FACULTY OF MEDICINE AND HEALTH SCIENCES

EVALUATION OF CERVICAL CANCER SCREENING UPTAKE, HPV GENOTYPING AND SELF-SAMPLING COLLECTION TECHNIQUES IN ETHIOPIA

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Dedication

I dedicate this doctoral work for women who are living and suffering from cervical cancer in the world and to my darling wife, Mrs.Betselot Worku and our lovely children Eyosiyas, Nataniam, and Mabel. This thesis is a result of your patience and trustful support. Even though it was a long journey, I have reached the end of the training, but it is also the beginning of a new and demanding life. I also dedicate this work to honorable Dr. Sharon Ransom, Mr. Moges, Mr. Dawit, and SAMH`s staff members who were supportive throughout this study.

Declaration

I declare that this doctoral research work titled "**EVALUATION OF CERVICAL CANCER SCREENING UPTAKE, HPV GENOTYPING AND SELF-SAMPLING COLLECTION TECHNIQUES IN ETHIOPIA**" is original and has not been submitted elsewhere. It does not infringe on the copyright of other persons or entities. All data apart from the research findings has been duly acknowledged.

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Abbreviations

AAU	Addis Ababa University
AML	Algemeen Medisch Laboratorium
ASCUS	Atypical squamous cells of undetermined significance
BCC	Behavior Change Communication
CC	Cervical Cancer
CCHF	Cervical cancer health facility
CDC	Centers for Disease Control and Prevention
CHAI	Clinton Health Access Initiatives
CIN	Cervical Intraepithelial Neoplasia
CT	Clinician-taken
DNA	Deoxyribonucleic acid
FMOH	Federal Ministry of Health
GAVI	Global Alliance for Vaccines and Immunization
HBM	Health Belief Model
HDA	Health development army
HEWs	Health extension workers
HF	Health Facility
HPV	Human Papilloma virus
HR	High Risk
HSIL	High grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICC	Invasive cervical cancer
IPRH	International Partnership for Reproductive Health
JHPIEGO	Johns Hopkins Program for International Education in Gynecology and Obstetrics
LEEP	Loop Electrical Excision Procedure
LMICs	Low- and middle-income countries
LR	Low Risk
MoH	Ministry of Health
NASS	Nurse Assisted Self-Sampling

NCCP	National Cancer Control Plan
NCR	National Cancer Registry
PAP	Papanicolaou
PATH	Program for Appropriate Technology in Health
qPCR	quantitative Polymerase Chain Reaction
RRP	Recurrent respiratory papillomatosis
SAMH	Sister Akelisia Memorial Hospital
SPSS	Statistical Package for the Social Sciences
SS	Self-Sampling
STA	Screen-and-Treat Approach
UNICEF	United Nations International Children's Emergency Fund
VIA	Visual Inspection with Acetic acid
VIAM	VIA with Magnification
VILI	Visual Inspection after application of Lugol's Iodine
WHO	World Health Organization

Summary

Invasive cervical cancer (ICC) is the fourth most prevalent malignancy and cause of death in women worldwide. It is the second most prevalent malignancy and cause of death among women between 15 and 44 years of age in Ethiopia. Ethiopia is the second most populated country in Sub-Saharan Africa, with more than 56 million females. It is also one of the least urbanized countries in the world, with only 21.7% of the population living in urban areas. Ethiopia has 31.5 million women aged 15 years and older and 7,095 women were diagnosed annually with ICC of whom an estimated 4,884 women died from this disease during 2019. The routine and standard method of cervical cancer screening in Ethiopia is Visual Inspection with Acetic Acid (VIA). Allthough 20 million women are eligible for cervical screening in Ethiopia, less than 1% of women have been screened.

The first National Cancer Control Plan of Ethiopia (2016 -2020) outlines the dire need for the national implementation of this cancer control plan. The plan outlines interventions to reduce the burden of cancer through changes in lifestyle, primary prevention, screening and early diagnosis, appropriate follow-up, treatment and provision of palliative care, and advanced stages management, when very little can be done to treat the disease. The low cervical cancer screening uptake is largely due to the low awareness of cancer signs and symptoms, inadequate screening and early detection and treatment services, inadequate diagnostic facilities and poorly structured referral. The country has very few cancer specialists (only 4 qualified oncologists for the entire population). This makes it difficult for a great majority of the population to access cancer treatment services, which results in long waiting times and cause many potentially curable tumors to progress to incurable stages.

The reason for this despondent situation is that the cancer-treatment infrastructure in Ethiopia is inadequate and some cancer-management options are not readily available within the health care system. Cancer is treated through medical, surgical or radiation therapy, but some patients seek cancer treatment abroad. Effective cancer treatment requires surgical, radiation and chemotherapy be available in the same setting to avoid distant referral and delays in treatment administration. Currently, the Ethiopian essential medicines list does not include chemotherapy for cancer. Even the essential medicines for cancer pain-management are rare to find in most public hospitals.

However, there are opportunities for a program to prevent and control cancer to be developed and expanded in Ethiopia. The country has adopted a comprehensive national action plan on the prevention and control of chronic non-communicable diseases, including cancer. Expansion of cancer treatment services is underway. The country plans a nation-wide scale up of the screening and treatment for cervical pre-cancer into 800 health facilities approximitaley (one health facility per district). The First Lady of Ethiopia guides and leads the cancer-control programme with the Minister of Health, as cancer research in Ethiopia is not proportionate to the magnitude of the problem. This is due to inadequate funding and training facilities in cancer research. There is also no comprehensive cancer surveillance system, and population-based cancer registry limited to the Addis Ababa region at present.

Weaknesses contributing to the poor primary health medical state Ethiopia finds itself in includes low awareness about cancer screening and prevention; inadequate and unskilled staff; lack of pathology laboratories and expertise; the public health service is inadequate and centralized; lack of expertise on cancer diagnosis and treatment as well as lack of diagnostic and treatment facilities. Public medical service is limited in tertiary hospitals and centralized. Cancer medicine and supplies are not available and if available it is not affordable. Minimal palliative care knowledge and practice by health workers, and no palliative-care structure in health care.

The Federal Ministry of Health (FMOH) therefore admits that there is an urgent need to make the most efficient use of the available limited resources for maximum impact, through the identification and implementation of cost-effective strategies and innovations in cancer control.

The cancer control policy notes the possibility of using new technologies, such as HPV DNA testing as well as outreach approaches to reach more women more efficiently to raise awareness of cervical cancer screening. Recently, in 2021, Ethiopia has started the HPV DNA test as a pilot project; however, the program faced several challenges like a shortage of supplies and reagents.

Other key interventions include:

- to train health workers on cancer prevention and advocacy
- to utilize opportunities like commemoration days to disseminate cancer prevention information to the community

- to early identify and refer patients suspected of cervical cancer
- to train health professionals on VIA and cryotherapy
- to conduct awareness campaigns
- to provide education and community support materials for patients with cancer
- to improve and increase access to diagnostic and treatment facilities
- to operationalize HPV DNA testing at regional and national laboratories
- to develop action plan for phased introduction of cancer care
- to develop a standard set of equipment required for supplying health facilities with diagnostic equipment
- to train medical doctors and nurses on the chemotherapy protocols identified as standard.
- to develop a staffing plan for optimal use of the radiotherapy unit and develop an education and in/service training plan to implement radiotherapy treatment.
- to improve access to surgery that help diagnose cervical cancer, determine how far the cancer has spread and treat the cancer (especially for early-stage cancers).

The FMOH also commits to develop a health workforce plan for cancer that addresses education as well as in-service capacity building opportunities, harnessing international, regional and national virtual as well as in-person training platforms for different levels of health professionals for cancer diagnosis and treatment.

A publication in January 2021, ' Availability and readiness of cervical cancer screening service at health facilities in Ethiopia' by Tigist Shumet Wasiyhun, *et al,* Ethiop. J. public health nutr. confirms that cervical cancer is the second prevalent cancer type. It is the most preventable and treatable type of cancer and can be screened and diagnosed early. The need for the availability and readiness of the health facility is inevitable for the provision of these services. This study aimed to assess the availability and readiness of cervical cancer screening service using the Ethiopian health facility surveys conducted in 2016 and 2018. Data were obtained from Ethiopia service

availability and readiness assessment (SARA) 2016 and 2018 which was a national cross-sectional facility-based survey. The availability and readiness of cervical cancer screening service using four tracer items such as; equipment, reagents, training completed and availability of the national cancer prevention and control policies. The results of this study showed: Nationally, 21% and 33% of the 632 health care facilities included in the study provided cervical cancer screening services in 2016 and 2018, respectively. Among those facilities that provide cervical cancer screening services, 30% of the hospitals and 29% of the health care centers had all tracer items for cervical cancer prevention and control. However, none of the health care clinics had all the tracer items to provide cervical cancer screening services and the service readiness score has remained similar in two periods.

In the conclusion the author states that the overall availability of cervical cancer screening services in health facilities was found lacking; the number of health care facilities rendering cervical cancer screening has increased by 33% in SARA 2018 when compared to SARA 2016, but the level of service readiness remained similar. The author recommends that the FMOH should distribute and ensure constant availability of guidelines, equipment, reagents, and provide refresher training to health care providers.

Although the FMOH did not fare well with the SARA 2016 and 2018 findings, a Press report from the WHO on 5 February 2021 confirms that Ethiopia successfully immunized over 2 million girls against human papillomavirus (HPV) from December 2018 to January 2021.

The HPV vaccinnation program was introduced in Ethiopia in December 2018, targeting 14-year-old girls. The FMOH lead the rollout and conducted the vaccination in collaboration with regional health bureaus and the education sector, key stakeholders, and different partners including WHO, UNICEF, CHAI, PATH, Jhpiego, Girls Effect and Save the Children. The quadrivalent Gardasil vaccines were acquired through the support of GAVI, the Vaccines Alliance.

The Human Papillomavirus (HPV) vaccination campaign targeting 2.4 million 14-year-old girls across the country in two cohorts, was completed the end of January 2021. One cohort took HPV – the first dose of the vaccine, while the second cohort was vaccinated the second dose of the vaccine (HPV), which they missed due to school closures in the wake of the COVID-19 pandemic. The vaccination was conducted in schools, communities and health facilities.

Advocacy, social mobilization and awareness creation was conducted in the weeks prior to the vaccination campaign. An expert panel discussion was held at national level, followed by sensitization workshops in five selected regions. Messages were broadcasted on the benefits of the HPV vaccine through national, regional and community media (TV and radio), on educational TV channels as well as in schools to ensure high vaccine uptake.

The WHO provided technical and logistical support to the campaign. WHO central and regional teams provided technical support in monitoring and supportive supervision for quality assurance.

The vaccination of the 2.4 million schoolgirls is a big milestone in the history of cervical cancer screening and prevention in Ethiopia. Many more similar interventions are desperately required by the FMOH, health care workers as well as the population of Ethiopia.

The prevalence rate of cervical carcinoma as well as abnormal lesions of the cervix are great concerns and must be addressed by all possible means in order to minimize the negative impact of this disease. The lack of national prevalence statistics is crippling all data related publications. It is known that the NCR of Ethiopia currently only collect data related to Addis Ababa. Other data utilized are known from studies done in the various districts of Ethiopia.

Allthough 20 million women are eligible for cervical screening in Ethiopia, less than 1% of women have been screened. The reasons for the low uptake of cervical cancer (CC) screening may also be due to health beliefs and lack of knowledge regarding the primary risk factors causing cervical cancer; the collection method of the cervical samples as well as the distance to travel in order to reach a health facility which provides cervical cancer screening.

The general purpose of this research study is:

- to endeavour to improve the uptake of cervical cancer screening service by evaluating the feasibility of self-sampling as well as HPV testing as alternative screening options in Ethiopia,
- to investigate the cervical cancer screening uptake where women's health beliefs and risk factors lead them to decide whether to be part of the cervical cancer screening program,

- to do a systematic review of the self-sampling HPV detection rate by comparing results from samples collected by clinicians in Africa, and
- to explore HPV genotype distribution as well as cervical cytology abnormality prevalence rates.

The first research is a cross-sectional study conducted in Adama town, Oromia region, Ethiopia. Women participated voluntarily in cervical cancer screening at St. Aklesia Memorial Hospital. Eighty-three (83) women provided a total of 166 coupled nurse assisted self-samples (NASS) and clinician-collected samples. Specimens were stored at room temperature and analyzed using the RIATOL qPCR HPV genotyping test. This is a quantitative Polymerase Chain Reaction (qPCR) high-throughput HPV test utilizing an assay reading the presence of E6 and E7.

The second research study conducted in Adama, Oromia, Ethiopia, involves 412 women participating in this study between September and December 2017. The purpose of this study was to assess the participating women's health beliefs and risk factors.

The third study is a systematic review and meta-analysis of 250 research articles related to self-sampling HPV testing performed in Africa. The data was analyzed by comprehensive electronic bibliographic databases of Pubmed, Cochrane, WHO Global health library as well as Popline.

The last study is an institutional-based cross-sectional study with 366 participants. The screening methods were HR HPV DNA testing analyzed using the Abbott Real-Time PCR system and cervical cancer screening performed using conventional PAP cytological techniques.

To summarize the main findings on the first research question (Chapter 2): Seventy-three women (87.9%) of the participants felt that nurse assisted self-sampling (NASS), using the ThinPrep plastic spatula and endocervical brush rinsed in Preservecyt Solution vial, was comfortable to use. An overall HPV, HR (High Risk) HPV, and LR (Low Risk) HPV prevalence was 22.7% (15/66), 18.2% (12/66) and 6.1% (4/66) respectively. The overall HR HPV prevalence was 17.2% (NASS) and 15.5% Clinician-taken (CT). The most prevalent HR-HPV type was HPV 51, and the overall measurement agreement between NASS- and clinician-taken samples was moderate with a kappa value of 0.576 ($p < 0.001$). Women with a history of sexual partners of more than two

men showed an HPV result associated with HR HPV positivity (P-value <0.001). There was a significant statistical association between HR HPV positivity and visual inspection with acetic acid (VIA) positive (p value<0.001).

The conclusion of the first research question is that NASS is a good alternative as a sample collection method for HPV testing for cervical cancer screening in Ethiopia. However, the quality of the collection of the sample does require improvement. Improved instruction or training of women by the health care workers how to collect adequate samples and to transfer the sample to the Thinprep PreservCyt vial by rinsing the collection device vigourously into the ThinPre PreservCyt may have a definite positive impact on the quality of the sample. NASS HPV testing may be a valuable tool for the follow-up of women in low-resource setting countries. Although our study revealed that HPV 51, 31, 16, 45, 52, and HPV 58 was predominantly identified, a large-scale study is required to study the prevalent genotypes in women of Ethiopia in order to aid in the selection of an appropriate HPV vaccine type accordingly. Our research was the first study on HPV detection on NASS using Cytobrush/plastic spatual ThinPrep PreservCyt vial and may be used as a platform for similar studies in the future.

The second research question (chapter 3) is to evaluate the cervical cancer screening uptake using the health belief model. Only 6.8% (28/412) women reported that they had visited a health facility (HF) previously for cervical cancer (CC) screening. Among those, thirteen, (3.2% in total) had undergone screening tests either by VIA or Pap test method. More than a third of the women (38.3%) recognized the need to go for regular Pap or VIA tests for early detection of CC. However, only 11.2% were aware that the first sexual intercourse at eairly age is associated with increased risk of CC. Cigarette smoking as an associated factor to intensify the risk of cervical cancer was recognized by 59.2% of the women.

There was a significant association between the educational background of the women and cervical cancer health facility visits (CCHF) (p<0.05). Women who had a family history of CC, showed an increase interest to visit the CCHF for check-up purposes (p<0.05). Eligible women did not feel threatened by the risk of developing cervical cancer. Only 41.5% of women partaking in this study, indicated that they knew the benefits of cervical cancer screening.

In this study, women believe that the main barrier factors for not visiting clinics for screening were because they douche vagina daily ($p < 0.05$) and no “screen-and-treat” approach (STA) cervical cancer screening modalities was available at the health care facilities ($p<0.005$). The women who visited clinics for CC screening were statistically associated with when they had symptoms, sex with many partners as well as those women taking contraceptive drugs or contraceptive devices ($p<0.05$).

The health beliefs model used to explore the reasons for the Ethiopian women’s lack of participation in cervical cancer screening as well as the factors for prevention of CC, and so on, may assist with the design of culturally appropriate cervical cancer screening interventions. Therefore, addressing issues of low screening uptake and visiting health clinics might require more than one theory, considering there may be no single theory suitable for all cases. Hence, further study is required to explore other possible factors contributing to low screening uptake and clinic visits for cervical cancer screening.

A systematic review of African studies conducted to explore self-sampling HPV detection rate and its acceptability compared with that collected by doctors (Chapter 4). Eight research articles from six countries in the African continent with a total of 3,476 women included in these studies, formed part of the systemic review. On average the high risk (HR)-HPV detection rate was 36% (7.2 - 84.8%) and 35% (6.8 - 87.8%) for self- and clinician-collected sampling, respectively. The average differences and variation of HPV rates between sampling methods were 2.6% (SD =1.7). There was correlation ($r=0.997$) between the HR-HPV detection of the two sampling methods. The moderate kappa agreement 0.71(0.47 to 0.89) between the two sampling techniques was found.

In general, women concluded that the self-collected sampling method was the preferred method of sample collectiom (86.3%) and easy to obtain (77.8%). The acceptability of self-collected HPV testing could be an alternative sampling method that provides equivalent and comparable HPV detection to that of clinician sampling methods and may therefore increase the uptake of screening services. Introducing standardized self-sampling and a diagnostic assay across African countries may be very useful for strengthening the cervical cancer screening strategy.

As this review study only focused on African-based studies, there are several concerns regarding the full introduction of self-sampling into the African health care systems. Most African countries

still use conventional PAP smear and VIA for cervical cancer screening programs due to the relatively low cost; however, skilled and trained nurses, doctors and pathologists are required for the least developed countries where these skills are extremely scarce. Thus, to introduce HPV tests using self-collected sampling, some level of infrastructure with relevant equipment, reagents, electricticity as well as a skilled workforce are required.

The fourth study aimed to assess the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities at selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia (chapter 5). The overall HR HPV burden of 13.7% and the abnormal cytology prevalence rate of 13.1% respectively were confirmed. The majority of HR HPV types were other than types 16 and 18. Of the total abnormal cytology results, 81.3% of the smears collected were diagnosed as low-grade squamous intraepithelial lesions (LSIL), 12.5% and 6.3% of the smears collected were diagnosed as atypical squamous cells of undetermined significance (ASCUS) and high-grade squamous intraepithelial lesions (HSIL), respectively. The HR HPV infection rate correlated well with the geographical area of residence of the patient, her occupation as well as her HIV serostatus. Other associated factors include the age of the patient, her age at first marriage as well as her education level. The overall agreement between Abbott Real-Time HR HPV DNA PCR results as well as Pap smear cytology screening results was 78.96% (Kappa value of 0.12, 95% CI (0.00–0.243), P=0.01).

Non-16/18 HR HPV genotypes represented the largest proportion of HR HPV infections in this study. Women without cervical cytology abnormalities had the highest frequency of HR HPV infection. This may be due to high sensitivity rate of the assay, Abbott Real-Time HR HPV DNA PCR, utilized in our study. The burden of HR HPV infection and cervical cytology abnormalities presented in this study are consistent with the few previous local studies and reviews done in Ethiopia, yet somehow lower than the estimated prevalence for sub-Saharan Africa.

The performance of the Abbott Real-Time HR HPV DNA PCR and Pap smear cytology screening methods require further evaluation using histology as the gold standard. A large-scale community-based cohort study is recommended in order to determine the national burden of HPV and cervical cytology abnormalities. The outcome of this large study must be designed to recommend the ideal screening algorithm in the local context and therefore will significantly contribute to the national preventative public health strategies against cervical cancer.

The last chapter is (chapter 6) is summarizing and discussing the overall findings of our studies. Accordingly, nurse assisted self-sampling could be used as an alternative sample collection method for HPV primary screening testing in Ethiopia particularly for the remote rural population areas since comparable results and moderate agreement between doctors versus self-sampling was found. However, the quality of the sample requires improvement by intensifying training of all relevant health workers on the proper collection of an endocervical sample and then transferring the sample to the vial by rinsing the collection device vigourously in the ThinPre PreservCyt vials. The HPV detection variation between the two sampling methods are expected due to, as noted in different research studies, sample collection steps, sample collection devices, the use of different HPV detection assays, and geographical location of the patient. For example, the overall HPV prevalence rate in our two studies, capital city (Addis Ababa) versus special zone of Oromia (Adama) town geographical area, was 13.7% and 22.7%, respectively.

Our study may show that screening uptake can be increased with the implementation of NASS and/or clinician collected samples for HPV testing. It is recommended that the government should design a cervical cancer screening model that reduce the number of follow-up clinic visits for women by implementing one-stop first visit STA health facilities customized for the Ethiopian health care system.

Even if HPV testing is resource-dependent, HPV testing is recommended above VIA. HPV testing should be provided where it is affordable, implementable and sustainable over time. This recommendation applies to women regardless of HIV and any other sexually transmitted disease status. Although recent cluster randomized trial study in Ethiopia revealed that self HPV testing significantly improved uptake over VIA, the authors recommended that the FMOH of Ethiopia may design a longitudinal comparative large scare study of HPV testing and VIA testing to determine variations in specificity, sensitivity, screening uptake, adherence to procedures, feasibility and cost-effectiveness and algorithim design.

Appropriate awareness and education of women when visiting the health facility have a significant positive impact on the outcome of low screening uptake. Timeous testing and confirmation of the HPV genotypes in the country is necessary. This information will advise the suitable HPV vaccines to be utilized in the future for national vaccination programs. Our study identified a wide range of genotypes and prevalence rates of HR HPV.

We assessed women's perception or health beliefs and risk factors towards cervical cancer disease and screening participation. Most women confirmed that they never visited health clinics for cervical cancer screening mainly due to misperception, e.g. assuming regular vagina douching prevents gynaecological challenges. Cultural and religious beliefs, fear of their husband's decision to agree with cervical examination, limited knowledge on risk factors, unawareness of which health facility provides the service, long waiting time, shortage of finance, etc. were added factors contributing for low visit of health clinics for purpose of cervical cancer screening. Most women visit clinics at the late stage of disease as to avoid repeated clinic visits and follow ups.

Designing culturally appropriate cervical cancer screening interventions through scientific studies of women's perception in detail is crucial. Therefore, addressing issues of low uptake of CC screening or health clinic visits may require more than one theory, since there may be no single theory that is suitable for all cases. Hence, a supplementary study is required to explore other possible factors contributing to the low uptake of clinic visits and screening for cervical cancer.

CHAPTER 1: GENERAL INTRODUCTION

1.1 Historical Background of Cervical Cancer

In 1842, Italian physician, Domenico Rigoni-Stern, published an original article in the Gionale per severe ai progressi della patologia e della terapeutic that was based on his observations of the differences in age of women diagnosed with cancer of the uterus compared to cancer of the breast. Of uterine cancer, he wrote, `cancer of the uterus`, was common in married women and widows. He noted that the incidence of uterine cancer had not increased through licentious practices of women; however, the risk was greater among women who were excessively sensitive morally and nervously irritable (1). The causative agent of the female genital tract infections and the subsequent development of 'cancer of the uterus' remained a mystery for almost a century.

In 1908, Walther Schauenstein's doctoral thesis titled "Histological Studies on the Atypical Squamous Epithelium on the Portio and Inner Surface of the Cervix Uteri" contributed to the theory that cancer of the uterine cervix was preceded by precancerous state restricted to the epithelium cells (2). This concept was essential for understanding the prevention of invasive cervical cancer and forms the basis of the elimination of precancerous leions at the early stage of the disease using cytological screening.

In 1928, George Papanicolaou presented his paper on the use of vaginal smears for detection of uterine cancer at the third Race Betterment Conference in Battle Creek, Michigan, USA. The diagnostic value of vaginal smears for carcinoma of the uterus"; was published in 1941 in the American Journal of Obstetrics and Gynecology (3).

The inauguration of a new era in cytology involved controversy. The question of whether Aurel Babes' work preceded the work of George Papanicolaou has, historically, generated questions about the origin of cervical cytology screening techniques (4). In 1949, direct sampling of the uterine cervix was discovered by a Canadian gynecologist/cytologist, J Ernest Ayre, 1949 (5). In 1956, cells described as koilocytes today, were derived from the term 'koilocytotic atypia' proposed by Koss and Durfee (6). The term reflected the hollow nature of the clear perinuclear

space (Greek: koilos = cavity, kytos = cell). The nuclei of koilocytes that contained viral particles was presented by Laverty et al. from Australia in 1978 (7-9).

The reason why among many young women infected with human papillomavirus only a very few progress to cervical cancer, is not understood fully, in keeping with the unpredictable behavior of precancerous lesions of the cervix in a long-term follow-up study (10). The possibility of one or more contributing factors explaining the relationship of viral infection to cancer still needs to be explored. Mysteries remain why HPV present in cancers of organs such as the cornea of the eye and the esophagus. However, cervical cancer is unique amongst the cancers that are caused by infections in that almost every cervical cancer diagnosed is associated with a Human Papillomavirus infection.

According to different natural history studies, it has clearly indicated the development of cervical cancer preceded by HPV infection in several years and sexual transmission is the predominant mode of HPV acquisition (11,12). In every cell of HPV associated lesion, the viral genome is present in the original tumour and in metastases. The natural history studies of HPV infections satisfy the historically linked to cervical cancer (13,14).

1.2 Burden of Cervical Cancer

Globally, cervical cancer (CC) is the fourth most frequent women cancer with an estimated 570,000 new cases and more than 270,000 deaths in 2018, representing 6.6% of all female cancers (15). Approximately 90% of deaths due to female cancers occur in low- and middle-income countries (LMICs). Judging by the current rate, it is estimated that the death rate from cervical cancer will rise by nearly 66 percent globally by 2030 (16, 17).

However, the global high mortality rate from cervical cancer could reduce through a comprehensive approach that includes prevention, early diagnosis, effective screening as well as a functional treatment program. There are currently vaccines that protect against common cancer-causing genotypes of HPV and can significantly reduce the risk of cervical cancer and other cancers (19-21).

In Africa, 111,632 new cases in 2018 in sub-Saharan Africa. In the same year, 68% of women died from cervical cancer. Most cancers (over 80%) in sub-Saharan Africa are detected at a late stage, predominantly due to a lack of information about cervical cancer and a dearth of prevention services (21).

In some LMICs cervical cancer is the commonest cancer and the leading cause of death from cancer among women. Recently, it was estimated that 31.5 million women were at risk of developing cervical cancer in Ethiopia with an estimated 7,095 and 4,884 annual numbers of new cases and deaths, respectively. Most cancers (over 80%) in sub-Saharan Africa are detected at a late stage, predominantly due to a lack of information about cervical cancer and a dearth of prevention services. It is known that the late-stage disease is associated with low survival rates after surgery, chemotherapy or radiotherapy. Also, these treatment modalities may be lacking, be limited, too expensive or non-accessible for many women in low-resource countries, including Ethiopia (22-23).

1.3 Human papillomavirus (HPV) Diagnosis and Pathogenesis

1.3.1 Viral Structure

HPV is a small, non-enveloped, double-stranded DNA virus that is approximately 55 nm in diameter and a member of the Papillomaviridae family (20). The viral DNA genome encodes eight open reading frames comprised of six early (E1, E2, E4, E5, E6, E7) proteins that maintain regulatory function and two late (L1 and L2) proteins (21, 22]. HPV has a characteristic icosahedral viral outer shell, primarily comprised of 360 molecules of the L1 major protein arranged as 72 star-shaped pentameric capsids (27, 28).

The L1 protein, which serves as the primary structural element, can spontaneously self-assemble into 72 pentamers, forming a virus-like particle (28). The viral shell also contains up to 72 molecules of the L2 major capsid protein, but the exact location and function of the L2 minor proteins remain poorly understood (29).

1.3.2 Classification of HPV Types

The HPV types that infect humans have a known specificity for epithelial cells both at mucosal and cutaneous sites (24). There are five major known HPV genera: ∝-papillomavirus, β-papillomavirus, γ-papillomavirus, mu-papillomavirus, and nu-papillomavirus (30). γ-genus today contains 79 HPV types and 27 species, surpassing ∝ and β genera with 65 and 51 HPV types respectively. HPV genotypes are classified as low-risk (non-oncogenic types) and high-risk (oncogenic types) according to their ability to cause cancer (27). The rate of HPV type discovery is increasing, probably because of metagenomic sequencing. Classification of HPVs is on the nucleotide sequence of the ORF coding for the capsid protein L1. HPV types belonging to different genera have less than 60% similarity within the L1 part of the genome. Currently, the HPV type reached more than 202, belong to 49 species in five genera.

1.3.3 Pathogenesis

HPV infection occurs at the basal cell layer of stratified squamous epithelial cells. Infection stimulates cellular proliferation in the epithelium, and infected cells display a broad spectrum of changes, ranging from benign hyperplasia to dysplasia to invasive carcinoma. To effectively replicate, HPV must utilize the host cellular components. During the process, the viral protein product encoded by E6 binds to the p53 tumor suppressor gene product, which results in the premature degradation of the p53 protein (28). The E7 protein binds to a tumor suppressor protein—the retinoblastoma protein—and inhibits its function (31). These protein products mediate much of the virus`s oncogenic potential and their production represents a difference between the low- and high-risk strains of HPV.

1.3.4 Transmission of Genital HPV

The transmission of genital HPV is predominantly associated with sexual activity. Although several lifetime sexual partners are associated with a higher likelihood of acquiring HPV, even a person with a few or even one-lifetime sexual partner can get infected with HPV. The transmission does not require the presence of visible lesions in the source individual and frequently occurs from persons who are asymptomatic or have a subclinical infection. Consistent and correct use of condoms partially reduces the risk for genital HPV acquisition or transmission, and therefore

may reduce some of the risk for HPV-associated diseases (e.g., genital warts and cervical cancer) (32). Condom use does not entirely prevent transmission of HPV, since exposure to HPV can occur in areas that are not covered or protected by a condom (e.g., scrotum, vulva, or perianal region). A person can get HPV infection by having vaginal, anal, or oral sex with someone who has the virus. It spreads mostly during vaginal or anal sex.

Treatment of warts or cervical cellular abnormalities will reduce but may not eliminate the risk of transmission. Although rare, genital HPV infection with low-risk types can be transmitted from mother to newborn during delivery, and it may cause respiratory tract warts known as recurrent respiratory papillomatosis (RRP); in children, this condition is called juvenile-onset RRP (JORRP) (32).

1.3.5 Natural History of HPV Infections

Available data suggest that more than 90% of individuals with genital HPV infections are asymptomatic and clear the infection within two years (33). The incubation period, representing the time from acquisition to clinical manifestations, is variable and ranges from three weeks to several months for genital warts and several months to years for cervical cellular abnormalities. If cervical cancer develops, it typically occurs decades after the initial infection and following the acquisition of HPV (34).

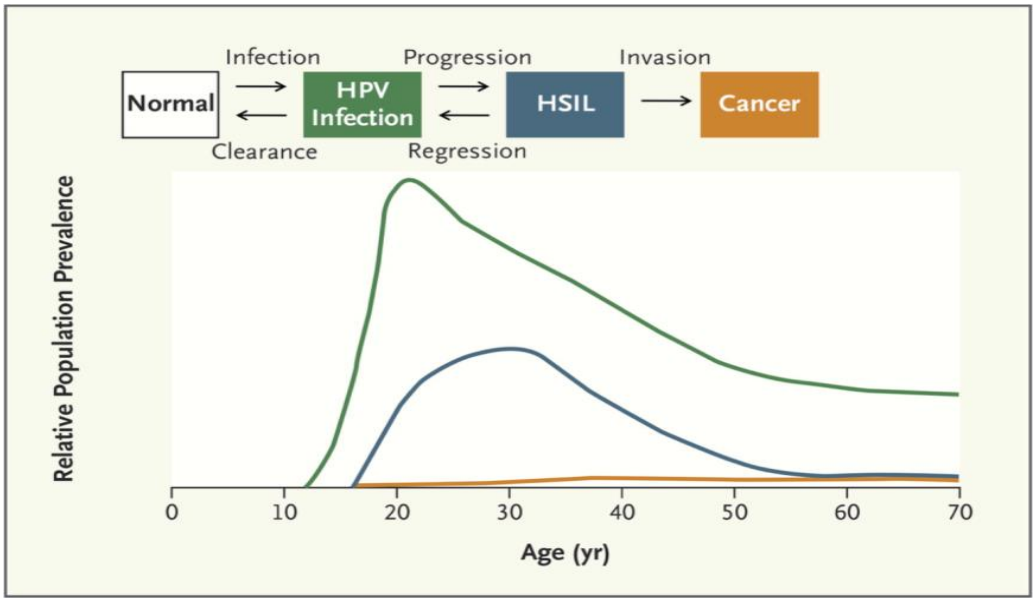

Figure 1. Age at Peak Prevalence for Each Stage in Cervical Carcinogenesis

The progression to cervical cancer is a dynamic process with a spectrum of potential outcomes that include immune-mediated clearance of HPV, to a precancerous lesion, regression of precancerous lesions as well as progression of precancerous lesions to cervical cancer with invasion of local tissue (35-38). The frequency of spontaneous regression is unclear. A few studies indicate a regression rate with cervical intraepithelial neoplasia (CIN) 2 of 19% to 40% over six months to two years (38-41). Available data strongly suggest that persistent HPV infection with high-risk HPV types is the most important risk factor for the progression of precancerous (high-grade) cervical cellular changes and cervical cancer. Additional factors associated with persistent infection include older age, smoking, and immunodeficiency.

1.4 Cervical Cancer screening

Several test methods are available to screen women for cervical precancers and cancers. Each screening test has its strengths and limitations, and the choice of test depends on the setting and application (42-45).

1.4.1 Visual Examination of Cervix

These methods are simple and can be performed by a trained health worker. The test methods are relatively inexpensive, do not require expensive laboratory infrastructure and provide relatively quick results, allowing the use of STA. The various visual examination methods are as follows:

- Visual inspection after application of acetic acid (VIA)
- Visual inspection after application of Lugol's iodine (VILI)
- Colposcopy

VIA is a naked eye visual inspection of the cervix after the application of 3 to 5% acetic acid to the cervix. When this test is performed with the naked eye, it is also called cervicoscopy or direct visual inspection. The application of 3 to 5% acetic acid to the cervix causes reversible coagulation or precipitation of the cellular proteins. Areas with dysplasia or invasive cancer have many undifferentiated cells in the epithelium and hence undergo maximal coagulation because of the higher content of nuclear protein. These areas prevent light from passing through the epithelium which causes the areas of abnormality to appear acetowhite. The accuracy of VIA to detect cervical neoplasia has been extensively studied and found to be satisfactory (44-45).

VIA is an evidence-based and affordable alternative approach for cervical cancer screening in low-resource settings (46). Studies have reported the sensitivity of VIA for detecting precancerous lesions somehow comparable to that of cervical cytology while requiring fewer resources and feasible to carry out in low-level health facilities (47,48). Besides, VIA provides immediate results, thus promoting the linkage of screening with treatment. The STA ensures adherence to treatment soon after diagnosis and reduces the risk that women get lost for follow-up in the referral system. VIA combined with cryotherapy (freezing of precancerous lesions of the cervix), ideally in a STA, is an effective and efficient strategy for secondary prevention of cervical cancer in low-resource settings and can be conducted by competent clinicians and nurses (49,50).

Lugol's iodine visual inspection application is known as Schiller's test and uses Lugol's iodine instead of acetic acid. Squamous epithelium contains glycogen, whereas precancerous cells and invasive cancer lacks glycogen. Iodine is glycophilic and is taken up by the squamous epithelium,

staining it mahogany brown or black. Precancerous lesions and invasive cancer do not take up iodine (because of the absence of glycogen) and appear as well-defined, thick, mustard, or saffron yellow areas (50).

Simple tests like VIA and VILI have generated considerable interest in several developing countries including Ethiopia. More than 208 public health facilities in Ethiopia deliver VIA service since 2018. The pooled sensitivity of VIA for CIN2 and above is 69% (95%CI: 54 to 81), and pooled specificity is 87% (95% CI: 79 to 92). The sensitivity and specificity of VILI was 87.2% and 84.7% respectively (51,52). Women have shown that screening once in a lifetime at the age of 35 years with a one or two visit screening strategies involving VIA would reduce the lifetime risk of cervical cancer by approximately 25 to 36% and cost less than 500 US dollars per year of life saved (51).

Another simple cervix examination technique is a colposcopy where closely examining the cervix and vagina. A colposcopy is a low power, stereoscopic, binocular field microscope containing a powerful light source, used for magnified visual examination of the uterine cervix. The reason for referral to colposcopy is a positive screening test result (52). This examination is not painful, has no side effects, and it can be performed safely throughout pregnancy. Unlike a Pap test which scrapes tissue from the entire cervix, colposcopy allows the examiner to take tissue samples (biopsies) from specific areas that do not look normal. The cervix biopsy enables the clinician to obtain deep enough tissue to get adequate stroma in order to exclude invasive lesions histologically.

A cost-effective STA, screening to treatment, is critical as this strategy minimizes the number of patients with abnormal screening results, being lost to follow-up and not receiving appropriate treatment - a major cause for low program performance (49,53-55). VIA-based programs using STA strategy has shown to reduce precancerous lesions of the cervix, cervical cancer incidence, and mortality (57).

When one-stop STA is not feasible, an alternative strategy STA with strong follow-ups program should be in place. STA is conducted with immediate results provided as well as and treatment, if needed. STA is performed later that day or at a designated time shortly after screening (47,58). If the STA strategy is utilized, it is essential that the participant is counselled at the time of

screening in order to minimize loss to follow-up of women requiring treatment (53, 57, 59). Ethiopia commenced the use of VIA combined with cryotherapy for cervical cancer prevention during 2009.

Both VIA and VILI have some drawbacks and the interpretation of a visual test of the cervix has limited value in older women as degenerating cervical epithelium and partial or lack of visibility of the transition zone with aging deems the VIA and VILI processes not useful. Indeed, studies have shown that the sensitivity of VIA declines substantially in women aged 40 years or older (60,61). VIA-based screening is also healthcare provider dependent and lacks reliable quality assurance system. Implementation of VIA screening at health facilities requires close supervision in order to maintain national level quality assurance.

Although newer literature questions the benefits of VIA in routine care, the FMOH of Ethiopia has identified VIA to be the standard screening method nationally. Ethiopia is largely rural in population and women are not keen on cervical examinations. The ministry therefore decided that VIA, one-stop STA and/or STA will be more beneficial to the larger part of the female population. There is no statistics available to reiterate the portion of women lost to follow-up, but the low screening uptake clearly shows that a one-stop STA is of utmost importance in order to address the prevention of cervical carcinoma and its precursors.

The author therefore recommends that the FMOH should also assess HPV testing as a screening method as it has many advantages over VIA, i.e. the HPV results are precise and less human-dependent; the results are available within hours and it has high sensitivy. Additionally, self-sampling for HPV testing showed to be very useful specially in hard-to-reach rural areas.

1.4.2 Cytology-based screening

Cervical cytology screening is recognized as the most successful way to reduce the incidence of cervical cancer. The conventional Papanicolaou smear (CPAP) was discovered in 1943. This method examines exfoliated cells by scraping cells from the cervix and manually spreading the smear onto a glass slides, fixing the cells, and staining the smears by Papanicolaou staining. The

stained smear is then examined microscopically by a cytotechnologist/pathologist. The challenge of the PAP smear is the inhomogeneous slide preparation technique from scraping, spreading, and staining. Conventional Pap smears can have false-negative and false-positive results because of inadequate sampling and slide preparation as well as errors in laboratory interpretation of the cells (62).

This technique has brought a reduction in the incidence and mortality of CC in many developed countries (62-64). CC screening is one of the most successful disease-prevention programs. However, this approach has failed to attain the same results in developing countries. A cytology-based screening program may require repeat testing and visits to manage women who need treatment. To guarantee the success of a screening program, training and continuous education of health care workers are essential (65). Previous experience has shown decline in the incidence or mortality of CC in LMICs (66).

Liquid-based cytology (LBC) was introduced in the mid-1990s to correct poor slide preparation. LBC is the collection of cervical exfoliated cells transferred into liquid preservative. During the LBC preparation method, debris, inflammatory cells and most of the red blood cells are removed by microfiltration. The specimen is prepared by automated equipment and the smear is spread in a monolayered circle on the glass slide. The smear is stained by the Papanicolau technique and examined microscopically by a cytotechnologist/ pathologist (47,53).

The remainder of the specimen in the LBC vial allows for ancilliary testing of the sample, such as human papillomavirus (HPV). The comparative accuracy of each technique has been studied extensively and has yielded conflicting results. Recent systematic reviews reported that there is convincing evidence to recommend the LBC method over the conventional PAP smear method (47,58).

In LMICs, only approximately 5% of eligible women undergo cytology-based screening in five years. In LMICs (46,67), cytology-based services are confined to teaching hospitals or private laboratories in urban areas. The barriers to scale-up cervical cytology-based screening programs in LMICs, including Ethiopia, includes the lack of trained and skilled professionals, lack of consumables, laboratory infrastructure as well as suitable equipment. Furthermore, the absence of a well-organized monitoring and evaluation system is a major obstacle for effective cervical

cancer screening policy implementation in order to monitor and evaluate screening uptake, incidenct rates, the management of the patients as well as to reduce loss to follow-up (47, 53, 58).

1.4.3 Human Papillomavirus DNA based screening techniques

The etiopathological role of HPV as a causative agent of cervical cancer is well established. The test detects whether a person is infected with one or more of the 14 high-risk HPV viral genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). It is used as a routine screening test for women above 30 to 35 years in many regions and is especially useful to evaluate women with equivocal Pap test results. HPV testing requires sophisticated laboratory equipment and is currently unaffordable in less-developed countries (68).

HPV testing is feasible in low-resource settings and could be the best strategy for cervical cancer. However, the high cost and health system requirements of HPV DNA testing is challenging for large-scale implementation in LMICs. A previous study showed that a single round of HPV DNA screening could reduce the incidence and mortality from cervical cancer by approximately 50%, whereas approaches based on VIA and cytology had little effect on these outcomes (46, 69-71).

Each infected cell contains a fixed amount of HPV DNA (1 to 500 copies), and the doubling time of the clonal population in a persistent infection is about 286 days (72). The higher number of infected cells will have a higher corresponding viral load and a greater probability for abnormal cytology. The minimum viral load associated with the visual detection of abnormal cytology (ASC-US+) is 6.5 HPV copies/cell. Some women with fewer HPV DNA copies per clonal (cancer) cell will take more time to be detected by the commercially available molecular tests since they use a fixed cutoff (73). Mean high-risk HPV16, -18, -31, and -33 viral loads of 1.9 × 106 copies/million cells have been associated with normal cervical cytology and not significantly associated with persistence or the subsequent development of cervical lesions (74).

HPV can be detected through tests that identify high-risk HPV types, either by detection of a viral DNA fragment (with or without genotyping) or through mRNA detection (Table 1). The HPV tests can identify the DNA of one or more oncogenic HPV type without prior DNA amplification. Other tests amplify a viral DNA fragment using polymerase chain reaction (PCR) to obtain copies, both

conventionally and in real-time. HPV genotyping identifies specific viral types (usually HPV 16 and 18). The mRNA tests identify the expression of HPV E6 and E7 oncoproteins.

Infection with high-risk human papillomavirus (HR HPV) is the cause of almost all CC cases. Early sexual debut, multiple sexual partners, young age at first delivery, multi-parity, immunosuppression, co-infection with other sexually transmitted infections (STIs), cigarette smoking, long-term use of hormonal contraceptives, estrogen-only hormone replacement therapy, and obesity are some of the factors that have been associated with an increased risk of developing CC.

Table 1: HPV tests used for cervical cancer screening

Test	Technique	Name
DNA	Direct: Genome detection	• Hybrid Capture 2 • CareHPV test
	Amplification	• GP5+/GP+bio PCR-EIA • Cervista HPV HR
	Amplification and genotyping of HPV-16 & HPV-18	• Cervista HPV 16/18 • Cobas HPV test • Xpert HPV • Abbott RealTime High Risk (HR) HPV assay • PapilloCheck
RNA	Amplification of E6/E7 mRNA	• Amptima HPV Assay • PreTect HPV-Proofer HV
	Monoconal antibodies	• Advantage HPV E6 Test

1.5 Treatment of Precancerous Lesions and Invasive Cervical Cancer

According to the WHO guidelines, VIA and immediate treatment with cryotherapy is recommended. Cryotherapy is the freezing of precancerous lesions of the cervix, an effective method for secondary prevention and can be performed in a one-stop STA when acetic acid, equipment (i.e cryoprobe, liquid oxygen gas cylinder) and a trained health provider is avaliable. Only health providers who have demonstrated clinical competencies in cryotherapy are permitted to perform the procedure. Treating is done by using a double-freeze (three-minute freeze, five minutes defrost, three-minute freeze) technique to achieve a 3-5 mm ice ball around the cryo-tip (75 -77).

Loop Electrical Excision Procedure (LEEP) is reserved for precancerous lesions that are not eligible for cryotherapy. The LEEP may be used in cases suspicious of cancer, but only as a diagnostic tool. The LEEP procedure can only be performed by those who have demonstrated clinical competence in the procedure. LEEP requires local anesthesia and is to be performed only in settings that can handle potential urgent complications related to this procedure (e.g. heavy bleeding). Follow-up screening with VIA in one year is recommended (78,79).

When lesions are not treated with cryotherapy, conization is a method of choice which involve the process of removing of a cone-shaped area from the cervix. It can be performed with a scalpel (cold knife conization/cone biopsy), laser, or electrosurgical loop and a clean specimen margin for microscopic diagnosis is obtained. Conization is typically associated with more bleeding than laser or LEEP (80, 81). This method helps to rule out ICC and allows taking tissue for biopsy for diagnostic confirmation (80-82).

Treatment of invasive cervical cancer includes surgery or radiation therapy with or without chemotherapy. Curative surgery in cervical cancer aims to remove the primary tumor with all its extensions in a single operation. The extent of the operation depends on the clinical stage of the cancer and metastases. Partial surgery is not recommended as it is deemed to cause more harm than good. If radical surgery cannot be performed, radiation should be the management of choice for most advanced cervical cancers (83,84).

Radiotherapy plays a crucial role in the treatment of most invasive cervical cancer. In this aspect, the tumor is treated with ionizing radiation - a ray of light with higher energy penetrates the body, damaging and destroying the cancer cells. A combination of external and intra-cavitary radiation therapy is most useful to improve treatment outcomes. Radiotherapy is given as a curative or palliative dosage depending on the stage of the disease (83, 84). Chemotherapy is not a primary mode of treatment for cervical cancer although it is shown to improve treatment outcomes when used concurrently with radiotherapy as it works synergistically by destroying the cancer cells (84-87).

1.6 Cervical Cancer Prevention and Control Strategy

1.6.1 Global perscpective

Two very effective prevention strategies for cervical cancer include - vaccination against the human papillomavirus (HPV) and cervical cancer screening with HPV testing followed by treatment of detected precancerous lesions. In 2019, WHO called for action towards achieving the global elimination of cervical cancer. A strategic plan was documented encompassing elimination goals and targets for the scale-up of HPV vaccination to 90%, cervical screening to 70% and treatment of the patients to 90% globally by 2030 (88-92). Estimates suggest that achieving rapid scale-up of both HPV vaccination and twice per lifetime cervical screening in all countries would avert up to 13.4 million cervical cancer cases over the next half-century, with the majority (but not all) countries achieving incidence rates of <4 per 100,000 women by 2100. However, there are significant challenges - including shortage of HPV vaccine manufacturing supply, delivery and hesitancy, cervical screening point-of-care evaluation, acceptability as well as scaling up the effective precancer treatment process. The configuration of appropriate referral pathways and cancer treatment services and palliative care for those women who do develop cervical cancer, as well as the financing of HPV vaccination and cervical screening are

problematic. The WHO anticipates that the call-to-action will stimulate concerted action to address these issues (90,92).

1.6.2 Ethiopian perspective

The FMOH of Ethiopia has developed a cervical cancer control roadmap that has started implementation in 2015 (21). This blueprint mainly focuses on advocacy, communication, and social mobilization that shared the goal of behavioral change or health beliefs (93-96). The FMOH provides VIA as a primary screening tool for women in more than 208 health facilities, and this may increase up to 823 health facilities throughout the country.

Advocacy programs primarily aims to influence stakeholders such as politicians, decision-makers and journalists. The awareness of cervical cancer control as well as the prevention program could improve cervical cancer screening uptake by considering, 1) conduct advocacy meetings at different levels, such as women groups, policymakers, politicians, development partners, religious leaders, and community champions; 2) promote advocacy campaigns at national, regional, district, village and community levels;. 3) behavior Change Communication (BCC) to increase awareness of primary cervical cancer prevention, influencing social norms and facilitates behavior change amongst all individuals or sub-populations to assist with the prevention of cervical cancer (21,97).

Social mobilization is a broad-scale movement of engagement of community participation in achieving a specific development goal of cervical cancer prevention and control by embracing the principle of community involvement. Accurate information is essential to improve understanding of both HPV and cervical cancer amongst health care workers, educators, policymakers, parents, and patients. Many do not know the cause and burden of cervical cancer and may not be able to understand the value of cervical cancer prevention activities. Without such understanding and strong advocacy, individuals are less likely to access services. Women, their partners and community members must be aware of the causes of cervical cancer, their potential risk of developing the disease as well as the location of the relevant facilities which they can access for cervical cancer prevention services (98).

Community readiness, willingness and acceptance assists to ensure access of women to cervical cancer screening and treatment services, which is essential for the success of a cervical cancer prevention program. Education and training of women and their partners must be suitable for all the socio-cultural realities in order to avoid social resistance. A combination of community, facility and media-based information systems must be implemented to educate the community of the benefits and the availability of cervical prevention services (98).

The FMOH recommends that information and education strategies should be directed to women who have never been screened before as well as their partners and family members who can encourage them to request screening and comply with follow-up instructions. Healthcare providers should pass on clear and consistent messages in a language that is understood by the audience.

The FMOH has deployed 39,000 Health Extension Workers (HEWs) and three million more members of the Health Development Army (HDA) to mobilize and disseminate health messages. In Ethiopia, HDA and HEWs are an essential part of the community and play a key role in promoting the availability of cervical cancer prevention services. The cervical cancer roadmap provides HEWs and members of the HDA with the correct information about the cervical cancer prevention program. The role of HEW`s and members of the HDA are advocating and providing information about cervical cancer prevention services; identifying the eligible groups and assisting women in making decisions to attend the health facilities for cervical cancer prevention services as well as engaging with cervical cancer survivors (persons who have been successfully treated for cervical cancer) in education and advocacy for cervical cancer prevention. People with first-hand knowledge of the importance of early detection can provide powerful messages based on their experience (21, 95-98).

In Ethiopia, more than 208 health facilities are providing VIA screening and cryotherapy treatment and more than 52,000 women were screened in 2017/18. Besides, LEEP service was scaled up from five to fifteen hospitals. The FMOH is working to scale up VIA screening and cryotherapy treatment into 823 districts. Even though 20 million women are eligible for cervical screening in Ethiopia only less than 1% has been screened.

The appropriate level of knowledge, attitude, and beliefs are key elements for adopting a healthy lifestyle, influencing human behaviors, accepting newly introduced preventive measures and determining the stage at which cancer patient presents to a health facility. Studies from many parts of the world including Ethiopia have shown a lack of awareness within populations regarding CC symptoms, early signs, and the role of screening and HPV vaccination for prevention. Cervical cancer's long latency and recognizable precancerous lesions make screening a particularly effective way of prevention as these precancerous lesions, once identified, can be managed or treated safely and inexpensively in an outpatient setting. It is important to create awareness among communities through educational programs on cancer prevention, preventable risk factors, benefits of early diagnosis, and availability of screening facilities. In developed countries, CC screening programs have reduced the incidence of invasive lesions up to 80%.

In general, Ethiopia has adopted WHO recommendation VIA as secondary prevention strategy together with immediate treatment with cryotherapy. This approach has been started since 2009; however, due to various factors including not well organized prevention strategy, unable to reach women living in rural areas, service available only at selected health facilities, huge awereness gaps, cultural barriers, lack of all round committments, lack of strong program monitoring and evaluation and so on where only 1% of women has been screened.

1.7 Introduction of HPV Vaccines in Ethiopia

IT has been suggested that full vaccination coverage could prevent future HPV-attributable cancers and potentially reduce HPV-associated cancer incidence. The introduction and use of safe and effective vaccines against common HPV types have a significant impact on the morbidity and mortality among HPV vaccinated members of the population [21, 99)].

While the HPV vaccine seems crucial for cervical cancer prevention, several challenges need to be addressed prior to introducing routine HPV vaccination. HPV vaccination programs may be cost-effective in countries where high-quality screening is not widespread, vaccination coverage is high (>70%) and the cost of a three-dose HPV vaccination course is low (< US$10-25). If used, HPV vaccination should be a part of a coordinated strategy, including appropriately targeted messages to different audiences and should not undermine or divert funding from an effective screening program (100).

Taking into concideration the age of the females to be vaccinated during HPV vaccination program, it must be noted that the incidence of cervical cancer will not be noticeably decreased for a few decades after the introduction of the HPV vaccination program. Therefore, widespread screening for cervical cancer needs to continue, even after an HPV vaccine program is fully implemented in order to detect cervical abnormalities in the unvaccinated and previously infected population, as well as cancer caused by other serotypes of the HPV not part of particular vaccine. Monitoring and evaluation of both screening program and vaccination program is of paramount importance (21,100).

Generally, adolescent girls age 9 – 14 years are the current target for HPV vaccinations. Administering the HPV vaccine to these target groups requires a systematic approach such as school-based, health facility-based as well as outreach approach. Ethiopia started HPV vaccination program in 2018 for schoolgirls aged 14 years. This initiative started as a pilot study but eventually was launched nationally (21, 101,102). HPV vaccination of 2.4 million schoolgirls was successfully completed at the end of January 2021. The quadrivalent Gardasil HPV vaccine was only administered to schoolgirls in Addis Ababa and surrounds. Immunization is currently not available to the general public.

1.8 Thesis rationale

Ethiopia has already developed a five-year national cervical cancer prevention and control roadmap 2016 to 2020, mainly focusing on advocacy, communication, and social mobilization; cervical cancer screening techniques; primary and secondary prevention strategies; tertiary care; infrastructure, equipment and supplies; monitoring and evaluationas well as training and competency qualifications. Based on literatures review and Ethiopian national cervical cancer prevention and control guideline, there are many unresolved challenges in Ethiopia as listed below:

- about 35.8% of women in the general population estimated to harbor cervical HPV infection at any given time;
- 76.5% of invasive cervical cancers attributed to HPV genotypes 16 or 18;

- the cervical cancer screening coverage is still very low with the percentage of 0.6 % for all women aged 18-69 years, 1.6% for women living in urban areas and 0.4% for women living in rural areas;
- Ethiopia has a population of 31.5 million women aged 15 years and older who are at risk of developing cervical cancer;
- Cervical cancer ranks as the second of the most frequent cancer among Ethiopian women between 15 and 44 years of age;
- Comprehensive data is not yet available on the HPV burden in the general women population and financial resources for laboratory testing and treatment are limited.

This doctoral research could fill some of the gaps through understanding woman`s attitude and health beliefs on cervical cancer disease which result in the low screening uptake documented. Thus, a study was conducted to understand one of the reasons and risk factors of low uptake of cervical cancer screening through a structured health belief model (Chapter 3). Generally, women in Ethiopia visit health clinics at a very late or advanced stage of the disease, specialiy women in living rural aleas. Timeous treatment is therefore not possible and leads to a poor outcome. However, if women undergo timeous screening for cervical cancer, it is possible to detect cancer in the early stages and reduce mortality and morbidity. Thus we aimed to understand the screening uptake program that may be broadly influenced by:1) lack of knowledge and beliefs about cervical cancer screening services; 2) the role of health care providers who come in contact with women in hospitals and the sources of information, and 3) availability of health care facilities.

Globally, cervical cancer screening has successfully reduced cervical cancer incidence and mortality, especially in settings with effective screening programs with good organization, coverage, and quality assurance. However, in resource-limited countries like Ethiopia, standard cervical cancer screening tests such as cervical cytology (Pap smear), and HPV testing are not widely available. The common gynecological examination approach of investigating cervical cancer is not deemed to be comfortable by most women for various reasons and that leads to a lower screening uptake. Thus, we conducted a comparative HPV testing study between self-collected versus doctor sampling techniques (chapter 2). HPV testing through self-collected specimens has gained attention for its potential to increase screening participation. For further

information, we conducted a systematic review of African studies on self-sampling acceptability and comparison with doctor sampling (chapter 4).

The burden of cervical cancer in Ethiopia has not been studied very well and no large-scale community-based cohort study data is available to determine the national burden of HPV and cervical cytology abnormalities in order to recommend ideal screening algorithms in the local context. Therefore, our study aimed to assess the burden of cervical cancer and the genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities (chapter 5) which can contribute to the national preventive public health strategies against cervical cancer.

1.9 Objectives of the thesis

1.9.1 General objective

To evaluate cervical cancer screening uptake, HPV genotyping, and self-sampling specimen collection techniques in Adama, Oromia, Ethiopia.

1.9.2 Specific objectives

- to determine the feasibility of vaginal/cervical Nurse Assisted Self-Sampling (NASS) and the agreement between HPV testing on self-samples versus clinician-taken (CT) specimens in Adama, Oromia, Ethiopia.
- To evaluate cervical cancer screening uptake using health beliefs model (HBM) and knowledge of risk factors in Adama, Oromia, Ethiopia,
- To compare the HPV detection rate and acceptability of HPV self/- versus clinician collected sampling in African studies via a systematic review,

- To assess the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities in selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia.

1.10 Organization of the Thesis

This thesis is organized into six chapters and the first chapter is a general introduction and rationale, describing the overview of the cervical cancer, the impact of HPV screenings and other prevention and control programmes as well as the relevance of the studies herein; in the second chapter HPV testing on vaginal/cervical nurse assisted self-samples versus clinician-taken specimens and the HPV prevalence are discussed; in the third chapter cervical cancer screening uptake and risk factors are assessed using a health beliefs model (HBM); published articles on HPV detection rate and acceptability between HPV self-vs clinician collected sampling in African studies are discussed in the fourth chapter; the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities at selected obstetrics and gynecology clinics are discussed in the fifth chapter and the last chapter presents a general discussion, conclusions and perspectives emphasizing the challenges related to cervical cancer prevention and control.

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CHAPTER 2: HPV TESTING ON VAGINAL/CERVICAL NURSE ASSISTED SELF-SAMPLES VERSUS CLINICIAN-TAKEN SPECIMENS AND THE HPV PREVALENCE, IN ADAMA TOWN, ETHIOPIA

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2.1 Abstract

This study aims to determine the feasibility of vaginal/cervical Nurse Assisted Self-Sampling (NASS) specimens and the agreement between Human Papilloma Virus (HPV) tests on self-collected as well as clinician-taken (CT) specimens. Women participated voluntarily for cervical cancer screening at St. Aklesia Memorial Hospital. Eighty-three (83) women provided a total of 166 coupled self and clinician taken specimens collected. Specimens were stored at room temperature for a maximum of 10 months and analyzed using the RIATOL qPCR HPV genotyping test, a quantitative Polymerase Chain Reaction (qPCR) high-throughput HPV E6, E7 assay. The average age of the participating women was 32 years. Seventy-three women (87.9%) felt that NASS was easy to use. An overall HPV, HR (High Risk) HPV and LR (Low Risk) HPV prevalence was 22.7% (15/66), 18.2% (12/66) and 6.1% (4/66), respectively. The overall HR HPV prevalence was 17.2% (NASS) and 15.5% (CT). The most prevalent HPV type was HPV51; HPV 16 was only detected in 1 woman (CT+NASS) and HPV18 only in 1 woman (CT). The overall measurement agreement between self- and clinician-taken samples was moderate with a kappa value of 0.576 ($p < 0.001$). Lifetime partnered with more than two men were associated with HR HPV positivity (P-value <0.001). There was a strong statistical association between HR HPV positivity and visual inspection with acetic acid (VIA) positive (p value<0.001). The Nurse assisted self-sampling for HPV testing could be seen as an alternative option and might be acceptable to Ethiopian women. The overall HR HPV prevalence was comparable with Sub-Saharan countries in the general population.

KEY WORDS: Cervical cancer, Nurse, self-sampling; HPV, ThinPrep PreservCyt solution, liquid cytology, clinician-taken, qPCR, Ethiopia.

2.2 Introduction

Invasive cervical cancer (ICC) is the fourth most frequent malignancy and cause of death in women suffering from cancer worldwide (1). In Ethiopia, ICC is second among women between 15 and 44 years of age. Ethiopia has 31.5 million women aged 15 years and older and 7.095 women were diagnosed yearly with ICC of whom 4.732 died from the disease (estimates for 2012), Currently, there is only sparse data on the Human Papilloma Virus (HPV) burden in the general population of Ethiopia (2).

A study in Nigeria for example, found 93% participation in the self-sampling arm, compared to only 56% in the hospital-collection arm (3). Another study in Sub-Saharan Africa indicated a comparable HPV prevalence for self- (14.6%) and physician (12.7%) samples, so similar accuracy of the test on both sampling methods (4). A study in Madagascar showed absolute acceptance (100%) of self-sampling (with a flocked swab) followed by HPV testing as cervical cancer screening method (5). Available data indicate that the HPV prevalence in Ethiopia among women with normal cervical cytology varies between 15.9 % and 17.5%, and 96.6% of the invasive cervical cancers are attributed to HPV16 (78.4%) and 18 (18.2%) (2).

Cervical cancer develops over a long period of time through precursor lesions. These lesions can be detected by (cytological or visual) screening, and progression towards cancer can then be stopped by treatment (ablation or excision) in an early phase (6). Currently in Ethiopia, 200 health facilities are providing VIA (Visual Inspection with Acetic acid) screening followed by cryotherapy (ablative treatment technique), and more than 52,000 women were screened in 2016/17. Of the 20 million women eligible for screening only 0.3% of them screened. In addition, Loop electrosurgical excision procedure (LEEP) service was scaled up from five to fifteen hospitals and the FMOH is working to expand VIA screening and cryotherapy into 823 districts (7). However, more efforts or other screening techniques are urgently necessary to scale up the cervical cancer screening coverage in Ethiopia.

This study aimed to determine the feasibility and acceptability of vaginal/cervical Nurse Assisted Self-Sampling (NASS) and the agreement between Human Papilloma Virus (HPV) test on self-samples versus clinician-taken (CT) specimens in the Ethiopian population.

2.3 Methodology

The study aimed to determine the feasibility of vaginal/cervical Nurse Assisted Self-Sampling (NASS) and the agreement between Human Papilloma Virus (HPV) testing on NASS versus clinician-taken (CT) specimens.

The study was conducted in Adama Town, Oromia region, having a total population of 1,356,342 people of whom 659,992 are females. The St. Aklesia Memorial Hospital (SAMH), located in

Adama Town, is a private hospital with a long-time history and expertise in cervical cancer screening.

To reach in an efficient way a lot of women for recruitment in the study, radio calls and face to face interactions were organized. Through these channels, women were encouraged to schedule an appointment for cervical cancer screening approximately two weeks (10-18 days) after the first day of their last menstrual period. Also, women visiting the hospital for reproductive health-related issues were called for participation in the study.

Women were eligible if they were 20 years or older, had an intact uterus, had no history of cervical cancer, were mentally competent and able and willing to provide informed consent. Based on the upset of this study, a cross-sectional and probability sampling technique was used. The sample size was calculated by considering 5% margin error; 95% confidence level, 659,992 female populations of East Shewa, and according to pilot study 95% of a time women were responded self-sampling was acceptable means of screening and by adding 10% of the non-respondent rate the minimum sample size was 73. Women who were interested in participating in the study were given following instructions: no douche 48 hours prior to the test; no use of tampons, birth control foams, jellies or other vaginal creams or vaginal medications for 48 hours prior to the test and also advised to refrain from intercourse 48 hours prior to the test.

After signing an informed consent document, women were subjected to two ways of sample collection, both performed within the clinic: 1) nurse assisted self-sampling with supervision; 2) clinician-taken specimens i.e. a physician collected the samples according to the standard procedure of the clinic. Women were also asked to fill in a questionnaire.

2.3.1 Nurse assisted self-sampling (NASS) at the clinic

Women were invited to the private area of the clinic and were given verbal and printed diagrammatic instructions by the trained nurse for collecting the vaginal specimen. When the women confirmed that all instructions were clear, the nurse opened the collection kit and handed over the collection devices (in sequence order of spatula followed by cytobrush) to the woman
The vaginal fornix and ectocervix was sampled before the endocervix. To start the NASS, women were instructed to take a sample of the ectocervix using a plastic spatula, without speculum. The

women were asked to insert the plastic spatula, laying on the bed, into their vagina and to rotate three times 360˚, to remove and to handover the collection device to the nurse. The nurse then rinsed the spatula into a labeled vial with ThinPrep PreservCyt solution.

In the next step, the nurse provided the cytobrush to the woman to sample the endocervix. It was inserted by the woman herself until it met with resistance, rotated 45-90°, removed and handed over to the nurse. The nurse inserted the cytobrush sample into the same ThinPrep PreservCyt labeled vial. This procedure was not involving any invasive steps rather non-invasive simple and easy collection techniques. Collected samples were kept at 22˚C (room temperature) for about 10 months, until shipment and processing.

2.3.2 Clinician-taken (CT) sample at the clinic

The clinicians collected cervical samples according to standard protocols i.e. both ectocervix and endocervix samples were collected with a cytobrush and rinsed in a labeled vial with ThinPrep PreservCyt solution. Collected samples were kept at 22˚C (room temperature) for about 10 months, until shipment and processing.

2.3.3 Visual inspection with acetic acid (VIA)

After the NASS and the CT sample, all women underwent VIA. A woman was classified as VIA positive when acetowhite lesions were visualized by the clinician. All VIA-positive women were eligible for cryotherapy and were treated.

2.3.4 Laboratory

Both CT and NASS specimens were tested for presence of HPV with the RIOTOL qPCR HPV genotyping test (Algemeen Medisch Laboratorium (AML), Belgium). This clinically validated and ISO certified lab developed (LDT) high-throughput HPV test, detects 14 HR HPV types i.e. 16,18,31,33,35,39,45,51,52,56,57,58,59,66 and 68, 4 intermediate/low risk HPV (LR HPV) types

i.e. 6, 11, 53 and 67; 68 and a cell control (8, 9). Samples less than 10 cell/µl are considered as invalid and reported as samples of poor quality.

2.3.5 Data source and analysis

Quantitative data was collected and for some of the demographic variables were decoded accordingly. Any missed variable identified during the collection of data, the supervisor was responsible to follow up the patients and correct it accordingly. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 software. The overall measurement agreement between self- and clinician-collected samples was calculated with a kappa value. The dependent variable was HPV outcome and independent variables are socio-demographic. Pearson's chi-squared test and 95% confidence interval (CI) were used and statistically significant if the p-value was less than or equal to 0.05.

2.4 Results

A total of 83 eligible women were enrolled between October 2015 and July 2016 at SAMH hospital, Adama, Oromia region, Ethiopia. The study had no missed data or variables.

2.4.1 Patient demographics

The average age of eligible women was 32 years - the youngest woman was 20 and the oldest 65 years. Forty-seven women (56.6%) had an education level below grade 10 (high school); 33.7% (28/83) and 27.7% (23/83) of the study population were laborers and housewives, respectively. Seventy-one women (85.5%) were married at the time of the study and 69.9% had one lifetime partner. A total of 80.7% (67/83) had gravidity equal to or above one, and 7.5% (5/67) of these women had a spontaneous abortion previously. Women who used birth control and smoking cigarettes were 39.8% (33/83) and 18.1% (15/83), respectively. Four (4.8%) women reported being infected with HIV at the time of the study (Table 1).

2.4.2 Acceptance and feasibility of Nurse Assisted-Self-Sampling (NASS)

Regarding feasibility assessment (Table 2), a high number of the women indicated that NASS was easy to use (87.9%); easy to insert and collect (79.5%) and user-friendly (91.6%). Especially the privacy of a NASS compared to a clinician-taken specimen scored very high (92.8%). More than 80.0% of the women had confidence in the results of their NASS. Furthermore, over 85.0% of the women were willing to perform NASS at the clinic or home, would go to a clinic that would provide the NASS and were even willing to pay for a NASS followed by an HPV test if it would be available over the counter.

2.4.3 Sample quality

Out of 166 samples (two specimens per woman), 26.6% (44/166) of the samples did not have enough cells (>10 cells/µl) and were considered as samples of poor quality. According to Fisher`s exact test, there was no statistically significant difference in the number of samples with poor quality between the two sample groups (NASS: 19/83 and CT: 25/83) (p=0.3794) (Table 3). For 17 women (20.5%), both the CT and the NASS sample were of poor sample quality (Table 4) and were excluded from further analysis.

Table 1: Characteristics of women enrolled in our cervical cancer screening study (N=83), between October 2015 and July 2016, at SAMH hospital, Adama, Oromia region, Ethiopia.
Categories

Categories	Variables	Count	%
Age Group	20-30	39	46.9
	31-40	34	40.9
	41-50	8	9.6
	51-60	1	1.2
	>=61	1	1.2
Education	Under grade 8	23	27.7
	Under grade 10	24	28.9

Categories	Variables	Count	%
	Preparatory (University)	3	3.6
	Diploma	19	22.9
	Degree	13	15.7
	PhD	1	1.2
Occupation	Student	3	3.6
	House wife	23	27.7
	Laborer	28	33.7
	Government Employee	7	8.4
	Private employee	15	18.1
	Self-employed	7	8.4
Marital Status	Married	71	85.5
	Single	7	8.4
	Separated	4	4.8
	Living with partners	1	1.2
Life time partners	1	58	69.9
	2	21	25.3
	3	4	4.8
Gravidity	0	16	19.3
	1	21	25.3
	2	32	38.6

Categories	Variables	Count	%
	3	6	7.2
	4	6	7.2
	5	1	1.2
	6	1	1.2
Abortion	Induced	5	7.5
	Spontaneous	5	7.5
	No abortion	57	85.1
Current use of any birth control	Yes	33	39.8
	No	50	60.2
Current Smoking	Yes	15	18.1
	No	68	81.9
HIV Status	Reactive	4	4.8
	Non-Reactive	70	84.3
	Unknown	9	10.8
Chief presenting symptoms	Dyspareunia	4	4.8
	Intermestral	6	7.2
	Urinary Symptom	34	41.0
	Backache	14	16.9
	Vaginal discharge	25	30.1
VIA results	No acetowhite lesion	57	68.7
	Acetowhite lesion	9	10.8

2.4.4 HPV test results from the NASS and CT specimens

The RIATOL qPCR HPV genotyping test was performed on all collected NASS and CT specimens. The HPV results of the remaining 66 women are presented in detail in table 5. The overall prevalence of HPV was 22.7% (15/66). The prevalence of HR HPV was 18.2% (12/66) and LR HPV types 6.1% (4/66). The CT samples had an HPV prevalence of 15.5% (9/58) (all types), with a prevalence of 12.1% (7/58) for the high-risk types and 3.4% (2/58) for the low-risk types. The results from the NASS samples showed a somewhat higher prevalence of 17.2% (11/64), and 14.1% (9/64) and 4.7% (3/64) for all HPV types, HR and LR types respectively (Tables 4 and 5).

The overall agreement of HPV test results between NASS- and CT samples was moderate, with a kappa value of 0.58 (95%CI: 0.41-0.76). A total of 47/66 (71.2%) CT and NASS samples were in agreement in terms of HPV test results. From the 15 positive HPV samples, only 33.3% (5/15) were positive in both the NASS and CT sample, while for the HPV negative results there was 82.4% agreement (42/51). The most prevalent HPV type was HR HPV51 (4/66, 6.1%), followed by HR HPV31, 58 and 68 and LR HPV6 and 67 which were all found twice (2/66, 3.0%). HPV16 was detected in 1 woman, in both the CT and the NASS sample (overall prevalence: 1/66=1.5%) and HPV18 also in 1 woman, but only in the CT sample (overall/CT: 1/66=1.5%, NASS: 0%). Two women were co-infected with at least two HPV types (multiple infections: 2/66=3.0%). One woman out of these two was co-infected with 5 HPV subtypes: HPV6, 16, 51, 67, and 68 (according to the NASS HPV DNA result). A total of 12 different HPV types were identified out of the 18 HPV types that were tested for (Table 5) in this study.

Table 2: Acceptability and feasibility of nurse assisted-self sampling by women enrolled in our cervical cancer screening study (N=83).

Categories	Variables	Count	%
Practicality	Easy	73	87.9
	Moderate	7	8.4
	Difficult	3	3.6
Is it easy to insert and collect sample with the device?	Yes	66	79.5

	No	17	20.5
Is collection device user friendly?	Yes	76	91.6
	No	7	8.4
Is self-sampling more private compared to sampling by clinician?	Yes	77	92.8
	No	6	7.2
Do you believe in the results that were taken by yourself?	Yes	69	83.1
	No	14	16.9
Do you have plans to visit the clinic that provides self-sampling?	Yes	71	85.5
	No	12	14.5
Preference of self sampling over clinician?	Yes	79	95.1
	No	4	4.9
Willing to pay for HPV self test if available over the counter?	Yes	71	85.5
	No	12	14.5
Willing to perform self-sampling at clinic or home	Yes	73	88.0
	No	10	12.0

Table 3: Sample quality comparsion between nurse assisted self-samples (NASS) and clinician-taken samples (CT) (N=166)

Sample types	Human DNA detected	No Human DNA detected	Total
NASS	64	19	83

CT	58	25	83
Total	122	44	166

Table 4: HPV test results of the NASS and clinician-taken (CT) samples (N=83). *Type specific qPCR (Riatol HPV test)*

Clinician taken (CT) Sample	Nurse assisted self-sample (NASS)			
	HPV (+)	HPV (-)	No DNA	**Total**
HPV (+)	5	3	1	**9**
HPV (-)	6	42	1	**49**
No DNA	0	8	17	**25**
Total	**11**	**53**	**19**	**83**

Table 5 : HPV distribution by type, of the NASS and clinician-taken (CT) samples. *Type specific qPCR (Riatol HPV test) (N=66)*

# of HPV positive women	Type of samples	High risk HPV typing									Low risk HPV typing			Total		
		16	18	31	45	51	56	58	59	68	**6**	**53**	**67**	**Overall**	**SS**	**CT**
1	CT	-	1	-	-	-	-	-	-	-	-	-	-	1		1
2	CT	-	-	1	-	-	-	-	-	-	-	-	-	1		1
3	NASS	-	-	-	1	-	-	-	-	-	-	-	-	1	1	1
	CT	-	-	-	1	-	-	-	-	-	-	-	-			
4	NASS	-	-	-	-	-	-	-	1	-	-	-	-	1	1	
5	CT	-	-	1	-	-	-	-	-	-	-	-	-	1	1	1
	NASS	-	-	1	-	-	-	-	-	-	-	-	-			
6	CT	-	-	-	-	-	-	-	-	-	-	1		1	1	1
	NASS	-	-	-	-	-	-	-	-	-	-	1				
7	NASS	-	-	-	-	-	1	-	-	-	-	-	-	1	1	
8	CT	-	-	-	-	-	-	-	-	-		-	1	1		1

9	CT	-	-	-	-	-	-	-	-	1	-	-	-	1		1	
10	NASS	-	-	-	-	-	-	1	-	-	-	-	-	1	1		
11	NASS	-	-	-	-	-	-	-	-	-	1		-	1	1		
12	NASS	-	-	-	-	1	-	-	-	-	-	-	-	1	1		
13	CT	-	-	-	-	1	-	1	-	-	-	-	-	1	1	1	
	NASS	-	-	-	-	1	-	-	-	-	-	-	-				
14	NASS	-	-	-	-	1	-	-	-	-	-	-	-	1	1		
15	CT	1	-	-	-	1	-	-	-	1	-	-	-	1	1	1	
	NASS	1	-	-	-	1	-	-	-	1	1	-	1				
Total														15	11	9	

2.4.4 Results from NASS and CT HPV tes versus Visual inspection with acetic acid (VIA)

A total of 66 women underwent VIA. In 9/66 (13.6%) women, acetowhite lesions were visualized. When excluding the CT samples with poor sample quality, five of the 9 women with a positive VIA result, were HPV positive (sensitivity of 55.5% (CI: 26.6% to 81.1%)) and 84.5% (49/58) respectively. On the other hand, 45 of the 49 women with no acetowhite lesions were HPV negative (specificity of 91.8% (CI: 80.8% to 96.8%). The overall agreement between HPV and VIA result from CT sample was 86.2% (Table 6).

Table 6: HPV test results versus VIA CT & NASS HPV test results (N=58, N=64).

HPV result	CT VIA test		
	Acetowhite lesion	No acetowhite lesion	Total
HPV (+)	5	4	9
HPV (-)	4	45	49
Total	9	49	58
HPV result	NASS HPV test		
	Acetowhite lesion	No acetowhite lesion	Total
HPV (+)	7	4	11
HPV (-)	1	52	53

Total	8	56	64

When excluding NASS samples with poor sample quality, 7 of the 8 women with acetowhite lesions, were HPV positive (sensitivity of 87.5% (95% CI: 52.9%-97.8%)) and 52 women of the 56 with no visual lesions, were HPV negative of 92.8% (CI: 83.0% to 97.2%). The overall agreement between HPV and VIA result from NASS samples was 92.2% (Table 6).

2.4.5 Pearson's Chi-squared test

Table 7 shows the result of Pearson's Chi-square test using the HR HPV test result (combined NASS and CT results) and all collected variables, with HR HPV-negative status as the reference group. Having more than two lifetime sexual partners (p=0.000447) and being VIA positive was causally associated with an HR HPV positive test result and not a difference by chance. Spontaneous abortion (p-value=0.021) and being a housewife (p-value=0.016) was also associated with HR HPV positive results. Younger age groups (<40 years) showed a trend towards a correlation with a positive HPV test result (p-value=0.058); there were about 19.6% (11/56) HR HPV positive women in the age groups under 40, while only 10% (1/10) in the combined age groups above 40. Housewife and laborer were statistically associated with HR HPV (Chi-square = 13.880 and p=0.0016). No statistical association was found between HR HPV positivity and all other collected variables.

2.5 Discussion

2.5.1 Feasibility/acceptability of self sampling

Nurse assisted self-sampling (NASS) devices are not commercially available in Ethiopia and not used for routine sample collection system on cervical cancer screening program. Thus, this study may be considered as first in kind to used NASS collection device in Ethiopia. The acceptability of the NASS method device was very high and women felt NASS device was easy to use, insert and collect and user-friendly. Women were willing to perform the self-sampling (SS) because of its private nature. Ghanaian women reported that 76.3% self-collected (SC) was very easy technique and easy to obtain, 57.7% preferred SS over clinician-taken sample (CT) and felt SC

would increase their likelihood to access cervical cancer screening which was comparable percentage of women felt same in our study too (10,11).

Our study was further supported by data from Bolivia where SS was generally preferred over CT for a screening program based on HPV detection (12). Furthermore, a number of studies report that HPV self-sampling was found to be highly acceptable and feasible among hard-to-reach women.

A study in El Salvador reported that self-sampling revealed acceptability of 68%, although lower than reported in our study (13). Other studies from American-Indian and Hopi women have also supported our findings where self sampling-HPV testing was feasible and acceptable that may contribute to an increase of uptake (14,16). Most women showed a willingness to pay for self-sampling services and believed their results which could be seen as a driving force for screening among hard-to-reach women (15).

According to recent systematic and a meta-analysis (35,36), self-sampling may increase population uptake of cervical cancer screening utilizing various self-sampling collection devices such as QvinTip (brush), ESwab, Delphi Screener (lavage), Evalyn Brush, Qiagen test kit (Cotton swab), Just For Me (Brush), Dacron swab, Digene (brush), Herswab, Dry nylon flocked swab, Viba-Brush, PantaRhei Sampler (lavage), dry cotton swab, novel self-sampling kit (brush), etc. with various degrees of success. However, in our study we did not use any of the abovementioned devices, bu rather used NASS Cytobrush/plastic spatula as specimen collection tools, rinsing the cytobrush and/pr spatula into a ThinPrep Vial containing PreservCyt.

Almost the same percentage of women of our study as opposed to a similar Japanese study reported they would use self-sampling again and found instructions easy to follow and reported no issues with the usability of the self-sampling device. However, women in our study reported that they had confidence in the results of NASS unlike women who lacked confidence in the test where Puritan Foam Swabs were used as self-collector deice (16). Similar studies supported our findings from Latinas and Haitian population groups where women agreed HPV self-sampling was faster, more private, easy to use, and would prefer to use it again (17). Furthermore, in Germany, self-sampling was rated to be easy by 89.0 % of the participants as well as user-friendly by 96.0% of the women (18). Therefore, Ethiopian women might use nurse assisted self-sampling method as an alternative option for cervical cancer screening.

2.5.2 HPV prevalence in general population

The authors reported that an overall HPV prevalence was 22.7% and a prevalence of HR HPV and LR HPV were 18.2% and 6.1% respectively. HPV prevalence in Africa varied within a range of 12% to 46% (19). Two studies elsewhere in Ethiopia reported that the HR HPV prevalence was 17.3% and 15.8% (20, 21). Thus, our study revealed HR HPV prevalence was consistent with sub-Saharan Africa report where ours slightly higher. The overall HPV prevalence of NASS and CT samples were 10.8% and 13.2% respectively. The authors couldn't find similar report on the prevalence of HR HPV among self-sampling and doctor sampling which were 14.1% and 12.1% respectively in the general population of Ethiopia.

In Rwanda, the HR HPV prevalence was 19.0% which was slightly higher than our result (22). The prevalence of HR HPV in Dakar was 17.4% as compared to ours 18.2% which geographical areas and population difference could be a reason (23). The HR HPV prevalence in Cameroon was 18.5% that was comparable to our findings (24).

A study from Northern Africa, a Muslim community, HPV infection was 6.3% (4.0% of them were high-risk types), with no significant variation by age (25). However, a study done by Traore IMA et al (26) in Burkina Faso reveled that HR HPV prevalence was 38.3% which was twice of our result. Therefore, HPV prevalence was varied based on geographical areas and population segment as indicated in entire previous studies.

A study done by Laia Bruni et al (19), the estimated prevalence of HPV in Sub-Saharan Africa and global prevalence was 24.4% and 11.7% respectively which was almost comparable to our study (19). Further studies from 11 countries (Nigeria, India, Vietnam, Thailand, Korea, Colombia, Argentina, Chile, the Netherlands, Italy, and Spain) without cytological abnormalities were included and age-standardized HPV prevalence varied from nearly 20 times between populations, from 1.4% in Spain to 25.6% in Nigeria where 22.7% HPV prevalence was presented in our study (27).

2.5.3 HPV type distribution

From our study, the most prevalent HPV type was HPV51 followed by HPV31, 58 and 68 (HR types) as well as HPV6 and 67 (LR types). Women were co-infected with at least two HPV types and others were co-infected with five HPV subtypes: HPV6, 16, 51, 67, and 68. A total of 12 HPV types were identified in this study out of 19 HPV types tested. HPV 16 was the most frequent genotype identified in samples from previous Ethiopia studies and HPV 52, 58 and 18 were the second, third and fourth most common genotypes identified respectively, whereas in our study HPV 51 and 31 were the common genotypes identified (28). Thus, even within the same country, it is possible to observe different prevalence rates among various segments of the population.

A study from South Africa showed HPV 16, 35, and 58 to be the most common high-risk HPV types with no major differences in the type distribution by HIV status (29). In Mozambique, the most frequent were HPV51, HPV35, HPV18, HPV31, and HPV52. Likewise, multiple infections were detected in HPV51 of HPVs 16/18 on normal cytology where HPVs 51 and 35 were the two most common types detected (30).

HPV positive women in Europe were significantly more likely to be infected with HPV16 than those in sub-Saharan Africa. Heterogeneity between areas of Asia was significant were that supported by previous Ethiopian studies (27, 31). A study from Burkina Faso HPV 52, HPV 33, and HPV 59 were most identified genotypes whereas HPV 51, 31, and 58 were the most prevalent in our study (25).

A study from Nigeria, the prevalence of HPV35 and HPV16 were equally frequent (32). HPV16 was the most common type among the general population of Guinea (7.3%) (33). These findings confirm that different genotypes were identified in different geographical areas, population groups and age groups.

2.5.4 HPV tests versus VIA

In this study, the overall agreement between NASS HPV and VIA results was higher than CT results. The sensitivity between HPV and VIA test results was relatively higher on self- sampling as opposed to clinician- taken samples. There was an almost equal specificity value found between NASS and CT samples. A combination of HPV-based and VIA screen-and-treat approach may be feasible in a low-resource context and may contribute to improving the

effectiveness of CC prevention programs. The combination of HPV-testing and VIA for CC screening may reduce over treatment (24).

2.5.5 Agreement between NASS and CT HPV test

The overall agreement of HPV test results between NASS and CT samples was moderate, with a kappa value of 0.58. A study from Bolivia showed good agreement between self- and physician collected samples where HR HPV detection (κ = 0.71) was higher as compared to our study (12). A study from Sub-Saharan Africa revealed that the overall HPV positivity agreement between Self- and doctor was κ value of 0.52, respectively which had similar agreement with our study (34).

2.6 Conclusions

There was a moderate agreement between NASS and CT sample for HPV detection. NASS may be used alternatively as a sample collection strategy for HPV testing in the cervical cancer screening program in Ethiopia; however, the quality of the sample requires improvement. Additional training for the health care workers is recommended. NASS HPV testing may be a valuable tool for the follow-up of women in low-resource settings. NASS may be used as alternative strategy to increase cervical cancer screening coverage in Ethiopia.

Several type of self-sampling devices available in the global market, in our study, NASS Cytobursh/plastic spatual (ThinPrep Vial of PreservCyt) collection tool were used and a comparative large-scale study against commonly known self-collection devices should be designed in the furture. Despite self-sampling may increase uptake of screening, further study may be initiated in due course in resource-limitted countries where accessing and cost of self-sampling are main bottleneck.

Although our study revealed that HPV 51, 31, 16, 45, 52, and 58 genotypes were mostly identified, a large-scale study is required to study circulated genotypes in Ethiopia and select an appropriate national HPV vaccine accordingly. Genotyping information is important to guide the vaccine policy. Our study was the first report on HPV detection on self sampling using Cytobursh/plastic

spatual (ThinPrep Vial of PreservCyt and may be used as a platform for similar studies in the future.

2.7 Limitations

Although this research was carefully prepared, we concluded that the sample size was small and we are unable to generalize.

2.8 Acknowledgments

The authors acknowledged SAMH`s staff for the support of sample collection activities and Hologic Inc Company, USA for donating ThinPrep PreservCyt solution, cytobrush collection devices and spatulas through IPRH. The laboratory analysis was done at, AML.

2.9 Ethical clearance

The ethical committee of the College of Natural Sciences, Addis Ababa University, has examined the proposal of the project and approved it. The SAMH Hospital also approved the project. All women signed informed consent forms before enrolling for the study.

The laboratory analysis was done at AML. The source of the fund was the University of Antwerp, Hologic Inc company, and International partnership for reproductive health. The authors report no conflicts of interest.

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2.10 Author's contributions

E.L., G.B., S.R, JP. B conceived and designed the study. E.L., S.R. took part in data collection. E.L., I.B, C.S and JP. B performed laboratory data analysis. E.L, C.S., JP. B analyzed the data. E.L., C.S., G.B, JP.B. JP.V. performed data interpretation.

E.L., C.S., G.B., JP. V, S.R, R.L, JP. B contributed to the writing of the manuscript.

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CHAPTER 3: EVALUATION OF CERVICAL CANCER SCREENING UPTAKE AND RISK FACTORS KNOWLEDGE: HEALTH BELIEFS MODEL (HBM)

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3.1 Abstract

Background: Even though 20 million women are eligible for cervical screening in Ethiopia only less than 1% of women are screened. Part of the explanation for the low uptake of cervical cancer (CC) screening could be rooted in women`s health beliefs and inadequate knowledge of risk factors. **Objectives**: To assess women's health beliefs on CC screening and CC risk factors knowledge who visited Sister Aklesia Memorial Hospital (SAMH) for any medical reasons in Adama town, Oromia, Ethiopia. **Methods**: A cross-sectional study was conducted and a total of 412 women participated between September and December 2017. **Results**: The average age of women was 44.6 years. Among 28 women who visited a health facility, thirteen (3.2%) had undergone screening tests either of VIA or Pap test. Association between women's education ($p<0.05$) and household income ($p<0.05$) with health facility visits for CC screening were found statistically significant. Women didn't visit clinics for screening purposes because they believe "douching every day" can prevent CC; and no "screen and treat" approach existed; "uncomfortable if a man does the procedure"; "no self-sampling device available" was the main barrier factors. Women believed that they are not susceptible to CC when they don't have sex with many partners ($p<0.05$) and don't have symptoms ($P<0.05$), and so they don't need a CC screening test. A significant number of women ($p<0.05$) didn't consider abnormal CC screening tests without treatment can lead to cervical cancer. **Conclusions**: The health belief model could be used to study factors influencing Ethiopian women's participation in cervical cancer screening. Therefore, changing the social structure and living conditions of women may improve health through increasing preventive beliefs and incentives for screening tests. This study is identified several factors influencing cancer screening uptake and compliance.

Key words: Cervical cancer; VIA; Pap test; Barriers; Screening; Ethiopia

3.2 Introduction

Cervical cancer (CC) is responsible for 230,200 deaths and 444,500 cases of the disease annually among women in the developing country [1, 2]. The mortality rates for CC are expected to increase by 25 % during the next decade, even though this is one of the most preventable cancers [2]. In resource-limited countries access to cervical cancer screening (CCS) and vaccination is poor [3]. In sub-Saharan Africa over 80% of CC is detected in late stages [3, 4]. There is a low survival rate when women had cervical cancer at an advanced stage of disease [5].

In Ethiopia, CC is the second most frequent female cancer with an incidence rate (16.3%) among women between 15 and 44 years of age next to breast cancer (29.6%) [7]. Ethiopia has 29,4 million women aged 15 years and older and 7.095 women are reported with CC of whom 4,732 die from the disease [7].

In Ethiopia, 208 health facilities are providing VIA screening and cryotherapy treatment and more than 52,000 women were screened in 2016/17. Besides, Loop Electrical Excision Procedure (LEEP) service was scaled up from five to fifteen hospitals. The FMOH is working to scale up Visual Inspection with Acetic Acid (VIA) screening and cryotherapy treatment into 823 districts [8]. Even though 20 million women are eligible for cervical screening in Ethiopia only less than 1% has been screened [8].

Infection with high-risk human papillomavirus (HR HPV) is the cause of almost all CC cases. Early sexual debut, multiple sexual partners, young age at first delivery, multi-parity, immunosuppression, co-infection with other sexually transmitted infections (STIs), cigarette smoking, long-term use of hormonal contraceptives, estrogen-only hormone replacement therapy, and obesity are some of the factors that have been associated with an increased risk of developing CC [9].

The appropriate level of knowledge, attitude, and beliefs are key elements for adopting a healthy lifestyle, influencing human behaviors, accepting newly introduced preventive measures and determining the stage at which cancer patient presents to a health facility [10]. Studies from many parts of the world [11- 14] including Ethiopia [21-23] have shown a lack of awareness within

populations regarding CC symptoms, early signs, and the role of screening and HPV vaccination for prevention. Cervical cancer's long latency and recognizable pre-cancerous lesions make screening a particularly effective way of prevention as these pre-cancerous lesions, once identified, can be expectantly managed or treated safely and inexpensively in an outpatient setting [13]. It is important to create awareness among communities through educational programs on cancer prevention, preventable risk factors, benefits of early diagnosis, and availability of screening facilities. In developed countries, CC screening programs have reduced the incidence of invasive lesions up to 80% [12].

3.3 Methodology

The goal of this study was to investigate health beliefs on uptake of cervical cancer screening and treatments program and knowledge on cervical cancer risk factors in Adama, Oromiya, Ethiopia. A cross-sectional of 412 women participated in this study between September to December 2017 at SAMH. The only inclusion criteria were participants had some level of knowledge and awareness about cervical cancer disease.

The study was conducted in Adama Town, Oromia region, having a total population of 1.356.342 of whom 659.992 are female. As the population of East Shewa also seeks medical care in Adama, this population was also part of the study population. The SAMH Hospital, which is located in Adama Town, is a private hospital with a history of cervical cancer screening programs and is currently a center in which cervical cancer screening is performed.

Women who came for general medical checkups not primarily for cervical cancer screening were recruited from this hospital. Women were eligible if they were able and willing to provide written or verbal informed consent. Information on the basic demographic potential barrier to the update of cervical cancer and treatments, knowledge on risk factors were collected from all consenting women by standardized questionnaires. Nurses who trained in interview questionnaires and had good experiences on cervical cancer interviewed the women in their native language, either Oromia or Amharic. The inclusion criteria were women between the ages of 20 and 70 years old.

The questionnaire was designed in English and translated into Oromifia and Amharic: the main language used in the study area and back translated to English with any discrepancies addressed

was pretested among a group similar to the study respondents. The questionnaire had three sections. The first section included questions on the participants' demographic characteristics such as age, education status, marital status, age at marriage, history of CC in her family, parity, household income, and use of contraception. The study identified two outcomes i.e. women visited a health facility for CC purpose previously (1= visited, 0= not visited), and women who underwent CCS (PAP or VIA) test (i.e. 1= Yes; 0= No).

The second section included nine questions that assessed the respondents' specific risk factors and knowledge about cervical cancer prevention. Questions are required "Yes" or "No" responses. The risk factors included unprotected sex, multiple sexual partnerships, smoking, use of contraception, previous exposure to sexually transmitted diseases, and early sex onset.

The third section examined women's health beliefs about cervical cancer screening. The HBM is a well-known health education model that is simple in design and has been used successfully in health interventions. The questionnaire was developed based on the HBM theory (17,18) to assess beliefs related to cervical cancer screening. Based on literature reviews on factors influencing screening practice, 71 items were identified and grouped into the five domains of the HBM and checked for clarity, and pilot questionnaires were used and corrected accordingly. All items were translated into Oromia and Amharic language since most participants was from Oromia. Dichotomous responses i.e. Yes, or No was used. The HBM focuses on five determinants: Perceived susceptibility, perceived severity, perceived benefits [Positive attributes of the action], and perceived barriers [Negative attributes of the action], and cues for action.

3.3.1 Data analysis

Statistical analysis was performed using the SPSS version 20 software. Means and standard deviations were used to describe continuous variables. An association was statistically significant if the p-value was less than or equal to 0.05. Descriptive statistics and bivariate analyses were conducted. Odds ratios and 95% confidence intervals were used as measures of association. Descriptive statistics were conducted to characterize the participants and provide frequencies on individual questions and risk factors knowledge. Bivariate analysis was conducted to determine the association between socio-demographic characteristics, health beliefs, and risk factors

knowledge about cervical cancer prevention. A binary outcome of risk factors knowledge was determined and women who had answered “yes” response were considered to be more correctly responded while those who said “no” were considered to have no knowledge.

3.4 Results

A total of 412 women participated in the study and those who had some level of knowledge and awareness about cervical cancer disease were included in this study. The mean age of women was 44.6 years (SD=9.3). Two hundred forty-seven women (59.9%) and 18.7% (77/412) women were under grade 10 and above certificate, respectively (Table 1).

One hundred ninety-three women (46.8%) were married at the time of study, 11.4% were living with partners and 15.8% (65/412) were never married. Women indicated that they were married below the age of 20 years, 73.5% (303/412), and rest was married at the age of 20 and older. A relatively higher number of women were used modern medicine of 69.4% (286/412) as compared to traditional treatment, 30.6% (126/412) (Table 1).

More than three-fourth of women 78.6% (324/412) responded that no history of cervical cancer in their families was known and 3.2% (13/412) reported that there was a cervical cancer family history documented. A total of 356/412 (86.2%) women had children less than three. Almost half of women had household income less than ETB1500 per month and only 3.6% had monthly income greater than ETB 5000. Women, 34.5% (142/412), were used contraception drugs or devices in their lifetime (Table 1).

A total of 6.8% (28/412) women reported that they were visited a health facility for purpose of getting cervical cancer service. Accordingly, from women who had visited a health facility, only 3.2% (13/412), women reported underwent cervical screening either of VIA or Pap test (Table 1).

Table 1: Socio-demographic characteristic of the women participants and association between women cervical cancer health facility (CCHF) visit and socio-demographic characteristics (n=412), SAMH, September to December 2017.

Categories	**Sub-categories**	**Frequency**	**Percent**	CCHF visit			
				Yes	**No**	X^2	p-value
Age group	20 – 29	39	9.5	39	0	4.684	0.321
	30 – 39	91	22.1	86	5		
	40 – 49	135	32.8	124	11		
	50 – 59	140	34.0	128	12		
	60 – 69	7	1.7	7	0		
Education status	Under grade 8	56	13.6	53	3	11.186	0.048
	Under grade 10	191	46.4	184	7		
	Preparatory [University]	8	1.9	8	0		
	Certificate	80	19.4	73	7		
	Diploma	68	16.5	58	10		
	Degree	9	2.2	8	1		
Marital status	Married	193	44.8	180	13	0.643	0.958
	Single	65	15.8	60	5		
	Separated	41	10.0	38	3		
	Widowed	66	16.0	61	5		
	Living with partners	47	11.4	45	2		
Age at marriage	<=20 years	303	73.5	281	22	0.390	0.532
	>20 years	109	26.5	103	6		
Type of treatment	Modern	286	69.4	267	19	0.034	0.853
	Traditional	126	30.6	117	9		
History of cervical cancer in your family	No	324	78.6	308	16	82.693	0.000
	Yes	13	3.2	4	9		
	Not Sure	75	18.2	72	3		
Parity	=<3	356	86.4	332	24	0.012	0.912

	>3	56	13.6	52	4		
Household income (ETB])/Month	<1500	212	51.5	211	1	55.739	0.000
	1500-5000	185	44.9	165	20		
	>5000	15	3.6	8	7		
Use of any contraception	No	270	65.5	384	15	184.095	0.000
	Yes	142	34.5	0	13		
Visit clinic for cervical cancer service	No	384	93.2	-	-	-	-
	Yes	28	6.8	-	-	-	-
Previous history of CC Screening test (VIA or PAP)	No	399	96.8	-	-	-	-
	Yes	13	3.2	-	-	-	-

Table 2 shows that a quarter of women (25.2%) didn't give the correct answer on risk factors knowledge for cervical cancer. A percentage of 41.4 and 38.3 of women aware that risk factors of having more children and not regularly checked for VIA or PAP screening test could be a likely risk factor.

Very few women (11.2%) were aware that *early sexual debut* (having had first sexual intercourse at or before age 14) was associated with the development of CC and 59.2% of women recognized smoking cigarettes as a risk factor. The use of the birth control pill for a long time was recognized as a risk factor by 56.4%, and multiple births by 41.4% of women (Table 2). On average (ẋ=5.6) women correctly identified out of the nine risk factors presented in this study.

Table 2: Women knowledge about risks factors for developing cervical cancer, (n=412), SAMH, September to December 2017.

A woman agreed that the following risk more likely develop cervical cancer if ….	(n=412) Percentage
Has unprotected sex	60.4%
Smokes cigarettes	59.2%
Used birth control pill for a long time	56.4%
Had many sexual partners	56.1%
Has many children	41.4%
Not going for regular [Pap] smears or VIA tests	38.3%
Has a sexually transmitted disease or virus	11.7%
Has a weakened immune system	11.2%
Started having sex at a young age	11.2%

Table 3: Total and average score participant response`s on Health Beliefs, (n=412), questionnaires items (PSU=14; PS=7; PB=8; PBA=31; CA=12); SAMH, September to December 2017.

Perception	Disagreed		Agreed		Total disagreed	Total agreed
	Mean	Count (above average)	Mean	Count (above average)	% (Count)	% (Count)
Perceived susceptibility	10.67	232	4.33	180	71.11 (4099/5768]	28.89 (1668/5768)
Perceived severity	4.77	256	2.23	156	68.17 (1966/2884)	31.83 (918/2884)
Perceived benefit	4.68	235	3.32	177	58.51 (1928/3296)	41.49 (1367/3296)
Perceived barrier	15.04	183	15.13	187	49.70 (614312360)	50.28 (6215/12360)
Cues to action	6.15	183	5.85	229	51.27 (2535/4944)	48.73 (2409/4944)

A total of 6.8% (28/412) participants had visited CCHF previously at least once for cervical cancer checkup (table 1). There was a significant association between women who had graduated at least certificate level and who had visited CCHF (p-value =0.048). A significant association was also found between women who had cervical cancer history in their family and a previous visit to the cervical cancer health facility for checkup purpose (p-value =0.000).

Moreover, women's household income of more than ETB 1500 was significantly associated with a previous visit to a cervical cancer health facility for checkup condition (p value=0.000). From a total of 28 women who had visited CCHF, 46.42% (13/28) participants underwent VIA or PAP screening test (p-value =0.000). Almost, 70% of participants with a history of CC in the family (9/13) had visited a CC health facility.

Variables like marital status, number of children, age, age at first marriage, and type of treatment were not statistically associated with women visit for any kind cervical cancer service.

3.4.1 Health belief model results

A total of 143/412 (33.3%); 134/412 (31.5%) and 117/412 (27.5%) women had misconceptions regarding the CCS test that the test was only required when they have symptoms and when they have had sex with many partners and used contraceptive drugs (table 4). Forty percent (172/412) and 30.8% (131/412) women correctly identified the perceived severity (table 4). Women 159/412 (37.3%) agreed that getting a CCS test allows for early detection of cervical cancer (Table 5).

Table 4: Women`s responses for perceived susceptibility (PSU) and perceived severity (PS) regarding cervical cancer screening and its association to CCHF visit, Pearson`s Chi-Square test, (n=412), SAMH, September to December 2017.

.	CCHF Visit					
Items [perceived susceptibility (PSU)	Disagreed		Agreed		X^2	p-value
	Count	%	Count	%		
1. I am not at risk for an abnormal CCS test	273	66.3	139	33.7		

2.	I am not at risk for developing cervical cancer	275	66.7	137	33.3		
3.	If I have cervical cancer, I can die.	270	65.5	142	34.5		
4.	Since I do not have a history of cervical cancer in my family, it is very unlikely that I will get cervical cancer.	285	69.2	127	30.8		
5.	Cervical cancer is one of the most common cancers among women my age.	306	74.3	105	25.5		
6.	*If I do not have symptoms, I do not need a CCS test.*	*269*	*63.1*	*143*	*33.6*	*14.567*	*0.000*
7.	If I have not had children, I do not need a CCS test.	279	67.7	133	32.3		
8.	If I do not have intercourse, I do not need a CCS test.	319	77.4	93	22.6		
9.	If I am sterilized, I do not need a CCS test.	285	69.2	127	30.8		
10.	If I am not pregnant, I do not need a CCS test	308	74.8	104	25.2		
11.	*If I do not have sex with many partner, I do not need a CCS test*	*278*	*65.3*	*134*	*31.5*	*17.089*	*0.000*
12.	If I do pray and fasting accordingly, I do not need a CCS test	280	68	132	32		
13.	If I do drink holy water, I do not need a CCS test	327	79.4	79	19.2		
14.	*If I do not take any contraceptive drug or device use, I do not need a CCS test*	*295*	*69.2*	*117*	*27.5*	*15.430*	*0.001*
Items [perceived severity (PS)							
15.	*An abnormal CCS test, without treatment, can lead to cervical cancer.*	*240*	*56.3*	*172*	*40.4*	*4.444*	*0.035*
16.	Not having a CCS test could result in a serious health problem.	276	67	136	22		
17.	*Cervical cancer may lead to death*	*281*	*66*	*131*	*30.8*	*4.591*	*0.032*
18.	Cervical cancer would make a women's life very difficult.	310	75.2	102	24.8		
19.	Cervical cancer may lead to having a hysterectomy.	308	74.8	104	25.2		
20.	Cervical cancer is not a serious health problem.	283	68.7	129	31.3		
21.	Cervical cancer can lead to a woman needing to receive chemotherapy or radiotherapy treatment.	268	65	144	35		

Table 5: Women`s responses for perceived benefit [PB] and cues to action (CA) regarding cervical cancer screening and its association to CCHF visit, Pearson`s Chi-Square test, (n=412), SAMH, September to December 2017.

	Disagreed		Agreed		CCHF visit	
					X^2	p-value
Items (perceived benefit)	Count	%	Count	%		
22. Getting a CCS test makes me feel good because it means that I take care of my health.	213	51.7	199	48.3		
23. Getting a CCS test allows for early detection of cervical cancer.	*253*	*59.4*	*159*	*37.3*	*16.803*	*0.000*
24. The CCS test can determine cervical cancer.	217	52.7	195	47.3		
25. Getting a CCS test is a good investment of my time in health.	233	56.6	178	43.2		
26. A CCS test can find cervical cancer when it is possible to cure it.	260	63.1	152	36.9		
27. The CCS can save my life.	235	57	177	43		
28. The CCS test can help to find infection disease.	258	62.6	154	37.4		
29. Getting a CCS test can find another reproductive problems [genitals problems]	259	62.9	153	37.1		
Items (cues to action)						
30. To take care of my health	334	83.5	68	16.5		
31. After hearing something about cervical cancer.	297	72.1	115	27.9		
32. Because a doctor or nurse or midwife told me.	*263*	*60.9*	*149*	*34.5*	*7.842*	*0.005*
33. Because a health center send me mobile text or phone call.	150	36.4	262	63.6		
34. Because my mother spoke to me about it.	190	46.1	222	53.9		
35. Because a friend spoke to me about it.	189	45.9	223	54.1		
36. Because members of my family told me to get it.	77	18.7	335	81.3		

37. Because I listened to or read something in the news or in a television or radio program on CCS	*262*	*60.6*	*150*	*34.7*	*7.666*	*0.006*
38. Because I had genital bleeding.	57	13.8	355	86.2		
39. Because I had pain in my genitals.	*277*	*64.1*	*135*	*31.3*	*8.103*	*0.004*
40. Because someone I know well [family, friend, neighbor] had cervical cancer.	225	54.6	187	45.4		

In table 6, women indicated that one of the obstacles or perceived barriers was that they disliked the cervical cancer screening method to be done by a male doctor (49.0% (202/412). The participants also did not like the use of a speculum during the CCS examination (51.0% (210/412)). One big misperception identified in this study was 53.9% (222/412) of women believe that douching daily deems a CCS test unnessasary.

The number of women who visited a health facility for cervical cancer screening service was statistically associated with perceived susceptibility when they had symptoms, sex with many partners, and took any contraceptive drug or device used with a p-value of 0.000, 0.000 and 0.001, respectively (Table 6).

Table 7 illustrated that women who visited a health facility for cervical cancer screening services were statistically associated with perceived severity when they had an abnormal cervical cancer screening tests and believed that cervical cancer may lead to death with p-value 0.0.035 and 0.032, respectively. Women's perceived benefit for having a screening test allows for early detection of cervical cancer were statistically significant (p-value=0.000) with the number of health facilities visited (Table 5).

Women indicated that the barrier factors for not visiting a health facility for screening purpose were "if they douche daily" (*p-value=0.000*); no "screen and treat" approach available (p-value=0.000); "uncomfortable if a man does the procedure" (p-value=0.001); "they believe cancer is God's will" (p-value=0.002); "fear of cancer detection and treatment" (p-value=0.000) and "no self-sampling device available" (p-value=0.004) (table 6).

Table 5 indicated that women need some information regarding cervical cancer screening and accordingly they visited a health facility when health professionals informed them about it (p-value=0.005); had pain in genital area (p-value=0.006) as well as when they heard about cervical cancer screening through media programs (p-value=0.006). In general, for all HBM domains, the mean score was relatively greater in women who visited CCHF as compared to those that did not. The mean scores for perceived susceptibility, perceived barriers and cues to action domains did show a significant difference between the group that visited CCHFs and those that did not visit with a p-value of 0.008, 0.003, and 0.022, respectively, as shown in Table 7.

Table 6: Women`s responses for perceived barriers [PBA] regarding cervical cancer screening and its association to CCHF visit, Pearson`s Chi-Square test, [n=412], SAMH, September to December 2017.

					CCHF visit	
	Disagreed		Agreed		X^2	p-value
	Count	%	Count	%		
41. I do not have time to get a CCS test.	74	18	338	82		
42. Getting a CCS test only will give me problems.	159	38.6	253	61.4		
43. A CCS test can move the intra uterine device.	202	49	210	51	9.158	0.002
44. Getting a CCS test is painful.	78	18.9	334	81.1		
45. Getting a CCS test gives me some insecurity about my health.	201	48.8	210	51.0		
46. I fan unmarried or single woman gets a CCS test, people may think that she is having sex.	202	49	210	51		
47. Getting a CCS test is expensive.	213	51.7	199	48.3		
48. Getting a CCS test is embarrassment.	213	51.7	199	48.3	6.532	0.011
49. I do not have a CCS test because I do not know where I need to go.	174	42.2	238	57.8		
50. I prefer that a female gives me the CCS test, because it is uncomfortable for me if a man does it	210	51	202	49	10.491	0.001
51. I have not taken the CCS test because they treat me badly in the health care center.	246	59.7	166	40.3		

52.	I have not taken a CCS test because when I go, I need to wait a long time to be seen.	238	57.8	174	42.2		
53.	I do not know if I need to have a CCS test.	202	49	210	51		
54.	If a woman has not had sex, a CCS test could take away her virginity.	249	60.4	163	39.6		
55.	My partner/husband does want me to get a CCS test.	255	61.9	157	38.1		
56.	It is difficult to get a CCS test because I do not have money for transportation [take a bus, taxi, train].	222	53.9	190	46.1		
57.	I have not taken the CCS test because I am afraid to find out if I have cancer.	267	64.8	145	35.2	8.578	0.003
58.	I have not taken the CCS test because the health care center is only open during hours when I cannot go.	241	58.5	171	41.5		
59.	I have not taken the CCS test because I am embarrassed to have a genital exam.	246	59.7	166	40.3		
60.	I do not know at what age it is necessary to have a CCS test.	207	50.2	205	49.8		
61.	I do not know how often I need to get a CCS test.	185	44.9	226	54.9		
62.	I have not taken a CCS test because it is difficult to get an appointment.	242	58.7	170	41.3		
63.	I have not taken the CCS test because the provider not have self-sampling device	277	67.2	135	32.8	8.103	0.004
64.	I have language barriers	75	18.2	337	81.8		
65.	I do not take CCS test because the clinic do no have a private screening room	261	63.3	151	36.7		
66.	I do not take CCS test if there is no voluntary consulting test [VCT] prior to screening tests	242	58.7	170	41.3	4.690	0.03
67.	I do not have CCS test because of no “screen and treat” approach available	222	53.9	190	46.1	18.956	0.000
68.	I have not taken a CCS because I`m not HIV positive	118	28.6	294	71.4	4.724	0.03
69.	I have not taken a CCS because cancer is God will`s or traditions of religions	204	49.5	208	50.5	9.480	0.002
70.	I have not taken a CCS because I do douching every day or every time	190	46.1	222	53.9	21.883	0.000
71.	I have not taken a CCS test because I do sex by condom	54	13.1	358	86.9		

In table 7, the largest difference was in the 'perceived barrier' domain, with merely a 1.73-point difference between the two groups. 'Perceived severity' and 'perceived benefit' have the same difference, 0.32, while 'cues to action' had a difference of 0.75. In all the domains, the group that visit CCHFs scored higher mean values.

Table 7: Mean total score for Health Belief Model domains between the group that visited and not visited cervical cancer screening facility (n=412), Independent T test.

Domains	Mean [SD]		95% CI	P-value
	Not visited CCHF [n=384]	Visited CCHF [n=28]		
Perceived susceptibility	4.26[2.05]	5.32[1.89]	-1.85, -0.28	0.008
Perceived severity	2.21[1.51]	2.53[1.57]	0.911, 0.25	0.266
Perceived benefit	3.29[1.40]	3.61[1.42]	-0.85, 0.23	0.259
Perceived barrier	15.84[2.93]	17.57[2.81]	-2.86, -0.61	0.003
Cues to action	5.79[1.65]	6.54[1.62]	-1.37, -0.11	0.022

3.5 Discussion

In this study, all women heard about cervical cancer via radio, TV, friends or family members previously used as inclusion criteria to participate in the health belief model study. This can also be as a result of the FMOH raising awareness by training women and health care professionals [8]. In this study, cervical cancer screening coverage was 3.2%, higher than the national screening coverage rate (<1%) [8]

Health behavior is a result of individual beliefs rather than objective reality. Understanding women's health beliefs is a crucial step for promoting cervical cancer screening uptake [18]. There is a difference among the age groups of women on health beliefs in the use of cervical cancer screening utilization and other health services. Our study was not able to determine the association between health beliefs among different age groups, yet older women's cervical cancer screening behaviors were influenced by their perception of barriers, whereas younger women's behaviors were not. [15]. A study done in Ethiopia by Wassie S et al. [36] revealed that 70% of

participants disagreed that cervical cancer treatment was effective by traditional medicine. This strengthened our study findings that women preferred modern medicine for cervical cancer treatment.

The women who were educated with better income and heard about cervical cancer from their family [22, 34] were more inclined to visit the health facility for screening. This finding was similar to a research report documented in the previous study in Ethiopia. [19, 36]. It revealed that women with a lack of knowledge about prevention and control of cervical cancer are not likely to present for the screening.

Most women in our study did recognize cigarette smoking, multiple births, sex at an early age, and use of birth control methods as risk factors of cervical cancer, as supported by Mukama et al. [30].

Women in this study believed that cervical cancer screening is required when they had symptoms, sex with many partners, and contraceptive drugs and agreed that getting a CCS test allows for early detection of cervical cancer. Similar results were found in a study reflected by Thanh Cong Bui et al. [37].

Women concluded that they were not comfortable if the doctor was a male and that they preferred to be screened if the clinic had a program of “screen and treat” approach.

Women believe that vaginal douching every day was the main reason not to visit the health center for cervical cancer screening. And women believed that it protects against sexually transmitted diseases; however, contradictory to this douching disturbs the normal vaginal flora [37].

In Ethiopia, the cervical cancer screening coverage is less than 1% currently [8], which was not supported by our study (3.2%). This could be due to participants` recall bias or a small size study population used [19].

In our study, only 6.8% of participants visited a health facility previously for cervical cancer screening. A study from the Southern part of Ethiopia found 33.3% of the respondents mentioned visual inspection with acetic acid as a screening method, and 11.4% of the respondents screened for cervical cancer [20].

The author summarized women`s beliefs are influenced by their culture, knowledge, health-style, social background and experience of health or illness of family members [16,21,23]. Women

positively perceived that they could monitor health situations if they are aware of it and have information about the disease [23]. The author identified various perceptions or beliefs and recommends relevant corrective actions to be designed for the diverse cultural and social groups [21].

Ethiopia needs structured awareness and, educational programs as well as screening services to address the different levels of the individual perceived barrier, susceptibility, and severity [16,21,23]. Behavioral change communication (BCC) is an interactive process with communities to develop tailored messages and approaches using various communication channels to address cues to action.

Changing women's beliefs could be more difficult than social and economical change factors. Thus, changing the social structure and living conditions may improve women's health through increasing awareness and incentives for screening tests [17].

Free cervical cancer screening tests may not be the last resort. Education of women to change their perceived susceptibility, severity, and barrier through various ways and an integrated health belief model may be helpful [16,32].

To explore the relationship between women`s health beliefs and behaviors, the conceptual model of health belief is used to study factors influencing Ethiopian women's participation in cervical cancer screening. We may design a culturally appropriate cervical cancer screening health belief model and understand specific woman`s positive and negative influencing factors that improve the coverage.

3.6 Conclusion

The health belief model could be used to study factors influencing Ethiopian women’s participation in cervical cancer screening and may be considered in designing culturally appropriate cervical cancer screening interventions.

3.7 Conflicts of interest

Funding: No funding sources and this research did not receive any specific fund from funding agencies in the public, commercial, or not-for-profit sectors.

3.8 Competing interests

None declared.

3.9 Ethical approval

The ethical committee of the College of Natural Sciences, Addis Ababa University has examined the project and approved. The SAMH Hospital also approved the project and conducted ethically.

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CHAPTER 4: COMPARISON AND ACCEPTABILITY OF HPV SELF-COLLECTED CERVICAL CANCER SAMPLES VERSUS DOCTOR-COLLECTED SAMPLES IN AFRICA: A SYSTEMATIC REVIEW

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4.1 Abstract

Self-collected cervical cancer (CC) samples might be considered alternative strategy and provided an equivalent comparable result on HPV (Human Papillomavirus) detection and acceptability with clinician-collected samples in Africa. A systematic review was performed using four electronic bibliographic databases (Pubmed, Cochrane, WHO Global health library and Popline) to compared HPV detection rate and acceptability of HPV self-vs clinician collected sampling from African studies. Specific search keywords were used. The study only focused on research articles that compared self-vs clinician-collected samples based on HPV testing and its associated data. Eight research articles and a total of 3,476 women were included from six countries in Africa continent. The mean age of women was 40.6 years with range of 16 – 89 years. Aggregately the high risk (HR)-HPV detection rate was 36% (7.2% -84.8%) and 35% (6.8% - 87.8) of self-vs clinician-collected sampling, respectively. The mean differences and variation in detection rates between sampling methods was 2.6% (SD =1.7). There was significant HR-HPV detection rate correlation between two sampling methods with value of R=0.997. The weighted average of kappa agreement was 0.71(0.47 to 0.89) was moderate. Overall women concluded that self-collected sampling method was a preferred method (86.3%), easy to obtain (77.8%), and 76.7% increased cervical cancer screening uptake. The acceptability of HPV self-sample testing could be an alternative sampling method and increased the uptake of screening services. Introducing standardized self-sampling techniques and diagnostic assay study in Africa is paramount.

Key words: Self samples, Clinical samples, cervical cancer, Screening, HPV, Africa, Review

4.2 Introduction

Human papillomavirus (HPV) is the main cause of cervical cancer [1]. In low- and middle-income countries (LMIC) implementation of HPV screening test could not be easy, simple and cost effective, however, Africa will not ignore these methods introduced into its national cervical cancer screening programme [2,3]. Self-sampling has several advantages over physician-collected samples for detection of HPV genital infection. Self-collected samples can be more easily obtained in settings with limited resources, or in populations difficult to reach. Numerous studies have reported that vaginal/cervical self-obtained samples in women were accurate and suitable for Deoxyribonucleic Acid (DNA) testing [3-5].

Previous studies revealed that self-sampling might increase willingness to participate in cervical cancer screening programs as it reduces patient`s financial and logistical burden; and increase sense of privacy and autonomy. Self-sampling therefore might remove some of the barriers that prevent women, especially those in low socioeconomic and minority populations, from participating in regular screening programs [4, 6]. Overall, self-sampling is believed to improve the subjective patient experience, lead to increased screening participation and ultimately reduce morbidity and mortality related to HPV infection and cervical cancer [3, 5, 7].

In some countries self-sampling for HPV testing has already been adopted and evaluated to incorporate into national cervical cancer screening programs. Several studies have shown that most women who have been under-screened but who tested HPV-positive in a self-obtained sample may have potential to visit a clinic for follow-up diagnosis and management [8-10].

The definition of HPV self-sampling is a process where a woman who wants to know whether she has HPV infection using a kit to collect a cervico-vaginal sample, which is then sent for laboratory analysis. Various collection methods/devices were available but not in Ethiopia which include lavage, brush, swab and vaginal patch. While HPV self-sampling cannot provide a diagnosis of cervical (pre-) cancer, it identifies those women at higher risk [10]. The aim of this systematic review was to reach consensus among different research articles outputs on the selected topics in Africa and to determine self-sampling acceptability and HPV detection comparability between self-collected sampling verses clinician–collected samples within Africa. We focused on detectability as the outcome of interest, i.e., any positive test, whether originating from self- or

from physician-sampling. Our intent was on virological detection only, not on comparing collection methods as per their ability to distinguish HPV testing performances for detecting cervical precancerous lesions. This review addressed the following research question: Should HPV Self sampling testing be considered as an alternative platform for resource limited countries in Africa? This study was to determine the level of agreement between self-vs clinician-collected sampling for HPV testing in Africa.

4.3 Methods

To answer the research question we performed a computerized literature search in multiple databases; Medline via PubMed, Embase (Excerpta Medica database), Google Scholar, Scopus, the Cochrane Library, OCLC, PAIS (Public Affairs International Service), International Database (EBSCO), WHO (World Health Organization) Global Health Library, and POPLINE (Population Information Online). The study was followed PRIMA systematic review procedures and flow diagram (figure 1). PRISMA (Preferred Reporting Items for *Systematic Reviews* and Meta-*Analysis)* is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. A combination of medical subject heading terms and free text terms relating to "human papillomavirus" or "HPV" and "self-" or "patient-" or "auto-" or "physician-" or "clinician-" or health professional-" combined with "collection" or "obtained" or "sampling" or "testing" as both medical subject heading (MeSH) terms and text words in Africa were used. Reference lists of review articles and all articles identified in the systematic search were checked. An updated search was performed on September 2019. All abstracts were screened, checked and reviewed by two independent reviewers (HL and EL). This review included women who screened for cervical cancer, sexually active populations, and Human Immunodeficiency Virus (HIV) (+/-) populations, in Africa. No exclusion criteria were setup in relation to commercially available HPV technology. Only studies analyzing vaginal and/or cervical HPV self-taken samples verses clinician HPV test results as a comparator where considered. The review focused on HPV detectability as the outcome of interest, i.e. any positive test, whether originating from self- or from physician-sampling.

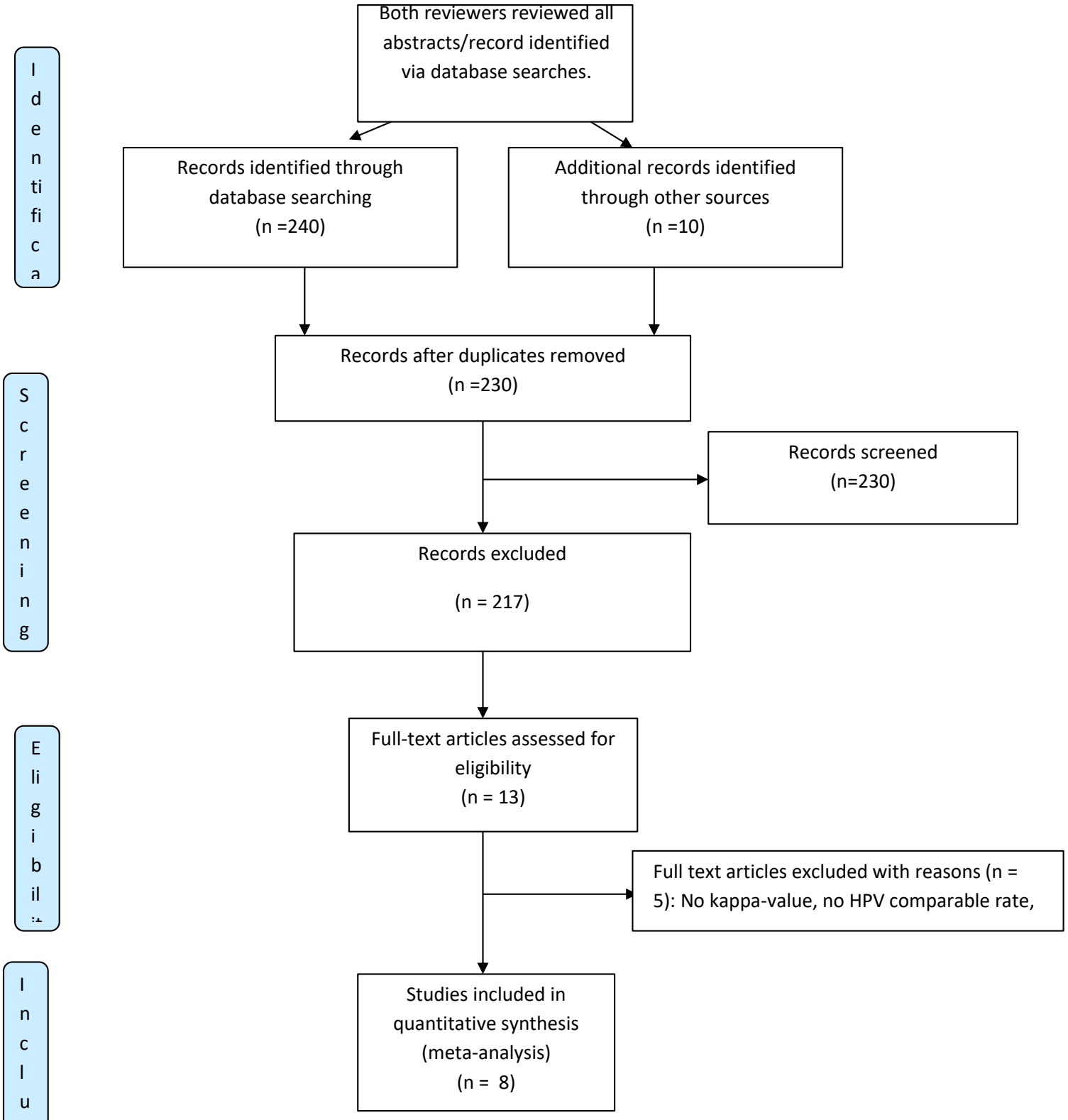

Figure 1: PRIMA systematic review processes

4.2 Statistical analysis

The kappa statistic, concordance and the difference in the proportions of HPV detection between clinician and self-sampling were calculated. Strength of agreement was used according to Landis and Koch-Kappa <0: poor; poor; 0 to 0.20: slight: 0.21 to 0.40; fair, 0.4 to 0.60, moderate: 0.61-0. 80: substantial: 0.81 to 1.0, almost perfect. Convert extracted data to common representation (usually average and SD (Standard Deviation).

4.3 Current status of knowledge

A total of 250 articles were found through search engine and any duplication and irrelevant articles were cleared and removed. There were only 8 relevant articles with total population of 3476 female participants (figure 1).

Studies from six African countries were included in this systematic review Ghana (1 paper), Nigeria (2 papers), Egypt (1 Paper), Cameroon (2 papers), South Africa (1 paper) and Ethiopia (1 paper) [11-18]. The average age of women was 40.6 years with range of 16 – 89 years. One study presented an age group of 16 -17 years that included sexually active South African adolescent women [17]. In this systematic review study, the method of sample collection differed. Self-sampling, cytobrushes, dry swabs, Cervex brushes as well as Care HPV brushes were used as sampling devices [17]. The overall detection rate of HR-HPV was moderately agreed upon between the self-and clinician- collected samples. The agreement between self- and physician-obtained samplings was good regardless of the disease prevalence in the tested population [3,7,9,19].

Study inclusion criteria varied from general population to specific patient groups (table 1), which included women who attended for cervical cancer screening service; HIV positive and negative women, and sexually active women. This is to our knowledge the first systematic review comparing the performance of self-collected cervical samples to clinician taken sample specifically focusing on Africa. P. Petignat et al [20] published an article to compare the detection rate of genital human papillomavirus (HPV) infection in self- and physician-obtained samples around the globe. However, the objective, scope and period of this study were quite different from our study. The first focus included only studies in Africa populations; secondary, the

systematic review period included recent studies and lastly we mainly focused on HR-HPV detection rate, results obtained from clinician-collected versus self-sampled. In this study we included all types of population groups without any restriction from general population to specific cases of HIV.

Table 1: Characteristics of study populations of eight review articles

No	Reference	Country	Sample size	Average age(yrs) /age range	Sample type (SS/CT)/sample quality control	Collection device (SS, CT)	Inclusion criteria	Exclusion criteria
1	Untiet et al- 11	Cameroon	789	44 (20-89)	Cervical samples	Flocked swab	Not pregnant women, aged between 20 and 89 years, having no previous cervical therapy or hysterectomy; women attending for routine cervical screening as well as hospital workers and wives of hospital employees	More than 6 months of stay
2	Modibbo et al- 12	Nigeria	400	40.8 (30 -65)	Cervicovaginal (SS: RNase P gene level =n=5 (2.7%) excluded from further analysis, CT= n=0 (not excluded)	Dry flocked swab	Women with age group 30 to 65 yrs	Pregnant, planning to relocate within six months, HIV positive, had unexplained cervical bleeding, history of hysterectomy, mental illness or cervical cancer from the study.
3	Kamal et al- 13	Egypt	1601		Cervical samples	-		-
4	Obiri-Yeboah et al., -14	Ghanaian	191	44.1 (>=18 years)	Vaginal/cervical	CareHPV brush	HIV (+) and HIV (-) women or general OPD population	Currently menstruating, previous treatment of cervical cancer
5	Olusegun et al- 15	Nigeria	194	43.4 (23-75)	Cervical	Cytobrush (cervexR	NA	NA
6	Viviano et al- 16	Cameroon	188	38.7 (30-49)	Endocervical (for HIV + women)	Dry swab	NA	pregnancy and previous total hysterectomy
7	Adler et al – 17	South Africa	30	(16-17)	SS: Vaginal swabs; CT: cervical swab	Dacron® swab	sexually active South African adolescent females	

8	Eshetu et al – 18	Ethiopia	83	32 (20-65)	Vaginal/cervical SS:<10 cells/ul: 22.8% excluded; CT: <10 cells/ul: 30.1% excluded)	Cytobrush	An intact uterus, no history of cervica cancer	Less than 20 years

There was a high HPV prevalence difference observed between reviewed studies when comparing HIV positive women versus general population. In the study with the highest HPV prevalence, 84.8-87.9% of women tested positive [13], while 6.2-9.8% were positive in the study with lowest prevalence [15]. There was variation (Mean=2.5, SD=1.7) among eight studies of HPV detection rate between self- sampling and clinician sampling (table 2). Aggregately HR-HPV detection rate was 36% with a wide range of (7.2% - 84.8%) and 35% (6.8% - 87.8) for self-and clinician-collected sampling, respectively. The absolute median differences in detection rates between sampling methods was 1.9% (table 2).

In three articles HPV detection rate was highest for self-collected samples [11,17-18], whereas in the remaining five studies clinician taken samples had the highest detection rate. Comparatively a high rate of HR-HPV detection was found on three studies where source of population was sexually active and HIV positive women.

Three papers from Ghana [12], Nigeria [14], and Ethiopia [18] compared acceptability and feasibility of self-collected samples, where different devices i.e Dry flocked swab, CareHPV brush, Cytobrush (cervexR), Cytobursh/plastic spatual (ThinPrep Vial of PreservCyt) were applied, over clinician-collected samples. Averagely 86.3%, 77.8%, and 76.7% of women reported that self-sampling techniques were preferred over clinician taken samples, easy to obtain, support cervical cancer screening, respectively. Most African women participating in the review articles concluded that self-sampling was a preferred choice which may decrease healthcare access challenge, health disparities, stigma, traditional cervical screening, providing samples at clinic which is uncomfortable, fear of doctors, fear of friends or family etc. Therefore, self-sampling could increase the uptake of cervical cancer screening in resource limited countries.

Most African women are not prone to visit clinic regularly for general check-up particularly for cervical cancer screening program, thus self-sampling could increase women participation in cervical cancer screening program [18, 20].

There was a significant HR-HPV detection rate correlation between sampling methods with R-value of 0.997, (Figure 2). The mean percentage difference of HR-HPV detection rate between self-vs clinician collection was 2.6% with range of 0.1% to 5.3%. Across all included studies there was no significant difference between the HR-HPV detection rate between self- vs clinician collected samples. The greatest difference between the two samples methods was observed at 5.3% (table 2), where sexually active women and HIV positive women were compared [16]. The variances can be due to collection techniques, procedures, study designs, source population, assay tests and clinical settings.

Table 2: Comparison of HPV detection percentage between self-vs clinician collected cervical cancer samples.

Reference	Country	Assay type	Type of HPV detect	HPV prevalence (%)		HPV prevalence (%) difference	Kappa value
				SS	CT		
Untiet et al- **11**	Cameroon	Abbott RealTime High Risk HPV assay (Abbott Laboratories, Abbott Park, IL)	HR-HPV	14.6	12.7	1.9	0.74
Modibbo et al- **12**	Nigeria	GP5+/6+ Luminex system	HR-HPV	8.9	10.3	1.4	-
Kamal et al- **13**	Egypt	Hybrid Capture 2 (HC2) assay	HPV	84.8	87.9	3.1	0.89
Obiri-Yeboah et al., -**14**	Ghanaian	careHPV (Qiagen)	HR-HPV	78.0	78.1	0.1	0.88
Olusegun et al- **15**	Nigeria	Hybribibo GenotArray	HR_HPV	6.2	9.8	3.6	0.47
Viviano et al- **16**	Cameroon	GeneXpert HPV assay	HR-HPV	14.3	19.6	5.3	0.57
Adler et al – **17**	South Africa	Roche Linear Array	HR-HPV/LR_HPV	47	43	4	0.80
Eshetu et al – 18	Ethiopia	Riotol qPCR	HR-HPV/LR_HPV	17.2	15.5	1.3	0.586

Only two studies compared sample quality between self-and clinician-collected samples [12, 18]. One study from Nigeria [12] showed that 2.7% of self-collected samples were rejected for further analysis due to poor quality, whereas none were rejected from clinician-collected samples (RNase p gene (cq values >40). However, a study from Ethiopia [18] indicated 22.8% of self-collected samples and 30.1% of clinician collected- samples were rejected for analysis due to poor samples collection (<10 cells/ul).

This systematic review showed a moderate kappa agreement between two sampling methods and 62.5% of reviewed articles showed that a higher detection rate was observed in clinician-collected sampling (gold standard) over self-sampling. Thus, we are expecting such difference due to poor self collection instruction/training and insufficient collection procedural demonstration. However, self-sampling approach with different collection tools would help the uptake of cervical cancer screening program where all necessary awareness and education on self-sampling techniques are provided to women.

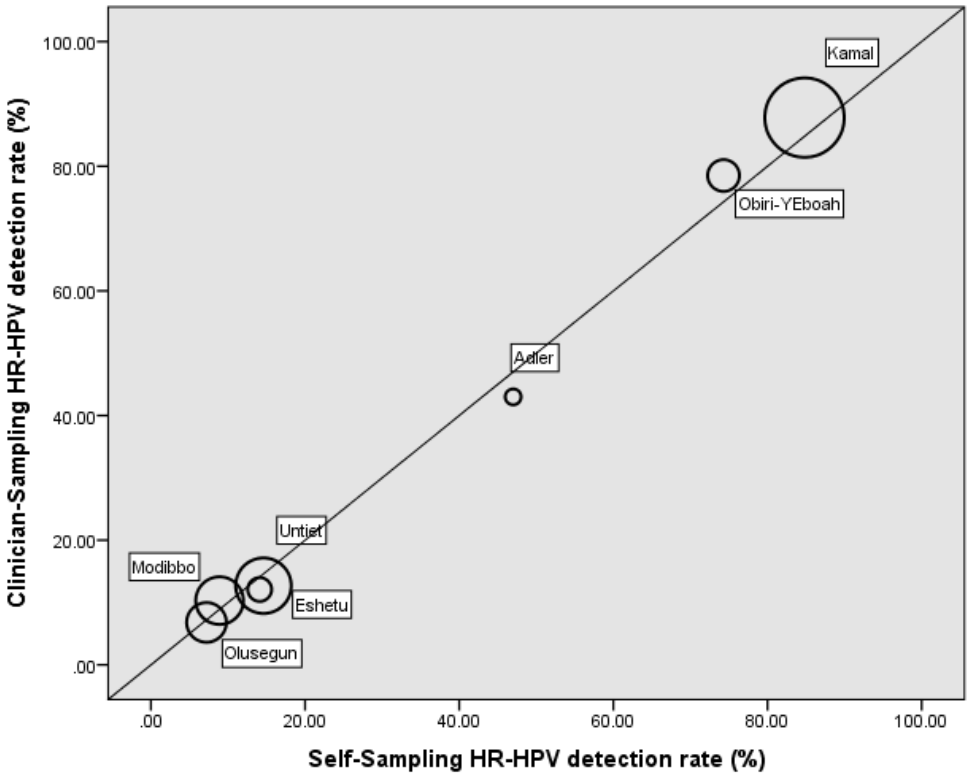

Figure 2: Correlation of self- and clinician-sampling for high-risk HPV in trials with data from 3,476 women. The sizes of the symbols are proportional to the sample sizes of the trials.

The average of studies trial of kappa agreement was 0.71 with range of 0.47 to 0.89 which was moderate. The overall agreement between self- and clinician collected HR-HPV detection rate was moderate with no significant variance (SD=0.16).

As this review study only focused on African based studies, there might be a number of concerns regarding full introduction of self-sampling into the health care system. Most African countries still used PAP (Papanicolaou Test) smear and VIA (Visual Inspection of cervix with Acetic Acid) for cervical cancer screening program due to relatively low cost and as no major infrastructure is required. Prior to the introduction of HPV testing on self-sampling collection technique, at least some level of infrastructure is needed like equipment, reagents, electrical power, and skilled manpower.

In Africa, HIV or Tuberculosis Bacillus (TB) diagnostic laboratory equipped with basic laboratory infrastructure, and without further investment, these labs can perform HPV testing at national or regional reference laboratories by availing HPV detection assays, supplies, materials and training. If self -sampling devices were available at every health center or in the near future at pharmacy stores, women could obtain it easily, take her sample and send it to the central laboratories for HPV detection and cytological analysis. This method will assist with early detection of cervical disease as well as increased uptake of screening. Point of care HPV testing at the various clinics must also be investigated as a method of cervical cancer screening.

4.4 Conclusion

In conclusion, self-sampling could be considered as alternative best sampling methods which provide a reproducible and comparable HPV detection to that of clinician sampling methods. Introducing standardized, easy, and simplified self-sampling and diagnostic assays across African countries may increase the uptake of cervical cancer screening coverage and contribute to a reduction of morbidity and mortality. We observed variations in study design. HPV detection methods and various sample collection devices utilized where some could have influenced the quality of the self-sample, influence the generalized conclusion regarding the use of the self-sampling HPV testing. A large study utilizing various self-sampling devices will be of great value. Further research is clearly needed to justify self sampling methods is an accurate and affordable approach in resource scarce setting.

4.5 What is already known on this topic

- HPV testing between self verses clinician collected samples could have comparable results.
- Self sampling could be used as alternative cervical cancer screening.
- Self-sampling could be helpful to increase the uptake of cervical cancer screening because of ease of use, self-sampling acceptability and feasibility in terms of easy to obtain samples. Women prefer this collection method.

4.6 What this study adds

- This study was focused on African studies only and confirmed that self-sampling could be used as alternative collection method to increase the uptake of cervical cancer screening.
- Various self-sampling devices must be tested, and easy collection procedure instructions could improve the quality of samples and may helps increase the uptake of service cancer screening program.
- Moderate agreement was observed between two sampling techniques which support the introduction of self-sampling in Africa continent.

4.7 Competing interest

There are no conflicts of interest i.e. financial and non-financial competing interests.

4.8 Authors' contributions

E.L., G.B., L.B, JP. B conceived and designed the study. E.L took part in data collection. E.L is performed data analysis. E.L and JP. B analyzed the data. E.L., L. B, JP. B andJP.Vare performed data interpretation.

E.L., G.B., JP. V, R.L, JP. B contributed to the writing of the manuscript.

4.9 Acknowledgments

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CHAPTER 5: BURDEN AND GENOTYPE DISTRIBUTION OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION AND CERVICAL CYTOLOGY ABNORMALITIES AT SELECTED OBSTETRICS AND GYNECOLOGY CLINICS OF ADDIS ABABA, ETHIOPIA

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5.1 Abstract

Background: Human papillomavirus is recognized as the major cause of cervical cancer. It is estimated that annually, 7,095 women are diagnosed with cervical cancer and 4,732 die from the disease in Ethiopia. Understanding that the screening practice is very poor, and the coverage is very limited, this disease burden is one of the major public health agendas in Ethiopia. This study aimed to assess the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities at selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia.

Methods: An institutional-based cross-sectional study design was employed from June to October 2015. Cervical samples were collected from 366 participants based on inclusion criteria. HR HPV DNA was analyzed using an Abbott Real-Time PCR system, and cervical cytology screening was performed using the conventional Pap-smear technique. Data were entered Epi-data version 13 and analyzed using STATA version 11.

Results: The overall HR HPV burden and abnormal cytology were 13.7 and 13.1%, respectively. The majority of HR HPV types were other than types 16 and 18. Of the total abnormal cytology results, 81.3% were low-grade squamous intraepithelial lesions (LSILs), and 12.5 and 6.3% were atypical squamous cells of undetermined significance (ASCUS) and high-grade squamous intraepithelial lesions (HSILs), respectively. Geographical residence, occupation, and HIV serostatus were significantly associated with HR HPV infection. Among the variables, age, age at first marriage, and education were the only factors associated with cervical cytology abnormalities. The overall agreement between the real-time PCR and Pap cytology screening methods was 78.96% (Kappa value of 0.12, 95% CI (0.00–0.243), P=0.01).

Conclusions : Non-16/18 HR HPV genotypes represented the largest proportion of HR HPV infections in this study. Women with normal cervical cytology had the highest frequency of HR HPV infection. A large-scale community-based cohort study shall be designed and implemented to further identifying the persistent genotype and assessing the changes in cervical epithelial cell lines. The quality of cytology screening must also be assessed.

Keywords: High-risk Human Papillomavirus, Cervical cytology, Obstetrics and gynecology, Genotype distribution, Real-time PCR, Pap cytology

5.2 Background

The World Health Organization estimates that nearly530,000 women worldwide are diagnosed with cervical cancer every year and that 275,000 die from the disease. Cervical cancer is renowned as the third most common cause of cancer in women globally, of which almost 70% occurs in developing countries [1, 2]. In Ethiopia, the age-standardized incidence and mortality rates are estimated as 26.4 and 18.4 per 100,000, respectively, four and nine-fold higher that the incidence and mortality rates in Western Europe [1].

Cervical cancer has been recognized as an outcome of a sexually transmitted infection, and the etiology is limited to a few human papillomavirus (HPV) genotypes. The association between HPV and cervical cancer is a universal fact, and variability among the different types is geographically limited. With optimal testing systems, HPV DNA can be identified in almost all specimens of invasive cervical cancer. [2]. One of the major reasons identified for the progression and development of cervical neoplasia among women who are repeatedly infected by HPV is ineffective cell mediated immunity [3].

Of all HPV genotypes, more than 40 have been identified from anogenital mucosa samples and most are transmitted sexually. HPV genotypes 16, 18, 31, 33, 35,39, 45, 51, 52, 56, 58, 59, 66 and 68 are classified as the high-risk (HR) group, which predicts cervical cancer [4]. The major phases in cervical oncogenes includes the infection of the metaplastic epithelium of the cervical transformation zone with high-risk HPV infection, viral persistence and clonal progression of the persistently infected epithelium to cervical pre-cancer, and invasion [5].

In sub-Saharan Africa, HPV-associated cervical cancer is one of the major causes of morbidity and mortality. A lack of strong initiatives as well as sustainable cervical cancer prevention programs and services have been identified as potential causes of the high incidence rate in most countries [6]. In Eastern Africa, approximately35.8% of women are estimated to harbor cervical HPV infection at any given time, and 76.5% of invasive cervical cancers are associated with HPV 16 or 18 [7]. Moreover, only 0.6% of the total female population aged 18–69 years in Ethiopia is screened every 3 years, representing1.6% urban women and 0.4% rural women, which demonstrates that screening practice is underdeveloped and that the overall coverage is very

limited [8, 9]. This study produced substantial information with relevant data regarding the burden of HR HPV infection and cervical cytology abnormalities in the intended setting.

5.3 Methods

An institutional-based cross-sectional study design was employed at three selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia, from June to October 2015. The study was conducted among women who visited the Family Guidance Association of Ethiopia Addis Ababa Area Reproductive Health Clinic, Hemen Maternal and Children Health Specialty Center, and SinamokshEthio Women's Health Special Clinic. The study population consisted of women who visited the clinics for any gynecological purposes, including cervical cancer screening, and fulfilled the inclusion criteria. A nonprobability convenience sampling technique was used to select the study sites, considering the scope and volume of services provided. As these health facilities provide cervical cancer screening services and have a significant volume of client visits, they were potential sites for this study and among the very few sites providing this service consistently in the city. All women who visited each clinic during the study period and who were eligible for this study were consecutively added until the number of clients reached the calculated minimum sample size. A total of 366 women were enrolled in the study.

Sociodemographic characteristics, sexual behaviors and other risk-factor variable responses were gathered using a structured questionnaire. Abbott Real-Time PCR system HR HPV DNA and Pap screenings were performed following the standard operating procedure. The cytological examination was performed by two pathologists whose degree of expertise was Medical Doctor with Diploma in Pathology and Cytology. Agreement between HR HPV and Pap smear results was assessed by Cohen's Kappa coefficient by recoding the findings into two categories (Negative and Positive). The results were entered onto EpiData software Version 13.0, and the data were analyzed using STATA Software Version 11.0. Descriptive statistics, proportions and the actual number of cases were used to describe frequency outputs for categorical variables and arithmetic means for the average age of the participants. Cross-tabulations were performed to explore and display relationships between two categorical variables. Chi-square statistics were employed to assess differences between two categorical variables. Multivariate logistic regression analysis (adjusted odds ratio) was applied to evaluate the strength of the association of the various potential

risk factors with the presence of HR HPV infection and cervical cytology abnormalities. Positive and negative percentage agreement and overall percentage agreement were assessed for HR HPV DNA PCR and Pap smear screening methods. A P-value of less than 0.05 was considered statistically significant.

5.4 Results

5.4.1 Study subjects and sociodemographic characteristics

A total of 366 participants between 18 and 68 years of age were enrolled in this study. The mean age was 42.7 ± 10.7 SD. Most study subjects, 296/366 (80.9%), were within the range of 31–60 years. In terms of residence, 352 (96.2%) participants visited the study clinics from the Addis Ababa area. Of the total number of participants, 287 (78.4%) were married; among these, 71(24.7%) was married for the first time before 18 years of age. Regarding parity, 29 (7.9%) of the participants had> 5 complete pregnancies and deliveries; 281 (76.8%) women were parity 1 to 5.

Participant employment status was also assessed, and248 (67.8%) of the study participants were self-employed. Regarding educational status, the highest proportion comprised those with Diploma or Degree and above qualification (158/366; 43.4%), and only 39 (10.7%) were unable to read and write (Table 1).

5.4.2 Burden of High-risk Human papillomavirus and its genotypes

The overall burden of HR HPV infection in this study was 50/366 (13.7%). Among the HR HPV-positive cases,8 (16%) were identified as having HR HPV 16 genotype,38 (76%) had “other HR HPV” (HR HPV genotypes 31,33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68), 2 (4%) had genotype 16 together with “other HR HPV” genotypes, 1(2%) had genotype 18 together with “other HR HPV” genotypes, and 1 (2%) had genotype 18. The HR HPV genotype distribution showed that “other

Table 1 Sociodemographic characteristics of the study participants, Addis Ababa, Ethiopia, June to October 2015

Variable	Number	%
Age		
18–30	53	14.48
31–60	296	80.87
> 60	17	4.64
Residence		
Addis Ababa	352	96.2
Outside Addis Ababa	14	3.8
Marital Status		
Single	32	8.7
Married	287	78.4
Widowed	28	7.7
Divorced	19	5.2
Age at first marriage		
< 15	39	10.66
15–17	32	8.74
> =18	295	80.6
Parity		
0	56	15.3
1 to 5	281	76.8
> 5	29	7.9
Employment status		
Employed (Government/Private/NGO)	108	29.5
Self-employed	248	67.8
Unemployed	10	2.7
Education		
Unable to read and write	39	10.7
Elementary	64	17.5
High school	105	28.7
Diploma/Degree and above	158	43.2

Despite the low proportion, multiple infections were identified for HR HPV 16 and “other HR HPV” as well as for HR HPV 18 and “other HR HPV”, with proportions of 4 and 2%, respectively. The proportion of HR HPV-positive cases was 26, 72, and 2% in age ranges 18–30, 31–60, and > 60, respectively. Age range 31–60was found to have the highest proportion of positivity (76, 95% CI (71.3–80.1%)), which was statistically significant.

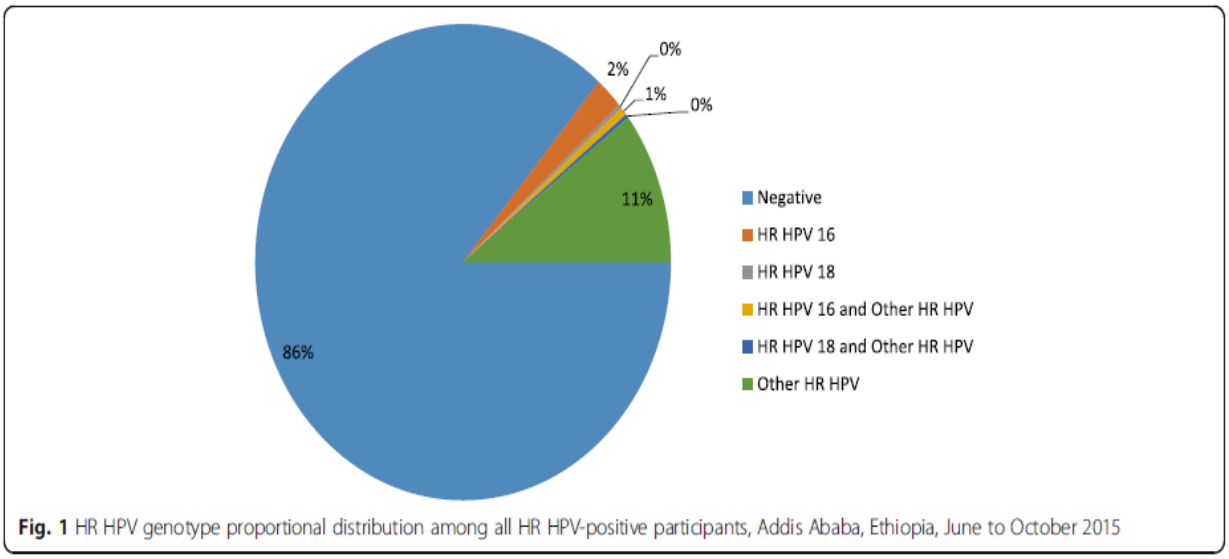

Fig. 1 HR HPV genotype proportional distribution among all HR HPV-positive participants, Addis Ababa, Ethiopia, June to October 2015

The association between HR HPV infection with sociodemographic and reproductive health, sexual behavior, and other risk factors was analyzed through bivariate analysis using the chi-square test. Age (P =0.000), parity (P = 0.017), age at first marriage (P =0.027), education (P = 0.003), condom use during sexual intercourse (0.011), cigarette smoking (0.000), and family history of cervical cancer (0.003) were significantly associated with HR HPV infection. Ever use of any type of contraceptive, age at first sexual intercourse, more than one lifetime sexual partnership, history of STD, alcohol consumption, and HIV serostatus, with P-values of0.106, 0.266, 0.334, 0.824, 0.227, and 0.688, were not significantly associated.

In multivariate analyses using logistic regression, only “other HR HPV” type was significantly associated with residence, employment status, and HIV serostatus, with P-values of 0.037, 0.01, and 0.041, respectively (Tables 2 and 3). Individuals who visited the clinics from outside Addis Ababa were 8.12 times more likely to have “other HR HPV” type infection than those who were from Addis Ababa. Furthermore, the likelihood of having “other HR HPV” infection among

unemployed individuals was 9.2 times higher than for employed individuals. Compared to diploma or degree holders, women who were not able to read and write were less likely to be infected with "other HR HPV" types (Table 2).

Table 2 Association of "other HR HPV" genotypes with sociodemographic factors, Addis Ababa, Ethiopia, July to October 2015

Sociodemographic	Response Category	"other HR HPV" positivity	*COR(95% CI)	*P*-value	**AOR(95% CI)	*P*-value
Age	18–30	10 (26.32)	Ref[a]			
	31–60	27 (71.05)	0.43 (0.19,0.96))	0.038	0.6 (0.01,1.77.9)	0.36
	> 60	1 (2.63)	0.27 (0.03,2.27)	0.228	0.33 (0.02,4.9)	0.42
Residence	Addis Ababa	35 (70.0)	Ref[a]			
	Out of Addis Ababa	3 (6.0)	2.35 (0.62,8.81)	0.207	8.12 (1.14, 57.9)	0.037[b]
Marital status	Married	28 (56.0)	Ref[a]			
	Unmarried	7 (14.0)	2.795 (1.096,7.128)	0.031	3.22 (0.73, 14.29)	0.123
	Widowed	3 (6.0)	1.05 (0.299,3.716)	0.934	1.80 (0.40,8.24)	0.445
	Divorced	0	0			
Age at first marriage	< 15	2 (4.0)	Ref[a]			
	15–17	4 (8.0)	0.25 (0.025,2.59)	0.248	2.15 (0.17,0.48)	0.55
	> = 18	32 (64.0)	0.14 (0.029,0.646)	0.012	4.98 (0.47,52.2)	0.18
Parity	0	7 (14.0)	Ref[a]			
	1 to 5	28 (56.0)	0.72 (0.3,1.8)	0.471	4.15 (0.90,19.2))	0.067
	> 5	3 (6.0)	0.79 (0.2,3.3)	0.743	6.78 (0.66,72.4)	0.101
Employment status	Employed (Government/Private/NGO)	12 (24.0)	Ref[a]			
	Self employed	22 (44.0)	0.79 (0.37,1.66)	0.531	1.22 (0.548, 3.07)	0.67
	Unemployed	4 (8.0)	5.1 (1.26,20.73)	0.023	9.17 (1.6, 52.22)	0.01[b]
Education	Unable to read and write	1 (2.0)	Ref[a]			
	Elementary	6 (12.0)	3.75 (0.43,32.48)	0.23	4.86 (0.4,59.4)	0.215
	High school	11 (22.0)	4.33 (0.54,34.77)	0.168	12.39 (01.01151.12.5))	0.049
	Diploma/Degree and above	20 (40.0)	5.34 (0.69,41.21)	0.108	14.06 (1.12,176.6)	0.041[b]

*COR-Crude Odds Ratio, **AOR-Adjusted Odds Ratio, [a]Reference, [b]There is a statistically significant association

Table 3 Association of "other HR HPV" genotypes with sexual behavior and other risk factor variables, Addis Ababa, Ethiopia, June to October 2015

Sexual behavior and other risk factor variables	Response Category	"other HR HPV" positivity	*COR(95% CI)	*P*-value	**AOR(95% CI)	*P*-value
Ever use of contraceptive	Yes	24 (48.0)	Ref[a]			
	No	14 (28.0)	0.01 (0.3,1.2)	0.164	0.62 (0.28,1.40)	0.251
Age at first sexual intercourse	< 15	3 (6.0)	Ref[a]			
	15–17	10 (20.0)	1.39 (0.35,5.53)	0.637	0.30 (0.03,2.62)	0.275
	> = 18	25 (50.0)	0.82 (0.23,2.9)	0.753	0.13 (0.01,1.04)	0.054
More than one lifetime partnership	Yes	25 (50.0)	Ref[a]			
	No	13 (26.0)	0.65 (0.32,1.31)	0.229	0.79 (0.34,1.86)	0.591
Condom use during sexual intercourse	Yes	14 (28.0)	Ref[a]			
	No	24 (48.0)	0.53 (0.3,0.9)	0.076	0.66 (0.27,1.66)	0.38
History of STD	Yes	6 (12.0)	Ref[a]			
	No	32 (64.0)	1.24 (0.5,3.1)	0.641	2.62 (0.7,9.8)	0.151
Cigarette smoking	Yes	2 (4.0)	Ref[a]			
	No	36 (72.0)	0.53 (0.1,2.6)	0.435	0.86 (0.13,5.6)	0.87
Family history of cervical cancer	Yes	4 (8.0)	Ref[a]			
	No	34 (68.0)	0.01 (0.2,1.9)	0.402	1.24 (0.3,5.)	0.76
Alcohol consumption	Usually	3 (6.0)	Ref[a]			
	Occasionally	16 (32.0)	1.32 (0.4,4.9)	0.68	1.33 (0.27,6.2)	0.72
	Never	19 (38.0)	0.75 (0.2,2.7)	0.67	0.8 (0.16,4.0)	0.79
HIV serostatus	Negative	25 (50.0)	Ref[a]			
	Positive	3 (6.0)	2.67 (0.7,10.3)	0.156	5.73 (1.06,30.9)	0.042[b]

*COR-Crude Odds Ratio, **AOR-Adjusted Odds Ratio, [a]Reference, [b]There is a statistically significant association

5.4.3 Abnormal cervical cytology

Overall, Pap smear abnormalities were observed in13.1% (48/366) of the study subjects. Among the abnormalities,3 (6.3%), 39 (81.3%), and 6 (12.5%) were ASCUS, LSIL, and HSIL respectively (Fig. 2). Among the abnormal cytology categories, LSIL abnormality showed the highest frequency. Low-grade squamous intraepithelial lesion (LSIL) and high-grade intraepithelial lesion (HSIL) rates in the 31–60 age category were33 (84.62%) and 6 (66.67%), respectively, higher compared to the other age categories (Table 4). The association between age category and abnormal cytology was assessed by Fisher's exact test and found not to be statistically significant (P-value = 0.180).

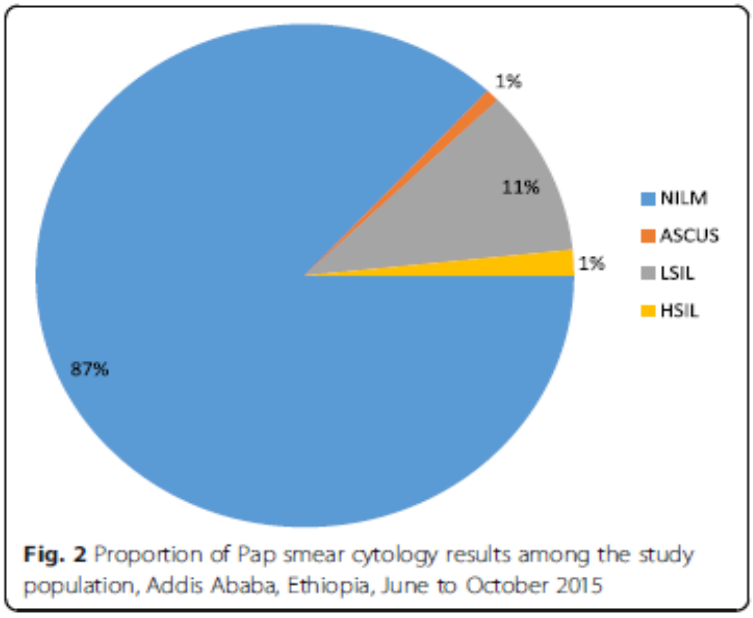

Fig. 2 Proportion of Pap smear cytology results among the study population, Addis Ababa, Ethiopia, June to October 2015

Table 4 Frequency of abnormal Pap smear cytology by age category, Addis Ababa, Ethiopia, June to October 2015

Abnormal Pap smear cytology	Age Categories (year)			*P*-value	Total
	18–30	31–60	> 60		
	No (%)	No (%)	No (%)		
ASCUS	0 (0.00)	3 (7.5)	0 (0.00)		3 (6.25)
LSIL	4 (10.26)	33 (84.62)	2 (5.13)	0.180	39 (81.3)
HSIL	0 (0.00)	4 (66.67)	2 (33.33)		6 (12.5)
Total	4 (8.33)	40 (83.33)	4 (8.33)		48 (100.0)

In addition, a significant association with any of the risk factor variables was not observed for LSIL abnormalities according to the Chi-square test. In contrast, HSIL abnormal cytology was significantly associated with age, age at first marriage and educational status, with P-values of 0.003, 0.004 and 0.014, respectively (Table 5).

Table 5 Association of HSIL abnormal cytology with "age, age at first marriage and educational status", Chi-square analysis, Addis Ababa, Ethiopia, June to October 2015

Variable		Frequency No (%)	Chi-square	*P*-Value
Age	18-30	0 (0)	11.84	0.003
	31-60	4 (66.67)		
	>60	2 (33.33)		
Age at first marriage	<15	1 (16.67)	10.99	0.004
	15-17	3 (50)		
	>=18	2 (33.33)		
Educational status	Illiterate	3 (50)	10.66	0.014
	Elementary	0 (0)		
	High School	1 (16.67)		
	Diploma/Degree and above	2 (33.33)		

Use of any type of contraceptive, age at first sexual intercourse, more than one lifetime sexual partner, frequency of condom use, frequency of cigarette smoking, history of STD and alcohol consumption were not significantly associated with abnormal Pap cytology (P-value > 0.05). HR HPV genotypes were compared with cytological abnormalities, and the results are summarized in Table 6. The overall HR HPV genotype frequency among the total normal cytology results was 40/318(12.6%). As shown in Table 6, 40 (80%) of HR HPV positive individuals had normal cytology (NILM); 5(10%), 4 (8%), and 1 (2%) had LSIL, HSIL, and ASCUS, respectively. Among the total number of HRHPV-positive individuals, HR HPV 16 was found in two of the cases of HSIL abnormality, and the remaining two were caused by "other HR HPV" genotypes.HR HPV 18 was only found in NILM, but HR HPV 16 was identified both in NILM and HSIL. Nonetheless, "other HR HPV" genotypes were found across all stages (Table 6).

Table 6 HR HPV genotypes compared to Pap smear cytology findings, Addis Ababa, Ethiopia, June to October 2015

HR HPV Genotypes	NILM	ASCUS	LSIL	HSIL
HR HPV 16	6 (12%)	0 (0%)	0 (0%)	2 (4%)
HR HPV 18	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Other HR HPV	30 (60%)	1 (2%)	5 (10%)	2 (4%)
HR HPV 16 and other HR HPV	2 (4%)	0 (0%)	0 (0%)	0 (0%)
HR HPV 18 and other HR HPV	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Total	40 (100%)	1 (100%)	5 (100%)	4 (100%)

5.4.4 Percent agreement between HR HPV DNA PCR and conventional pap smear cytology

Agreement between HR HPV DNA PCR and conventional Pap smear cervical cancer screening methods was analyzed using positive, negative, and overall percentage agreement as well as the Kappa statistics. The positive and negative percentage agreement was found to be 87.7 and 22.4% respectively. However, the overall percentage agreement was 79.0%, and the Kappa value was 0.12 (95% CI (0.00–0.24), P-value =0.01). The overall percentage agreement findings reveal significant agreement between HR HPV DNA PCR and conventional Pap smear cytology screening methods ($P < 0.05$).

5.5 Discussion

This study mainly aimed to assess the burden of HR HPV and cervical cytology abnormalities, along with potentially associated sociodemographic, sexual behavior, and reproductive health variables, in three Obstetrics and Gynecology and reproductive health clinics in Addis Ababa, Ethiopia. In this study, the overall HR HPV burden was 13.7%. “Other HR HPV” genotypes (31, 33, 35,39, 45, 51, 52, 56, 58, 59, 66, or 68 types) were the most frequent (76%) genotypes identified in this study, followed by HR HPV 16 (16%). The overall prevalence of abnormal cytology was also 13.1%. Approximately three-quarters (72%) of the HR HPV-infected women were in the age range of 31 to 60 years and this was significantly associated with abnormal cytology. HR HPV was found in 12.6% of normal cytology reports. Moreover, geographical residence, occupation, and HIV serostatus were significantly associated with HR HPV infection.

In this study, the overall HR HPV burden was 13.7%, a finding that was consistent with previous studies reported from different parts of Ethiopia [14, 15], at 13.2 and 15.8%, respectively. In contrast, our finding was much lower than those in two other studies from Ethiopia [16, 17]. This difference might be because the participants in the first study [16] were women with cervical complaints and all samples were cases of cervical dysplasia, which may result in higher values. In our study, however, cytological samples were obtained from women who did not necessarily have cervical dysplasia or gynaecological complaints. Similarly, the difference from the other report [17] may be due to the study site chosen, as that study was conducted in the only

specialized cancer center in Ethiopia, which would increase the probability of observing a large number of positive HR HPV cases.

In addition, approximately 34% of those study participants were HIV positive, which may also have contributed to the higher rate of HR HPV [12]. Our finding was lower than the estimated prevalence rate reported for all HPV genotypes (high-risk and low-risk types) from sub-Saharan African countries (21.8%) [11] and Nigeria (21.6%) [12].

To date, studies conducted in Ethiopia [14, 16] have reported that HR HPV 16 is the predominant HrHPV genotype. In contrast, the most frequent genotypes identified in the present study were “other HR HPV” genotypes (31, 33,35, 39, 45, 51, 52, 56, 58, 59, 66, or 68 types), contributing 76%, followed by HR HPV 16 (16%). Our finding is comparable with that in a worldwide meta-analysis review [10], which reported that the predominant genotype in Eastern Africa was HR HPV 52, followed by HPV 16. Another study [18] found that HPV-positive women in sub-Saharan Africa were less likely to be infected by HPV 16 than were women in Europe. Similarly, another study [19] examining paraffin-embedded cervical tissues reported that HPV 52 (25.5%) and 58(22%) were the most frequent genotypes. This difference in genotype frequency in various studies might be due to geographic variation and host immunogenetic factors. Regardless, HPV 16 appears to be less influenced by immune status than other HPV genotypes. This fact, coupled with impairment in cellular immunity, may contribute to the presence of HPV genotypes other than HPV 16 in some populations [19].

Multiple HR HPV type infections were found in 7.9% of HR HPV-positive individuals in a study by Mohammed et al. in Northeastern Nigeria [20], which is comparable to the findings of the present study (6%). In contrast, the17.5% of multiple infections in a study conducted on Ethiopian and Sudanese women [19] was relatively higher than that in the present study. This may be due to the nature of the samples processed in that study [19], which included tissue blocks with cervical intraepithelial neoplasia or carcinoma, and the possibility of infection by more than one type of HR HPV may increase in such cases [16].

An age-specific HPV infection study in South Africa [13] reported that the highest frequency (74.6%) of infections was found in women older than 25 years. Similarly, another study from Addis Ababa, Ethiopia, reported that 50.6% of HR HPV-infected women were in the age range of 30–50

years [17]. These studies are consistent with our finding that 72% of the HR HPV-infected women were 31–60 years of age. However, the significant association between age group in the bivariate analysis (P <0.05) was not significant in the multivariate analysis. This is similar to the results of the study conducted in Gurage Zone, Ethiopia [14]. In contrast, a study by Andall B in Trinidad (33) showed that the highest (63%) prevalence of HPV infection was observed among women aged < 30 years (P < 0.0001), with a peak in the age range of 21 to 25 years. This might be due to the detection of low-risk HPV in addition to HR HPV.

In this study, residence, occupation, and HIV serostatus were significantly associated with HR HPV infection in multivariate analysis. This finding was comparable with a study [24] reporting that occupation and residence are significantly associated with HPV infection. Nonetheless, the study by Muluken et al. in TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia [17], reported that HIV and residence were not significantly associated with HR HPV prevalence. This might be due to differences in sampling, type of participants, and data collection methods.

In our study, use of any type of contraceptive, age at first sexual intercourse, and more than one lifetime sexual partnership were not associated with HR HPV infection. This outcome is comparable to the findings of Mega AC et al. in rural Nigeria [21].

The overall abnormal cytology burden in the present study was 13.1%, which was lower than that in a similar study from Ethiopia [17, 22] and another from South Africa [13]. This difference might be due to the presence of a large number of HIV-infected individuals, who are not easily able to resolve infection and experience progression to the development of precancerous to cancerous lesions [23]. In our bivariate analysis, age at first marriage and educational level were significantly associated with HSIL Pap smear abnormality (p-value 0.004 and 0.014), consistent with a study reported by Abel et al. [22].

Furthermore, our study presents high-risk HPV genotypes with cervical cytology findings. HR HPV 16 was found in 50% of HSIL reports, and “other HR HPV genotypes” were the most frequent finding for LSIL. Similarly, for women who had normal cervical cytology results, the most frequent genotypes were “other HR HPV” genotypes. According to the meta-analysis by Gary C. et al. [18], the most common HR HPV type in HSIL among women with and without cervical neoplastic diseases was HR HPV 16, which was consistent with our findings. In contrast to the same study

[18], which reported HR HPV 16 as the predominant genotype inLSIL and NILM, all the LSIL and NILM results in our study were attributed to “other HR HPV” genotypes. Moreover, “other HR HPV” genotypes were observed across all grade levels of cytological findings.

As reported in various studies, HPV-positive women in sub-Saharan Africa are less likely to be infected with HR HPV 16 than are their counterparts in Europe ([18–20]. Interestingly, the present study also revealed that 12.6%of women with NILM were positive for any type of HR HPV infection. This is comparable to a study [25] from West Africa reporting that 13% of women with normal cytology results were positive for HR HPV. In such situations, the women may continue to have an increased risk of HSIL during the interval between the first and next screening [26].

5.6 Conclusions

The prevalence rates of HR HPV infection and cervical cytology abnormalities presented in this study are consistent with the few previous local studies and reviews in Ethiopia but somehow lower than the estimated prevalence for sub-Saharan Africa. Unlike previous studies, “other high risk HPV” genotypes contributed considerably to the overall HR HPV burden. Multiple-type infections were found in sexually active women. The highest frequency of HR HPV positivity was in women without cervical cytology abnormalities. Hence, the interval between the primary and secondary HPV screening for HR HPV positives and negatives needs to be defined separately.

The performance of the Abbott Real-Time HR HPV DNA PCR and Pap smear cytology screening methods may need to be further evaluated against histologically confirmed results. In addition, the screening program for early-age sexually active women should be further promoted in various health settings. The FMOHshould also further consider the possibility of introducing vaccines targeting other oncogenic HPV types in addition to genotypes 16 and 18. A large-scale community-based cohort study shall also be designed and implemented to determine the national burden and the molecular epidemiology of persistent HR HPV types and cervical cytology abnormalities which will help to recommend the ideal screening algorithm considering the local context. This will significantly contribute to the national preventive public health strategies against cervical cancer.

5.7 Abbreviations

ASCUS: Atypical squamous cells of undetermined significance
HIV: Human immunodeficiency virus;
HRHPV: High-risk human papillomavirus;
HSIL: High grade squamous intraepithelial lesion;
LSIL: Low-grade squamous intraepithelial lesion;
NILM: Negative for intra-epithelial lesions and malignancy;
PCR: Polymerase chain reaction;
STD: Sexually transmitted disease

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5.9 Association Author contributions

Conceived and designed the experiments: KE, IA, KD, MN, DS, ZL, and TH. Performed the experiments and investigations: KE, MN, and DS. Analyzed and reviewed the data: KE, THK, and KD. Wrote the paper: KE, KD, and RT. Reviewed and edited the manuscript draft: IA, MN, DS, ZL, TH, THK, EL, and RT. All authors read and approved the final manuscript.

5.10 Funding

Not applicable

5.11 Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

5.12 Ethics approval and consent to participate

The study proposal was reviewed and approved by the Departmental Research and Ethics Review Committee (DRERC) of the Medical Laboratory Sciences, School of Allied Health Sciences, College of Health Sciences; Addis Ababa University (Letter Ref Number: MLS/388/15) on 08/04/2015. Formal individual written consent was collected from each participant. Informed consent was obtained by interpretation in the participant's local dialect. The privacy and confidentiality of each individual participant was ensured. An appropriate coding system was used rather than any personal identifiers. All client results were reported to their clinicians in the standard result format with a specified turnaround time and utilized for clinician judgment in addition to being used for these research purposes.

5.13 Consent for publication

Not applicable

5.14 Competing interests

The authors declare that they have no competing interests.

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CHAPTER 6: GENERAL DISCUSSION AND RECOMMENDATION

6.1 General discussion

The FMOH has set a target to screen at least 80 % of the appropriate target population as well as treat the pre-invasive cervical cancer cases by 2016 - 2020 (2). This target is very far from reality. Cervical cancer screening coverage in Ethiopia is very low (3,4). Only 1% of the eligible 20 million Ethiopian women have been screened thus far (3). The main reasons for the low cervical cancer screening total are mainly due to the poor education of the women, low household income status, inaccecibility and readiliess of CC screening health facilities as well as lack of knowledge and awareness. Health care education, behavioral change communication and changing the lifestyle of women could improve the screening coverage significantly.

Understing Ethiopian women's health belief motivational factors remain important as they influence screening coverage. A detailed study on perceived vulnerability, a belief of consequence (perceived severity), positive benefits, barriers to action, and exposure to factors that prompt action (cues to action) is required. In Ethiopia, women who visit clinics for cervical cancer screening are unsure of any available screening and treatment. They come to the clinics when they are in severe pain and suffering, yet with no hope.

This implies the need for awareness program and close monitoring and evaluation of screening services to increase the coverage and sustainability of the cervical cancer prevention program in Ethiopia. The collaborative effort among different stakeholders through engagement in advocacy, social mobilization and information dissemination is crucial.

Upon investigating and evaluating the cervical cancer screening uptake using the health belief model, it was found that only 6.8% women had visited a health facility previously for cervical cancer screening. There was a significant association between educational background and the number of cervical cancer health facility visits (CCHF). Most women confirmed that they never visited Health Facility (HF) for cervical cancer screening mainly due to misperception, limited knowledge on risk factors, not knowing which HF provides the service, long waiting times, shortage of finance, etc. The main reason women didn't visit HF was due to the practice of daily vaginal douching which they believe prevents cervical cancer as well as associated sexually transmitted diseases. However, several other studies indicated that douching causes physical

epithelium abrasions and/or disrupt the normal protective vaginal microenvironment, thus facilitating HPV acquisition (5). Furthermore, there is no one-stop " screen and treat" approach in every health facility. Most women visit clinics at the late stage of disease as to avoid repeated clinic visits and follow up visits.

The authors applied the health beliefs model to understand the root cause of Ethiopian women's low participation in the cervical cancer screening program. The authors concluded that motivational factors in the health-promoting behavior of low screening uptake require more than one theory - there is no single theory suitable for all cases. Hence, further studies are required to explore other possible factors contributing to the low screening uptake.

Ethiopia has been using the "screen-to-treat" approach for VIA and cryotherapy since 2019. Even though VIA is an inexpensive, simple, quick, free of charge, and single-visit approach screening method, it enhances challenges such as diagnostic sensitivity, identifying precancerous lesions accurately and precisely; reproducible (inter-operator variability); quality assurance; supplies, equipment maintenance; level of training and skill are questionable. The positive predictive value of VIA may vary with age, parity, and underlying cervical disease burdens (7-12). Thus, it may be helpful to study in detail the VIA program in Ethiopia to avoid underlying cervical cancer due to program failures.

There is a serious cervical cancer screening coverage (<1%) in Ethiopia and to mitigate the high morbidity/mortality, screening of eligible women is essential. The routine and standard method of screening in Ethiopia is VIA. HPV testing appears feasible as a primary screening even in LMICs because of the poor sensitivity of VIA. Despite all drawbacks of VIA screening and with no HPV test available, VIA has played a role, compared to none screening program. The government should re-evaluate VIA against avaible screniing model and design a model that reduces follow-up visits by availing a one-stop first visit "scrren and treat" approach customized for the Ethiopian health care system.

Nurse assisted self-sampling could be used as an alternative sample collection method for HPV primary screening testing in Ethiopia for women living in urban or rural areas. However, standard self-sampling collection device in place, the quality of the samples requires improvement and a proper method of sampling and standard collection protocols must be relayed to the relevant members of the population.

HPV self-sampling collection materials are not commercially available in Ethiopia, is only used for research purposes. HPV detection using NASS Cytobrush/plastic spatula ThinPrep PreservCyt vial may be used as a platform for similar studies in the future. Single NASS device, either cytobrush, spatula, or both, should be evaluated to conclude that whether single or double collection tools better than others. Thus, a randomized trial may consider in the future.

HPV testing is a valuable test to improve the screening uptake and follow-up of women in a low-resource setting. Although our study revealed that HPV 51, 31, 16, 45, 52, and HPV 58 was predominantly identified, a large-scale study is required to study the prevalent genotypes in women of Ethiopia in order to select an appropriate national HPV vaccine program.

Even if HPV testing is resource-dependent, HPV testing is recommended above VIA. HPV testing should be provided where it is affordable, implementable and sustainable. This recommendation applies to women regardless of their HIV status. Ethiopia should design a longitudinal study of HPV testing to determine the feasibility, cost-effectiveness, cost-benefit analysis and cost-utility analysis (i.e quality-adjusted life year, QALY) of women's health.

The feasibility and acceptability of NASS over CT were relatively higher, was comparable with other studies (1). NASS is a choice of screening because of its high acceptance, ease to use, insert and collect, user-friendly, private nature, and easy to follow instructions for the hard-to-reach and unscreened population (2,3). A clear conclusion from our study regarding the use of NASS in the Ethiopian context may not be possible to generalize and requires further studies. However, recent study in Ethiopia indicated that self-collection HPV testing at the local health facility may significantly improve the uptake of cervical cancer screening in Ethiopia (23). Further studies from high-income countries with existing heterogeneity suggest that HPV self-sampling can increase cervical cancer screening uptake compared with the current standard of care and linkage to clinical assessment or treatment (3).

The contribution of HPV NASS in the fight against cervical cancer may be crucial to increase HPV detection, cervical cancer screening management as well as increase the screening coverage. Although a moderate kappa agreement was found between the two sample methods in our study, NASS could still be helpful in the fight against cervical cancer; incidence rate and mortality of invasive cervical cancer; increase the chance of early HRHPV detection; determine the

genotyping distribution, and increase the uptake of cervical cancer screening and prevention (14-16).

A systematic review and meta-analysis of 250 research articles related to self-sampling HPV testing performed in African studies were analyzed by comprehensive electronic bibliographic databases of Pubmed, Cochrane, WHO Global health library as well as Popline. This systematic review explored the self-sampling HPV detection rate and its acceptability compared to that of doctor collected. In general, women indicated that self-collected sampling method was the preferred method of sample collection (86.3%) and easy to obtain (77.8%). The acceptability of self-collected HPV testing could be an alternative sampling method that provides comparable HPV detection rates to that of clinician sampling methods and may therefore increase the uptake of screening services. Introducing standardized HPV self-sampling and a diagnostic assay across African countries may be very useful for strengthening the cervical cancer screening strategy (17-19).

An institutional-based cross-sectional study was conducted with 366 women that aimed to compare the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection with cervical cytology abnormalities at selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia. Accordingly, the overall HR HPV burden and cytology abnormality rate was found to be 13.7 and 13.1%, respectively. Most HR HPV types were other than types 16 and 18. The HR HPV infection rate compared significantly with the geographical area of residence of the patient, her occupation as well as HIV serostatus. Other associated factors included the age of the patient, her age at first marriage as well as her education level. The overall agreement between HPV real-time PCR results as well as Pap cytology screening result was 78.96% (Kappa value of 0.12).

Non-16/18 HR HPV genotypes represented the largest proportion of HR HPV infections in this study. Women with normal cervical cytology had the highest frequency of HR HPV infection. This may be due to the high sensitivity rate of the assay utilized for this study. The burden of HR HPV infection and cytology abnormalities presented in this study are consistent with the few previous local studies and reviews done in Ethiopia, yet somehow lower than the estimated prevalence for sub-Saharan Africa.

The performance of the Abbott Real-Time HR HPV and Pap smear cytology screening methods require further evaluation against histologically confirmed results. A large-scale community-based cohort study is recommended in order to determine the national burden of HPV and cervical cytology abnormalities. The outcome of this large study must be designed to recommend the ideal screening algorithm in the local context and therefore will significantly contribute to the national preventive public health care strategies in prevention of cervical cancer.

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Appropriate awareness and education for all women while visiting the health facility will have a significant positive impact on the outcome of the low national screening uptake. Timeous HPV testing and confirmation of the existing circulating HPV genotypes in the country is necessary. This information will help to determine the vaccine required as a national vaccination roll-out. Our study revealed that HR HPV prevalence in the general women population is like other African studies with a wide range of detection rate variation.

6.2 Conclusion and general reflection

Self-sampling platform with nurse-assisted self–sampling (NASS) is easy to use, acceptable, and a feasible alternative collection method in Ethiopia. Women, particularly those in the rural areas, should receive appropriate self-sampling instructions on how to collect, transfer the specimen, pack and transport the samples.

The self-sampling method has the potential to improve the uptake of cervical cancer screening and testing in Ethiopia. However, standard devices for self-collection are not yet available at local markets. Furthermore, evidence from comparable studies, doctors- vs self-sampling, indicates that more training is required to standardized collection instructions. Successful implementation of self-sampling program requires further studies through evaluating various self collection samplers, collecting techiques, testing, resources, laboratory infrastructure as well as equipment. Financial support for these programs requires buy-in from the government and corporations. The overall investment in cervical cancer screening through self-sampling will create a robust laboratory network for HPV testing and will decrease the incidence of cervical cancer.

The introduction of HPV test self-sampling may increase uptake of screening and further determine HPV circulation genotype in the country. Potential and timely identification of high-risk

HPV types support early case treatment and management. Our results identified mixed types of high-risk HPV (16, 18, 31, 45, 51, 58, 59) and low-risk HPV (6, 53, 67) among the populations in this study.

Currently, visual inspection with acetic acid (VIA) is the scandard screening method used in Ethiopia, although its sensitivity and specificity are lower compared to HPV testing. The performance of VIA has faced the problem of many false-positive cases, leading to a low positive predictive value, and requires many confirmatory colposcopies under gynecological review. Thus, the introduction of HPV tests at the health facilities is essential. Additionally, the use of radio, TV, and social media can be useful in educating the population and therefore increasing awareness of the importance of cervical cancer screening and the prevention thereof.

In our study, we assessed the impact of health beliefs and risk factors on cervical cancer screening uptake. Even though there are different approaches to evaluate health beliefs, we used the health belief model (HBM) to reveal the health behavior of women concerning perceived susceptibility, perceived severity, perceived benefit, perceived barriers, and cues for action.

Accordingly, most women confirmed that they never attended health clinics for cervical cancer screening mainly due to misperception, limited knowledge on risk factors, not knowing health facilities that offer such service, long waiting time, shortage of finances, etc. Women indicated that the main reason they did not visit the health facility for cervical cancer screening was they believed regular douching would prevent cervical cancer and associated sexually transmitted diseases. Women were not offered cervical cancer screening due to the absence of a one-stop “screen and treat” approach at most health facilities. Sadly, most women visited clinics at the late stage of disease due to perceived barrier, lack of income, clinics not found everywhere, avoiding repeated clinic visits and case follow-up, lack of awareness, etc.

The number of women who underwent screening tests was less than expected. One-third of women recognized screening could help for the early detection of cervical cancer. The main reason for screening was women`s level of education and had a history of cervical cancer in their families. This information could help with designing educational materials and the utilization of community volunteers to assist in educating women in their community. Information that is designed to encourage women to obtain regular cervical cancer screening service as well as

communications through various media outlets has the potential to reach 70% coverage of 35-45 years old women by 2030, one of the WHO targets towards cervical cancer elimination on a public health level.

Fewer numbers of women understood the risk factors that contribute to cervical cancer, such as HPV infection, early sexual debut, cigarette smoking, and multiple sex partners. Our study showed that the main reasons why women were not attending health facilities for cervical cancer screening:

1) A high degree of inconvenience, expense, absence ofone-stop “screen and treat” approach, perceived side effects, discomfort, pain as well as emotional upset due to method of screening and sample collection method.

2) Women are reluctant to receive cervical related medical examination and recommendations on health care interventions from male doctors.

3) Women are not motivated to have some form of cervical cancer screening intervention due to fear of screening outcomes.

4) Wmen believe that cervical cancer is not a severe disease and they don’t understand the deleterious consequences of cervical cancer.

5) Women believe that regular douching practices diminishes the chances of developing cervical cancer.

Designing culturally relevant cervical cancer screening interventions through scientific studies of women’s perceptions is critical. Therefore, addressing issues of low uptake of CC screening might require more than one theory, since there may be no single theory that is suitable for all cases. Hence, more studies are required to explore all other possible factors contributing to low uptake of screening and fewer clinic visits for cervical cancer.

Our systematic review study revealed that there is no significant difference in the detection and acceptability of self-collected HPV testing versus specimens collected by the doctors. Women were receptive to self-collected methods and indicated a preference for this method. However, the

detection rate could vary between study subjects due to the use of different HPV assay, the sample collection procedure, collection devices as well as population variability.

Introducing large scale standardized self-sampling techniques and diagnostic assays in Africa is of paramount importance and very useful for future cervical cancer screening strategies. A systematic review on African based self-sampling studies concluded that there may be several concerns regarding full introduction of SS collection method into the health care system. Most African countries still use Pap smear and VIA for cervical cancer screening programs due to cost and infrastructure. However, these screening methods require skilled and trained nurses or doctors and cytotechnologists/ pathologists for the collection of the specimen as well as the diagnosis of the tests. Introducing HPV test and self-sampling will require training for women and health providers; avail infrastructure, equipment, reagents, electrical power as well as a skilled workforce.

Lastly, we assessed the burden and genotype distribution of high-risk human papillomavirus (HR HPV) infection and cervical cytology abnormalities. We saw a moderate statistical agreement between the HPV real-time PCR and Pap cytology screening methods. The abnormal cytology results found in cervical lesions in order of prevalence are low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells of undetermined significance (ASCUS) as well as high-grade squamous intraepithelial lesions (HSIL). HPV infection is associated with geographical residence, education level, awareness, occupation, and HIV serostatus. In general, non-16/18 HR HPV genotypes represented the largest proportion of HR HPV infections in our study. The highest frequency of HR HPV positivity was in women with normal cervical cytology.

A large-scale community-based cohort study is required to determine the national burden of HPV and cervical cytology abnormality rates to recommend the ideal screening algorithm in the local context. These could significantly contribute to the national preventive public health strategies against cervical cancer.

6.3 Recommendations

Ethiopia implemented the NCCP in 2015, and VIA and cryotherapy have been used as standard screening and treatment care to improve access to cervical cancer prevention despite of all drawbacks. Cervical cancer screening using HPV testing, is the best alternatives to VIA or cytology-based screening with accuracy to detect precancerous lesions at a rate better than former.

However, several concerns and questions still require answers:

1) Does all VIA screening health facilities provide the service as expected?
2) Does the service provide one-stop “screen-and-treat” approach on a regular and consistent basis?
3) Are women getting screening services as planned?
4) Are the minimum resources available and show readliness to provide effective and sustainable services?
5) Are all options for cervical cancer treatment available?
6) Does the ministry of health expand the cervical cancer screening program to the rural areas as well?
7) Are health providers gaining and maintaining expected knowledge, skills and qualifications?
8) Are screening services accessible to all women in the target groups particulary the poorest, most vulnerable and hardest to reach?

Addressing these questions will require commitment, support, and involvement from government agencies, policymakers, communities, schools, religious sectors, non-governmental organizations, private sectors, broadcasting services, health professional’s workforce as well as family members. The introduction of the HPV test as a primary screening test following international testing algorithms demands a significant level of investment. Planning and arrangement with Ethiopian FMOH to address the challenges existed in the current screening program will be crucial.

It is true that without HPV testing in combination with one-stop “screen-and-treat” approach at health care facilities, VIA will have a role in cervical cancer screening, compared to no screening. Reduced cervical cancer mortality is possible when VIA or cytology screening co-exists followed by timeous and appropriate treatment managmenet of the relevant patients. Benefits outweigh the harms, but screening uptake and accurate diagnosis may gain by far when HPV test is introduced instead of VIA. In 2021, Ethiopia has started the HPV DNA test as a pilot project; however, the program faced several challenges like a shortage of supplies and reagents. The FMOH should direct and gain political commitment to operationalize HPV tests together with cryotherapy throughout the country to reduces the number of repeat visits and loss to follow-up.

Even if HPV testing is resource-dependent, the authors support the use of HPV tests over the VIA, where it is available, affordable, implementable and sustainable in the future. This recommendation applies to women regardless of HIV status and any other sexually transmitted disease.

Ethiopia needs to design longitudinal and cohort studies on HPV testing with all other alternatives to determine the feasibility, cost-effectiveness analysis, cost-benefit analysis and cost-utility analysis (i.e quality-adjusted life year (QALY).

The main challenges with the Pap test are keeping quality assurance programs intact and maintenance of certification for skilled personnel at various levels during the preparation, staining and screening of the smear. Initiating reliable and accurate quality control programs that are regularly monitored by external national laboratories is required. Additionally, the proficiency test (PT) program can design a platform where all participant laboratories are able to improve their quality issues.

In general, pathology tests for cervical cancer screening, including PAP tests, have not gained attention due to other priorities diseases, such as malaria, TB, and HIV. Pap smear, Liquid-based cytology (LBC) and HPV testing is mainly offered by the few private laboratories in Ethiopia and is found to be an expensive alternate to VIA. The shortage of technologists and pathologists to microscopically screen these smears reiterates the massive challenge should Pap smear/LBC screening be implemented nationally. Resource constraints, limited number of histotechnologists

and pathologists as well as infrastructure remain a major challenge. The incidence of cancers is showing a drastic increase at an alarming rate.

LBC screening has several advantages over the VIA or Pap test. However, due to its expensive nature, it may not be feasible at every health facility. The authors look forward to the government formulating a way to increase the availability of HPV testing at least at regional and university hospitals, where samples may be refered via a sample referral linkage system. The government could also design an efficient self-sampling and laboratory business model whereby sampling devices are distributed to health facilities. This approach could have dual benefits in terms of determining HPV genotypes prevalances throughout the country using data generated through such a model. The turnaround time (TAT) should be defined and communicated to patients. Patients must be informed on the date of result return and a follow up SMS or other electronic means will drastically reduce loss to follow up and dropout rate.

Self-sampling HPV test is promising and although comparable results to that of doctor collected samples were found in our study, we recommend studying its effectiveness and feasibility with expanded population-based studies before deploying HPV testing assays and machines throughout the country. Fragmented and unstandardidized HPV genotyping studies in different geographical areas will have a negative impact on policy decisions. Therefore, for the success of the national CC prevention and control program, nationwide pathology laboratories should be epnaned and integrated into existing diagnostic laboratory systems. Due to the high sensitivity nature of the HPV test, which may lead to overtreatment, the government should develop HPV test algorism and builf robust cytology programs for answering the issues of quality control, training, and waiting time.

Treatment for precancerous lesions involves cryotherapy and LEEP equipment and supplies. It is recommended that the number of screening centers be increased, procurememt and placement of the required equipment using public-private partnership platforms as well as mobile clinics where women with high risk HPV results and/or cytologically diagnosed abnormal lesions get immediate treatment would be crucial for a positive outcome on cervical cancer screening and management.

The pilot HPV vaccination project launched in Ethiopia in 2015 targeted adolescent girls in the 9 – 13 years' age group in Oromia and Tigray regions. Further, in 2018 Ethiopia launched HPV vaccination for schoolgirls aged 14 years as a primary prevention strategy and it was successful. The main reason for the shift of age in the cohort was due to a global shortage of HPV vaccine supplies. This shortage forced the government to continue vaccinating only 14-year-old girls every year. The best way of avoiding high treatment costs while saving the lives of women is the implementation of HPV vaccination nationally. Therefore, these remain serious challenges that Ethiopia and other least developed countries have faced challenges in terms of securing, buying and distributing HPV vaccines after GAVI graduation and international financial support were discontinued.

According to the GAVI vaccine alliance eligibility graduation policy, the least developed countries like Ethiopia would not be eligible when the Gross National Income (GNI) is greater than $1,000. This means the country must arrange to self-finance. Questions to be answered - when will Ethiopia have access to the graduated GAVI Vaccine Alliance support? Will Ethiopia achieve the HPV vaccination coverage target 90% in 2030?

Previous researches, including ours, have demonstrated that HPV genotype distribution in Ethiopia is very diversified. GARDASIL 9 – valent vaccine could be the best available option for vaccinations that protect girls from the risk of cervical cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.

To redirect from where we are now, expressions of women`s lower screening coverage, biological science and vaccination are not enough. Social, psychological, and cultural health behavioral change studies are required now on a large scale in Ethiopia. Most eligible women are not visiting health facility regularly because of misperception or altered health beliefs about cervical cancer. Detailed studies on women`s health beliefs and perceptions might assist to convert fear of developing cervical carcinoma and the treatment thereof into an opportunity that leads to reduced late-stage cancer presentation, reduced treatment cost, less government investment as well as reduced family problems. Finally, improved quality of life of women will advance the frequency medical checkup, visit clinic for CC screening purpose, manage her own health, become productive and patcipate in economic growth. Utilizing the extended health belief model and self-

determination theory in future longitudinal studies could help the country to save the lives of millions of women.

6.4 What should be done? The way forward

To conclude this doctoral research project, the authors would like to recommend in specific ways on cervical cancer screening program in Ethiopia and beyond:

- Health professional guided or nurse assisted HPV self- sampling should be designed for the hardest to reach the population with proper sample collection instruction and standard devices.
- High quality and less expensive HPV self –sampling collection devices should be available for commercial use to the entire nation.
- HPV-Point of Care (POC) diagnostic test should be available for resource-limited countries to allow the one-stop “screen-and-treat” approach at a clinician’s office, an ambulance, the patient’s home, mobile clinics or in the hospital.
- Massive cervical cancer awareness programs, sexual reproductive educational programs, media campaigns (TV, Radio, electronic short message service (SMS), social media, etc.) outreaches in the form of organizing a great run, a celebration of World Cancer Day amongst others may be considered and thereby improve screening uptake and treatment.
- Longitudinal studies on the effect of health motivation, belief, external factors, barriers, perception, and self-efficacy using the health belief model and self-determination theory could determine the root cause for low women screening participation and intervention strategy.
- A national cancer standard electronic registry and management program should be available in such a way that all relevant information, based on the WHO international coding system, is captured and managed. Analyzed data on cancer cases can be utilized for monitoring and evaluation as well as for research and policy decision-making.
- Policy decision-making research should be conducted to determine the cervical cancer-screening interval and test algorithm on the bases of individual and co-testing with VIA, HPV, cytology, colposcopy, or a combination approach. Parallel studies are needed to define the appropriate age for cervical screening and intervals based on test method and average risk level.

- Unorganized, ineffective, and unstructured routine cervical cancer screening and treatment programs in Ethiopia should transform into electronic information management systems and be integrated with the current Hospital management information system (HMIS).
- Cervical cancer post-treatment surveillance on the recurrence of gynecologic cancer in women who have had completed the management of primary cancer therapy is crucial. However, its cost-effectiveness should be studied in small-scale pilot survey. The survey will help to determine post-treatment survival rate, women`s quality of life, risk factors as well as the success of treatment.
- Effective monitoring of a national cervical cancer prevention and control programs should be the backbone to advise on the delivery of expected services.
- University-level educational curriculum should be designed to permit laboratory technologists to qualify as cytotechnologists and histotechnologists at the master level to join the pathology workforce (which is very small in numbers). This could transform the current traditional sectioning-and-staining technology skill to higher competencies in various techniques, which include screening slides and interpreting results which brings a high positive impact on the diagnostic fields.
- Cervical cancer screening and treatment operational related research should be initiated through international and national partners to fill the gaps.
- Extensive health providers service training and qualification may be arranged at the national level, zonal and district level.
- One-to-ten functional relationship platform should be designed where a college female student engages on advicing ten community women on the current cervical cancer screening and treatment situation and ways to increase the update of screening and treatment.
- Sharing the success stories of cervical cancer surviors` through media outlets through motivational and inspirational TV or radio series, could influence and impact millions of women's lifes to change the perception of screening and treatment.

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ANNEX I: SCIENTIFIC OUTPUT

Publications in peer-reviewed scientific journals

Eshetu Lemma Haile, Cindy Simoens, Ina Benoy, Gurja Belay, Jean-Pierre Van geertruyden, Sharon A. Ransom, Ramokone Lisbeth Lebelo, Johannes Paul Bogers. HPV testing on vaginal/cervical nurse assisted self-samples versus clinician-taken specimens and the HPV prevalence, in Adama town, Ethiopia. Medicine (2019) 98:35 (e16970).

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ANNEX II: PROJECTS UNDERWAY –RESEARCH (PI)

1) Anti-breast and cervical cancer clinical studies: Phytochemistry screening and cytotoxicity studies for selected traditional medicinal plants. Eshetu L Haile
   Status: Proposal and grant writing, AC3T Study.
2) Covid-19 and pathology laboratory safety practice in Africa: online survey. Eshetu L Haile
   Status: submitted for publication, Funder: ASCP, USA
3) Assessment of Knowledge, Attitudes, and Practices (KAP) towards covid-19 in Ethiopia: online/phone call cross-sectional survey. Eshetu L Haile
   Status: Data analysis and manuscript writing, EPHI, Ethiopia
4) Determination of SARS-COV-2 (covid-19) antibody dynamics on Ethiopian patients: longitudinal sampling. Eshetu L Haile
   Status: Seeking international collaboration and fund