variables of the study sample and obtained means, medians and proportions for the independent variables and outcome. We also compared the baseline characteristics of the sample with the primary outcome. Since the principal exposure variable in this analysis was patient-reported HIV status, we estimated the mean age of women who received a cervical cancer screening by patient-reported HIV status. We performed the Student's t-test of differences in means between two groups (mean age of women who were "HIV infected" as group 1, and mean age of women who were HIV uninfected as group 2. In this analysis, women who did not know their HIV status were treated as missing. We also compared the baseline socio-demographic characteristics of the sample by age at first screening <35 years compared to ≥35 years.

Bivariable and multivariable logistic regression model: To further understand the independent effect of patient-reported HIV on the age at first CCS, we performed bivariable logistic regression analysis using various demographic variables as independent variables and dichotomizing the age at first CCS as either < 35 years as the primary outcome "1" or age at first CCS ≥ 35 years as the referent category "0". We also created dummy variables for other socio-demographic variables such as smoking, alcohol, years of completed education (< 7

years as group 1, 7-12 years as group 2 and > 12 years as group 3), history of ever been diagnosed with an STI, age at first coitus, history of vaginal infection, total lifetime number of sex partners, parity, and provider-referral. We first performed a bivariable logistic regression on each of these reported characteristics with age at first CCS < 35 years as the primary outcome. We then used a multivariable logistic regression model to assess the independent predictive effect of patient-reported HIV on the likelihood of having a first CCS at age <35 years in our cervical cancer screening population. We used the backward selection method to build our final predictive model. We estimated 95% confidence intervals for each of these measures of association and corresponding p-values. We assessed model fit by the Hosmer-Lemeshow goodness-of-fit statistical test.[26] A p-value of greater than 0.05 was considered a good model-fit.

Results

During the study period 14,054 out of the 14,088 (99.8%) women reported the age at first screening. The proportion of women who screened at < 35 years was significantly higher in women who were HIV infected (51.5%) compared to women who were HIV uninfected (40.2%) (p <0.001). The mean age at first screening for HIV infected women was 35.0 ± 7.4 years compared to 38.2 ± 10.2 years for HIV uninfected women (p-value=0.001). The Boxplot in Fig. 2.5 in the supplementary section in chapter 7 of this dissertation showed a significant difference in the age at first CCS for HIV infected women versus HIV uninfected women. Figs. 2.3 and 2.4 showed the normal distribution of age at first screening in HIV infected compared to women HIV uninfected. Most women had their first CCS between the age of 31-40 years (37.3%; 95% CI: 36.5, 38.1). Fig. 2.8 showed the pie chart distributions of the age groups at which women had their first CCS in the sample population. The baseline comparability for other socio-demographic

variables in relation to screening at < 35 years compared to ≥ 35 years have been summarized in Table 4.1.

In the bivariable logistic regression analysis shown in Table 4.2, we found that being HIV infected was significantly associated with having a first CCS at <35 years with an unadjusted OR=1.58, 95% CI: 1.36-1.84. Other sociodemographic characteristics that were significantly associated with first CCS at < 35 years were: 7-12 years of completed education (OR=3.12, 95% CI: 2.75, 3.53); >12 years of completed education (OR=1.53; 95% CI: 1.36, 1.72); total life-time number of sex partners ≥3 (OR=1.14; 95% CI: 1.05, 1.24); history of condom use during sex (OR= 2.26; 95% CI: 1.98, 2.58); history of vaginal infection (OR=1.39; 95% CI: 1.27, 1.53); and past diagnosis of an STI (OR=1.23; 95%CI: 1.10, 1.37). In the bivariable logistic regression, we also found that women who received a provider referral (OR=0.75; 95% CI: 0.70, 0.80), parity ≥5 (OR=0.83; 95% CI: 0.47, 0.55), age at first sexual debut ≤22 years (OR=0.83; 95% CI: 0.77, 0.90), and alcohol consumption (OR=0.61; 95% CI: 0.53, 0.71) were significantly less likely to have their first CCS before age 35 years.

In the multivariable logistic regression model adjusting for the effect of education years completed, history of vaginal infection, use of condoms and history of smoking, the effect of HIV on the age at first CCS was not statistically significant (adjusted OR= 1.18; 95% CI: 0.99 - 1.41). The adjusted effect of these covariates has been summarized in Table 4.2, and notably, women who completed 7-12 years of education or more were 1.27 to 3.51 times more likely to have had first CCS at less than 35 years compared to women with less education. The adjusted model was fit for these covariates with a Hosmer-Lemeshow goodness-of-fit test p-value=0.538.

Discussion

This analysis provides knowledge on the age at which women initiate cervical cancer screening and the possible factors associated with the age at first cervical cancer screening in Nigeria. We hypothesized that women with reported HIV infection were significantly more likely to have their first cervical cancer screening at younger age compared to women HIV uninfected.

The first principal finding in this analysis showed that women in the study sample had their first cervical cancer screening at a median age of 37 years (IQR 30-45). We also found that on average, women who were HIV infected had their first CCS at a younger age than women who were HIV uninfected (35.0 ± 7.4 years versus 38.2 ± 10.2 years). Also, in the adjusted model, though the effect of patient-reported HIV infection was not significantly associated with first CCS at < 35 years, this association showed a trend towards statistical significance (aOR=1.18; 95% CI: 0.99, 1.41, p=0.058). The second principal finding in our analysis showed that women who completed 7-12 years of education or more were 1.27 to 3.51 times more likely to have had their first CCS before age 35 than women with less education.

Our study findings have significant implications for cervical cancer prevention and screening in Nigeria. First, the median age at first cervical cancer screening is relatively late at 37 years and this is of concern for cervical cancer prevention and control given the evidence that invasive cervical cancer occurs at a median age of 35 years in HIV infected women, 40 years in HIV uninfected women, and 38 years in women with unknown HIV status.[22] The relatively late screening age in our sample suggests that many women may have already developed precancerous conditions of the cervix or invasive cancer. This finding could also explain the high rate of late presentation of invasive cervical cancer with high death rate as reported in previous studies related to cervical cancer survival in Nigeria and similar settings in Africa.[27-30] Also of

greater concern is the finding that HIV infected women had their first cervical cancer screening at the mean age of 35.0 ± 7.4 years, which is the corresponding age at diagnosis of most invasive cervical cancer cases in HIV infected women reported in Zambia.[22] Related to the age at first cervical cancer screening, an earlier study report from a district hospital in Abuja, Nigeria's federal capital, found a mean age of 32.0 ± 6.6 years at first cervical cancer screening by visual inspection with acetic acid (VIA).[31] Compared to the mean age of 35.0 ± 7.4 years at first CCS in our study sample, the slightly lower mean age at first screening in the Abuja HIV population could partly be explained by the mode of screening using VIA, and the specific program intervention, which involved active interaction between HIV infected women receiving antiretroviral therapy and provider-initiated cervical cancer screening with VIA during the intervention period.[31] VIA is technically less sophisticated than cytology-based screening which is usually done in tertiary health care facilities with cytopathologic support. However, cytology-based screening methods have been shown to be more specific in detecting cervical precancer in HIV infected populations irrespective of immune status and antiretroviral treatment.[32] Overall, the findings on age at first screening in our study population have broadened our knowledge and understanding of the current situation on cervical cancer screening services in Nigeria and the need to utilize these important findings for health policy advocacy at states and federal ministries of health to guide the next steps for effective cervical cancer prevention and control in Nigeria.

Our analysis also revealed the critical role of educating women and girls as a social capital intervention to improve cervical cancer screening utilization, particularly with regard to early initiation of cervical cancer screening. We found that women who completed 7-12 years of education or more were 1.27 to 3.51 times more likely to have had their first CCS before age 35 than women with lesser educational attainment. Similar findings in Kenya showed that women with at least a secondary education were more likely to have a cervical cancer screening

compared to women with primary level education or less.[33] Our study findings support the existing literature on the impact of women's education on health outcomes including cervical cancer screening utilization. For instance, several study reports have shown that educational attainment significantly improves utilization of maternal health care services including cervical cancer screening.[34-38] Related to the role of education improving cervical cancer outcomes is the association between country-level socio-demographic index (SDI) and cervical cancer burden, with high SDI countries having a significantly lower ICC burden compared to Nigeria and other low SDI countries.[39] In brief, the SDI ranges between 0 and 1, and is a summary indicator derived from measures of income per capita, educational attainment, and fertility.[39] An SDI of 1 represents a location with the highest observed educational attainment, the highest log income per capita, and the lowest fertility rate.[39] A previous related index, the human development index (HDI), which also includes adult literacy rate and primary to tertiary education enrollment rates, has been shown to correlate inversely with incidence and mortality from invasive cervical cancer, with greater reductions in cervical cancer incidence in very high HDI compared to low HDI countries.[40]

We also found that women with reported use of condoms for sex (aOR=1.96; 95% CI: 1.70, 2.27) and vaginal infection (aOR=1.29; 95% CI: 1.15, 1.43) were significantly more likely to have their first cervical cancer screening before age 35. These findings could be related to the perceived risk for cervical cancer in the presence of these sexual risk factors and could have triggered either provider-referral or self-referral for cervical cancer screening at a relatively younger age compared to women without these risk characteristics in the study population.

The strength of our study findings is related to the relatively large sample size of 14,088 women who provided age at first cervical cancer screening in 99.8% (14,054) of the sample population. This health services data also spanned a decade of cervical cancer screening offered

in an opportunistic setting in a cosmopolitan Nigerian city that also offers care to a large population of HIV infected adults in West Africa. To the best of our knowledge this is the first secondary analysis of CCS data in Nigeria that provides precise estimates of the age at which women had first cervical cancer screening. We feel that our findings have external validity and could be generalized to other settings in West Africa with ongoing HIV care and availability of opportunistic cervical cancer services. We however, recognize and acknowledge the limitations of self-reported risk factors in this analysis. It is possible that some women may have concealed some information that could affect the internal validity of our estimates. Related to the limitations of self-reported data, the age at first CCS provided in this study population may not be correct and our findings should be interpreted in the context of self-reports.

Our future research will focus on understanding provider and patient perspectives on the facilitators and barriers to cervical cancer screening in an opportunistic screening setting using qualitative research methodology. However, our current findings could guide health decision makers in the implementation of cervical cancer screening guidelines particularly in our settings were cervical cancer screening are largely opportunistic. Specifically, our findings of a relatively late age at first cervical cancer screening particularly in HIV infected women population will require a more focused effort and investment on awareness creation that women will benefit more by starting screening at a younger age in order to maximize the benefits of CCS to prevent morbidity and mortality due to ICC in the population. Our findings also provides evidence to design interventions focusing on health care providers to discuss risk, counseling and recommendation for women to initiate CCS at age 21 in accordance with most CCS guidelines.[4,41,42] At the moment, Nigeria does not have a national guideline for cervical cancer screening; therefore, our findings provide evidence supporting the adoption and implementation of CCS guidelines by health care providers in Nigeria. This could lead to significant improvement in screening, detection and

treatment of precancerous cervical lesions at an early age, particularly in high-risk women who are HIV infected.

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Chapter 5: Predictors of Abnormal Cervical Cytology Screening Outcome among Women at First Cervical Cancer Screening in Jos, Nigeria

Abstract

Background

Cervical cancer screening services offer opportunities for early detection and treatment of precursor cervical cancer lesions. Efficient use of limited resources, particularly in Low and Middle-Income Countries (LMICs) could be streamlined to screen women with high probability for underlying cervical precancer or cancer. We sought to assess the factors associated with abnormal cervical cytology outcome at first CCS in an opportunistic screening setting.

Methods

We utilized a database of women who had utilized cervical cancer screening at the OSCC in Jos, Northern Nigeria covering a period of 10 years (2006-2016). The de-identified records of women who had their first CCS was used to analyze the association of patient-reported HIV and the likelihood for an abnormal cervical cytology outcome at first CCS. We performed descriptive statistics with relevant tests of association using a t-test for continuous variables and a chi square or Fisher exact test where applicable, for categorical variables. We also used a bivariable and multivariable logistic regression models to estimate the independent effect of patient-reported HIV on the likelihood of an abnormal cervical cytology outcome at first CCS. All statistical tests were performed on STATA version 14.1, College Station, Texas, USA. Level of statistical significance was set at 0.05.

Results

During the study period, 14,081 (99.95%) women had cervical cytology reports out of the total 14,088 women that had first CCS in the database. Mild and severe cervical dysplasia was reported in 9.7% and 4.6% of the sample, respectively. Specifically, 4.11% with ASCUS, 5.62% with LSIL, 1.61% with ASCUS-H, 0.22% with AGUS, 2.50% with HSIL, and 0.23% with HSIL with suspicion for invasion. The median age for the various cytology categories were: 43 years for ASCUS, 45 years for LSIL, 47.5 years for ASCUS-H, 40 years for AGUS, 47 years for HSIL, and 52 years for HSIL with suspicion for invasion. There was no statistically significant difference in either mild or severe cervical dysplasia with reported HIV status in the study sample (p-value=0.930). The sociodemographic variables significantly associated with an abnormal cervical cytology outcome at first CSS were: age at first CCS ≥ 35 (aOR=3.57; 95% CI: 2.74, 4.64), multiparity ≥ 5 (aOR=1.27; 95% CI: 1.03, 1.56), and provider-referral (aOR=1.34; 95% CI: 1.09, 1.64).

Conclusion

HIV infection alone is not significantly associated with an abnormal cervical cytology outcome. In resource-limited settings such as Nigeria, it is more efficient to recommend and support CCS for women who are 35 years, of high parity, and who received a recommendation for screening from a health care provider irrespective of HIV status. Women with these characteristics have a higher probability for underlying precancer.

Introduction

Although invasive cervical cancer (ICC) has a well-known natural history with treatable precancerous abnormalities detectable through screening, it is a significant public health burden in Low-and Middle-Income Countries (LMICs). Of the half million new cases of ICC reported globally each year, over 80% occur in LMICs[1]. Nigeria is one of these countries with a huge burden of CC incidence and mortality.[2] The Global Burden of Cancer 2013 ranked cervical cancer the 2nd most common in incidence and mortality for all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health care service intervention for reducing ICC incidence and mortality. The precancerous abnormalities detectable at screening ranges from minor atypical cells, low-grade epithelial cell abnormalities to severe or high-grades epithelial cell abnormalities that could progress to invasive cervical cancer if not detected and treated. The reporting of these epithelial cell abnormalities detected through screening by the Papanicolou smear test (pap test) and cytologic interpretation is guided by the 2001 Bethesda system.[4]

The benefits of CCS are evident from data in developed countries, where organized CCS programs have led to a substantial decline in ICC incidence and mortality. [5-11] In Nigeria the high prevalence of HIV and the lack of organized CCS programs could be significant contributing factors to the high burden of invasive cervical cancer. In such setting where organized CCS programs are lacking, the opportunity to have a screening test likely depends on several factors including the availability of a screening service and system support to overcome barriers to accessing such services; patient-related factors such as risk perception for ICC, illiteracy, and lack of awareness of CCS, or where to go for such screening.[12-15] Other patient-related factors such as cost of screening, health insurance coverage, education, perception of screening benefits and ability to overcome barriers to accessing services are significant contributors.[13,16] Indeed, the

"perception of screening benefit" is one of the important constructs related to taking a preventive behavioral action as explained in the HBM.[17,18] Since the aim of cervical cancer screening is to prevent cervical cancer through identification and treatment of precancerous cervical lesions, understanding the predictors of having an underlying precancerous lesion at first screening and in subsequent follow up screening could provide evidence for educating women and providers on the benefits of screening, particularly in women with certain characteristics. These predictors could also guide development of country-level screening guidelines for cervical cancer. For instance, a French healthcare database on cervical cancer screening provided evidence for not starting cervical cancer screening before age 25,[19] in comparison to the USPSTF guideline[20,21] that recommends starting cervical cancer screening at age 21.

Precancerous cervical lesions if identified and treated early will prevent progression to invasive cervical cancer. However, previous studies have shown that development of invasive cervical cancer occurs at a lower median age of 35 years in HIV positive women compared to a median age of 40 years in women who are HIV negative.[22] Also, among women age less than 35, being HIV positive confers a 4-fold higher risk of having ICC compared to being HIV negative.[22] In a large cervical cancer screening program in Zambia, data on age at screening showed that the median age at first cervical cancer screening was unexpectedly higher in HIV seropositive compared to HIV seronegative women.[23] In Nigeria the age at first cervical cancer screening is not known, and we also do not know the sociodemographic characteristics associated with an underlying abnormal cytology outcome at first cervical cancer screening.

This manuscript utilized secondary data of women who had their first cervical cancer screening and the corresponding cytology reports to understand the predictors of abnormal cervical cancer screening outcomes at first cervical cancer screening. We hypothesized that women with HIV infection are more likely to have underlying cervical cancer abnormalities at

first cervical cancer screening than HIV uninfected women in Nigeria. The secondary aim of this chapter utilized a subset of women who had a normal cervical cytology at the first CCS and also had a follow up Pap test to understand the effect of patient-reported HIV and other sociodemographic characteristics on the hazard of abnormal cervical cytology in the sub-sample. Our hypothesis for this sub-aim is that women with reported HIV infection have a significantly higher hazard of an abnormal cervical cytology at subsequent follow up compared to the HIV uninfected women.

Methods

Study design and setting

We performed a retrospective cross-sectional analysis of data on a sample of women who had received a cervical cancer screening at the "Operation Stop" cervical cancer (OSCC) unit in, Jos, Nigeria over a 10-year time period (2006-2016). The OSCC unit commenced cervical cancer screening and treatment in 2006 with funding from Exxon Mobil, Texas, USA, through the African Organization for Research and Training in Cancer (AORTIC). This project offered opportunistic cervical cancer screening services to women in Jos, neighboring towns, and states in northern Nigeria. Also, the project has maintained an up-to-date electronic database and backup paper records of all women utilizing the service. This database has records of patient demographic and risk factor variables that are obtained from women at the first screening visit prior to cervical sample collection for Pap smear test. Each woman utilizing the service is given a unique medical record number, and all subsequent records including the cytopathology reports are entered into an operational database on FileMaker Pro version 8.0.[24]

Study sample

This study utilized de-identified patient data in the OSCC electronic database. After obtaining relevant IRB approvals for this study, we accessed the sociodemographic, risk factors and cervical cancer screening cytology outcome variables for this analysis. Our source database included all women who had received cervical cancer screening with documented cytology report in the database. We excluded follow-up entries, and utilized only the records at the first cervical cancer screening for the primary analysis.

For the analysis of the secondary aim, we utilized data of women who had a result of negative for intraepithelial lesion or malignancy (NILM) at the first cervical screen and had a follow up cytology test to analyze time to first detection of abnormal cervical cytology outcome. The detailed description of the study sample derivation is illustrated in Fig. 2.4 in chapter 2 of this dissertation.

Key independent and primary outcome variables

The electronic database has important variables ranging from age at first screening, socio-demographic variables, source of referrals, patient-reported HIV status, presence of STIs, age at first sexual debut, smoking history, alcohol consumption, reported lifetime number of sexual partners, parity, years of completed education, use of contraceptives and other risk factors. The primary outcome variable for this aim is the cytology result as described in the 2001 Bethesda system for reporting pap cytology.[4] This variable is categorical and the description of these categories as provided in the 2001 Bethesda system of reporting pap cytology are summarized in Box 2. The primary independent variable is patient-reported HIV status documented at the time of first cervical cancer screening. The operational definition of other independent variables has been described in Box 1 in chapter 2 of this dissertation.

Box 2. Summary of Terminologies for Cytology categories by the 2001 Bethesda system[4]

Negative for intraepithelial lesion or malignancy (NILM): This category is reported for cervical pap specimens for which no epithelial abnormality is identified

Cell abnormalities could be squamous or glandular as categorized below:

Epithelial Cell Abnormalities (Squamous cell)

Atypical squamous cells of undetermined significance (ASCUS): This category is reported for cellular abnormalities that were more marked than those attributable to reactive changes but that quantitatively or qualitatively fell short of a definitive diagnosis of squamous intraepithelial lesion (SIL)

Atypical squamous cells of undetermined significance, cannot exclude high-grade squamous intraepithelial lesion (ASCUS-H): This category is reported for cellular abnormalities reflecting a mixture of high-grade SIL (HSIL) and its mimics. It is intermediate between ASCUS and HSIL

Low-grade squamous intraepithelial lesion (LSIL): This category encompasses human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1

High-grade squamous intraepithelial lesion (HSIL): This category encompasses moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3

Epithelial Cell Abnormalities (Glandular cell)

Atypical glandular cells, favor neoplastic: This category is reported if the cells are glandular in origin. The presence of this cells is associated with underlying high-grade disease than in ASCUS

Statistical Analysis of primary aim

Descriptive statistics: We estimated the relative proportions of the various categories of pap cytology report according to the Bethesda system and the corresponding 95% CI. The median age at first CCS for each of the cytology outcome categories and the corresponding interquartile range (IQR) were estimated. We then categorized the cytology report into three sub-categories as follows: Negative for intraepithelial lesion or malignancy (NILM) as category 1 (referent category); ASCUS and LSIL (mild cervical dysplasia) as category 2; and ASCUS-H, AGUS, HSIL, HSIL with suspicion for invasion (severe cervical dysplasia) as category 3. We also estimated the proportions for each of these sub-categories. We compared the baseline socio-demographic characteristics of the study sample by cervical cytology sub-categories using the Pearson's chi square or Fisher's exact test where applicable and obtained corresponding p-values.

Bivariable logistic regression: to performed bivariable logistic regression to obtain the odds ratios of the association between baseline socio-demographic variables and having an abnormal cervical cytology, dummy variables were created for each of the sub-categories with category 1 (NILM) as referent. We then performed separate bivariable logistic regression to estimate the likelihood of having mild cervical dysplasia (category 2) and severe cervical dysplasia (category 3) respectively at first CCS for patient-reported HIV and other socio-demographic characteristics in the study sample. For each of these categories, we estimated the unadjusted odds ratio, 95% Cis, and the corresponding p-values.

Multivariable logistic regression: We built a multivariable logistic regression model to assess the independent effect of patient-reported HIV and other socio-demographic characteristics on the likelihood of having an abnormal cervical cytology outcome report at first cervical cancer screening. As in the bivariable logistic regression model, we used category 1

cytology report (NILM) as referent. We then performed separate multivariable logistic regression models each for mild cervical dysplasia (category 2) and for severe cervical dysplasia (category 3). We used the backward selection method in deciding the covariates that remain in each of the final predictive models. We estimated the 95% confidence intervals for each of these measures of association, and the corresponding p-values. The assessment of each model fit was by the Hosmer-Lemeshow goodness-of-fit statistical test.[25] A p-value of greater than 0.05 was considered a good model-fit.

Statistical Analysis of secondary aim

We analyzed the sub-sample of women who had NILM at first pap and had at least one follow up cytology result for time to detection of any epithelial cell abnormalities (ECA) at subsequent follow up Pap. We determined follow-up time in years from date of first NILM to the date of first ECA report or date of last NILM follow up report with censoring at last follow up date or December 31st, 2016 whichever came first. The primary outcome for this secondary aim was development of any ECA as described by the Bethesda 2001 reporting system.[4]

We performed descriptive statistics of the sub-sample and compared means of continuous variables with the Student's t-test, while categorical variables were compared using the Pearson chi square or Fisher's Exact test where applicable. The corresponding p-values were estimated.

To estimate the hazard ratios for development of any ECA during follow-up, we first subcategorized the cytology report into 2 categories as follows: Negative for intraepithelial lesion or malignancy (NILM) as category 1 (referent category); any ECA report (ASCUS, LSIL, ASCUS-H, AGUS, HSIL, HSIL with suspicion for invasion) as category 2 (primary outcome). We also created dummy variables for patient-reported HIV and other socio-demographic characteristics of the study sample to estimate the effect of these covariates on the hazard of development of an

ECA during the follow up period. Specifically, for patient-reported HIV, we treated HIV unknown as “missing” and categorized HIV uninfected as “referent category” and HIV infected as “primary exposure”. We also created dummy variables for other sociodemographic variables such as parity (> 3 as “0” and ≥ 3 as “1”), age at first sex (< 20 years as “0” and ≥ 20 years as “1”), smoking (No as “0” Yes as “1”), alcohol (No as “0 and Yes as “1”), lifetime number of sex partners (< 3 as “0” and ≥ 3 as “1”), history of vaginal infection (No as “0” and Yes as “1”), and history of ever diagnosed with an STI (No as “0” and Yes as “1”). We then performed bivariable and multivariable analyses using Cox regression models with relevant Kaplan-Meier methods. The unadjusted and adjusted hazard ratios with their corresponding 95% Cis were estimated for patient-reported HIV and other sociodemographic variables in the sub-sample. We used the log-rank test of equality of survival function to compare differences between groups. A p-value of <0.05 was considered a significant difference in development of outcome event between the groups. We used Stata version 14, college station, Texas, USA for all statistical analyses.

Results

Results of analyses for primary aim

Descriptive statistics of the sample

During the study period, 14,081 (99.95%) women had cervical cytology reports out of the total 14,088 women that had their first cervical cancer screening. As shown in Table 2.1, 85.7% of the study sample had NILM, while 9.7% and 4.6% had mild and severe cervical dysplasia respectively. Specifically, 4.11% (95% CI: 3.80, 4.46%) with ASCUS, 5.62% (95% CI: 5.25, 6.01) with LSIL, 1.61% (95% CI: 1.41, 1.83) with ASCUS-H, 0.22% (95% CI: 0.15, 0.31) with AGUS, 2.50% (95% CI: 2.26, 2.78) with HSIL, and 0.23% (95% CI: 0.16, 0.32) with HSIL with suspicion for invasion. The median age for the various cytology categories were: 36 years (IQR; 30-43) for

NILM, 43 years (IQR; 36-50) for ASCUS, 45 years (IQR; 35-52) for LSIL, 47.5 years (IQR; 38-55) for ASCUS-H, 40 years (95% CI: 34-52) for AGUS, 47 years (IQR; 39-55) for HSIL, and 52 years (IQR; 43-60) for HSIL with suspicion for invasion. As shown in Fig. 5.1, the scatter plot of the median age at first screen and the predicted cytology outcome category suggest a positive linear relationship between median age and severity of cytology outcome at first cervical screen.

Self-reported HIV status was not significantly associated with mild of severe cervical dysplasia in the study sample (p-value=0.930). The association between other socio-demographic variables with cervical cytology outcomes are displayed in Table 5.1 in the supplementary section in chapter 7 of this dissertation.

Unadjusted and adjusted logistic regression model of patient-reported HIV and other sociodemographic variables and mild cervical dysplasia

In the unadjusted regression model, patient-reported HIV infection was not significantly associated with mild cervical dysplasia (OR=0.99; 95% CI: 0.77, 1.28). The sociodemographic factors that were significantly associated with mild cervical dysplasia were: age at first CCS ≥35 years (OR=2.83; 95% CI: 2.48, 3.24), multiparity ≥5 (OR=1.46; 95% CI: 1.31, 1.64), age at first sexual intercourse ≤22 years (OR=1.23; 95% CI: 1.08, 1.41), provider-referral (OR=1.88; 95% CI: 1.67, 2.11), history of ever smoked cigarettes (OR=1.84; 95% CI: 1.01, 3.35) and history of alcohol consumption (OR=1.50; 95% CI: 1.23, 1.83). One notable finding in the unadjusted model is that women with 7-12 completed years or more of education were significantly less likely to have mild cervical dysplasia at first CCS than women with less than 7 completed years of education (7-12 years, OR=0.68; 95% CI: 0.56, 0.84; >12 years, OR=0.82; 95% CI: 0.68, 0.96). These unadjusted ORs are presented in Table 5.2.

In the adjusted logistic regression model including age at screening ≥ 35, provider-referral, multiparity ≥ 5, history of vaginal infection and alcohol consumption, the effect of patient-reported HIV infection was not significantly associated with mild cervical dysplasia (aOR=1.04; 95% CI: 0.80, 1.36). The sociodemographic variables that were independently associated with mild cervical dysplasia were: age at first CCS ≥ 35 (aOR=2.56; 95% CI: 2.23, 2.95), multiparity ≥ 5 (aOR=1.21; 95% CI: 1.08, 1.36), provider-referral (aOR=1.75; 95% CI: 1.56, 1.98) and history of alcohol consumption (aOR=1.38; 95% CI: 1.38; 95% CI: 1.13, 1.70). These adjusted ORs are presented in Table 5.2.

Unadjusted and adjusted logistic regression model of patient-reported HIV and other sociodemographic variables and severe cervical dysplasia

In the unadjusted regression model, patient reported HIV infection was not significantly associated with severe cervical dysplasia (OR=0.93; 95% CI: 0.64, 1.35). The sociodemographic factors that were significantly associated with severe cervical dysplasia were: age at first CCS ≥ 35 years (OR=4.24; 95% CI: 3.40, 5.29), multiparity ≥ 5 (OR=1.85; 95% CI: 1.58, 2.17), age at first sexual intercourse ≤ 22 years (OR=1.32; 95% CI: 1.08, 1.60), provider-referral (OR=1.27; 95% CI: 1.08, 1.49). Similar to the unadjusted model for mild dysplasia, women with 7-12 completed years or more of education were significantly less likely to have severe cervical dysplasia at first CCS than women with less than 7 completed years of education (7-12 years, OR=0.46; 95% CI: 0.34, 0.62; > 12 years, OR=0.63; 95% CI: 0.49, 0.80). The unadjusted ORs are presented in Table 5.3.

In the adjusted logistic regression model including age at first screening ≥ 35, provider-referral, multiparity ≥ 5, history of vaginal infection, 7-12 years of completed education, and > 12 years of completed education, the effect of patient-reported HIV infection was not significantly associated with severe cervical dysplasia (aOR=1.26; 95% CI: 0.83, 1.92). The sociodemographic

variables that were independently associated with severe cervical dysplasia were: age at first CCS ≥ 35 (aOR=3.57; 95% CI: 2.74, 4.64), multiparity ≥ 5 (aOR=1.27; 95% CI: 1.03, 1.56), and provider-referral (aOR=1.34; 95% CI: 1.09, 1.64). Women with 7-12 completed years of education (aOR=0.65; 95% CI: 0.48, 0.88), > 12 completed years of education (aOR=0.75; 95% CI: 0.58, 0.98), and history of vaginal infection (aOR=0.67; 95% CI: 0.53, 0.84) were significantly less likely to have severe cervical dysplasia at first CCS. These adjusted ORs are presented in Table 5.3.

Results of analyses for secondary aim

During the study period, 1,599 women with NILM at first pap had at least one follow-up pap cytology screening. Of the 1,555 women who reported their HIV status, 3.7% (57/1,555) were HIV infected. The median age at first pap was 39 years (IQR; 33-45), and HIV infected women were significantly younger (36.3 ± 8.1) than those uninfected (39.3 ± 6.6; p=0.005). The mean follow-up time was similar for women who had ECA compared to those with NILM at follow up (2.3 ± 1.6 vs 2.4 ± 1.6 years, respectively; p-value=0.383). The baseline comparability of women with NILM versus women with ECA at follow-up is presented in Table 5.1.1.

After a total accrued follow up time of 3,809 years, 243 women (15%) had an ECA at follow up with an event rate of 6.38 per 100 person-years (PYs). Women ≥ 35 years old at first pap were significantly more likely to have an ECA at follow-up compared to women younger than 35 (7.5 per 100 PYs vs 3.8 per 100 PYs, HR=1.96; 95% CI: 1.4, 2.8). Self-reported HIV infection was not significantly associated with developing ECA in either unadjusted (7.4 per 100 PYs vs 6.4 per 100 PYs, HR=1.17; 95% CI: 0.53, 2.3) or adjusted analyses (aHR=1.78; 95% CI: 0.87, 3.65). Fig. 5.1.1 shows the Kaplan-Meier of patient-reported HIV and hazard of an ECA at follow up with no significant difference between HIV infected and uninfected women. However, Fig. 5.1.2 shows a significant hazard for an ECA during follow up in women age ≥ 35 years at first CCS. The

unadjusted and adjusted hazard ratios for an ECA for other sociodemographic variables of the sample are displayed in Table 5.1.2.

Discussion

These analyses provide significant knowledge about the characteristics that are associated with having an abnormal cervical cytology outcome at the time of first cervical cancer screening in a large sample of women in Nigeria. It also provide us with evidence that though HIV infection is known to be associated with higher prevalence of precancerous lesions of the cervix and to also accelerate progression to invasive cancer stages, it alone is not sufficient to explain these associations. Our data suggest that other sociodemographic variables such as late age at first screening and multiparity are additional significant factors for underlying precancerous cervical lesion at the time of first screening and during subsequent follow-up Pap cytology.

Our primary analysis shows that patient-reported HIV was not significantly associated with having either mild or severe cervical dysplasia at the time of first cervical cancer screening in our study sample. The adjusted OR representing the effect of HIV on having mild cervical dysplasia was 1.04 (95% CI: 0.80, 1.36) and 1.28 (95% CI: 0.83, 1.92) for severe dysplasia. However, we found that women who had first cervical cancer screening at age ≥ 35 years were 2.56 (95% CI: 2.23, 2.95) and 3.57 (95% CI: 2.74, 4.64) times more likely to have an underlying mild and severe cervical dysplasia, respectively, at the time of first cervical cancer screening. Indeed, the utility of HSIL for early detection of cervical cancer has been studied in older women and its sensitivity for cancer was 89% in women screened at age 40-69 and 83% in women screened at age ≥ 70 years.[26] Therefore, our study findings showing a severe dysplasia rate of 4.6% and that older age is a significant predictor of underlying severe dysplasia are therefore a critical finding for cervical cancer screening in Nigeria.

Furthermore, taking a closer assessment of the relationship between age at first screening and abnormal cervical cytology outcome, we observed a trend towards significant positive correlation between median age at first CCS and the severity of underlying cervical cytologic abnormality, as shown in Fig. 5.1. The median age at diagnosis of these abnormalities and the corresponding interquartile range suggest that implementing a Nigerian cervical cancer screening policy between age 30 and 60 years may be a more effective screening recommendation for our women population. Although our data are limited to one federal academic tertiary referral medical institution in northern Nigeria, these data provide preliminary justification for a subsequent cost-effectiveness analysis to understand the value of extending CCS outside this age range in the Nigerian population. Such understanding is crucial in resource-constrained settings where health insurance coverage is lacking. If subsequent cost-effectiveness analysis supports screening within this age range, health policy makers could implement health insurance coverage for cervical cancer screening for women ages 30 to 60 in Nigeria. However, there is need to obtain more large-scale screening data across the country to increase the precision of these estimates.

Our analysis also found that multiparity ≥ 5 was significantly associated with mild or severe cervical dysplasia at first CCS. Specifically, women with parity ≥5 were 1.85 (95% CI: 1.58, 2.17) and 1.27 (95% CI: 1.03, 1.56) times more likely to have an underlying mild or severe cervical dysplasia, respectively, at the time of first cervical cancer screening. Indeed, studies on the cofactors in cervical pre-cancer and progression to invasive cancer have demonstrated that women of multiparity 3+ were significantly more likely to have pre-cancer compared to nulliparous women.[27] In Nigeria, according to the Nigeria Demographic Health Survey 2013, the national average number of births per woman is 5.5.[28] Indeed, in many settings in sub-Saharan Africa and Nigeria, women place a high premium on parity, and this socio-cultural norm could contribute to the burden of pre-cancer and invasive cervical cancer.[29] Other sociodemographic characteristics

such as smoking, sexually transmissible infections, number of sexual partners, and age at first sexual intercourse have been identified as significant cofactors in cervical carcinogenesis.[30] These identified cofactors associated with abnormal cervical cytology outcomes at first screening further provide evidence that could guide prioritization of cervical cancer screening targeting women with these identified characteristics, particularly in settings where resources are limited.

We also found that women who were referred by providers for first cervical cancer screening were 1.34 times more likely to have severe cervical dysplasia outcome compared to women who self-referred for first CCS (aOR=1.34; 95% CI: 1.09, 1.64). The plausibility of this finding is not fully understood, though it may be related to the role of providers in identifying women with risk factors for cervical cancer and offering selective referral for screening in this population. Moreover, our previous analysis in chapter 3 found that women who received provider referral were more likely to be older and have known risk factors for cervical cancer.

We previously reported in Chapters 3 and 4 that educated women were more likely to self-refer for first CSS and to have their first CSS before age 35. Our analysis further confirms the role of women education in improving cervical cancer screening utilization and outcomes. We found that completing at least 7-12 years of education significantly reduces the odds for severe cervical dysplasia by 25% to 35% compared to women who had fewer years of completed education. These findings are supported by previous studies showing the critical role of women education in improving cervical cancer outcomes. For instance, cervical cancer incidence and mortality are correlated with the socio-demographic index (SDI) of the population, with high SDI countries having a significantly lower ICC burden compared to low SDI countries.[31] In brief, the SDI ranges between 0 and 1 and is a summary indicator derived from measures of income per capita, educational attainment, and fertility.[31] An SDI of 1 represents a location with the highest observed educational attainment, the highest log income per capita, and the lowest fertility rate.[31] A previous

related index, the human development index (HDI), which includes adult literacy rate and primary to tertiary education enrollment rates, has been shown to correlate inversely with incidence and mortality from invasive cervical cancer, with greater reductions in cervical cancer incidence in very high HDI compared to low HDI countries.[32] In Nigeria there is a wide regional disparity in median years of educational attainment: it is highest in the south-western states (8.5 years) and lowest in the far north-east and north-western states (0.0 years).[28] The median years of educational attainment in the study area according to the NDHS 2013 report is 2.9 years.[28] Compared to this population-based report on the median years of education attainment, the women in our study were significantly more educated with a median of 13 years of completed education.

The findings described in this paper imply that screening guidelines in Nigeria should support a policy for initiation of pap test in women starting at age 30 because the probability of detecting an underlying abnormal cytology outcome seems to be higher after this age in our screening population. A similar analysis of a large sample of pap tests in Israeli women provided age estimates at which various precancerous cervical abnormalities and invasive cancer conditions were diagnosed and supported the review of screening guidelines to cover ages 25 to 65 years among Israel's population.[33] Indeed, the optimal age for initiating cervical cancer screening has been a subject of continuing debate, and recommendation depends on several variables. The USPSTF recommends starting screening at age 21,[20,21] while the French guidelines expresses concerns about the benefits and risks of screening, detection and treatment of abnormal cervical lesions for pap test performed earlier than age 25 years.[19] Also, the adoption of HPV vaccination in most developed countries has provided new evidence necessitating the review of current guidelines on both the age and mode of cervical cancer screening. For instance, a trial report in a HPV vaccinated population in Australia showed that primary HPV screening was significantly more effective in the detection of high-grade cervical abnormalities compared to

cytology-based screening in women aged 33 years or younger where HPV vaccine uptake was high.[34] Also, mathematical modelling based on HPV vaccination status and effectiveness of HPV as primary screening for cervical cancer showed that one-time and two-time HPV screening per woman was a cost-effective option for women who have been vaccinated with the nanovalent HPV vaccine and the quadrivalent HPV vaccine types, respectively.[35] However, in Nigeria and most other LMICs in Africa where HPV vaccination is not widely available, current evidence supports alternative screening strategies such as the "screen-and-treat" options endorsed by the World Health Organization screening guidelines.[5] Moreover, evidence of visual aided inspection with acetic acid (VIA) in the detection of high-grades precancerous lesions of the cervix supports this screening option in both HIV and non-HIV infected population.[36]

Adherence to guidelines by healthcare providers is critical to the success of cervical cancer prevention and control. In the future, it will be appropriate to understand the perception of health care providers in Nigeria about the value of adoption and adherence to cervical cancer screening guidelines in cervical cancer prevention efforts. For instance, a prior survey of US obstetricians and gynecologist revealed persistent barriers to adherence to screening guidelines and recommended interventions to promote adherence to guidelines for improving the quality of cervical cancer prevention.[37]

Similar to the findings in our primary aim, our secondary aim also found that self-reported HIV at first CCS was not significantly associated with the hazard of an abnormal cervical cytology at follow up (aHR=1.78; 95% CI: 0.87, 3.65). We also found that age at first CCS ≥ 35 years and multiparity were significantly associated with hazard for abnormal cervical cytology at a subsequent follow-up pap after prior normal cytology outcome. Our confidence in the findings of abnormal cervical cytology at a subsequent follow-up Pap test reported in this study is supported by the sensitivity and specificity studies of pap cytology compared to other screening modalities

for cervical dysplasia in an HIV-infected population showed that Pap test screening has superior specificity irrespective of immune status or antiretroviral treatment.[38]

A main strength of this analysis is the relatively large sample size, which provides relatively precise estimates of the association between the independent variables and the primary outcomes. To the best of our knowledge, this type of analysis of healthcare service data to understand the association between sociodemographic factors and underlying precancerous cervical lesions has not been done previously in Nigeria. Our findings provides baseline evidence that could guide health policy decision makers in designing action steps in cervical cancer prevention efforts in Nigeria and similar settings in Africa. We recognize the limitations of using self-reported data in our analysis and acknowledge that our findings should be interpreted and applied in the context of self-reported outcomes. We also recognize that our statistical estimates are potentially biased by missing data, and our findings are based on reports from a population that has overcome barriers to access and received a cervical cancer screening. Therefore, our findings may not be representative of the larger population of women, particularly those in rural and suburban communities in Nigeria. A future population-based study of a nationally representative sample of Nigerian women in urban and rural settings could provide a more generalizable evidence for guiding health policy decisions for effective cervical cancer screening and control nationally and at sub-national levels in Nigeria.

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Chapter 6: Summary, Conclusions and Future Research

Of the half million new cases of invasive cervical cancer (ICC) reported globally each year, over 80% occur in Low-and Middle Income Countries (LMICs)[1]. Nigeria is one of these countries that bears a notable burden of ICC incidence and mortality.[2] As reported in the Global Burden of Cancer 2013, cervical cancer is ranked the 2nd most common in incidence and mortality for all cancers in Nigeria.[3]

Cervical cancer screening (CCS) is an important health services intervention known to reduce significantly the incidence and mortality from invasive cervical cancer, particularly in developed countries where organized CCS programs are available. [4-10] However, organized CCS programs are currently lacking in Nigeria and most other LMICs. The opportunity for CCS likely depends on several factors ranging from availability of screening and offering screening recommendations by providers to health system support to overcome barriers to accessing services. Indeed, the literature on cancer screening suggests that, screening is a process of care, consisting of several steps and interfaces between patients, providers, and health care organizations.[11] In this context, screening rates are largely driven by strategies that limit the number of interfaces across organizational boundaries; recruiting patients, promoting referrals, and facilitate appointment scheduling; and promoting long-term patient care and engagement.[11] The organizational capability of the health care system to address these boundaries could explain the relatively higher CCS rates of 83% in the US[12], in comparison to Nigeria and similar LMICs in sub-Saharan Africa where rates range between 6-8%.[13,14] For over a decade, the PEPFAR program has provided continuing support for HIV screening, treatment and care in Nigeria. PEPFAR has also worked through the Centers for Disease Control and Prevention (CDC) and country-level ministries of health to support the integration of cervical cancer screening services as a standard of care for all HIV infected women given the high-risk of

precancer in HIV infected women.[15] Although the federal ministry of health of Nigeria[16] endorses the CDC recommendation to offer counseling and cervical cancer screening as a standard of care for all HIV infected women receiving treatment in PEPFAR supported facilities, the Pap test is only available in few tertiary health facilities, and there is currently no national cervical cancer screening program in Nigeria. Also, there is no national program for HPV vaccination in Nigeria, and cervical cancer screening to date has been largely opportunistic, depending on either recommendation by healthcare providers or when women are aware of the service and decide to seek screening. The current organizational structure makes it critical for healthcare providers to have the necessary training and support to engage patients in screening counseling and to also offer cervical cancer screening recommendations, particularly to those at risk.

Indeed, we have an established body of evidence about the effectiveness of provider recommendation for screening on cervical cancer screening participation.[11,17-20] Also, we have evidence in HIV (Human Immune deficiency Virus) infected populations, suggesting women's awareness that HIV infection increases the risk of ICC and having a strong provider-patient relationship were significant facilitators for CCS utilization.[21] These cross-sectional analyses were conducted on the premise that in an opportunistic screening setting, patient-reported HIV infection is significantly associated with cervical cancer screening utilization and outcomes. This dissertation is based on 3 interrelated but distinct questions with key findings that contribute to the cervical cancer screening and prevention literature in Nigeria with potential applicability in other LMICs where organized screening services are lacking. The 3 research questions, hypotheses and key findings are summarized in the following paragraphs:

The relationship between provider-patient interaction with respect to cervical cancer screening referral is important in Nigeria given the high burden of HIV and evidence of high prevalence of precancerous conditions of the cervix in HIV infected population.[22-24] We, however,

do not understand the relationship between patient-reported HIV infection and provider behavior in providing a cervical cancer screening referral during the care process, particularly in settings where cervical cancer screening is largely opportunistic. Therefore, our first research question: Is there a significant association between patient-reported HIV and the likelihood of provider referral for a cervical cancer screening? *We hypothesized that women with reported HIV infection are significantly more likely to receive a CCS referral by a provider compared to women who are HIV negative.*

Our key findings related to this questions suggest that: 1. Women who are HIV infected are currently receiving more referrals for cervical cancer screening than those HIV uninfected. Our analysis showed that women who reported being HIV infected were more than 2 times more likely to be referred by a provider at the time of first cervical cancer screening than women who were HIV uninfected (aOR=2.35; 95% CI: 1.95, 2.82). We also found that women who had completed 7-12 years of education were less likely to received provider-referral compared to women with less than 7 years of completed education (aOR=0.77; 95% CI: 0.71, 0.84). Other socio-demographic factors that were significantly associated with provider-referral for first cervical cancer screening were age ≥35 years, parity ≥5, age at first sex ≤22 years, smoking history, and use of condoms. Overall, our analysis for this question suggests the need for strengthening provider-patient communication during routine clinical care process and also designing health systems that support recommendations for cervical cancer screening and other preventive care services to women at risk.

We also analyzed the median age at first cervical cancer screening to understand if age at first cervical cancer screening differs by HIV infection status among women who have received a pap test. We have evidence from similar settings in sub-Saharan Africa that development of invasive cervical cancer occurs at a lower median age of 35 years in HIV positive women

compared to a median age of 40 years in women who are HIV negative.[25] Also, among women less than 35 years, being HIV positive confers a 4-fold higher risk of having ICC compared to being HIV negative.[25] Also, in a large cervical cancer screening program in Zambia, data on age at screening showed that the median age at first cervical cancer screening was unexpectedly higher in HIV seropositive women compared to HIV seronegative women.[26] In Nigeria, the age at which women initiate CCS is not known; therefore, our second research question: Is there a significant association between patient-reported HIV status and the age at which women have their first cervical cancer screening? *We hypothesized that the median age at first CCS is lower in women with reported HIV compared to the median age of women who are HIV negative.*

The first key finding from our second question suggests the need for a concerted effort to promote early onset of cervical cancer screening. We found that women in the study sample had their first cervical cancer screening at a median age of 37 years (IQR 30-45). We also found that on average, women who were HIV infected had their first CCS at a younger age than women who were HIV uninfected (35.0 ± 7.4 years versus 38.2 ± 10.2 years). The cervical cancer prevention program in Zambia (CCPZ) has been considered an effective model for resource-limited settings by PEPFAR.[15] Data from the CCPZ showed that women with HIV infection developed invasive cervical cancer at the median age of 35 years.[25] It seems that the age at which HIV infected women have their first cervical cancer screening in our population (35.0 ± 7.4 years) is rather late. Therefore, our finding implies that if health systems do not enable women to initiate screening earlier than the median age found in our study population, we may not achieve much progress in cervical cancer prevention and control.

Our analysis also confirms the central role of educating women as a social capital investment for improving cervical cancer outcomes. We found that women who completed at least

7-12 years of education were 1.27 to 3.51 times more likely to have had first CCS at less than age 35 than women with less education. A study about acceptability of cervical cancer screening in an HIV treatment facility in south western Nigeria indicated that women with tertiary level education were significantly more likely to accept and complete cervical cancer screening than women with a primary level of education or none.[27] The possible role of education in this context could be related to empowering women to make independent health decisions, particularly in northern Nigeria where health decisions rest on the shoulders of men even when it affects women's health. Education also empowers women economically and enables them to navigate the health care system and overcome barriers to access.

Precancerous cervical lesions, if identified and treated early, will prevent progression to invasive cervical cancer. However, previous studies have shown that development of invasive cervical cancer occurs at a lower median age of 35 years in HIV positive women compared to a median age of 40 years in women who are HIV negative.[25] Also, among women less than age 35, being HIV positive confers a 4-fold higher risk of having ICC compared to being HIV negative.[25] In a large cervical cancer screening program in Zambia, data on age at screening showed that the median age at first cervical cancer screening was unexpectedly higher in HIV seropositive compared to HIV seronegative women.[26] In Nigeria the age at first cervical cancer screening is not known, and we also do not know the sociodemographic characteristics associated with an underlying abnormal cytology outcome at first cervical cancer screening. Therefore, our third research question: Is there a significant association between patient-reported HIV and abnormal cervical cytology outcomes at the time of first cervical screening? *We hypothesized that the likelihood of an abnormal cytology outcome at first CCS will be significantly higher in women who were HIV infected compared to those who were HIV uninfected.*

The key findings related to the third question are: 1. We found that late age at first screening was significantly associated with an underlying precancerous abnormality at the time of first CCS. We also examined the median age at first CCS and observed a positive correlation between age and severity of underlying precancerous cervical abnormalities. Our findings related to median age associated with the various categories of precancerous abnormalities provides preliminary evidence for health policy makers in Nigeria to advocate that for efficient use of limited resources, CCS with the pap test should be recommended within the age range 30-60 years. Also, we recommend that since the probability of detecting an underlying precancerous cervical lesion is higher within this age range in our population, health policy and decision makers should advocate for health insurance coverage for CCS within this age limit as an efficient way of maximizing scarce resources. However, more data are needed, including a subsequent cost-effectiveness analysis, to better inform decisions in this regard.

Our findings further support the value of investing in girls' and women's education as a social capital-based intervention to improve both cervical cancer screening utilization and better screening outcomes in Nigeria. We found that completing at least 7-12 years of education significantly reduces the odds for severe cervical dysplasia by 25% to 35% compared to women who had fewer years of completed education at the time of first CCS.

Finally, we found that although women with reported HIV infection have a higher hazard of precancerous abnormalities of the cervix at follow-up, women aged 35 years or older at first cervical cancer screening were significantly more likely to develop precancerous cervical abnormalities compared to younger women.

Further Research and Action Steps

Our current analysis has provided us with quantitative evidence about the epidemiology of cervical cancer screening utilization and screening outcomes in a population of women that

have had a pap test. However, our findings can only be interpreted within the limits of self-reported data. Most of our statistical models explain only a small proportion of the changes in outcomes observed. These findings suggest the need for further research to better understand the underlying factors that are critical to utilization of cervical cancer screening. Some of these factors may not possibly be captured in a secondary data set, thus limiting our understanding of the barriers and facilitators of screening utilization in the current analysis.

We need to understand the perception of the benefits of cervical cancer screening among Nigerian women, the barriers they face in obtaining screening, and the type of societal and health care system support that will enhance screening utilization. We also need to better understand the perception of providers on the barriers and facilitators of cervical cancer screening including their knowledge on cervical cancer risk and prevention, their knowledge on screening guidelines and availability of such guidelines at the point of care. It is also important to understand how other health services support at the point of care, such as clinical decision support systems, could enhance patient-provider interaction and engagement, counseling and recommendation for screening. Nevertheless, our findings can make a significant contribution by broadening our knowledge on the cervical cancer screening processes with respect to Nigeria, where cervical cancer screening is largely opportunistic.

Going forward, the Nigerian government through the ministry of health should interpret these health services research data and utilize them for health policy decisions toward the design and implementation of an effective national program for prevention and control of cervical cancer in Nigeria. The immediate action step is to integrate cervical cancer screening services into existing sexual and reproductive health services across Nigeria. Service integration in this context has been shown to reduce structural barriers to access and improve service utilization especially in high-risk HIV infected population in LMICs.[28] Related to service integration is evidence of the effectiveness of a policy of “screen-and-treat” with cryotherapy and low-tech screening methods

such as VIA in LMICs.[4,26,29-31] While service integration for early detection and treatment of precancerous cervical lesions is important, one of the most cost-effective intervention for improving cervical cancer outcomes in LMICs is the implementation of a national HPV vaccination program.[32] This has been successfully implemented in Rwanda, an example of a LMIC that has made substantial progress in prevention and control of cervical cancer in Africa.[33-35] Indeed, a recent commentary on the need for societal investment to improve cervical cancer outcomes in Nigeria recommends wide coverage of HPV vaccination as one of the cost-effective option for cervical cancer prevention and control.[36] Going by the lessons from Rwanda, these implementation steps for improving cervical cancer prevention and control in Nigeria will require political will, cross-sectoral collaboration and planning, innovative partnerships as well as continuing data monitoring and evaluation.[34] Also the role of women's health advocates such as the Society of Gynecology and Obstetrics of Nigeria in facilitating these implementation steps is critical. Indeed, the Promoting Action in Research Implementation in Health Services (PARiHS) framework recognizes the critical role of utilizing evidence and facilitation in the right context for successful implementation efforts.[37,38]

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Chapter 7: Supplementary Materials-Tables, Figures and Graphs

This Chapter provide details of Tables, Figures and Graphs/Plots relevant to the statistical analyses and results sections of this dissertation. These Tables, Figures and Graphs have been referenced in the corresponding chapters of the dissertation.

Table 2.2. Summary statistics of the socio-demographic and baseline cytology outcomes of women who received first CCS in an opportunistic cervical cancer screening program in Jos Nigeria (N=14,088)

Characteristics	**Descriptive statistics (Mean ± SD, Median, IQR or % in parentheses)**	**95% Confidence intervals**
Age at first CCS	37; IQR, 30-45	
Age groups at first CCS		
<21 years	1.1	1.0, 1.3
21-30	24.7	24.0, 25.4
31-40	37.3	36.5, 38.1
41-50	25.4	24.6, 26.1
51-60	8.9	8.5, 9.4
61-70	2.1	1.8, 2.3
≥71	0.2	0.2, 0.3
Missing	0.2	0.2, 0.3
Age at first sex	20; IQR, 18-22	
Education years completed	13; IQR, 12-14	
Annual household income in USD	3,300; IQR, 1,920-4,800	
HIV status		
Infected	703 (5.0)	4.6 - 5.5
Not infected	13,155 (93.4)	93.0 - 93.8
Unknown (missing)	230 (1.6)	1.4 - 1.9
History of Vaginal infection		
Yes	80.0	79.4 - 80.7
No	16.6	16.0 - 17.2
Missing	3.4	3.1 - 3.7
Use of condoms		
Yes	7.4	6.8 – 7.6

No	86.2	85.6 – 86.8
Missing	6.6	6.2 – 7.1
Ever diagnosed with an STI		
Yes	10.0	9.5 – 10.5
No	60.8	60.0 – 61.6
Missing	29.3	28.5 – 30.0
Types of STIs		
Gonorrhea	17.0	14.0 – 20.5
Trichomonads	6.7	4.8 – 9.2
Hepatitis	40.5	36.4 – 44.8
Chlamydia	28.7	17.3 – 47.1
HPV/Genital warts	5.9	4.2 – 8.3
Syphilis	4.8	3.3 – 7.0
Herpes	3.4	2.2 – 5.4
PID/Unspecified	18.3	15.6 – 22.3
# of Lifetime sex partners	2; IQR, 1-3	
Parity	3; IQR, 2-3	
History of smoking		
Yes	0.6	0.5 – 0.7
No	98.5	98.3 – 98.7
Missing	1.0	0.8 – 1.1
History of Alcohol		
Yes	6.5	6.1 – 6.9
No	92.5	92.1 – 93.0
missing	1.0	0.9 – 1.2
Race		
Black	99.7	99.6 – 99.8
Others	0.1	0.1 – 0.2
Missing	0.2	0.1 – 0.30
Cytology outcome at first CCS		
NILM	85.7	85.1 – 86.3
ASCUS	4.1	3.8 – 4.5
LSIL	5.6	5.3 – 6.0
ASCUS-H	1.6	1.4 – 1.8
AGUS	0.2	0.2 – 0.3
HSIL	2.5	2.3 – 2.8
HSIL, suspicion for invasion	0.2	0.2 – 0.3
Cytology category at first CCS		
Normal cervical cytology	85.7	85.1 – 86.3
Mild cervical dysplasia	9.7	9.3 – 10.2
Severe cervical dysplasia	4.6	4.2- 4.9

SD (standard deviation), IQR (Interquartile range), % (Percent)

Table 2.3. Baseline socio-demographic characteristics of the study sample comparing women with reported HIV infection and HIV uninfected

Variable	HIV uninfected	HIV infected	p-value
Age at first CCS(Mean ± SD)	38.2 ± 10.2	35.0 ± 7.4	0.001‡
Age at first sex (Mean ± SD)	20.1 ± 4.0	19.4 ± 3.5	0.001‡
Total # of sex partners(Mean ± SD)	2.1 ± 1.8	3.2 ± 2.6	0.001‡
History of Vaginal infection			
No	2,234 (17.7)	84 (12.2)	0.001†
Yes	10,454 (82.3)	606 (87.8)	
History of STIs			
No	8,508 (98.7)	11 (1.6)	0.001†
Yes	574 (6.3)	669 (98.4)	
Use of condom			
No	11,464 (93.4)	483 (72.6)	0.001†
Yes	807 (6.6)	182 (27.4)	
History of smoking			
No	12,949 (99.4)	697 (99.2)	0.317†
Yes	73 (0.6)	6 (0.8)	
History of Alcohol			
No	12,174 (93.5)	648 (92.4)	0.254†
Yes	842 (6.5)	53 (7.6)	
Education years completed(Mean ± SD)	11.8 ± 3.1	11.4 ± 2.9	0.001‡
Annual household income in USD(Mean ± SD)	4,188.7 ± 4,075.1	3,708 ± 2,811.4	0.027‡
Parity	3.6 ± 2.5	2.7 ± 1.9	0.001‡
Cytology category at first CCS			
Normal cervical cytology	11,261 (85.6)	605 (86.1)	0.930†
Mild cervical dysplasia	1,288 (9.8)	68 (9.7)	
Severe cervical dysplasia	599 (4.6)	30 (4.2)	

‡Student t-test and †Pearson's chi². Percent in parenthesis, SD (standard deviation)

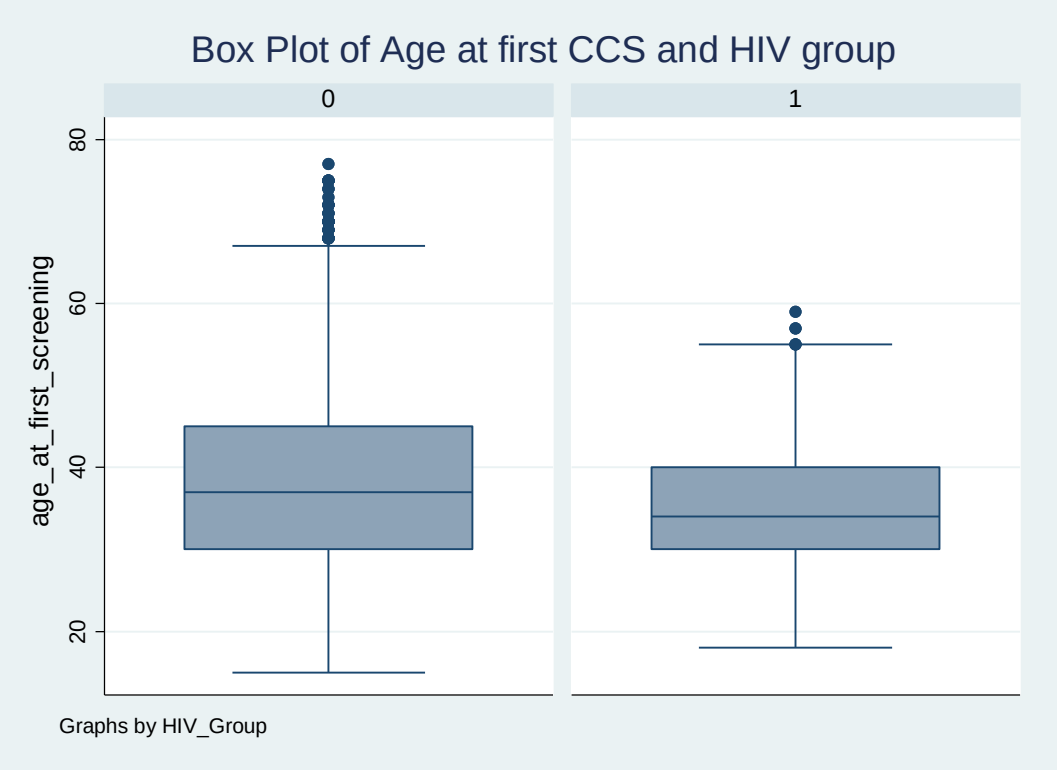

Fig. 2.5. Box Plot of Age at first CCS by patient-reported HIV ("0"=HIV uninfected and "1" HIV infected")

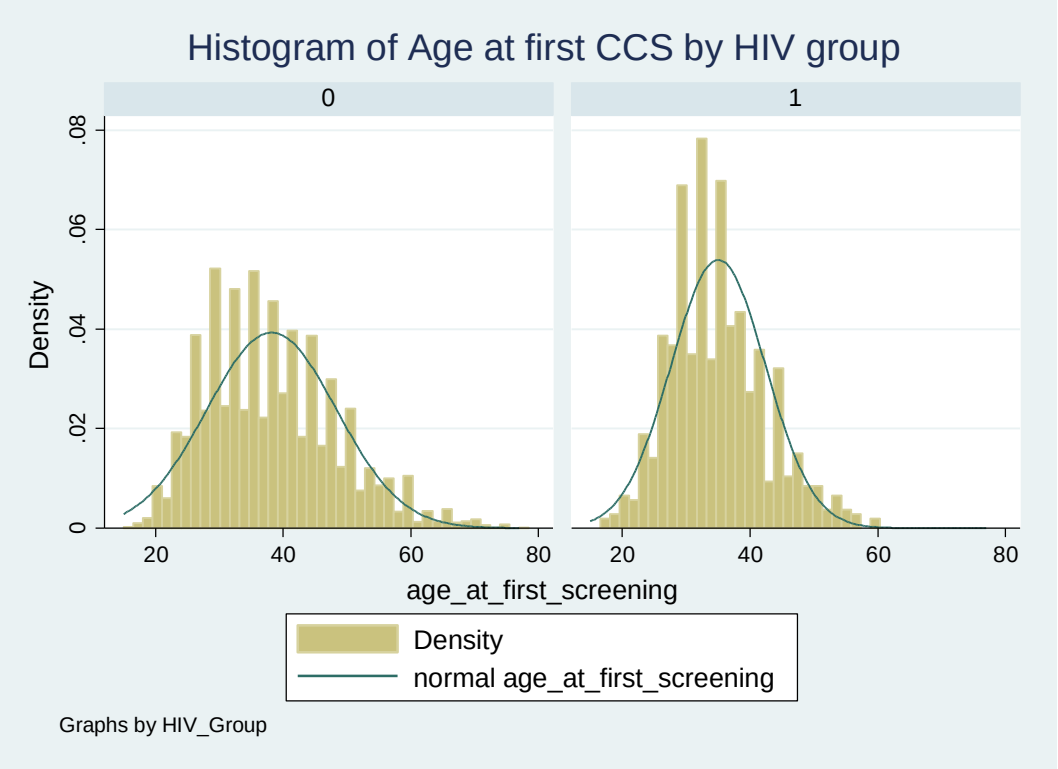

Fig. 2.6. Histogram and normal density plot of age at first cervical cancer screening by patient-reported HIV status *(HIV group o (not HIV infected), HIV group 1 (HIV infected))*

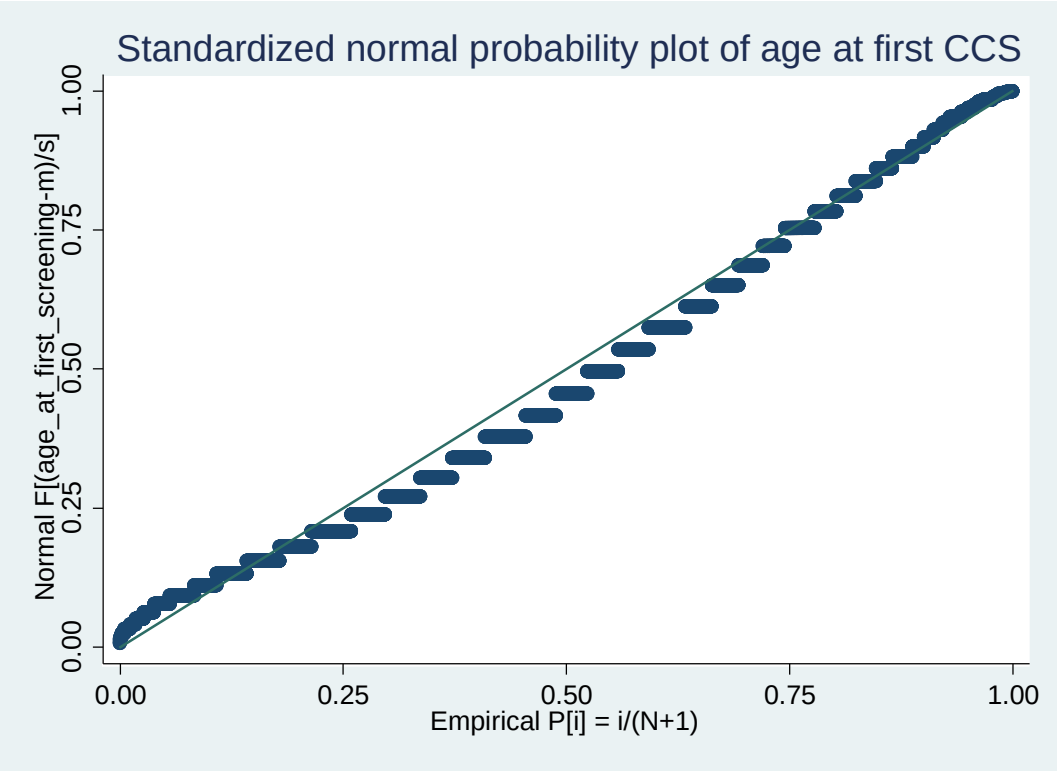

Fig. 2.7. Normal probability plot of age at first cervical cancer screening in an opportunistic screening unit in Jos, Nigeria

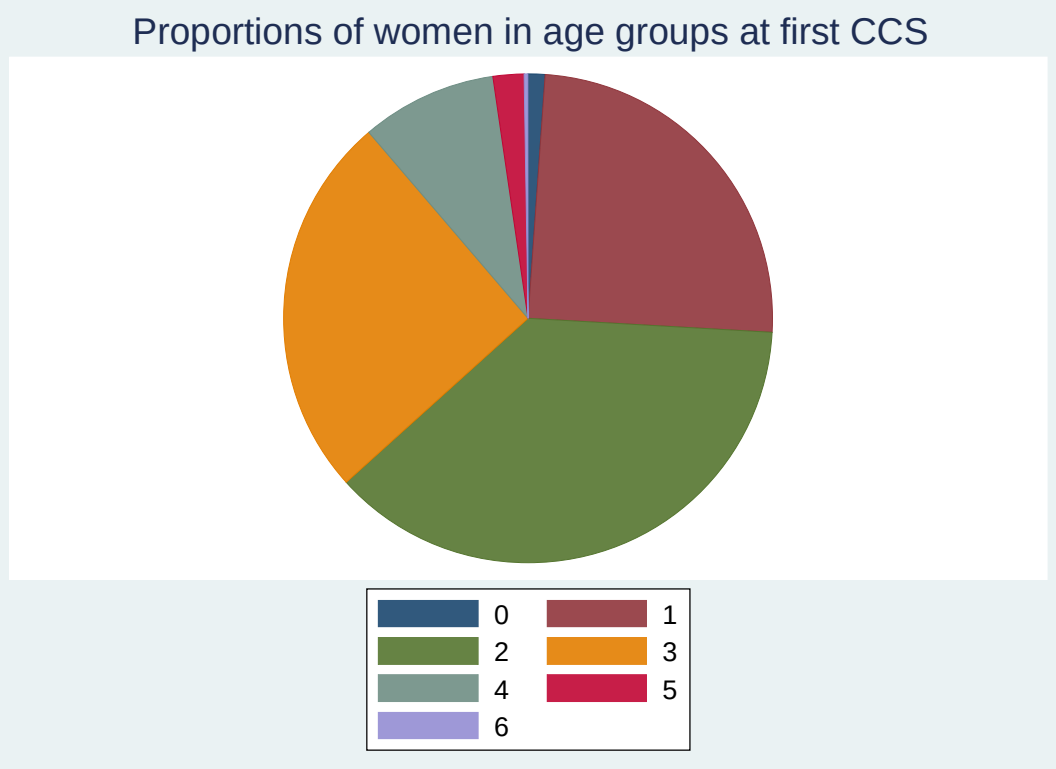

Fig. 2. 8. Pie chart distribution of age groups at first cervical cancer screening in an opportunistic screening unit, Jos, Nigeria

Note: 0 (<21 years), 1 (21-30), 2 (31-40), 3 (41-50), 4 (51-60), 5 (61-70), 6 (≥71)

Table 3.1. Baseline socio-demographic characteristics by referral type in women at first CCS in an opportunistic screening program in Jos, Nigeria (N=14,088)

Variable	Self-referral	Provider-referral	p-value
HIV status			0.001†
Not infected	6,682 (50.8)	6473(49.2)	
Infected	220 (31.3)	483 (68.7)	
Age at first CCS(Mean ± SD)	37.5 ±10.1	38.6 ±10.0	0.001‡
No of Lifetime sex partners(Mean ± SD)	2.2±1.8	2.2±1.9	0.074‡
Use of condom			
No	6,304 (51.9)	5,841 (48.1)	0.001†
Yes	398 (39.4)	611 (60.6)	
History of smoking			
No	6,949 (50.1)	6,926 (49.9)	0.001†
Yes	18 (22.8)	61 (77.2)	
History of Alcohol			
No	6,542 (50.2)	6,493 (49.8)	0.061†
Yes	428 (47.0)	483 (53.0)	
History of vaginal infection			
No	1,154 (49.3)	1,189 (50.7)	0.477†
Yes	5,648 (50.1)	5,625 (49.9)	
Ever diagnosed with STI			
No	4,814 (56.2)	3,747 (43.8)	0.001†
Yes	628 (44.8)	778 (55.3)	
Age at first sex	20.5±3.9	19.8±3.9	0.001‡
Education years completed(Mean ± SD)	11.8±2.9	11.7±3.2	0.439‡
Parity(Mean ± SD)	3.4±2.4	3.7±2.6	0.001‡
Annual household income in USD(Mean ± SD)	4,374.5 ± 4,263.7	3,971.7 ± 3,851.2	0.001‡

‡Student t-test and †Pearson's chi². Percent in parenthesis, SD (standard deviation)

Table 3.2. Bivariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association between patient-reported HIV, other socio-demographic factors and provider-referral for CCS at first screening in Jos, Nigeria (N=14,088)

Variable	OR (95% CI)	p-value	aOR (95% CI)	P-value
HIV status				
Uninfected	1.0			
Infected	2.27(1.93, 2.67)	0.001	2.35(1.95, 2.82)	0.001
Age in years				
<35 years	1.0			
≥35 years	1.34(1.25, 1.43)	0.001	1.25(1.15, 1.35)	0.001
Education (years completed)				
<7years	1.0			
7-12years	0.65(0.57, 0.73)	0.001	0.77(0.71, 0.84)	0.001
>12years	0.81(0.72, 0.90)	0.001	-	-
Parity				
< 5	1.0			
≥5	1.27(1.18, 1.36)	0.001	1.18(1.09, 1.28)	0.001
Age at first sex				
>22 years	1.0			
≤22 years	1.38(1.28, 1.49)	0.001	1.27(1.16, 1.39)	0.001
Total life-time sex partners				
<3	1.0			
≥3	1.05(0.97, 1.14)	0.234	-	-
Use of condoms during sex				
No	1.0			
Yes	1.66(1.45, 1.89)	0.001	1.47(1.28, 1.70)	0.001
History of vaginal infection				
No	1.0			
Yes	0.97(0.89, 1.06)	0.477	-	-
Ever diagnosed with STIs				
No	1.0			
Yes	1.59(1.42, 1.78)	0.001	-	-
History of Smoking				
No	1.0			
Yes	3.40(2.01, 5.76)	0.001	3.20(1.67, 6.12)	0.001
Alcohol consumption				
No	1.0			
Yes	1.14(0.99, 1.30)	0.061	-	-

Hosmer-Lemeshow goodness-of-fit p-value=0.223, LR (chi2)=275.9, Pseudo R^2=0.0186

Table 4.1: Baseline socio-demographic characteristics by age at first CCS <35 years versus ≥ 35 years in an opportunistic screening program in Jos, Nigeria (N=14,051)

Variable	Age first CCS ≥ 35 years	Age first CCS < 35 years	p-value
HIV status			0.001†
Not infected	7,870 (59.8)	5,285 (40.2)	
Infected	341 (48.5)	362 (51.5)	
Age at first CCS (Mean± SD)	8,305 (44.5 ±7.7)	5,749 (22.7 ±3.7)	0.001‡
No of Life-time sex partners(Mean± SD)	6,185 (2.2±1.9)	5,104 (2.2±1.8)	0.503‡
Use of condom			
No	7,307 (60.2)	4,838 (39.8)	0.001†
Yes	404 (40.0)	605 (60.0)	
History of smoking			
No	8,222 (59.3)	5,653 (40.7)	0.272†
Yes	42 (53.2)	37 (46.8)	
History of Alcohol			
No	7,625 (58.5)	5,410 (41.5)	0.001†
Yes	635 (69.7)	276 (30.3)	
History of vaginal infection			
No	1,536 (65.6)	805 (34.4)	0.001†
Yes	6,517 (57.8)	4,756 (42.2)	
Ever diagnosed with STI			
No	4,963 (58.0)	3,598 (42.0)	0.001†
Yes	744 (52.9)	662 (47.1)	
Age at first sex (Mean± SD)	8,193 (19.9±4.1)	5,651 (20.4 ± 3.8)	0.001‡
Education years completed (Mean± SD)	6,610 (11.8±3.4)	5,117 (11.9±2.6)	0.062‡
Parity (Mean± SD)	7,818 (4.4±2.5)	4,317 (2.1±1.7)	0.001‡
Annual household income in USD(Mean ± SD)	4,579 (4320.4± 4366.9)	2,365 (3848 ± 3144.4)	0.001‡

‡Student t-test and †Pearson's chi^2. Percent in parenthesis, SD (standard deviation)

Table 4.2. Bivariable and multivariable Logistic regression model with unadjusted and adjusted odds ratio of the association between patient-reported HIV, other socio-demographic factors and the likelihood of first CCS at age <35 years in an opportunistic cervical cancer screening program in Jos, Nigeria (N=14,051

Variable	OR (95% CI)	P-value	aOR (95% CI)	P-value
HIV status				
Not infected	1.0			
Infected	1.58 (1.36, 1.84)	0.001	1.18 (0.99, 1.41)	0.058
Referral group				
Self-referral	1.0			
Provider-referral	0.75 (0.70, 0.80)	0.001	-	-
Education (years completed)				
<7years	1.0			
7-12years	3.12 (2.75, 3.53)	0.001	3.07 (2.69, 3.51)	0.001
>12years	1.53 (1.36, 1.72)	0.001	1.43 (1.27, 1.62)	0.001
Parity				
< 5	1.0			
≥5	0.51 (0.47, 0.55)	0.001	-	-
Age at first sex				
>22 years	1.0			
≤22 years	0.83 (0.77, 0.90)	0.001	-	-
Total life-time sex partners				
<3	1.0			
≥3	1.14 (1.05, 1.24)	0.001	-	-
Use of condoms during sex				
No	1.0			
Yes	2.26 (1.98, 2.58)	0.001	1.96 (1.70, 2.27)	0.001
History of vaginal infection				
No	1.0			
Yes	1.39 (1.27, 1.53)	0.001	1.29(1.15, 1.43)	0.001
Ever diagnosed with STIs				
No	1.0			
Yes	1.23 (1.10, 1.37)	0.001	-	-
History of Smoking				
No	1.0			
Yes	1.28 (0.82, 2.0)	0.273	1.63 (0.93, 2.83)	0.086
Alcohol consumption				
No	1.0			
Yes	0.61 (0.53, 0.71)	0.001	-	-

The Hosmer-Lemeshow goodness-of-fit p-value=0.538, Pseudo R^2=0.0363, LR (chi^2) =521.35

Table 5.1. Baseline socio-demographic characteristics by cervical cytology category at first CCS in an opportunistic screening program in Jos, Nigeria (N=14,081)

Variable	NILM	Mild Dysplasia	Severe dysplasa	p-value
HIV status				
Not infected	11,261 (85.7)	1,288 (9.8)	599 (4.6)	0.930†
Infected	605 (86.1)	68 (9.7)	30 (4.3)	
Age at first CCS				
< 35 years	5,367 (93.4)	288 (5.0)	94 (1.6)	0.001†
≥ 35 years	6,701 (80.4)	1,083 (13.0)	548 (6.6)	
Total # lifetime sex partners				
< 3	6,727 (85.5)	763 (9.7)	374 (4.8)	0.001†
≥ 3	3,035 (88.7)	271 (7.9)	114 (3.3)	
Use of condom				
No	10,436 (86.0)	1,166 (9.6)	540 (4.4)	0.002†
Yes	904 (89.5)	81 (8.0)	25 (2.5)	
History of smoking				
No	11,899 (85.8)	1,340 (9.7)	630 (4.5)	0.145*
Yes	63 (79.8)	13 (16.4)	3 (3.8)	
History of Alcohol				
No	11,212 (86.1)	1,230 (9.4)	588 (4.5)	0.001†
Yes	743 (81.7)	123 (13.5)	44 (4.8)	
History of vaginal infection				
No	1,919 (82.0)	276 (11.8)	145 (6.2)	0.001†
Yes	9,752 (86.6)	1,036 (9.2)	480 (4.2)	
Ever diagnosed with STI				
No	7,431(86.8)	763 (8.9)	365 (4.3)	0.843†
Yes	1,228 (87.3)	122 (8.7)	56 (4.0)	
Age at first sex				
≥ 22 years	8,025 (84.5)	996 (10.5)	476 (5.0)	0.001†
<22 years	3,843 (88.5)	345 (8.0)	153 (3.5)	
Education years completed				
< 7 years	1,366 (83.8)	172 (10.5)	93 (5.7)	0.001†
7-12 years	3,078 (89.8)	256 (7.5)	93 (2.7)	

>12 years	5,834 (87.6)	584 (8.8)	244 (3.6)	
Parity				
< 5	7,382 (88.2)	699 (8.4)	288 (3.4)	0.001[†]
≥ 5	2,894 (77.0)	563 (14.9)	303 (8.1)	

[†]Pearson's chi[2]. [*]Fisher's Exact. Percent in parenthesis

Table 5.2. Bivariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association of patient-reported HIV and other sociodemographic variables and mild cervical dysplasia at first CCS in Jos, Nigeria (N=14,081)

Variable	OR (95% CI)	P-value	aOR (95% CI)	P-value
HIV status				
Uninfected	1.0			
Infected	0.99 (0.77, 1.28)	0.953	1.04 (0.80, 1.36)	0.747
Age at first CCS				
<35 years	1.0			
≥35 years	2.83 (2.48, 3.24)	0.001	2.56 (2.23, 2.95)	0.001
Referral group				
Self-referral	1.0			
Provider-referral	1.88 (1.67, 2.11)	0.001	1.75 (1.56, 1.98)	0.001
Education (years completed)				
<7years	1.0			
7-12years	0.68 (0.56, 0.84)	0.001	-	-
>12years	0.82 (0.68, 0.96)	0.025	-	-
Parity				
< 5	1.0			
≥5	1.46 (1.31, 1.64)	0.001	1.21(1.08, 1.36)	0.001
Age at first sex				
>22 years	1.0			
≤22 years	1.23 (1.08, 1.41)	0.002	-	-
Total life-time sex partners				
<3	1.0			
≥3	0.80 (0.69, 0.93)	0.003	-	-
Use of condoms during sex				
No	1.0			
Yes	0.82 (0.65, 1.04)	0.103	-	-
History of vaginal infection				
No	1.0			
Yes	0.76 (0.69, 0.87)	0.001	0.81 (0.70, 0.94)	0.004
Ever diagnosed with STIs				
No	1.0			
Yes	0.97 (0.79, 1.19)	0.772	-	-

History of Smoking				
No	1.0			
Yes	1.84 (1.01, 3.35)	0.045	-	-
Alcohol consumption				
No	1.0			
Yes	1.50 (1.23, 1.83)	0.001	1.38 (1.13, 1.70)	0.002
Hosmer-Lemeshow Goodnes-of-fit p-value=0.145, LR (chi2) =365.90, Pseudo R^2=0.0425				

Table 5.3. Bivariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association of patient-reported HIV and other sociodemographic variables and severe cervical dysplasia at first CCS in Jos, Nigeria (N=14,081)

Variable	OR (95% CI)	P-value	aOR (95% CI)	P-value
HIV status				
Uninfected	1.0			
Infected	0.93 (0.64, 1.35)	0.704	1.26 (0.83, 1.92)	0.276
Age at first CCS				
<35 years	1.0			
≥35 years	4.24 (3.40, 5.29)	0.001	3.57 (2.74, 4.64)	0.001
Referral group (N=14,081)				
Self-referral	1.0			
Provider-referral	1.27 (1.08, 1.49)	0.004	1.34 (1.09, 1.64)	0.005
Education (years completed)				
<7years	1.0			
7-12years	0.46 (0.34, 0.62)	0.001	0.65 (0.48, 0.88)	0.006
>12years	0.63 (0.49, 0.80)	0.001	0.75 (0.58, 0.98)	0.034
Parity				
< 5	1.0			
≥5	1.85 (1.58, 2.17)	0.001	1.27 (1.03, 1.56)	0.025
Age at first sex				
>22 years	1.0			
≤22 years	1.32 (1.08, 1.60)	0.006	-	-
Total lifetime sex partners				
<3	1.0			
≥3	0.69 (0.56, 0.86)	0.001	-	-
Use of condoms during sex				
No	1.0			
Yes	0.55 (0.36, 0.82)	0.004	-	-
History of vaginal infection				
No	1.0			
Yes	0.67 (0.56, 0.82)	0.001	0.67 (0.53, 0.84)	0.001
Ever diagnosed with STIs				

No	1.0			
Yes	0.93 (0.70, 1.24)	0.627	-	-
History of Smoking				
No	1.0			
Yes	0.83 (0.26, 2.64)	0.751	-	-
Alcohol consumption				
No	1.0			
Yes	1.08 (0.79, 1.47)	0.651	-	-

Hosmer-Lemeshow Goodnesss-of-fit p-value 0.798. LR (chi^2)-178.15, Pseudo R^2=0.0497

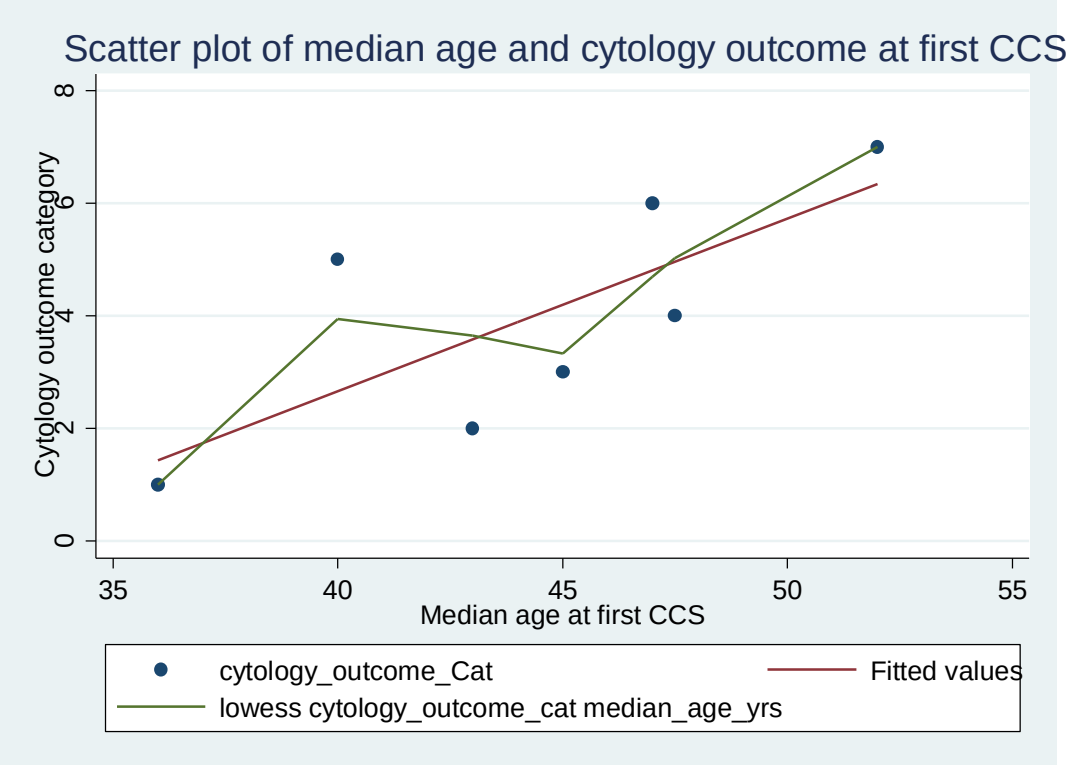

Fig. 5.1. Scatter plot of the median age at first CCS and the cytology outcome category (1=NILM, 2=ASCUS, 3=LSIL, 4=ASCUS-H, 5=AGUS, 6=HSIL and 7=HSIL with suspicion for invasion)

Table 5.1.1: Baseline socio-demographic characteristics and follow up cervical cytology outcome of women with normal cervical cytology category at first CCS in an opportunistic screening program in Jos, Nigeria (N=1,599)

Variable	Normal cytology	Abnormal cytology	p-value
Patient-reported HIV			
Not infected	1,272 (84.9)	227 (15.1)	0.894†
Infected	48 (84.2)	9 (15.8)	
Mean follow up time in yrs(Mean ± SD)	2.4 ± 1.6	2.3 ± 1.6	0.383‡
Age at first CCS			
<35 years	422 (90.6)	44 (9.4)	0.001†
≥35 years	934 (82.4)	199 (17.6)	
Age at first sex			
<20 years	496 (83.8)	96 (16.2)	0.451†
≥20 years	829 (85.2)	144 (14.8)	
Parity			
< 3	426 (90.4)	45 (9.6)	0.001†
≥3	830 (81.6)	187 (18.4)	
Total life-time Sex partners			
<3	928 (84.3)	173 (15.7)	0.364†
≥3	408 (86.1)	66 (13.9)	
Smoking			
No	1,339 (84.8)	241 (15.2)	0.536*
Yes	9 (90.0)	1 (10.0)	
Alcohol			
No	1,261 (84.5)	232 (15.5)	0.101
Yes	80 (90.9)	8 (9.1)	
Vaginal infection			
No	199 (80.6)	48 (19.4)	0.043†
Yes	1,124 (85.6)	189 (14.4)	
Ever diagnosed with STI			
No	908 (84.9)	161 (15.1)	0.844†
Yes	136 (85.5)	23 (14.5)	

‡Student t-test and †Pearson's chi². *Fisher's Exact. Percent in parenthesis, SD (standard deviation)

Table 5.1.2. Bivariable and multivariable Cox regression model with unadjusted and adjusted hazard ratio for abnormal cervical cytology with patient-reported HIV and other sociodemographic variables at follow up after normal cervical cytology at first CCS in Jos, Nigeria (N=1,599)

Variable	HR (95% CI)	p-value	aHR (95% CI)	P-value
HIV status				
Uninfected	1.0			
Infected	1.25 (0.65, 2.41)	0.535	1.78 (0.87, 3.65)	0.116
Age at first CCS				
<35 years	1.0			
≥35 years	1.98 (1.43, 2.75)	0.001	1.63 (1.11, 2.41)	0.013
Parity				
< 3	1.0			
≥3	2.0 (1.45, 2.78)	0.001	1.65 (1.14, 2.37)	0.008
Age at first sex				
>20 years	1.0			
≤20 years	0.89 (0.69, 1.16)	0.391	-	-
Total lifetime sex partners				
<3	1.0			
≥3	0.89 (0.67, 1.18)	0.426	-	-
History of vaginal infection				
No	1.0			
Yes	0.70 (0.51, 0.96)	0.025	0.67 (0.48, 0.93)	0.015
Ever diagnosed with STIs				
No	1.0			
Yes	0.97 (0.63, 1.50)	0.885	-	-
History of Smoking				
No	1.0			
Yes	0.50 (0.07, 3.60)	0.488	-	-
Alcohol consumption				
No	1.0			
Yes	0.51 (0.25, 1.02)	0.059	0.49 (0.22, 1.05)	0.067

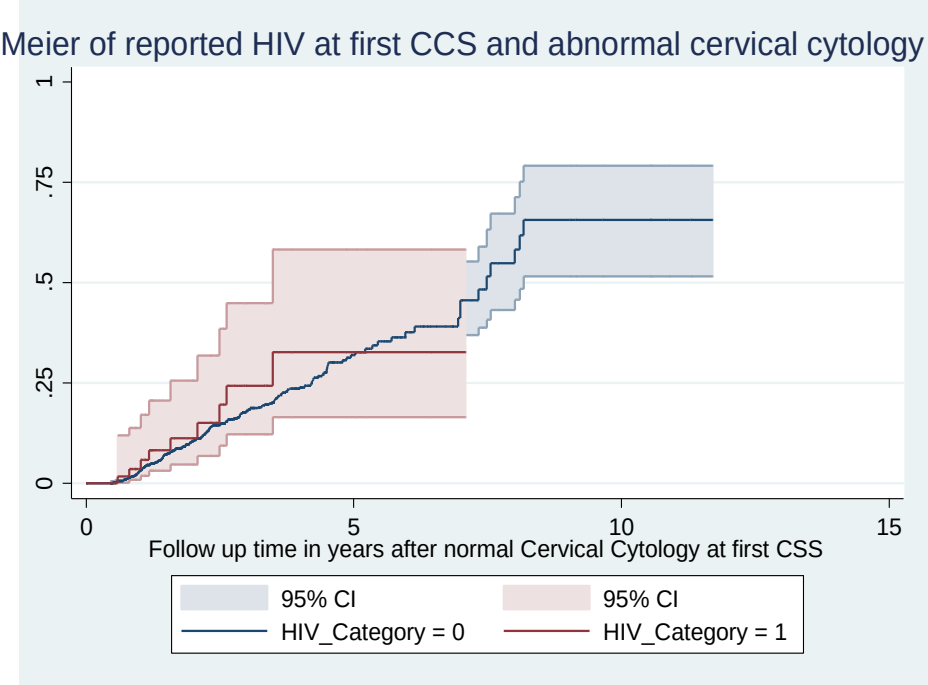

Fig. 5.1.1. Kaplan-Meier Plot of patient-reported HIV at first cervical cancer screening with normal cytology and hazard of abnormal cytology at subsequent follow up Pap cytology (log-rank test, p-value=0.534)

Note: HIV_Category=0 (not HIV infected), HIV_Category=1 (HIV infected

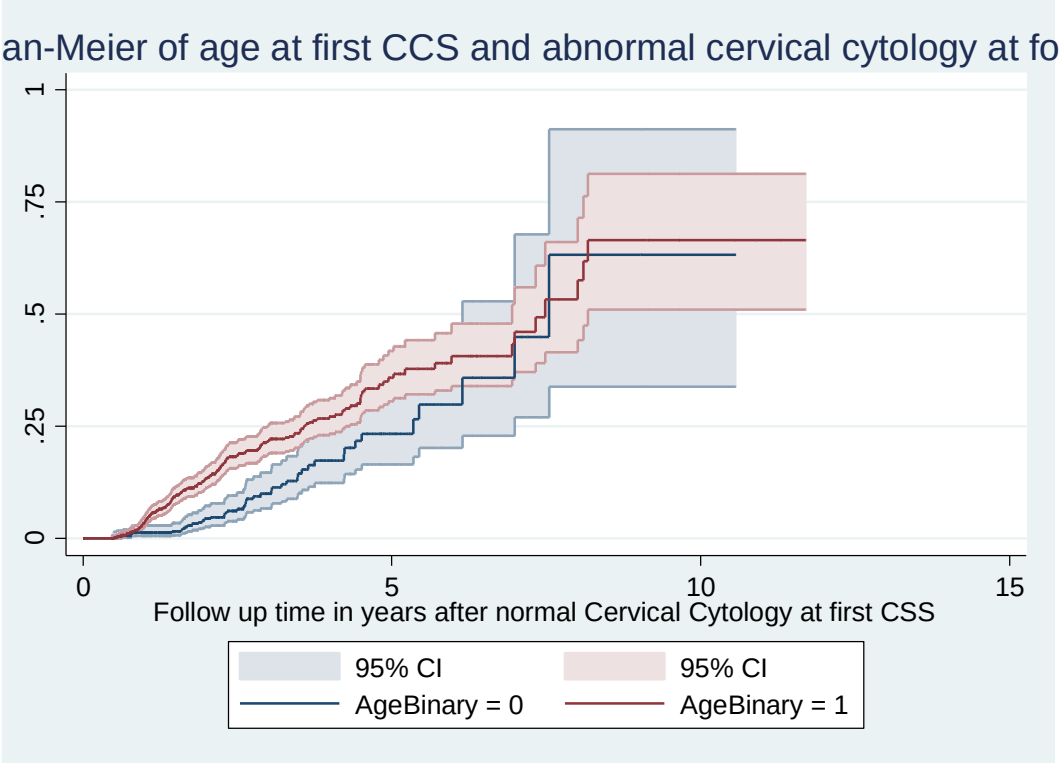

Fig. 5.1.2. Kaplan-Meier Plot of patient-reported age at first cervical cancer screening with normal cytology and hazard of abnormal cytology at subsequent follow up Pap cytology (log-rank test, p-value=0.001)

Note: AgeBinary=0 (Age at first CCS <35 years), AgeBinary=1 (Age at first CCS ≥ 35 years)

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