Medical Faculty
of the Martin Luther University Halle-Wittenberg

The need for optimizing cervical cancer screening in Ethiopia

Thesis to obtain the academic degree of
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Summary Report:

This dissertation reports the Ph.D. project comprised of five academic studies. Findings from the baseline studies reported that more than 80% of women diagnosed with cervical cancer in Ethiopia presented at the late stage without curative intervention options. Accordingly, due to late-stage and longer waiting times, only 13.5% of the patients received curative therapy. Given this concerning facts, we conducted the cluster-randomized population-based trial that enrolled 2356 women from 22 clusters into two arms to investigate the uptake of cervical cancer screening by comparing new strategy using self-sampled human papillomavirus testing and the standard care of screening in our case visual inspection with acetic acid. The objective of this dissertation, therefore, is to discuss the need for optimizing cervical cancer screening at a community level so that to reduce the burden of the disease, patients suffering, and improve their survival by instituting acceptable screening method.

Referat:

Diese Dissertation berichtet über das aus fünf akademischen Studien bestehende Ph.D.-Projekt. Die Ergebnisse der Basisstudien zeigten, dass mehr als 80 % der Frauen, bei denen in Äthiopien Gebärmutterhalskrebs diagnostiziert wurde, in einem späten Stadium ohne kurative Interventionsmöglichkeiten auftraten. Dementsprechend erhielten nur 13,5 % der Patientinnen aufgrund des späten Stadiums und der langen Wartezeiten eine kurative Therapie. In Anbetracht dieser besorgniserregenden Tatsachen führten wir die cluster-randomisierte bevölkerungsbasierte Studie durch, in die 2356 Frauen aus 22 Clustern in zwei Armen aufgenommen wurden, um die Inanspruchnahme des Gebärmutterhalskrebs-Screenings zu untersuchen, indem wir die neue Strategie mit dem Selbsttest auf humane Papillomaviren und die Standardversorgung des Screenings in unserem Fall die visuelle Inspektion mit Essigsäure verglichen. Ziel dieser Dissertation ist es daher, die Notwendigkeit einer Optimierung des Gebärmutterhalskrebs-Screenings auf Gemeindeebene zu erörtern, um die Belastung durch die Krankheit und das Leiden der Patientinnen zu verringern und ihr Überleben durch die Einführung einer akzeptablen Screening-Methode zu verbessern.

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Muluken Gizaw, Brhanu Teka, Friederike Ruddies, Konjit Kassahun, Dawit Worku, Alemayehu Worku, Andreas Wienke, Rafael Mikolajczyk, Ahmedin Jemal, Andreas M. Kaufmann, Tamrat Abebe, Adamu Addissie, and Eva Johanna Kantelhardt (2020): Reasons for not attending cervical cancer screening and associated factors in rural Ethiopia. *Cancer prevention research* (Philadelphia, Pa.) 13(7).

Friederike Ruddies, Muluken Gizaw, Brhanu Teka, Sarah Thies, Andreas Wienke, Andreas M. Kaufmann, Tamrat Abebe, Adamu Addissie, and Eva Johanna Kantelhardt (2020): Cervical cancer screening in rural Ethiopia: a cross-sectional knowledge, attitude, and practice study. *BMC Cancer* (2020) 20:563.

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Abbreviations and Acronyms:

CC	cervical cancer
CCPs	cervical cancer patients
CD4	cluster of differentiation 4
FIGO	The International Federation of Gynecology and Obstetrics
HDSS	health and demographic surveillance site
HIV	human immune-deficiency virus
HPV	human papilloma virus
IARC	International Agency for Research on Cancer
NCDs	non-communicable diseases
PhD	Doctor of Philosophy
UICC	Union for International Cancer Control
VIA	visual inspection with acetic acid
WHO	World Health Organization

Abkürzungen und Akronyme:

CC	Gebärmutterhalskrebs
CCPs	Gebärmutterhalskrebs-Patientinnen
CD4	Cluster der Differenzierung 4
FIGO	Die Internationale Föderation für Gynäkologie und Geburtshilfe
HDSS	Gesundheit und demografische Überwachung Website
HIV	Humanes Immundefizienz-Virus
HPV	Humanes Papillomavirus
IARC	Internationale Agentur für Krebsforschung
NCDs	nicht übertragbare Krankheiten
PhD	Doktor der Philosophie
UICC	Union für Internationale Krebsbekämpfung
VIA	Sichtprüfung mit Essigsäure
WHO	Weltgesundheitsorganisation

1. **Introduction and Objectives**

Chronic, non-communicable diseases (NCDs), including cancers, have emerged as a global epidemic in the 21st century, and are the leading cause of morbidity and mortality (Fitzmaurice et al.,2019). Cancer is the second leading cause of death globally. Amongst different types of cancers, the global burden of cervical cancer is still high, especially in low and middle-income countries. In 2018, 570,000 women developed cervical cancer, and it claimed 311,000 lives (Bray et al., 2018). Cervical cancer is the most commonly diagnosed cancer in the lowest income countries; it ranks as the fourth most commonly diagnosed and fourth leading cause of death globally. However, cervical cancer was the second most incident cancer in developing countries, including Ethiopia (Bray et al., 2018; Timotewos et al., 2018). Unlike other reproductive health cancers, cervical cancer can be prevented and even possibly cured if identified in its early stages. Therefore, public health interventions using primary and secondary prevention modalities such as screening are acknowledged as the most effective approach for cervical cancer control efforts (WHO, 2019; Jeronimo et al., 2017).

Human papilloma virus (HPV) is a necessary cause for cervical cancer development, with more than 14 high-risk types that are mainly responsible for cervical carcinogenesis (Walboomers et al., 1999; Burd, 2003). Cervical cancer is described as "a disease of poor", mainly because developed countries have managed to reduce the incidence of the disease considerably, by increased detection and effective treatment at the pre-invasive stage of the disease (Arbyn et al., 2019). In developing countries, including Ethiopia, women still present at the late-stage, which considerably compromises curative treatment (Feuchtner et al., 2019; Gizaw et al., 2017; Begoihn et al., 2019).

The World Health Organization (WHO) has now launched a global action initiative for cervical cancer elimination during the 21st century by scaling up vaccination, screening, and treatment coverage (Canfell, 2019). As an initial target, the WHO envisaged to reach a goal of 90% coverage of vaccination, 70% of eligible women to be screened by highly precise testing (HPV testing), and 70% of women diagnosed for cervical cancer to get appropriate treatment by 2030 (WHO, 2019).

For countries without long-established vaccination programs for cervical cancer prevention, intensifying the coverage of screening might be the only option to save the lives of many women who have passed the age of vaccination (Beddoe, 2019). As part of this effort, the Ethiopian government developed a cervical cancer prevention guideline and started a national cervical

cancer screening service at few hospitals in 2015. According to the guideline, the standard care for screening, as in many developing countries, is a "see and treat" approach using the visual inspection with acetic acid (VIA) (FMOH, 2015). Although a VIA screening approach has been recommended by the WHO as an appropriate innovation for developing countries, the method has been criticized due to its many shortcomings, such as maintaining quality assurance, the invasiveness of a pelvic examination and user variability of the procedure, having a low positive predictive value and lack of evidence on periodic screening performance (Moses et al., 2015; Gizaw et al., 2019; Sritipsukho and Thaweekul, 2010).

In addition, the low uptake of VIA based screening has become a major challenge, and other new approaches to assure the high coverage of cervical screening among the eligible women are needed. At this junction, an innovative method of self-sampled HPV testing was suggested due to its higher test performance and simple application (Jeronimo et al., 2017; Gizaw et al., 2019). In developing countries, including Ethiopia, to curb the impact of the disease and reach the desired coverage of screening to effectively prevent the disease, a highly precise, and at the same time a point of care test, must be established. Despite the presence of a high unmet need for cervical cancer screening for eligible women in Ethiopia, the coverage of the screening service and the uptake of women of the available service are very limited. Although there is no data on the national coverage of cervical cancer screening by VIA, small-scale studies in different parts of the country, including our baseline survey, have documented cervical cancer screening in only 2–10% of age-eligible women (Kasa et al., 2018; Aweke et al., 2017; Ruddies et al., 2020).

In the current context of cervical cancer screening, the acceptability and simplicity of the screening method is crucial to enhance the coverage and improve the uptake by targeted women. The success of existing and new tests highly depends on the women's level of participation and adherence to the procedures.

The screening optimization trial was conducted in the Health and Demographic Surveillance Site (HDSS) of Addis Ababa University which is located in Butajira district. Conducting a comparative trial in this HDSS gave us the possibility to easily identify the required targeted women as it has updated defined population with basic demographic background information. Moreover, it provided additional advantage for a population-based follow up through unique identifiers of each household, thus to estimate the proportion of women reached with the program and to identify women who participated in the screening and who did not.

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The aim of this work was first to describe cervical cancer patient characteristics, presentation, survival, and community level screening practice as first-hand information to better understand the disease of interest in the study area context. Then, a robust investigation was done to evaluate which method of cervical cancer screening would be feasible, with better uptake. Furthermore, from this work, we explored reasons and factors that affect women's participation in cervical cancer screening by applying direct comparison between women who underwent screening and those that did not. The following research questions have been answered:

1. How large is the uptake of self-sampled HPV testing compared to VIA at a population level?
2. How different is the uptake of VIA screening after triaging by self-sampled HPV testing?
3. What are the main reasons reported by women for not attending cervical cancer screening?
4. Which demographic characteristics are significantly associated with the non-participation of cervical cancer screening?
5. What is the knowledge, attitude, and screening practice of cervical cancer at a community level?
6. What is the clinical stage of cervical cancer patients at presentation, predictors of advanced stage, and prolonged patient interval?
7. What is the overall survival of cervical cancer patients and how does it differ according to HIV status?
8. Which clinical and demographic characteristics were associated with the survival of cervical cancer patients and longer patient intervals?

These findings were discussed by consulting studies conducted globally and mainly based on the current recommendations by the WHO and other key stakeholders such as the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC) and other regional cancer control plans moving towards elimination of cervical cancer in this century. Therefore, it is intended to provide setting-specific results for action towards the global aim of preventing and controlling cervical cancer, especially in resource-limited settings. This dissertation is based on the five publications presented below.

2. Synopsis of the Publications

Publication one: Muluken Gizaw, Brhanu Teka, Friederike Ruddies, Tamrat Abebe, Andreas M. Kaufmann, Alemayehu Worku, Andreas Wienke, Ahmedin Jemal, Adamu Addissie, and Eva Johanna Kantelhardt (2019): Uptake of cervical cancer screening in Ethiopia by self-sampling HPV DNA compared to visual inspection with acetic acid: A cluster randomized trial. *Cancer prevention research* (Philadelphia, Pa.) 12(9):609–616. DOI: 10.1158/1940-6207.CAPR-19-0156

Contribution as an author:

I was the main person responsible for the conception of ideas, formulation of the research questions, design, and conducting the actual fieldwork together with the main supervisor. I supervised the actual screening of women, data collection, and other field activities such as the follow-up of women and their treatment, as per the protocol. I was also responsible for maintaining quality assurance, analyzing the data, writing the results, and developing the manuscript. Also, I was responsible for all the required actions until the paper was published.

Publication two: Muluken Gizaw, Brhanu Teka, Friederike Ruddies, Konjit Kassahun, Dawit Worku, Alemayehu Worku, Andreas Wienke, Rafael Mikolajczyk, Ahmedin Jemal, Andreas M. Kaufmann, Tamrat Abebe, Adamu Addissie, and Eva Johanna Kantelhardt (2020): Reasons for not attending cervical cancer screening and associated factors in rural Ethiopia. *Cancer prevention research* (Philadelphia, Pa.) 13(7) DOI: 10.1158/1940-6207.CAPR-19-0485

Contribution as an author:

I was the main person responsible for the conception of ideas, formulation of research questions, design, and conducting of the actual fieldwork, with support from the main supervisor. I was also responsible for quality assurance, analysis of the data, writing of the results, and development of the manuscript with support from my supervisors. I was also responsible for all the required actions until the paper was published.

Publication three: Friederike Ruddies, Muluken Gizaw, Brhanu Teka, Sarah Thies, Andreas Wienke, Andreas M. Kaufmann, Tamrat Abebe, Adamu Addissie, and Eva Johanna Kantelhardt (2020): Cervical cancer screening in rural Ethiopia: a cross-sectional knowledge, attitude, and practice study. *BMC Cancer* (2020) 20:563. DOI: 10.1186/s12885-020-07060-4

Contribution as an author:

I actively participated in supervising the data collection process, results, and discussion writing, along with other authors. I also revised the manuscript and approved it for publication.

Publication four: Muluken Gizaw, Adamu Addissie, Sefonias Getachew, Wondimu Ayele, Israel Mitiku, Ulrike Moelle, Tigist Yusuf, Mathias Begoihn, Mathewos Assefa, Ahmedin Jemal, and Eva Johanna Kantelhardt (2017): Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study. *Infectious agents and cancer* 12:61. DOI: 10.1186/s13027-017-0171-4

Contribution as an author:

I was the main person responsible for conducting the analysis, report writing, including quality assurance, producing tables and graphs, manuscript writing, and undertaking the whole process of publication.

Publication five: Matthias Begoihn, Assefa Mathewos, Abreha Aynalem, Tigeneh Wondemagegnehu, Ulrike Moelle, Muluken Gizaw, Andreas Wienke, Christoph Thomssen, Dawit Worku, Adamu Addissie, Ahmedin Jemal, and Eva Johanna Kantelhardt (2019): Cervical cancer in Ethiopia - predictors of advanced stage and prolonged time to diagnosis. *Infectious agents and cancer* 14:36. DOI: 10.1186/s13027-019-0255-4

Contribution as an author:

I actively participated in writing results and discussion with other authors, revised the manuscript, and approved it for publication.

Uptake of Cervical Cancer Screening in Ethiopia by Self-Sampling HPV DNA Compared to Visual Inspection with Acetic Acid: A Cluster Randomized Trial

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Abstract

In Ethiopia, the standard method of cervical cancer screening is using Visual Inspection with Acetic Acid (VIA). Self-collection–based human papillomavirus (HPV) testing is assumed to improve the uptake of screening, especially for hard to reach populations. We investigated whether HPV DNA testing with the self-collection of cervical samples would be associated with increased uptake and adherence to procedures at the population level compared with VIA within defined rural population in Ethiopia. A total of 22 clusters (comprising 2,356 women ages 30–49 years) were randomized in two arms. Following the community mobilization, women of the clusters were invited to go either to the local health post for a self-collection–based HPV DNA testing (arm A) or Butajira Hospital for VIA screening (arm B). In the HPV arm, of the 1,213 sensitized women, 1,020 (84.1%) accessed the health post for self-sampling compared with the VIA arm, where 575 of 1,143 (50.5%) visited the hospital for VIA ($P < 0.0001$). Of those women who attended the VIA and HPV arms, 40% and 65.4% adhered to all procedures expected after screening, respectively. Out of women positive for high risk HPV, 122 (85%) attended VIA as a follow-up test. The trial demonstrated significantly higher levels of population-based uptake and adherence for self-collection HPV testing. Women were more receptive for VIA after their HPV testing result was positive. Self-collection HPV testing can be done at the local health facility and may significantly improve the uptake of cervical cancer screening in Ethiopia.

Introduction

Cervical cancer remains a major public health problem globally, with an estimated 570,000 new cases diagnosed and 311,000 deaths occurring annually with the large share of these cases and deaths occurring in low and middle income countries (1). In most developing countries, cervical cancer is the leading cause of cancer-related death among women (2, 3). In Ethiopia, cervical cancer is the second leading cause of morbidity and mortality from all cancers in women (4). In Ethiopia, almost all women with cancers present to healthcare facilities at advanced disease and poor prognosis (4). Cervical cancer can be prevented and even possibly cured if identified in its early stages, and this could be achieved in developed countries (5, 6). However, the risk of developing invasive cervical cancer continues to be higher in developing countries as the regions do not have well-organized prevention strategies (7, 8).

Currently, cervical cancer screening by visual inspection with acetic acid (VIA) and immediate treatment with cryotherapy is recommended by the World Health Organization (WHO) for low and middle income countries as this method requires trained nurses, few resources, and the results are available immediately (9–11). However, accessing VIA is difficult for many rural women as the service is only available at the district hospital level in very few places (12–14). Although VIA is accepted by the government in many low income countries, yet maintaining quality assurance, the invasiveness of a pelvic examination, and user variability of the test remain critical barriers (15).

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The detection of high risk human papillomavirus (hrHPV) in the cervix is a very sensitive method and has been recommended by the WHO in settings wherever technically and financially possible (9, 16, 17). This approach is found to be less examiner-dependent, reduces the burden on the healthcare system, enhances accuracy and efficiency, and reduces cultural barriers (10, 15, 18, 19). Moreover, a self-collected sample for HPV DNA testing was found to be acceptable and feasible by underserved women (20–23). Therefore, HPV test might be a future option in low and middle income countries.

In Ethiopia, screening with VIA followed by cryotherapy started in 2009 first for HIV-positive women in few selected hospitals (4, 11). Currently, the Federal Ministry of Health in Ethiopia has expanded the service to general health facilities, but the uptake of VIA remains low (24).

So far, few studies have been conducted in African settings to assess the uptake and acceptability of different screening approaches at a population-based level (15, 25). A study in sub-Saharan Africa reported a higher uptake of HPV-based cervical cancer screening than VIA in clinical settings (15). In Ethiopia, there is no evidence of the uptake and acceptability of self-sampling–based HPV testing as a primary cervical cancer screening method. Therefore, the objective of this study was to compare the uptake and adherence to procedures between HPV testing with the self-collection of cervical samples and using visual inspection with acetic acid by including all women residing within the predefined clusters.

Materials and Methods

Study design and population

A cluster-randomized trial was employed. This trial has been registered in clinical trial.gov (NCT03281135). We have used the Butajira Health and Demographic Surveillance Site population as a platform. It provides a well-defined number of women with their basic demographic features (26). The clustering process was performed using the existing health system of the country. According to the Ethiopian cervical cancer screening guideline, women ages between 30 and 49 years were targeted for screening in both arms (11). All women included in this study had never been screened before. We used a total of 22 clusters, each comprising 80 women as a minimum required sample. The clusters were divided equally between two arms: self-collected HPV testing and VIA. Women were excluded if they were pregnant, actively bleeding, had a previous hysterectomy, and refused to give consent before the screening.

Randomization

We followed a step-wise randomization process; we first divided a total of 10 villages or kebeles (the smallest administrative unit of the country, Ethiopia) into 22 clusters where proportionally four of the clusters belong to the urban setting. Finally, we generated 11 clusters for each arm, which contained the minimum of 80 targeted women in each cluster and a buffer zone between the clusters to control contamination of information. All clusters were linked with responsible community health workers. The randomization list was created by using a unique allocation ID. The randomization was also performed for each village separately, which means two clusters in each village were randomly allocated to one of two trial arms: the HPV arm or the VIA arm. The randomization was conducted using Research Randomizer Software (27).

Procedure and intervention

Community mobilization was conducted in each village using health extension workers (HEW) under the supervision of a facilitator. Targeted women were invited to attend the sensitization program in their vicinity. A trained team provided information on cervical cancer and screening during the community sensitization conducted in every cluster for the HPV and VIA arms separately. The sensitization was performed independently for each cluster using different tailored pretested sensitization materials. Accordingly, we sensitized and invited an equal number of women to either Butajira hospital for VIA arm where the service was available in the district or the primary health care unit at their vicinity for HPV self-sampling. In both arms, a reminder was given once through HEWs in the middle of the allocated screening period.

In the HPV self-sampling arm, women were offered an Evalyn Brush (Rovers) to collect a swab under active supervision by a trained health professional. Women collected samples in a private area in the health post. Samples were immediately placed in a plastic bag provided by the Evalyn Brush Company after giving a unique ID. Samples were stored and transported by the end of the week to the Molecular Laboratory of the Department of Microbiology, Immunology and Parasitology, College of Health Sciences, Addis Ababa University (Ethiopia) for DNA extraction. A DNA aliquot was sent to Charité Universitätsmedizin Berlin, Department of Gynecology (Germany) for HPV genotyping. The genotyping was performed using GP5+/GP6+ PCR with MPG-Luminex assay read out.

Training was provided to local health workers on postscreening counselling information and instructions. After receiving the results back, the health workers communicated results based on the counselling instruction in person at the health post where the specimens had been collected. Women who tested positive for hrHPV were cautiously counselled and appointed for further screening by VIA at Butajira Hospital. Women who tested positive for hrHPV and VIA were treated by cryotherapy.

In the VIA arm, women were appointed on any of 5 consecutive days given to visit the hospital. They could choose a convenient day to reduce the attrition rate. VIA screening was done for all women who visited the hospital

and were eligible for the procedure. A trained and certified nurse was responsible for performing the screening. All women who tested VIA positive were rescreened by a gynecologist for quality assurance. A WHO see-and-treat approach was implemented to screen-and-treat with cryotherapy for women who tested positive (16).

Data analysis

The primary analysis of the endpoint "adherence to procedure" was analyzed on the intention-to-treat principle (based on previous categorization) by comparing the number of women sensitized in the HPV self-sampling arm and the VIA at hospital arm. Descriptive analysis was carried out to calculate the uptake and characterize the sociodemographic characteristics of participants. Descriptive statistics were done to compare the two arms with different socio-demographic and economic factors. The χ^2 test was employed to compare the significance of the two screening approaches for the uptake of screening with the significance level of $P < 0.05$. Fisher exact test was used when the expected values are too low. Continuous variables such as age and waiting time were changed to categorical variables for ease of reporting.

Ethical consideration

Ethical approval was obtained from the Institutional Review Board of the College of Health Sciences, Addis Ababa University (Ethiopia) and Martin Luther University (Halle, Germany). Further approval was obtained from the National Research Ethics Review Committee for transferring samples to Germany using a material transfer agreement bilaterally signed between two institutions. The study is in line with the declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects. Oral consent was obtained from the women under the study for both screening and exit interviews. Screening was performed in a way in which privacy and confidentiality was maintained. Treatment was provided for women who were positive in both arms according to the national cervical cancer treatment guideline.

Results

The 22 clusters were divided in the HPV self-sampling arm or VIA arm. A total of 1,213 women from 11 clusters were sensitized for HPV self-sampling, of which 1,020 [84.1%; 95% confidence interval (CI), 81.95–86.07] attended the self-sampling (Fig. 1). Moreover, of the total women sensitized in the HPV arm, 794 (65.4%) adhered to all procedures of the study protocol. Of the 1,143 women sensitized to attend VIA in the hospital, 575 (50.5%; 95% CI, 47.41–53.2) attended the hospital. Of the total women sensitized in the VIA arm, 458 (40%) have adhered to all procedures of study protocol. There was a statistical significant difference in uptake and adherence to procedures between HPV self-sampling and VIA ($P < 0.0001$).
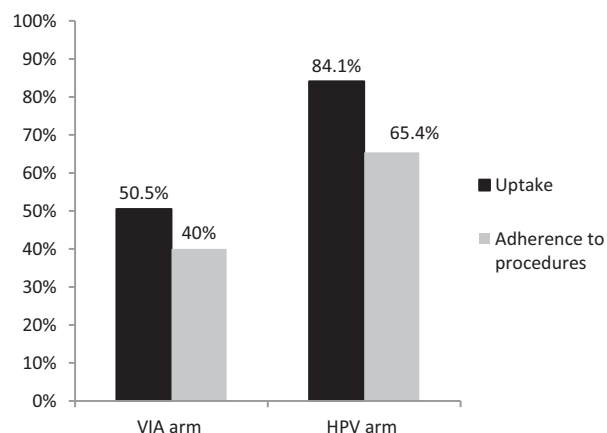
Figure 1.
Proportion of adherence to the uptake and procedures for women who participated in screening for cervical screening, Butajira, Ethiopia, 2018.

Study participant characteristics

Table 1 shows the demographic and reproductive characteristics of women according to their study arm. The majority of the study participants, 682 (81.7%) and 403 (86.9%) came from rural villages in the HPV self-sampling

Table 1. Sociodemographic characteristics of women who participated in screening for cervical cancer, Butajira, Ethiopia, 2018

Demographic characteristics	Total (N = 1,299) n (%)	Study arm	
		HPV self-sampling arm (N = 835) n (%)	VIA arm (N = 464) n (%)
Residence			
Urban	214 (16.5)	153 (18.3)	61 (13.1)
Rural	1,085 (83.5)	682 (81.7)	403 (86.9)
Marital status			
Married	1,212 (93.3)	763 (0.2)	449 (96.8)
Single	2 (0.15)	2 (0.2)	—
Divorced	39 (3.0)	33 (4.0)	6 (1.3)
Widowed	36 (2.77)	28 (3.4)	8 (1.7)
Separated	10 (0.77)	9 (1.1)	1 (0.2)
Age category			
30–34	735 (56.6)	519 (62.2)	216 (46.6)
35–39	364 (28)	203 (24.3)	161 (34.7)
40–44	126 (9.7)	72 (8.6)	54 (11.6)
45–49	73 (5.6)	40 (4.8)	33 (7.1)
Educational status			
Illiterate	838 (64.5)	546 (65.4)	292 (62.9)
Primary level (1–8)	397 (30.5)	249 (29.8)	148 (31.9)
Secondary level and above (9–12)	64 (5.0)	40 (4.8)	24 (5.2)
Occupation			
House wife	995 (76.6)	686 (82.2)	309 (66.6)
Farmer	129 (9.9)	38 (4.6)	91 (19.6)
Merchant	143 (11)	83 (9.9)	60 (12.9)
Government employee	9 (0.7)	6 (0.7)	3 (0.6)
Daily laborer	20 (1.5)	19 (2.3)	1 (0.2)
Other	3 (0.2)	3 (0.4)	—
Husband education			
Illiterate	684 (52.6)	471 (56.4)	213 (45.9)
Primary level (1–8)	504 (38.8)	297 (35.6)	207 (44.6)
Secondary level (9–12)	111 (8.6)	67 (8.0)	44 (9.5)

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Table 2. Service accessibility of women who participated in screening for cervical cancer, Butajira, Ethiopia, 2018

	Study arm	
	HPV self-sampling arm (N = 835)	VIA arm (N = 464)
Service accessibility	n (%)	n (%)
Means of travel to point of screening		
Foot	835 (100)	65 (14)
Horse cart	—	5 (1.1)
Car(Bajaj)	—	394 (84.9)
Distance to hospital		
<5 km	251 (26.1)	173 (23.8)
5–10 km	266 (27.7)	232 (31.9)
>10 km	444 (46.2)	323 (44.4)
Perceived difficulty of travel		
Yes	5 (0.6)	141 (30.4)
No	830 (99.4)	323 (69.6)
Mean (SD) of waiting time in minutes at point of screening	4.5 (2)	36 (12)

and VIA arms, respectively. Age distributions were similar in both arms; the majority of participants were between the age of 30 and 39. The mean ($\pm$ SD) age at first pregnancy of the HPV arm and VIA arm was 18.4 ($\pm$4.8) and 18.6 ($\pm$4.6), respectively. Most of the participants were illiterate and housewives by occupation. Moreover, the majority of the participant's husbands were illiterate and farmers by occupation. Furthermore, we compared the service accessibility between two arms. All women in the HPV arm travelled to the point of care on foot while the majority of participants 394 (85%) travelled to the hospital using a car in the VIA arm. The majority of women, 323 (44.4%), who came for VIA screening were from furthest places where the distance was greater than 10 km from the hospital. While participants rated for perceived difficulty of travelling to the point of care, the majority responded that they did not perceive difficulty travelling to either of the health facilities. However, about one third of the participants in the VIA arm reported that travelling to hospital was difficult, while very few participants reported similarly in the HPV arm. The mean waiting time at the point of care before receiving the service of HPV arm and VIA arm was 4.5 and 36 minutes, respectively (Table 2).

HPV DNA testing arm

Of the total 721 women who were screened, there were 171 (19.2%) reported to have a too low cell count to detect any HPV type and required rescreening. Following the recommendation to rescreen women with a low cell count, of the 171, 73 (42.7%) were willing to provide a second self-collected sample, 76 (44.4) refused to resample, and 22 (13%) were not accessible during two consecutive follow-ups. According to the guidelines for cervical cancer screening, those who were found to be positive for hrHPV had to go for further screening or examination, in this case VIA examination. Accordingly,

of all women who were positive for a single or multiple HPV infection, 122 (85%) attended VIA examination and 22 (15%) did not attend the point of care. Of the HPV-positive women who underwent VIA, 10 were VIA positive and consequently treated with cryotherapy (Fig. 2).

VIA arm

Of the 466 women screened by VIA, 22 (4.7%) were positive; 15 (3.2%) examinations were inconclusive, because the squamo-columnar junction zone (SCJZ) was not adequately visible. Two women refused the procedure after counselling. As part of the quality assurance, we rescreened all women found to be positive or inconclusive by a well-trained gynecologist. Accordingly, of the 22 women found positive by trained nurses, 11 (50%) were found to be positive by reexamination, 6 (27.3%) were negative, and 5 (22.7%) did not attend their appointment. Of the women who were positive on rescreening, 8 women received cryotherapy, and 1 was highly suspicious for cervical cancer and therefore referred for hysterectomy at the Butajira General Hospital. Cryotherapy was postponed for 1 woman due to pregnancy and 1 woman refused the cryotherapy treatment (Fig. 3).

Discussion

In this randomized trial, we compared the uptake and adherence of procedures for cervical cancer screening between self-sampled HPV testing with VIA in a population-based setting in Ethiopia. By using the lowest administrative unit in the community, including local health extension workers to invite the women, and selecting the unique IDs of 80 women in each cluster, we assured targeting a random population sample. Reducing the current burden of cervical cancer can only be achieved through a high uptake of cervical cancer screening by the targeted population (19). This study demonstrated higher uptake and adherence of HPV-based screening than of VIA, the standard method in Ethiopia. About 84% of sensitized women from the HPV arm attended screening, while only 50.5% attended VIA. Of those women attended screening in both arms, 65.4% and 40% adhered to all procedures expected after screening in the HPV and VIA arm, respectively. The improvement of screening uptake through self-sampled HPV-based testing has been reported by several studies. Self-sampling avoids multiple barriers associated with VIA, such as, taboo related with medical vaginal examination, fear of pain, long travel to the point of care, and long waiting time at health facilities (19, 28).

Study findings highlighted that the HPV triage eventually showed an increased uptake of VIA in this population. Accordingly, 85% of the women positive for hrHPVs underwent VIA screening. Similarly, studies
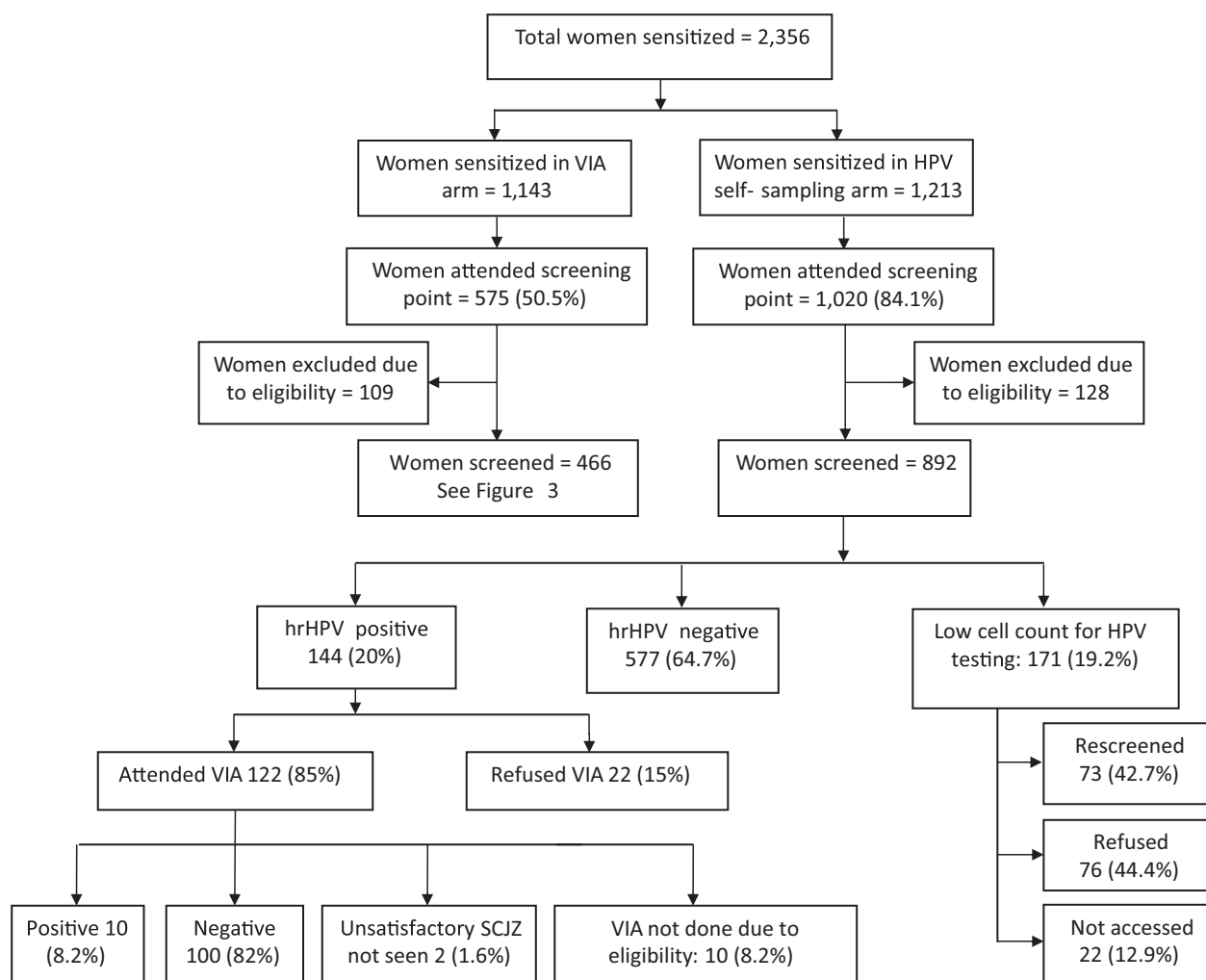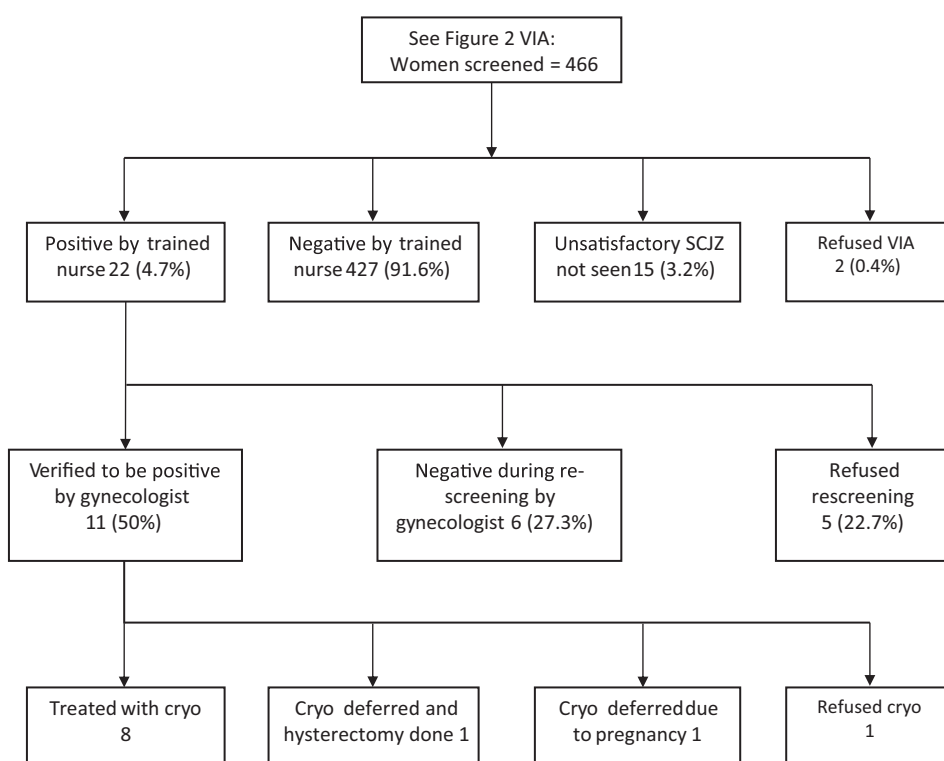
Figure 2.
Study trial flow chart and screening adherence outcomes for women who participated in HPV arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

conducted elsewhere reported that the majority of women who tested HPV positive will more likely comply with the subsequent medical advice (19). Among the women positive for hrHPV in the HPV arm, only 10 (8.2%) were positive in the triage test, VIA in this case. About 171 (19.2%) of women did not perform the sample collection properly. As a result, these samples were inadequate for the detection of HPV infection. In the VIA arm, a lack of consistency in interpreting the result by different providers has been a critical challenge in this study. Of the women who attended VIA screening, 22 (4.7%) of women were first identified as VIA positive or inconclusive by a trained nurse. However, only half of the women were found to be positive for VIA during the verification by an experienced gynecologist. Similarly, the subjective variability has been identified as one of the pitfalls of the VIA screening (16, 29, 30). In both arms, the

majority of VIA-positive patients were treated by cryotherapy at the point of care; otherwise, they were sent to the gynecologist for further investigation and treatment at the district hospital.

Despite various advantages of the screening test used, maintaining a higher coverage of screening among targeted individuals must be assured. To improve the coverage of screening, the service must be accessible, with a short waiting time and simple protocol to comply with. Regarding the accessibility of both screening approaches, the HPV test was offered in the women's vicinity (accessible on foot), while women randomized to the VIA arm had to travel (mainly motor-vehicle) to undergo the screening, which may have contributed to the lower uptake and adherence to screening procedures. Women did not report any perceived difficulties in accessing the HPV testing, whereas 30% of the women

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Figure 3.
Study trial flow chart and screening adherence outcomes for women who participated in VIA arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

reported difficulties reaching the VIA and a long waiting time as an additional barrier. Although the HPV testing for cervical cancer screening had a better uptake by the eligible women in this study, there have been several challenges to providing HPV-based cervical cancer screening. Because HPV-based sampling requires a strict working protocol, there needs to be an adequate health and laboratory structure in place or a point of care test can be considered after the development of new tests.

The lack of a point-of-care test in the HPV arm in our study may have led to delays in disclosing the results. In addition, organizing follow-up is another critical problem of HPV-based screening. Moreover, laboratory procedures to process the results require trained health personnel, several machines, and numerous consumables. Hence, full scale up of the HPV-based screening might be difficult in countries where having constrained health system.

This study has limitations. We are aware that the distance to the VIA service was rather far in our setup, so providing a VIA service closer to the population would possibly increase the uptake. There were additional charges of travel to the place at which VIA screening was done. Moreover, this study did not consider costing analysis to compare the feasibility of HPV-based screening over the conventional screening approach.

Conclusion

With proper and rigorous community sensitization, self-sampled HPV testing is feasible, resulting in the high uptake of screening for cervical cancer in Ethiopia. The study demonstrated that women who tested positive for HPV were more likely to go for follow-up screening. Regardless of the better uptake of HPV testing, to scale-up HPV-based screening in Ethiopia, the capacity of the health system must be properly evaluated and strengthened by assuring the presence of a point of care to efficiently process the collected samples.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Gizaw, B. Teka, F. Ruddies, T. Abebe, A.M. Kaufmann, A. Worku
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Gizaw, T. Abebe, A.M. Kaufmann, A. Worku, A. Wienke, A. Jemal, A. Addissie, E.J. Kantelhardt
Writing, review, and/or revision of the manuscript: M. Gizaw, B. Teka, F. Ruddies, T. Abebe, A.M. Kaufmann, A. Worku, A. Jemal, A. Addissie, E.J. Kantelhardt
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Gizaw, B. Teka, T. Abebe, A. Worku, E.J. Kantelhardt
Study supervision: B. Teka, F. Ruddies, T. Abebe, A. Worku, A. Wienke, A. Addissie, E.J. Kantelhardt

Acknowledgments

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Uptake of Cervical Cancer Screening in Ethiopia by Self-Sampling HPV DNA Compared to Visual Inspection with Acetic Acid: A Cluster Randomized Trial

Muluken Gizaw, Brhanu Teka, Friederike Ruddies, et al.

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Reasons for Not Attending Cervical Cancer Screening and Associated Factors in Rural Ethiopia

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ABSTRACT

Social, economic, and cultural factors have been associated with the level of participation in cervical cancer screening programs. This study identified factors associated with nonparticipation in cervical cancer screening, as well as reasons for not attending, in the context of a population-based, cluster-randomized trial in Ethiopia. A total of 2,356 women aged 30 to 49 years in 22 clusters were invited to receive one of two screening approaches, namely human papillomavirus (HPV) self-sampling or visual inspection with acetic acid (VIA). Participants and nonparticipants were analyzed according to their sociodemographic and economic characteristics. Reasons were determined for the refusal of women to participate in either screening method. More women in the VIA arm compared to the HPV arm declined participation in the screening [adjusted OR (AOR) 3.5; 95% confidence interval (CI), 2.6–4.8]. Women who declined attending screening were more often living in rural areas (AOR = 2.0; 95% CI, 1.1–3.5) and were engaged in informal occupations (AOR = 1.6; 95% CI, 1.1–2.4). The majority of nonattendants perceived themselves to be at no risk of cervical cancer (83.1%). The main reasons given for not attending screening for both screening approaches were lack of time to attend screening, self-assertion of being healthy, and fear of screening. We found that perceived time constraints and the perception of being at no risk of getting the disease were the most important barriers to screening. Living in rural settings and informal occupation were also associated with lower participation. Offering a swift and convenient screening service could increase the participation of women in cervical cancer screening at the community level.

Introduction

Cervical cancer is one of the most common cancers among women in developing countries (1). In Ethiopia, it is the second leading cause of morbidity and mortality among all cancers in women (2). The World Health Organization (WHO) recommends early detection of cancer through organized screening programs in developing countries to reduce the growing burden of disease (3, 4). Unlike other cancers, cervical cancer can be prevented and possibly cured if identified at an early stage through organized screening, and this can possibly also be achieved in developing countries (5). The WHO envisages the elimination of cervical cancer as a public health problem in the next 100 years, mainly through organized comprehensive prevention and control approaches (6, 7). This program prioritizes placement of screening activities and ensures active participation of the targeted population (4, 7).

According to Ethiopian cervical cancer screening guidelines, women aged 30 to 49 years are targeted for visual inspection with acetic acid (VIA) screening, which is the method of choice for cervical cancer screening (2). The Ministry of Health in Ethiopia has been actively working to make VIA screening available in many district hospitals and health centers throughout the country (8); however, its coverage and uptake has been low. Accordingly, small-scale studies in different parts of the country have documented cervical cancer screening in only 5% to 20% of age-eligible women (9–11).

Several barriers hindering women from participation in cervical cancer screening have been identified. Common reasons for its low use stem from a false perception of cervical cancer and its screening due to knowledge deficits (12). The educational level of women is often mentioned as a reason for declining a screening invitation (13). Fear of embarrassment during the screening is also associated with poor uptake (14). Different studies have indicated that cultural and societal barriers related to the taboo of the genital area being touched were linked with declining a cervical cancer screening

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offer (15, 16). The perceptions of women as to their risk of developing cervical cancer were also critically associated with poor uptake (12). In addition, fear of the results and general reluctance to make time for screening were frequently reported factors for its low use (12, 17).

Self-sampling for human papillomavirus (HPV) testing was more acceptable among women in different countries, and was associated with higher uptake and accessibility (18, 19). Unlike VIA, HPV testing can be done at the doorstep through women's self-collection of samples (18). However, studies have identified multiple barriers to women participating in HPV self-sampling tests. Knowledge of women regarding HPV and its screening has been linked with their level of participation in this procedure (20, 21) and with misconceptions about its modality (21). Unlike other methods of cervical cancer screening, women were concerned about how to perform the procedure correctly (22, 23). In addition, fear of pain and discomfort during the procedure were reasons mentioned for nonparticipation (23).

Hence, this study used data from the randomized controlled trial conducted at the Butajira Health and Demographic Surveillance Site in Ethiopia to compare the uptake of cervical cancer screening for HPV self-sampling and VIA (24). The trial demonstrated that there was much better uptake by women for HPV testing than that for VIA. As part of the project activities, the current study compared women who refused to participate in the screening (in both arms) with those who participated, and the reasons for refusal were determined.

Methods

Study design and population

The cluster-randomized trial had a total of 22 clusters, each comprising 80 women, as a minimum required sample, divided equally between two arms: HPV self-sampling and VIA (23). Women aged 30 to 49 years were targeted for screening in both arms. Of the 2,356 women sensitized for screening in both arms, 761 (568 from the VIA arm and 193 from the HPV arm) failed to attend screening. Of those women who did not attend screening, 390 (51%; 264 from the VIA arm and 126 from the HPV self-sampling arm) were interviewed (**Fig. 1**).

Procedure and data collection

For the cluster-randomized trial (24), for all women in both arms, community mobilization was conducted in each village using health extension workers under the supervision of a facilitator. Similar approaches to sensitization were employed using the tailored pre-tested guiding sensitization material for both screening arms. After sensitization, all targeted women were invited to either the Butajira hospital for the VIA arm, where the service was only available during the study period, or to the primary health care unit at their vicinity for HPV self-sampling. In the HPV self-sampling arm, women were provided an Evalyn Brush (Rovers, the Netherlands) at a primary health post to collect a swab by themselves under active supervision by a trained health professional. Samples were stored and transported to the Central Molecular Laboratory Addis Ababa University for DNA extraction and testing. A DNA aliquot was sent to the Department of Gynaecology at Charité Universitätsmedizin Berlin, Germany, for validation and HPV genotyping. The genotyping was performed with MPG-Luminex Assay read out. During the sensitization, all women who attended the education events were registered with their name, specific residence, and contact information. Women were told to visit the screening locations on any of five consecutive days after the sensitization. The women were able to choose a day convenient to them to help reduce the attrition rate. All women who appeared at the screening locations were listed in a separate file, whereas women who did not show up during this period were considered nonattendants. The research team reconciled files from both arms of the study to select women who failed to attend any of the screening locations for inquiry as to the reasons for their absence. Trained research assistants were deployed to the household of each nonattendant to collect information using a structured questionnaire. An open question was asked to solicit the main reason for not attending the screening. Women who were not traced or assessed after two attempts were considered to be not accessible.

Data analysis

Descriptive analysis was undertaken to determine the sociodemographic characteristics of participants according to their screening status. Continuous variables, such as age, were changed to categorical variables for ease of reporting. ORs and adjusted ORs (AOR) with 95% confidence intervals (CI) were calculated to assess differences between participants and nonparticipants according to sociodemographic and economic characteristics. Reasons for not attending the screening were categorized into personal barriers, health facility–related barriers, and societal barriers as the identified themes belonged to both previously assigned arms of HPV self-sampling and VIA.

Ethical considerations

Ethical approval was obtained from the institutional review boards of the College of Health Sciences, Addis Ababa University (058/17/SPH), and Martin-Luther University, Halle, Germany (2017-143). The study was in line with the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Oral informed consent was obtained from screening participants and nonparticipants asked about reasons for their nonparticipation and was documented. To ensure women's privacy, the list of women who did not participate in screening was not transferred to any third body or local administrators. In addition, interviews were performed in a manner that maintained privacy and confidentiality.
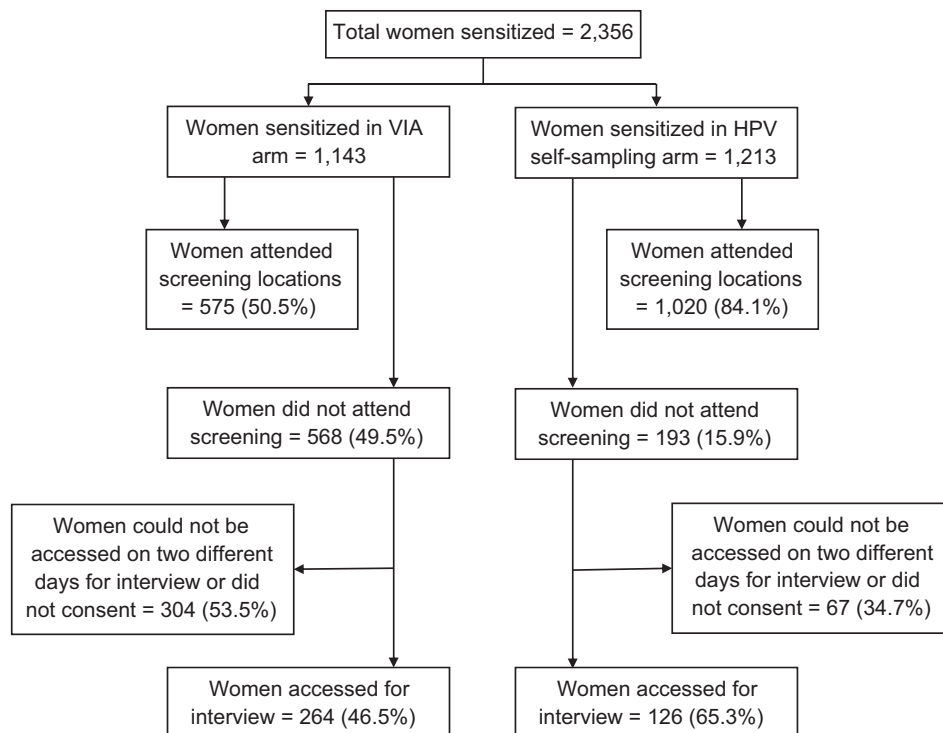
Results

Study participants' characteristics

The demographic characteristics of participants and nonparticipants in screening are summarized in **Table 1**. The majority of women in both arms of the study were Muslim

Figure 1.
Schematic flow of study participants in Butajira District, Ethiopia, 2018.

Total women sensitized = 2,356

Women sensitized in VIA arm = 1,143

Women sensitized in HPV self-sampling arm = 1,213

Women attended screening locations = 575 (50.5%)

Women attended screening locations = 1,020 (84.1%)

Women did not attend screening = 568 (49.5%)

Women did not attend screening = 193 (15.9%)

Women could not be accessed on two different days for interview or did not consent = 304 (53.5%)

Women could not be accessed on two different days for interview or did not consent = 67 (34.7%)

Women accessed for interview = 264 (46.5%)

Women accessed for interview = 126 (65.3%)

(71.3% screening nonattendants and 72.6% attendants), consistent with the predominant religion, and resided in rural settings (82.8% screening nonattendants and 83.5% attendants). Two-thirds (67.7%) of nonattendant women were from the VIA arm. Women who did not attend screening were more often unmarried compared to those who accepted screening (9.5% vs. 6.5%). Women who did not attend screening were more often in the age category of 35–39 years compared with those who accepted screening (39.2% vs. 28.7%). The majority of screening nonparticipants and participants had no formal education (54.5% and 64.5%, respectively). However, a larger portion of nonattendants had attended primary school and secondary school only (39.1% and 6.4%, respectively) compared with those who accepted screening (30.6% and 4.9%, respectively). In addition, more nonattendants had some form of offsite occupation, such as being day laborers or small traders (20.3%), compared with those who accepted screening (13.2%).

Factors affecting nonparticipation of women in cervical cancer screening

After adjusting for demographic characteristics of women and husbands, women in the VIA arm had three times higher odds of deferring participation in cervical cancer screening compared to women in the HPV arm (AOR = 3.5; 95% CI, 2.6–4.8). Women residing in rural settings had twice the chance of not attending (AOR = 2.0; 95% CI, 1.1–3.5) compared to those who lived in the urban part of the district. Women aged 35 to 39 years were more likely to defer participation (AOR = 1.5; 95% CI, 1.1–2.1) when compared to women aged 30 to 34 years. Attendance was significantly associated with primary educa-

tion of women (AOR = 1.4; 95% CI, 1.1–1.9) and their husbands (AOR = 1.5; 95% CI 1.1–2.1) when compared with those who had no formal education. In addition, women engaged in some form of outdoor work were more likely to not attend screening (AOR = 1.6; 95% CI, 1.1–2.4) compared with housewives (**Table 1**).

Main reasons given for not attending the screening

Of the 390 women who refused screening from the VIA and HPV self-sampling arms, 186 (70.5%) and 97 (77.0%) reported being busy with other activities or having no time to go for screening, respectively. Of the women assigned in the VIA arm compared with the HPV self-sampling arm, 43 (16.3%) suggested that screening would not help them because they considered themselves healthy. In addition, 14 (5.3%) and 9 (7.1%) women reported that fear of receiving bad news from others in the community influenced their decision to go for screening in the VIA and HPV arms, respectively. Other reasons contributing to screening nonattendance were as follows: women not being convinced that screening was necessary because of the information provided, the influence of their husband, fear of positive results after screening, and the feeling of shame because screening involved their genitalia being touched (**Table 2**).

Perceived barriers to participation in screening

Of the 390 women who did not participate in either of the screening approaches and could be accessed for interview, 353 (90.5%) women believed that cervical cancer was a serious disease that causes death. However, 324 (83.0%) women considered that they were not at risk of developing the disease in

Table 1. Sociodemographic characteristics and factors affecting nonparticipation of women in cervical cancer screening in Butajira District, Ethiopia, 2018.

Demographic characteristics	Total ($N = 1,689$) n (%)	Screening nonattendant ($N = 390$) n (%)	Adjusted OR[a] (95% CI)	P
Screening arms				
Self-sampled HPV arm	961 (56.9)	126 (32.3)	1	
VIA arm	728 (43.1)	264 (67.7)	3.51 (2.56–4.82)	**<0.000001**
Religion				
Christian	468 (27.7)	112 (28.7)	1	
Muslim	1,221 (72.3)	278 (71.3)	1.47 (1.07–2.00)	**0.016**
Residence				
Urban	281 (16.6)	67 (17.2)	1	
Rural	1,408 (83.4)	323 (82.8)	1.99 (1.13–3.48)	**0.016**
Distance to hospital				
<5 km	424 (25.1)	111 (28.5)	1	
5–10 km	498 (29.5)	143 (36.7)	1.26 (0.79–1.99)	0.322
>10 km	767 (45.4)	136 (34.9)	0.70 (0.45–1.10)	0.114
Marital status				
Married	1,567 (92.8)	353 (90.5)	1	
Unmarried	122 (7.2)	37 (9.5)	3.6 (1.41–9.18)	**0.007**
Age category (years)				
30–34	879 (53.8)	176 (47.6)	1	
35–39	508 (31.1)	145 (39.2)	1.51 (1.10–2.07)	**0.009**
40–44	155 (9.5)	29 (7.8)	0.75 (0.42–1.32)	0.321
45–49	93 (5.7)	20 (5.4)	0.97 (0.50–1.87)	0.940
Education of women				
No formal education	1,050 (62.2)	212 (54.5)	1	
Primary (1–8)	549 (32.5)	152 (39.1)	1.43 (1.05–1.93)	**0.020**
Secondary and above	89 (5.3)	25 (6.4)	1.52 (0.82–2.82)	0.183
Occupation				
Housewife	1,438 (85.1)	311 (79.7)	1	
Day laborers and merchants	251 (14.9)	79 (20.3)	1.64 (1.13–2.39)	**0.009**
Education of husbands				
No formal education	836 (49.5)	152 (39)	1	
Primary (1–8)	701 (41.5)	197 (50.5)	1.54 (1.14–2.10)	**0.004**
Secondary and above	152 (9.0)	41 (10.5)	1.03 (0.63–1.72)	0.886

Note: P values < 0.05 are highlighted in bold.
[a]Data adjusted for place of residence, age of women, occupation of women, marital status, religion, occupation of husbands, age of husbands, education of husbands, and screening arm.

their lifetime. Of all women who did not participate, 79 (20.3%) reported that their husbands would not allow them to go for screening. In addition, 58 (15.0%) nonparticipants reported that failure to attend a screening was due to a lack of trust in the health professionals working at the nearby health facilities. However, 352 (90.2%) women acknowledged that sensitization and awareness information were adequate in helping them decide to participate (**Table 3**).

Discussion

This study assessed factors associated with the participation of women in cervical cancer screening by two different methods and their reasons for not attending. Findings from this study demonstrate that VIA-based screening, being 35 to 39 years of age, working status, health perception, culture, place of residence, marital status, and educational level affected the uptake of cervical cancer screening. The main reasons reported for being unable to attend the screening were being busy with other daily tasks, women's perceived health, and the fear of receiving bad news from others in the community.

The current study showed that the majority of women (83.1%) perceived themselves to not be at risk of developing

Table 2. Main reasons for not attending the screening according to the screening strategy among respondents who had not attended screening in Butajira District, Ethiopia, 2018.

Reasons for not attending screening	VIA-based screening Frequency ($N = 264$), n (%)	HPV self-sampling Frequency ($N = 126$), n (%)
No time to attend	186 (70.5)	97 (77)
Perceived health	43 (16.3)	10 (7.9)
Fear of bad news from others	14 (5.3)	9 (7.1)
Not convinced to attend	13 (4.9)	7 (5.6)
Feeling of shame about screening	2 (0.8)	3 (2.4)
Influence of husband	3 (1.1)	—
Fear of positive result	3 (1.1)	—

Table 3. Perceived barriers to undergo cervical cancer screening among respondents who had not attended screening in Butajira District, Ethiopia, 2018.

Self-belief and health facility–related factors	Frequency (N = 390), n (%)
Cervical cancer is a serious disease	
Yes	353 (90.5)
No	37 (9.5)
I am not at risk of the disease	
Yes	324 (83.1)
No	66 (16.9)
My husband would not allow me to go for screening	
Yes	79 (20.3)
No	311 (79.7)
I was not satisfied with a previous visit to the hospital	
Yes	52 (13.3)
No	338 (86.7)
Providers are not trustworthy	
Yes	58 (14.9)
No	332 (85.1)
Fear of long waiting time at the hospital	
Yes	19 (4.9)
No	371 (95.1)
The information provided was adequate	
Yes	352 (90.2)
No	38 (9.8)
Fear of the results of screening	
Yes	24 (6.2)
No	366 (93.8)

cervical cancer. This result was consistent with previous studies conducted in Southern Ghana and Saudi Arabia, where respondents scored themselves at below average risk in terms of contracting the disease (25, 26). A possible explanation for this might be that the knowledge surrounding cervical cancer was poor in women from developing countries in general, and particularly those from Ethiopia (11, 26–28).

The current study further elaborated on the main reasons for declining screening by using open questions. Personal factors mentioned by women were as follows: not having time to attend the screening, perceiving themselves as healthy and viewing the screening as being for diseased persons, fear of a long-time commitment, inadequate information on screening, and fear of positive results. The single health facility–related barrier was a lack of satisfaction in the health facility where the screening was to take place. Societal-related barriers included fear of bad news from the screening activities, cultural taboos involving the touching of genitalia by others, and the influence from husbands to not attend. Despite all of these factors contributing to nonattendance at screenings, the majority of women claimed lack of time as the most important issue. A possible explanation for this might be the engagement of women in routine businesses in rural settings of the country, as well as their occupational status. These findings were consistent with other reports in which personal, health facility, and cultural factors influenced women not to attend cervical cancer screenings in different settings (14, 25, 29, 30).

The data revealed that participation by women in VIA-based screening was lower compared with HPV self-sampling. The acceptability of VIA compared with other screening modalities has been found to be low in many countries (30). This might be due to the invasiveness of pelvic examination and related cultural taboos (31). However, self-sampling for HPV testing has been found to be more acceptable, as the procedure is easy for women to perform and samples can be collected at their doorstep (32, 33).

The findings from this study suggest that women from rural areas are more likely to refrain from attending cervical cancer screening compared to those from urban locations. This finding is consistent with previous reports elsewhere, indicating that nonparticipation was due to a knowledge gap, the distance to the screening service, and cultural and societal views (29, 34–36). It is evident that knowledge related to cervical cancer and its prevention is poor in Ethiopian women, particularly among those who reside in rural areas, where there is also a shortage of services (11, 28).

The findings from this current study indicate that married women used cervical cancer screening more often than unmarried women. This finding was consistent with previous reports suggesting that being married was an independent factor influencing the uptake of different cancer screening services, as well as disease outcomes and treatment (37, 38).

In this study, women aged 35 to 39 years were less likely to attend cervical cancer screening than younger women. A possible explanation for low acceptance of screening in this age group might be practical challenges related to their outdoor working practices and other social circumstances compared to their younger peers. Moreover, the findings from this study indicate that older women were relatively more receptive to cervical cancer screening than younger women. This might possibly be explained by their availability at home and thereby their avoidance of some of the practical challenges in undergoing screening.

Our findings indicate that women who engaged in both formal and informal occupations were more likely to decline screening compared with housewives, which might be dictated by time constraints due to their work. This finding was consistent with a previous study (39). In Ethiopia, especially in rural settings, women are engaged in making money by selling goods and working as day laborers, which means that they may travel long distances and get home late at night, affecting their ability to attend screening. In addition, having a husband who works was negatively associated with screening uptake likely because those women would need to tend to the home and take care of the children, and therefore they would not be able to attend screening.

We acknowledge the following limitations of the study. First, data could not be collected from all of the women who failed to attend screening, even if we tried twice to access them. Background information was available only for the interviewed

study subjects. As a result, we are unable to extrapolate reasons and factors associated with nonattending among the noninterviewed study subjects. We assumed that the missing data were random; however, it was possible that the comparison did not show a true difference in reasons for nonattending between the two different screening approaches. Moreover, we assumed that women who worked outside the home were underrepresented. Second, the choice of a 5-day window to participate in screening might have affected the turnout of women for screening during the study period. Approximately half of the women invited to participate in the VIA arm did not undergo screening in that 5-day window. Some of those women who did not participate might have undergone screening had they been given more time. Notably, those who had a rural residence, and therefore likely had fewer transportation options, were less likely to participate. Those with jobs, and who therefore may not have been able to attend on those dates, were also less likely to participate.

In addition, it would have been better to have formal qualitative information, using focused group discussions and in-depth interviews with some of the women who did not attended screening, to obtain precise information as to why they did not attend. However, we used open questions, although self-reporting reasons for not attending screening might have been affected by recall and information biases. Even so, this study had some strengths: (i) the women were part of a study employing a robust design, which had an adequate sample size; (ii) direct comparisons were made between participants and nonparticipants in screening from the same population; and (iii) the influences of different screening approaches on attendance rates were assessed in the same population.

In conclusion, this study demonstrates that some of the population needed special consideration to increase attendance at cervical cancer screenings in Ethiopia. Additional efforts must be made for women who reside in rural settings, are engaged in time-consuming and outdoor jobs, and are not married. The perception of women about their health was associated with poor knowledge about cervical cancer and its prevention, which contributed to women not attending the screening. This study also suggests that to increase participation, a swift and convenient screening service should be offered, which can be completed quickly at the doorstep. Culturally sound behavior-changing education should be aimed at resolving misconceptions related to screening. Moreover, while providing education, the influence of the different factors at the household level and in the community should be considered.

Disclosure of Potential Conflicts of Interest

Authors' Contributions

Conception and design: M. Gizaw, F. Ruddies, K. Kassahun, A. Worku, T. Abebe, A. Addissie, E.J. Kantelhardt
Development of methodology: M. Gizaw, B. Teka, K. Kassahun, A. Worku, T. Abebe, A. Addissie, E.J. Kantelhardt
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Gizaw, B. Teka, F. Ruddies, K. Kassahun, A. Worku
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Gizaw, K. Kassahun, D. Worku, A. Worku, A. Wienke, A. Jamal, T. Abebe, A. Addissie, E.J. Kantelhardt
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Study supervision: A. Worku, A. Wienke, E.J. Kantelhardt

Acknowledgments

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Reasons for Not Attending Cervical Cancer Screening and Associated Factors in Rural Ethiopia

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BMC Cancer

Cervical cancer screening in rural Ethiopia: a cross- sectional knowledge, attitude and practice study

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Abstract

Background: Cervical cancer is the fourth most common cancer among women worldwide. Sub- Saharan Africa has a high incidence, prevalence and mortality due to shortage and underutilization of screening facilities. This study aims to assess knowledge and attitude towards cervical cancer and its prevention, as well as practice of cervical cancer screening.

Methods: This cross-sectional community- based study was conducted in Butajira, Ethiopia in February 2018. Systematic cluster randomized sampling was used to select households from which women in the targeted age group of 30–49 years were invited to participate. Data was collected using a quantitative door to door approach. The questionnaire included socio-demographic data, obstetric history, general knowledge, risk factors, attitude and practice. Logistic regression was used to assess factors associated with knowledge, attitude and practice after dichotomizing the scores using the median as cut off point.

Results: Three hundred forty-two out of 354 women completed the interviewer administered questionnaire making the response rate 96.3%. 125 women (36%) were aware of cervical cancer and 14 (4.7%) knew symptoms. None of the women named HPV as a risk factor. 61% thought it was a deadly disease, 13.5% felt at risk of developing cervical cancer and 60.7% said cervical cancer is treatable. Eight women (2.3%) had previously been screened. 48.1% had a source of information concerning cervical cancer, of which 66.5% named nurses. Better knowledge was associated with 1–8 years of education (OR = 2.4; CI: 2.4–1.3), having a source of information (OR = 9.1, CI:4.0–20.6), use of contraceptives (OR = 2.3, CI: 1.3–4.0) and a higher income (OR = 1.009, CI: 1.00–1.01). Naming nurses (OR:5.0, CI:2.4–10.3), another source of information (OR = 3.3, CI:1.2–9.0), use of contraceptives (OR = 2.2, CI: 1.2–3.8) and living in an urban area (OR = 3.3, CI:1.2–9.0) were associated with a positive attitude. Naming nurses (OR = 21,0, CI:10.4–42.3) and another source of information (OR = 5.8, CI:2.4–13.5) were associated with participating in cervical cancer screening.

Conclusion: Most women were unaware of cervical cancer, HPV-infection as a risk factor and did not feel susceptible to cervical cancer. As Health workers were the most commonly mentioned source of information, focus should be put on their further education.

Keywords: Cervical cancer, Ethiopia, Health intervention, Acceptability, Human papillomavirus

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Background

Cervical cancer is still the fourth most common cancer among women worldwide [1]. According to the GLOBOCAN data of 2018 the incidence of cervical cancer is 563,847 new cases worldwide, of which 52,633 occur in Eastern Africa [2]. In Ethiopia incidence and mortality rates of cervical cancer are 26.4 and 18.4 / 100,000 [3, 4]. The most relevant cause of cervical cancer is a persistent infection with high risk genotypes of HPV (e.g. 16, 18, 31, 52). Other co-risk factors are smoking, a weakened immune system, multi-parity, early sexual initiation and many sexual partners, as well as a family history of cervical cancer [5]. Cervical cancer mostly develops slowly, and when detected early as precancerous lesion, it can be treated effectively. Treatment options for advanced cervical cancer are expensive and often unavailable in Ethiopia [6, 7]. In developed countries the incidence of cervical cancer has decreased due to effective screening programs [2]. Due to more pressing health issues such as HIV, TB, Malaria and gastrointestinal infections, cancer and other noncommunicable diseases were long ignored in developing countries but are rapidly becoming an issue [8, 9]. Shortage of screening facilities, financial issues, cultural factors and lack of awareness limit the uptake of cervical cancer screening in developing countries [10] such as Ethiopia [9]. In a case control study in the Tigray region, Ethiopia, lack of knowledge and low risk perception were most commonly named as reasons for no-attendance to cervical cancer screening [11]. In a qualitative study from 2012 conducted in Jimma and Addis Ababa, Ethiopia the participants named limited access, lack of awareness and financial resources, the symptomless nature of cervical cancer and the stigma associated to the disease as common barriers towards screening procedures [12]. Studies conducted in Addis Ababa, Ethiopia on HIV- positive patients identified the cost, feeling healthy, lack of awareness and fear of the test results as barriers towards cervical cancer screening [13, 14]. Fear of marital disturbance and religious reasons have also been mentioned [12, 13]. The conceptual framework of the health belief model is often used to understand determining factors for a person's attitude and preventive health behavior [15, 16] and has been used in this study to assess the participant's attitude. This study was carried out before starting a cervical cancer screening intervention within the same community to assess possible barriers [17]. The objective was to assess women's knowledge, attitude and practice of cervical cancer and its screening on population level with a focus on influencing personal and cultural factors for further consideration while implementing cervical cancer screening.

Methods

Study design and setting

This cross-sectional community- based study was conducted in Butajira, Ethiopia in February 2018 to collect baseline information prior to a cluster-randomized trial that has been registered in clinicaltrials.gov (NCT03281135) [17]. Butajira is a district located 130 km southwest of the capital Addis Ababa in central Ethiopia with approximately 75,000 people, where the Addis Ababa University maintains a Health and Demographic Surveillance Site (HDSS) to track birth and death rates as well as migration in one urban and 9 rural Kebeles, the smallest administrative unit [18] Prior to this intervention, there were VIA- trained nurses at the general Hospital in Butajira, but no formal cervical cancer screening program. The health services in the district are organized according to the Ethiopian health sector development program with a system of health extension workers for primary health care, information distribution and community mobilization [19–21]. Health extension workers were used to reach and identify participants and distribute information.

Participants

The WHO recommends cervical cancer screening for all women at the age of 30–49 years [22]. All women in this targeted age group who were living in the HDSS zone in Butajira and were home during the time of data collection were considered eligible. The HDSS zone in Butajira was divided into 22 clusters of 80 women each. Systematic random sampling was used to first select the household and from each household women in the targeted age group were invited to participate. The single population proportion formula was used to calculate the sample size. Sample size calculation was based on the proportion of participants who were aware of cervical cancer. This proportion of participants was assumed to be 30% based on other studies conducted in Ethiopia [9, 13, 14, 23, 24]. Most of these studies, conducted in an urban setting, stated a higher level of awareness. Since this study was conducted in a rural setting, lower awareness was assumed. 322 participants were needed to construct a 95% confidence interval with an accuracy distance from estimate to limit of the CI of 5%. The final sample size was set at 354 women to account for the expected 10% non-responders.

Variables and operational definitions

Knowledge was measured with 14 questions assessing general knowledge and 15 questions asking for the perception of risk factors, with a maximum score of 35 points. **Attitude** was evaluated with 12 questions on a Likert scale from 1 to 5 with the options of "sure no, no, maybe, yes and for sure yes" to ensure understandability

with a maximum of 12 points. The questions were based on the health belief model with proxy variables selected for the items susceptibility, severity, social acceptability, access, cues for actions, barriers and self-efficiency [15]. The cervical cancer screening **practice** was measured with 3 questions with a maximum of 3 points assessing screening history, screening intention and access to screening facilities (supplement 1).

Independent variables were the socio-demographic data on income, age, occupation, religion, ethnicity, marital status, residency and obstetric history. Dependent variables were the scores of knowledge, attitude and practice. The median of the score was used as a cut-off point for knowledge, attitude and practice independently [25]. Those who scored on and below the median were considered to have a bad outcome.

Data sources /measurements

Extensive literature review was done to gather all relevant information in the field using the mesh terms cervical cancer, cervical cancer and KAP, cervical cancer Ethiopia, validity and reliability of KAP questionnaires, cervical cancer Africa, cervical cancer prevention, and cervical cancer pathology. The structure, scales and ranges of a WHO questionnaire on KAP [26] were used and adapted to the Ethiopian setting [3, 4, 9, 23, 27]. After item generation appropriate scales were selected using a nominal polytomous scale for knowledge and practice section and a bounded continuous scale for the attitude section [28]. Content validity was established by a panel of experts including a gynecologist and an epidemiologist [29]. Construct validity was tested using exploratory factor analysis.

Prior to the study, FGD were conducted in Butajira and results were used to select items. A pre-test was done to examine understandability and consistency with 30 participants in Butajira, Ethiopia in January 2018. Afterwards small changes were made to wording and scoring system of the questionnaire. The option "I don't know" was included in the knowledge section to avoid incomplete questionnaires. The questionnaire (Additional file 1) was developed in English, translated into Amharic and back into English to check for consistency. Reliability of the questionnaire was checked by testing for internal consistency using Cronbach's alpha [30]. Cronbach's alpha was 0.69 for the general knowledge section, 0.847 for risk factors, and 0.737 for the attitude section.

The questionnaire consisted of 67 closed questions in 7 sections on socio-demographic data, obstetric history, general knowledge, risk factors, attitude, practice and source of information.

Before starting the study, all health extension workers and data collectors were educated on cervical cancer, symptoms, HPV and possible screening methods. In the beginning of the study data collectors were trained on the questionnaire by explaining the questions, their purpose, possible answers, as well as the skip pattern. The questionnaire, the purpose and topic of the study were explained to the participants by the data collectors. Data was collected after verbal consent by five trained data collectors through interviewer- administered face to face interviews in February 2018 using a door to door approach. Verbal consent is commonly used in Ethiopia due to the high illiteracy rate in rural region. The use of oral consent was discussed and recommended with the institutional review board of Addis Ababa University. The collection process was supervised by two trained supervisors. All data collectors were observed intermittently during the data collection process to ensure the quality of the interview. Before leaving a Kebele the questionnaires were checked for consistency and completeness. Incomplete questionnaires were taken back for re-interviewing.

Methods of analysis

Incomplete questionnaires were excluded from all analysis. Descriptive and summary statistic was done for dependent and independent variables using SPSS 25. The variables marital status, occupation and ethnicity were summarized, and the household income was converted from Ethiopian Birr to USD, using the exchange rate of the February 26, 2018 (1 USD = 27.25 ETB). Independent variables were checked for multicollinearity using the Pearson correlation and chi square test. Some minor, but tolerable associations were found.

Sensitivity analysis was done using the Hosmer-Lemeshow test to analyze goodness of fit of the regression model. As a result, the Hosmer-Lemeshow test was 0.957 for the knowledge section, 0.903 for the attitude section and 0.00 for the practice section. The Practice section contained only 3 questions, so all analyses done to test for sensitivity might be inconclusive. Results of the logistic regression model to assess the practice of cervical cancer screening were included for their face validity. Logistic regression was used to create odds ratios in order to determine the strength of association in between independent and dependent variables using a level of significance of $p < 0.05$. Variables were included individually to select a robust model.

Results

The response rate was 96.3% with 341 out of 354 women completing the questionnaire. 251 (73.6%) participants were Muslims, 64 (18.7%) Ethiopian Orthodox Christian, and 26 (7.6%) protestant Christians. The majority was married, housewife and lived in a rural setting. The mean age was 35.5 years (SD = 5.6 years). In February 2018 the mean household income was 31.95 $ (SD =

47.56 $). Most women had no formal education with a mean of 2.0 years (SD = 2.74 years). Only 9 women had further education after high school. In average the women had 4.4 children with a range of 0–12 children. (see Table 1).

Only a third of the women had heard about cervical cancer and most were unable to name symptoms. Only few women correctly named screening as a method for reducing the risk of developing cervical cancer. None of the women named HPV as a risk factor. Commonly mentioned risk factors were smoking, HIV, multiple sexual partners, early sexual initiation, and STDs. 38 women correctly identified "middle" (30–49 years) as the age at risk of developing cervical cancer. The median of the score was 2 points out of 35 for the risk factor and general knowledge section combined. 139 (40.8%) were considered knowledgeable (see Table 2).

Almost two third of the women thought cervical cancer was deadly and more than half stated it was a serious disease, but only 13.5% felt susceptible to cervical cancer. Half of the women thought screening was possible. Barriers were evaluated by asking for fear of screening procedure. A quarter of the women was scared of screening. For self-efficacy the proxy variables wish for screening, treatment possibilities and wish for treatment were selected. The majority of women wanted to know if they have cervical cancer. Most women thought cervical cancer was treatable and wanted to get treated, if they had cancer. For social acceptability the husband's

perspective towards screening and treatment as well as community and personal support were assessed. Women were asked to describe their husband's perspective on screening and treatment of cervical cancer. The majority stated their husband would allow them to go for screening and treatment. 260 women (76.2%) would personally support women with cervical cancer and 230 (67.4%) said their community would be supportive of cervical cancer patients.

The median of the attitude score was 8 points out of 12, so accordingly 202 (59.2%) women had a negative attitude towards cervical cancer and its screening (see Fig. 1).

Only eight women (2.3%) had been screened before. 240 women (70.4%) had the intention to be screened, however only 107 (31.4%) said they had access to a screening facility. The median of the practice score was one point out of three, so 102 (29.9%) women were considered to have good screening practice.

16 participants (4.7%) felt well informed about cervical cancer. Additionally, 300 (88%) answered they would like to learn more about it. Most women had no source of information (see Fig. 2).

Women with 1–8 years of education had 2.4 times the odds to be knowledgeable (CI:1.36–4.3) than those without any education. Women who had any source of information concerning cervical cancer were 9.1 times more likely to have good knowledge (CI:4.0–20.6), than those who had no source of information. Nurses as a source of

Table 1 Socio- demographic information of participating women in Butajira, Ethiopia

Variable	Category	Frequency (n)	Relative frequency (%)
Religion (n = 341)	Muslim	251	73.6
	Not Muslim	90	26.4
Marital Status (n = 341)	Married	325	95.3
	Not Married	16	4.7
Occupation (n = 336)	Housewife	297	88.3
	Not Housewife[a]	39	11.7
Residence (n = 341)	Urban	34	9.7
	Rural	307	90.3
Education (n = 341)	No formal education	217	63.6
	Elementary school (1-8 yrs)	104	30.5
	Education beyond 9 years	11	3.3
	Higher education beyond high school	9	2.6
Household income per month in USD (n = 339)	< 10 USD	81	23.9
	10–50 USD	204	60.2
	50–100 USD	32	9.4
	> 100 USD	22	6.5
Use of contraceptives (n = 340)	yes	203	59.7
Current use of contraceptives (n = 341)	yes	83	24.3

[a]private employee 14, governmental employee 6, merchant 15, farmer/ daily labor 3, student 1

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Table 2 Women's knowledge on cervical cancer, screening, and risk factors in Butajira, Ethiopia

Variable	Yes n (%)	No n (%)	I don't know n (%)
Heard of CC (n = 341)	125 (36.7)	2 (0.6)	214 (62.7)
Mentioned symptoms (n = 341)	14 (4.1)	7 (2.1)	320 (93.8)
Bleeding	14 (4.1)		
Discharge	2 (0.6)		
Risk reducing possible (n = 341)	19 (5.5)	7 (2.1)	315 (92.4)
Methods for risk reducing (n = 341)			
Lifestyle	3 (0.9)		
Screening	13 (3.8)		
Screening available in community (n = 340)	113 (33.1)	4 (1.2)	223 (65.4)
Screening methods (n = 340)			
VIA	0 (0)	(0)	340 (100)
HPV test	4 (1.2)	2 (0.6)	334 (97.9)
Cytology	3 (0.9)	1 (0.3)	336 (98.5)
Age at risk for CC (n = 341)			
Young (< 30 yrs.)	30 (8.8)		
Middle (30–49 yrs.)	38 (11.1)		
Old (50–70 yrs.)	9 (2.6)		
Senile (> 70 yrs.)	5 (1.5)		
I don't know	271 (79.5)		
HPV as risk factor (n = 338)	**0 (0)**	1 (0.3)	337 (98.8)
HIV as risk factor (n = 341)	74 (21.7)	12 (3.5)	255 (74.8)
Multiple sexual partners as risk factor (n = 341)	86 (25.2)	6 (1.8)	249 (73.0)
Early sexual initiation as risk factor (n = 341)	82 (24.0)	11 (3.2)	248 (72.8)
History of STD as risk factor (n = 341)	84 (24.6)	4 (1.2)	253 (74.2)
Multi-parity as risk factor (n = 341)	68 (19.9)	31 (9.1)	242 (71.0)
Use of contraceptive as risk factor (n = 340)	40 (11.7)	23 (6.7)	277 (81.2)
Smoking as risk factor (n = 341)	110 (32.3)	5 (1.5)	226 (66.3)

information compared to those without information did not significantly raise the odds to be knowledgeable. Having used contraceptives before made it 2.3 times more likely for women to have good knowledge compared to those who never used contraceptives (CI: 1.3–4.1). Every additional dollar per month made it 1.009 times more likely for women to have good knowledge about cervical cancer (CI:1.00–1.01) (see Table 3).

Women who named nurses as a source of information had 4.28 times the odds of having a positive attitude towards cervical cancer (CI:2.4–7.4) and women who named any other source of information had 5.06 times the odds of having a positive attitude (CI:2.4–10.3). Living in an urban setting made it 3.35 times more likely to have a positive attitude towards cervical cancer screening compared to women living in rural areas (CI:1.2–9.0). Women who ever used contraceptives had 2.2 the odds of having a positive attitude compared to those

who never used contraceptives before (CI:1.2–3.8) (see Table 4).

Women who named nurses as a source of information had 21.05 times the odds to have a good practice score than those who named no source (CI: 10.4–42.3) and women who named any source of information had 5.8 times the odds to have a good practice score than those who had no source of information (CI:2.4–13.5) (see Table 5).

Discussion

As one of the few community-based studies conducted in rural Ethiopia with a door to door approach, external validity can be considered high [31]. In comparison to studies conducted in Ethiopia and other African countries awareness of cervical cancer was low in Butajira, since only a third of the participants had heard about the disease before. Other Ethiopian studies conducted in an urban setting reported

Fig. 1 Women's attitude towards cervical cancer and cervical cancer screening
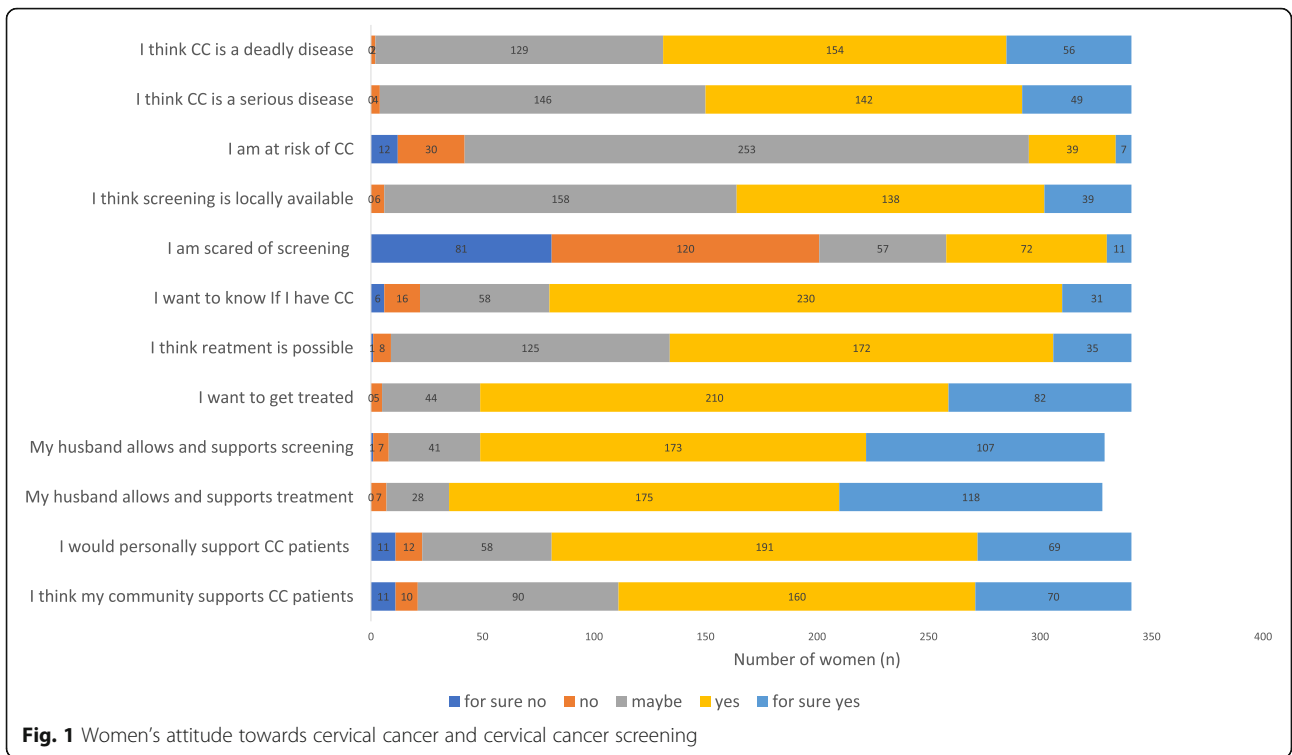
a higher level of awareness; in Dessi town, 57.7% of the study population were aware of cervical cancer [27], in Mekelle, 85% [3], in Gondar 78.7% [23] and in Addis Ababa 50% [14]. Lack of awareness has proven to be one of the major barriers towards cervical cancer screening [10]. In a qualitative study conducted in Burkina Faso it was mentioned as the second most common reason for underutilization [32].

57.8% of the population in Butajira did not know any risk factors. This result was similar to those in Dessie town, Ethiopia (58.1%), in Gondar, Ethiopia (47.5%) and in Hossana, Ethiopa (58.3%). None of the participants in Butajira identified HPV as a risk factor of cervical cancer. In Hossana, Ethiopia 8.9% named HPV as a risk factors and in Kenya 16.9% [33]. Awareness and knowledge of HPV as a risk factor is becoming increasingly

Fig. 2 Women's source of information concerning cervical cancer and cervical cancer screening
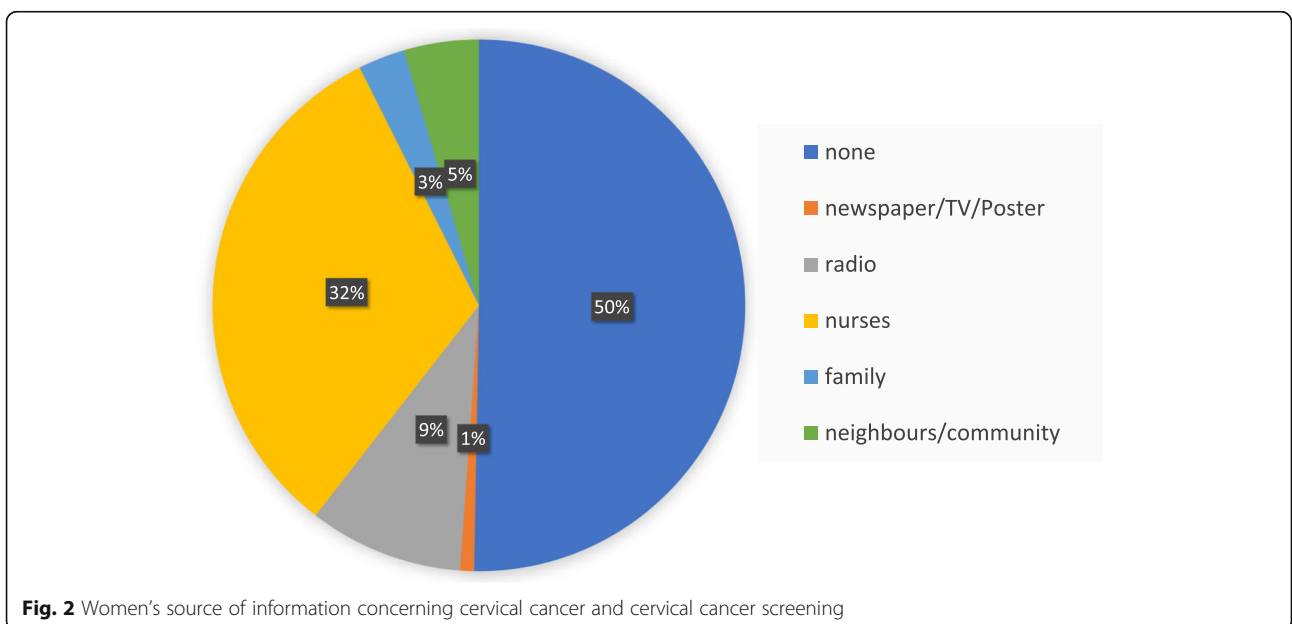
Table 3 Factors associated with good knowledge of women in Butajira, Ethiopia

Variable	OR	95% CI for OR	*p*-value
Education (1–8 yrs. vs none)	2.42	1.36–4.30	**0.002**
Education (9 or more yrs. vs none)	2.30	0.67–7.82	0.18
Higher age	1.02	0.97–1.07	0.415
Source (nurse vs none)	1.52	0.86–2.66	0.143
Source (another source vs none)	9.10	4.00–20.66	**< 0.001**
Residence (urban vs rural)	0.79	0.29–2.15	0.646
Religion (not Muslim vs Muslim)	1.44	0.82–2.55	0.2
Occupation (any occupation vs housewife)	1.58	0.73–3.42	0.244
Contraceptive (ever used vs never used)	2.35	1.34–4.11	**0.003**
Household income per month (USD)	1.009	1.001–1.016	**0.024**

important, as HPV vaccine campaigns and HPV-based screening methods are scaled up in many countries and is also part of the guideline for cervical cancer prevention and control in Ethiopia [21, 34, 35]. The Ethiopian government included raising awareness about cancer related infections such as HPV in the national program 2015 [20, 21] In contrast to other studies, in which participants most commonly named multiple sexual partners [9, 27, 33],or STDs [23], the most commonly named risk factor in Butajira was smoking (110; 32.3%). Perception of risk factors like smoking, HIV, multiple sexual partners, and history of STD might be biased by a generally negative attitude against them. Women who used contraception were more knowledgeable and had a better attitude towards cervical cancer screening, than those who did not. Similar results have been found in rural Kenya [36] and Uganda [37] and could be explained by the contact to medical care and better health seeking behavior.

Only 13.5% of the participants felt at risk of developing cervical cancer. In Finote Selam, Ethiopia, 51.5% of the women felt at risk [24], and in Uganda 76% [38]. In Hossana, Ethiopia, 54% of the participants stated cervical cancer was curable [9], which is comparable to Butajira,

where 60.7% said cervical cancer was treatable. In contrast to many studies, women in Butajira felt supported by their husbands to go for screening (82.1%) and for treatment (85.9%), while in Kenya many women mentioned fear of marital dispute and commonly did not feel supported by their partners [39], the same was recorded in Uganda [37]. In the qualitative study conducted in Jimma, Ethiopia and Addis Ababa, Ethiopia, women also named fear of divorce and shame as one of the major barriers to cervical cancer screening utilization [12].

In Butajira only 2.3% of the women had been screened before. There was no existing cervical cancer screening program in Butajira at the time of data collection. This is less than found in other Ethiopian studies conducted in urban areas such as Hossana (9.9%) [9], and in Yirgalem (9.2%) [18], but higher than the average screening rate in Ethiopia of 0.6% [13]. Studies in Ethiopia focusing on HIV positive women revealed higher screening rates of 11.5% [13].

Health professionals were the most commonly named source of information. Participants in Hossana, Ethiopia also mostly named health professionals or media as a source [9, 14]. Studies conducted in Ethiopia revealed misconceptions about causes, risk factors, risk reduction

Table 4 Factors associated with positive attitude towards screening of women in Butajira, Ethiopia

Variable	OR	95% CI for OR	*p*-value
Education (1–8 yrs. vs none)	1.39	0.78–2.47	0.264
Education (9 or more yrs. vs none)	1.24	0.38–4.00	0.718
Higher age	1.01	0.96–1.06	0.63
Source (nurse vs none)	4.28	2.46–7.43	**< 0.001**
Source (another source vs none)	5.06	2.48–10.33	**< 0.001**
Residence (urban vs rural)	3.35	1.23–9.07	**0.017**
Religion (not Muslim vs Muslim)	1.13	0.65–1.97	0.658
Occupation (any occupation vs housewife)	0.54	0.23–1.28	0.164
Contraceptive (ever used vs never used)	2.21	1.28–3.84	**0.004**
Household income per month (USD)	1.001	0.995–1.007	0.747

Table 5 Factors associated with good practice of women in Butajira, Ethiopia

Variable	OR	95% CI for OR	*P*-value
Education (1–8 yrs. vs none)	1.66	0.83–3.29	0.147
Education (9 or more yrs. vs none)	0.66	0.16–2.67	0.563
Higher age	1.00	0.94–1.06	0.883
Source (nurse vs none)	21.05	10.47–42.34	**< 0.001**
Source (another source vs none)	5.82	2.49–13.59	**< 0.001**
Residence (urban vs rural)	1.02	0.32–3.27	0.962
Religion (not Muslim vs Muslim)	0.57	0.29–1.11	0.099
Occupation (any occupation vs housewife)	0.29	0.08–1.103	0.07
Contraceptive (ever used vs never used)	0.92	0.48–1.76	0.814
Household income per month (USD)	0.99	0.99–1.00	0.855

and screening among health workers [4, 40]. Only 11.4% [4] and 22% [40] of the female health workers had been screened for cervical cancer. Appropriately informed nurses can inspire women to utilize offered cervical cancer screening programs [41]. Surprisingly, naming nurses as a source of information was not statistically significantly associated with a better outcome of the knowledge score. This can raise questions about the health education provided by health workers among the communities. However, naming nurses as source of information was positively associated with the attitude and practice score, putting further emphasis on the relevance of their education. Since brochures, posters and newspapers together were named by 0.6% only, campaigns should focus on oral information distribution. Religion has been mentioned as a source of information by 1.6% of participants in a study conducted in southern Ethiopia among health workers [4], but has not been mentioned as a source of information in Butajira. In contrast to other African studies communication about cervical cancer seems low in the communities in Butajira, since only 2.9% named family and 4.1% neighbors as a source of information. In a qualitative study in Uganda, participants mostly named their aunts and elders within the community as a source of information [37] and in Congo most participants said they heard about cervical cancer from conversations with other people [25]. Having sufficient information on cervical cancer has been linked with better uptake of screening procedures [42]. This further proves the need for accurate awareness campaigns concerning cervical cancer.

Many other studies in Ethiopia have been conducted in urban areas, providing better access to health care and information. The urban setting of Butajira was also associated with a higher attitude score, possibly due to better access to information and health care.

Findings from this study were used to develop appropriate sensitization material and identify possible barriers for the following study on adherence to screening [17]. Furthermore, women who had previously been screened

were not included in the upcoming trial, therefore defining the screening rate in Butajira was an important part of this study. Health extension workers were used for community mobilization during the trial. Since naming health workers as a source of information was not statistically significantly associated to a better outcome on the knowledge score, special emphasis was put on their training to ensure the accuracy during the upcoming trial.

Several limitations have to be named concerning the study conducted in Butajira, Ethiopia. There is no standardized tool to assess knowledge, attitude and practice concerning cervical cancer and its prevention, therefore the comparability is limited. The study population was relatively homogenous in respect to residential area, religion and occupation. There are several limitations to knowledge, attitude and practice studies, as people might give socially desired answers [25] and sensitive subjects might not be answered correctly. Despite careful clustering, selection bias was possible, since participants absent during the time of data collection and those who did not want to participate were not included; this could affect the internal validity of the study [25].

Conclusion
Awareness and knowledge of cervical cancer prevention and risk factors, especially HPV, was low in Butajira, rural Ethiopia. Women's sense of low susceptibility towards cervical cancer was often not favorable for screening practice. Focus should be put on distributing information on risk factors, screening methods and their availability within the area of Butajira, Ethiopia. A higher level of education, having sources of information concerning cervical cancer and use of contraceptives were the most relevant socio-demographic factors for a positive outcome of knowledge, attitude and practice on regression analysis. Special emphasis should be put on training health care providers extensively on cervical cancer and its screening, since they are the primary source of information among the population in Butajira.

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Supplementary information

> **Additional file 1.** Questionnaire for women. Questionnaire used within this study.

Abbreviations
CC: Cervical cancer; CI: Confidence interval; HDSS: Health development surveillance site; HIV: Human immunodeficiency virus; HPV: Human papilloma Virus; KAP: Knowledge, attitude and practice; OR: Odds ratio; SD: Standard deviation; STD: Sexually transmitted disease; TBC: Tuberculosis; VIA: Visual inspection with acidic acid; WHO: World health organization; YRS: Years

Availability of data and materials
The datasets used and analyzed during the current study are not publicly available due to data privacy of participants but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethical approval was obtained from the Martin Luther University review board (2017–143) and the Ethiopian national research committee (339/19/11) after reviewing the study protocol. The method in which consent to participate was obtained was also approved by the Ethiopian research committee. Verbal consent was obtained from every participant before conducting the interview and consent was document by checking off the informed consent form after informing the participants about the study, its purpose and voluntary participation.

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no competing interests.

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Infectious Agents and Cancer

RESEARCH ARTICLE

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Cervical cancer patients presentation and survival in the only oncology referral hospital, Ethiopia: a retrospective cohort study

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Abstract

Background: Women infected with Human Immune Deficiency Virus (HIV) are assumed to be at higher risk of developing Cervical Cancer (CC). This is due to a rapid progression of pre-invasive to invasive lesions. However, evidences suggest, due to the availability of antiretroviral therapy (ART) and care services; an improved survival and treatment outcome of CC patients (CCPs) with HIV infection is expected.

Objective: The aim of this study is to examine the clinical characteristics and survival of of CCPs registered at the radiotherapy center of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa University, Ethiopia.

Methods: We conducted a retrospective cohort study. Data from 1655 CCPs diagnosed between September 2008 and September 2012 were included. The primary endpoint was death from any cause. Kaplan-Meier estimates were compared using the log-rank test. Cox proportional hazards regression model was used to identify predictors of death. Data were analyzed using STATA version IC/14.

Results: The mean age of all patients was 49 years (SD = 11.6 years). Of all CCPs, 139 (8.4%) were HIV positive, 372 (22. 5%) patients had a known negative HIV status and 1144 (69.1%) patients were asymptomatic with unknown HIV status. Due to late stage and waiting times, only 13.5% of the patients received curative radiotherapy doses. HIV-positive CCPs presented more often with advanced disease compared to HIV negative CCPs ((44.6%) versus 39.7%, $p = 0.007$). There was no significant difference in survival between HIV-positive and HIV-negative CCPs. Older age (HR = 2.01; 95% CI, 1. 01,-4.05), advanced disease (HR = 2.6; 95% CI, 1.67–4.04) and baseline anemia (HR = 1.65; 95% CI, 1.24, 2.20) were independent predictors for higher risk of death.

Conclusion: Survival rates of CCPs did not differ according to HIV status. The risk of death was higher for patients with older age, advanced disease and anemia. HIV patients should be screened for CC according to guidelines to avoid late presentation.

Keywords: Uterine cervical neoplasms, HIV, Survival, Africa, Ethiopia

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Background

Cancer and other non-communicable diseases (NCDs) have become leading causes of disability and death in developing countries, including Ethiopia [1]. Cervical Cancer (CC) is a leading cause of cancer morbidity and mortality in women globally. In 2012, 528, 000 new cases and 270,000 deaths were estimated to have occurred worldwide, with the majority of these cases and deaths (90%) occurring in low- and middle-income countries [2]. In Ethiopia, CC is the second most commonly diagnosed cancer and the leading cause of cancer death in women, with about 8000 newly diagnosed cases and 4700 deaths every year [3]. Most CC patients in Ethiopia seek healthcare at an advanced stage, when the effectiveness of treatment is limited [4].

Women infected with HIV are presumed to be more likely to have high risk Human Papilloma Virus (HPV) and have at least a 10% higher risk of developing CC [5–8]. HIV-positive patients are reported to more likely present with advanced stages of CC. It has been shown that HIV changes the natural history of HPV infection, resulting in a rapid progression to invasive lesions, and are associated with adverse survival probabilities [9]. The overall HIV prevalence in adult population of Ethiopia was 1.18% in 2016 with highest prevalence in Addis Ababa and Gambela regions with 4.9 and 4% respectively [10].
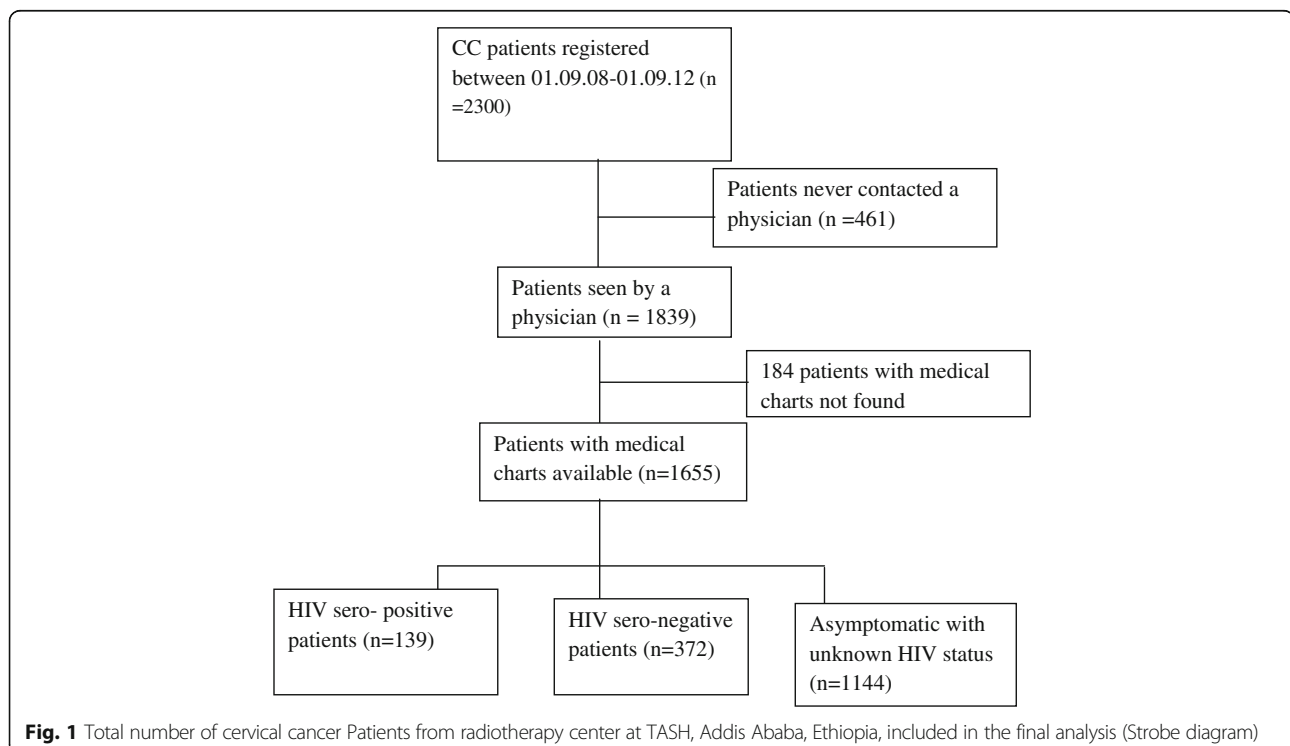
However, in the current context, due to the availability of ART and care services, an improved survival and treatment outcome of cervical cancer patients with HIV infection is expected. There is no adequate information documenting this evidence in Ethiopia. Hence, we conducted a retrospective cohort study to assess the survival rate of cervical cancer patients according to HIV status. We reviewed 1655 charts of women with cervical cancer from Tikur Anbessa University Hospital in Addis Ababa, Ethiopia.

Methods

Study design and population

We conducted a retrospective cohort study among cervical cancer patients diagnosed at Tikur Anbessa (Black lion) Specialized Hospital (TASH) from September 2008 to September 2012. TASH is the national teaching and referral hospital with more than 800 beds and offers diagnosis and treatment for approximately 400,000 in-patients and out-patients a year. The hospital receives patients who are referred from across the country, as well as patients from Addis Ababa. The hospital is the only one with a radiotherapy facility in Ethiopia. Patients were treated with surgery in the early stages and according to locally adapted guidelines at the radiotherapy center. Brachytherapy was not available at the time. Patients also may have registered but there after not received any treatment. Demographic and clinical characteristics of the patients were retrieved from individual patient charts. The survival status of patients was collected from the cancer registry which obtained information from patient cards or via telephone calls,

Fig. 1 Total number of cervical cancer Patients from radiotherapy center at TASH, Addis Ababa, Ethiopia, included in the final analysis (Strobe diagram)

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Study variables and data collection

HIV status identification

The HIV status of each patient was retrieved from medical charts by trained medical staff. Only half of the patient's charts contained a registered HIV status. HIV status was documented if the patient had been screened for HIV. Since September 10, 2011 every patient registered at TASH had been screened for HIV on a regular basis. Before this, only patients with a high risk profile (e.g., HIV-positive partner) or clinically suspicious patients were screened. The HIV status was tested using the enzyme-linked immunosorbent assay method. We grouped HIV status into three categories: HIV-positive, HIV-negative and HIV unknown.

Study outcome and definition

The primary objective of this study was to compare the overall survival of CC patients according to HIV status. We estimated follow-up time between the date of first presentation and the last date of observation. The last date of observation was defined as either death or censoring at the last known alive.

Data analysis

STATA version IC/14 (StataCorp, College Station, TX, USA) was used for statistical analyses. The overall survival of HIV positive and negative patients was estimated using Kaplan-Meier methods. Kaplan-Meier estimates were compared using the log-rank test. Cox proportional hazards regression model was used to identify predictors for survival. Influences of prognostic factors were estimated using hazard ratios with 95% confidence intervals (CI).

Ethical considerations

Ethical approval was obtained from the institutional review board of the College of Health Sciences, Addis Ababa University and Martin Luther University, Halle Germany. The confidentiality of the patient status was maintained by avoiding personal identifiers during analysis.

Results

Of the 1839 cervical cancer patients registered and seen by physicians at TASH, medical charts were retrieved for 1655 (90.0%). Of the 1655 patients with a medical chart, 139 (8.4%) were HIV-positive, 372 (22.5%) were HIV-negative and 1144 (69.1%) were asymptomatic with unknown HIV status (see Fig. 1).

Of all patients, 1081(65.3%) patients received any form of radiotherapy, 190 (11.5%) underwent surgery and 206 (12.4%) received chemotherapy. Among patients treated by radiotherapy, non- radical radiotherapy was provided for 770 (71.0%) of stage IIIB and IVA patients. Of the 190 patients who underwent surgery, 155 (81%) received

Table 1 Demographic and clinical characteristic of cervical cancer patients according to HIV status, TASH, Addis Ababa, Ethiopia, 2008–2012

Patient demographic characteristics	HIV status		
	HIV negative n (%)	HIV positive n (%)	HIV unknown n (%)
Residence			
Urban	128 (34.4)	82 (59)	431 (37.7)
Rural	244 (65.6)	57 (41)	713 (62.3)
Marital status			
Single	3 (0.8)	5 (3.6)	4 (0.4)
Married	297 (79.8)	113 (81.3)	928 (81.1)
Unknown	72 (19.4)	21 (15.1)	212 (18.5)
Age category			
< 30	15 (4.0)	29 (20.9)	47 (4.1)
30–39	81 (21.8)	58 (41.7)	243 (21.2)
40–49	131 (35.2)	40 (28.8)	389 (34)
50–59	88 (23.7)	10 (7.2)	295 (25.8)
60+	57 (15.3)	2 (1.4)	170 (14.9)
FIGO stage at presentation			
I-IIA	59 (15.8)	10 (7.2)	95 (8.3)
IIB-IIIA	148 (39.8)	57 (41.0)	51 (45.1)
IIIB-IVA	144 (38.7)	62 (44.6)	458 (40.0)
IVB	6 (1.6)	5 (3.6)	15 (1.3)
Post-operative	7 (1.9)	2 (1.4)	23 (2.0)
Recurrence	7 (1.9)	3 (2.2)	28 (2.5)
Unknown	1 (0.3)	0	9 (0.8)
Anemia Status			
No anemia ≥12	186 (50)	51 (36.7)	437 (38.2)
> 10 and <12	93 (25)	38 (27.3)	373 (32.6)
8–10	36 (9.7)	24 (17.3)	153 (13.4)
> 5 and <8	24 (6.5)	12 (8.6)	73 (6.4)
< 5	15 (4.0)	12 (8.6)	60 (5.2)
Unknown	18 (4.9)	2 (1.4)	48(4.2)
Co-morbidity status			
No co morbidity	341 (91.7)	124 (89.2)	1045(91.3)
Any co morbidity	31 (8.3)	15 (10.8)	99 (8.7)
Treatment modalities			
Radiation	187 (63.8)	105 (79.5)	789 (75.0)
Surgery	71 (24.2)	12 (9.0)	107 (10.0)
Chemotherapy	35 (12.0)	15 (11.5)	156 (15.0)
Patient outcome			
Alive	331 (89.0)	108 (77.7)	930 (81.3)
Dead	41 (11.0)	31 (22.3)	214 (18.7)
Total	372	139	1144

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radical hysterectomy and nine received a simple hysterectomy (see Table 1).

Patient characteristics

Table 1 shows the demographic and clinical characteristics of patients according to their HIV status. The mean age of all patients at entry was 49 years. The majority of cervical cancer patients with HIV-positive status came from urban areas (59%), while the majority of patients with HIV-negative, HIV unknown status were rural residents (62 and 66%, respectively). The majority of HIV-positive cervical cancer patients were between 30 and 39 years old (42%), with mean age of 39 (SD = 9) whereas HIV negative, HIV unknown cervical cancer patients were between 40 and 49 years (35 and 34%, with mean age of 50, respectively). About 81% of cervical cancer patients were married. The International Federation of Gynecology and Obstetrics (FIGO) stage at presentation for HIV-positive patients was IIB-IIIA (41%) and IIIB-IVA (44.6%); for HIV-negative/unknown patients IIB-IIIA (40 and 45%, respectively) and IIIB-IVA (39 and 40%, respectively). A total of 120(86.3%) of HIV positive women were on ART.

Survival according to HIV status

A total of 286 (17.3%) cervical cancer patients died during the follow-up period. The median survival time was 38 months.. Of the total deaths, 41(11%) and 31(22.3%) were HIV negative and HIV Positives. The median survival of HIV positives and HIV negative was 29 and 28 months respectively.

Crude survival probabilities did not differ between patients according to HIV status. After adjusting for place of residence, age, FIGO stage, co-morbidity (yes/no) and baseline anemia status, no difference in survival
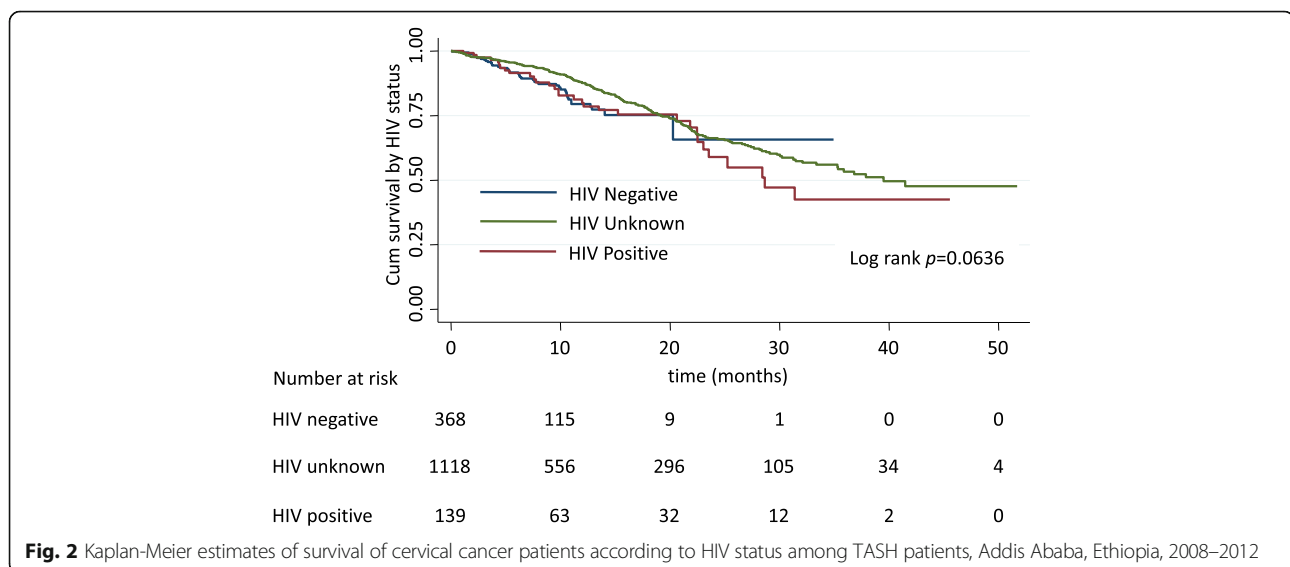
probability was seen between HIV-positive and HIV-negative/unknown cervical cancer patients (HR = 1.16, 95%CI 0.70–1.91) (see Fig. 2).

Survival according to other clinical and demographic characteristics

After adjusting for place of residence, HIV status, FIGO stage, co-morbidity and baseline anemia status, older CC patients had a two-fold higher risk of death than younger patients (HR = 2.02, 95%CI: 1.01–4.05). CC patients with higher cancer stage (FIGO IIB-IIIA and recurrence) had a higher risk of death, with HR = 2.60 (95%CI: 1.67–4.04) and HR = 2.77 (95%CI: 1.35–5.68), respectively, compared to those with a lower stage. Cervical cancer patients with anemia at baseline were more likely to die than non-anemic patients with HR = 1.65 (95%CI: 1.24–2.20) and HR = 1.84 (95%CI: 1.27–2.66) for a hemoglobin level of greater than 10 and between 8 and 10, respectively. Place of residence and co-morbidity status did not show any differences in overall survival of CC patients (see Table 2).

Discussion

This study showed that CC patients with known HIV infection constituted 8.4% of all CC patients registered in the largest referral hospital in Ethiopia. The survival rate was similar among CC patients with and without known HIV infection in this cohort where only 14% of patients received any form of therapy considering only the curative radiotherapy. The majority of patients with known HIV infection came from the urban area, compared to patients without HIV infection. About 86% of the HIV positive CCPs were on ART. A slightly higher proportion of patients with HIV infection presented with late-

Fig. 2 Kaplan-Meier estimates of survival of cervical cancer patients according to HIV status among TASH patients, Addis Ababa, Ethiopia, 2008–2012

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Table 2 Demographic and clinical characteristic associated with the survival of cervical cancer patients, TASH, Addis Ababa, Ethiopia, 2008–2012

Characteristics	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P*-value
HIV status			
Positive	1.00	1.00	
Negative	1.13(0.70,1.81)	1.16(0.70,1.91)	0.564
Unknown	0.77(0.53,1.13)	0.76(0.51,1.15)	0.206
Residence			
Rural	1.2(0.94,1.51)	1.16(0.91,1.48)	0.212
Urban	1.00	1.00	
Age group			
< 30	1.00	1.00	
30–39	1.52(0.78,2.97)	1.43(0.73,2.82)	0.290
40–49	1.50(0.78,2.86)	1.47(0.75,2.87)	0.259
50–59	1.12(0.57,2.20)	1.17(0.58,2.36)	0.650
60+	1.83(0.93,3.61)	2.01(1.01,4.05)[a]	**0.049**
FIGO stage at presentation			
I-IIA	1.00	1.00	
IIB-IIIA	1.32(0.86,2.03)	1.22(0.79,1.88)	0.372
IIIB-IVA	3.07(2.00,4.71)	2.60(1.67,4.04)[a]	**<0.001**
IVB	3.77(1.13,12.55)	2.54(0.74,8.68)	0.137
Post-operative	1.17(0.45,3.07)	1.04(0.40,2.74)	0.930
Recurrence	2.46(1.21,5.00)	2.77(1.35,5.68)[a]	**0.005**
Anemia: Hgb level at presentation (g/dl)			
No anemia ≥12	1.00	1.00	
> 10 and <12	1.82(1.38,2.40)	1.65(1.24,2.20)[a]	**0.001**
8–10	2.20(1.54,3.14)	1.84(1.27,2.66)[a]	**0.001**
< 8 and ≥5	1.47(0.90,2.42)	1.35(0.81,2.25)	0.242
< 5	1.24(0.67,2.31)	1.12(0.60,2.10)	0.706
Unknown	1.74(0.23,12.73)	1.21(0.16,8.96)	0.846
Co-morbidity status			
No co-morbidity	1.00	1.00	
Any co-morbidity	0.98(0.68,1.40)	0.99(0.68,1.43)	0.969

HR hazard ratio, *CI* confidence interval, *HIV* Human Immune deficiency Virus, *FIGO* International Federation of Gynecology and Obstetrics
values in boldface are statistically significant at alpha of 0.05

stage cancer. The median time of observation in patients without event was 38 months. Older age, late-stage disease and anemia were factors significantly influencing overall mortality probabilities of cervical cancer patients.

The survival of CC patients with positive HIV status was similar to those with negative or asymptomatic with unknown HIV status. The observed survival of HIV positive patients could have been compromised for two reasons: either because they die due to the HIV infection or second because the CC is more aggressive. Since we do not have information on cause of death in our study, we can only suggest that the widespread use of ART in

this cohort may prevent HIV related deaths and also fast progression of CC [11–13].

A higher proportion of HIV-infected cervical cancer patients presented with advanced stages of cancer compared to those with negative/unknown HIV status. This is probably because the HIV infection decreases the progression time of cervical cancer to more advanced stages [9, 14].

In our Cox model, we found older age, baseline anemia and advanced stage to be significantly associated with higher all-cause mortality of cervical cancer patients. This finding is consistent with studies conducted

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in similar settings elsewhere. According to a Nigerian study, there was a 41% higher proportion of death for advanced stages compared to early stages [15]. Moreover, a Kenyan finding showed that the 2-year survival of cervical cancer patients at advanced stage was less than 20% [16].

Baseline anemia independently predicted a higher risk of death; moderate anemia was significantly associated with higher mortality compared to patients with no anemia. In this study, anemia was defined as a hemoglobin level below 12 g/dl. Another similar study from north-central Nigeria indicated baseline anemia to be an independent predictor of lower survival in cervical cancer patients [15]. Furthermore, older (≥60 years) patients had a significantly higher risk of death compared to younger patients. Several other studies have also reported this [17, 18]; this might be due to fact that young patients are more likely to respond to treatment and present in an early stage [17]. In addition, it has to be considered that the probability for all-cause death is higher in the older age groups.

The strength of this study is the large number of all CC patients with medical charts available during a 4-year period in TASH, the only hospital for cancer treatment in Ethiopia and the inclusion of those patients who only registered but never received treatment were included. However, a limitation is the large proportion of CC patients with only asymptomatic with unknown HIV status. Since their characteristics were very similar to those with negative HIV sero-status we assume they are more likely to be HIV sero-negative. However, this may have underestimated the effect of HIV on the survival of CC patients. Moreover, about 20% of all cervical cancer patients who registered at TASH and were scheduled to see a physician for treatment planning during the study period did not come back; these patients may have had very advanced disease. We assume that the 10% of charts missing were random cases due to problems of misplacing, or miss-spelling names or numbers. The huge efforts that would have been needed to retrieve these charts were out of scale.

Conclusion

In conclusion, known HIV-positive patients constitute a considerable proportion of CC patients in a hospital cohort in Ethiopia and are diagnosed at a more advanced stage of disease compared to those with negative and unknown status. Survival did not differ between HIV-positive and HIV-negative and -unknown CC patients after adjusting for other prognostic factors. The high proportion of advanced stage cancer in HIV-positive patients suggests the need to increase the implementation and awareness of cervical cancer screening among HIV-positive women and remove barriers to accessing screening. Anemia at presentation probably reflects the severity

of disease and therefore shows adverse survival. Attention should be given generally to those CC patients who are diagnosed at older age and with advanced stage of disease, as these are contributing factors for lower survival rates. Finally, a high proportion of unknown HIV status justifies screening for HIV in all CC patients, this is now in place.

Availability of data and materials

- The datasets analyzed are available from the corresponding author on reasonable request.

Authors' contributions

MG performed statistical analysis and draft the manuscript. EK and AA participated in designing the study, analysis, reviewing and editing the final manuscript and contributed to the discussion. UM, TY and MB carried out the conception, designing the study and data collection. SG, WA, IM, MA and AJ have been involved in revising the manuscript critically with valid inputs. All authors read and approved the final form of the manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board of the College of Health Sciences, Addis Ababa University and Martin Luther University, Halle Germany.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Cervical cancer in Ethiopia – predictors of advanced stage and prolonged time to diagnosis

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Abstract

Introduction: In Ethiopia, most cervical cancer patients present at advanced cancer stages, long time after they experience first symptoms. We investigated possible predictors of long time spans between symptom onset and pathologic diagnosis (patient intervals). We also aimed to seek out predictors for advanced cancer stage diagnosis.

Methods: We conducted a retrospective cohort study among 1575 cervical cancer patients who were registered at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia between September 2008 and September 2012. Cox proportional hazards regression was used to find predictors of long patient intervals. Cumulative odds ordinal logistic regression was used to identify predictors of cancer stage at diagnosis.

Results: Median patient interval was 30 weeks, with the interval substantially longer in patients residing in rural than urban areas. Longer patient intervals were associated with more advanced cancer stages at pathologic diagnosis. HIV-positive women had an almost 1.5 times increased risk of diagnosis at a more advanced stage.

Conclusion: Cervical cancer patients are diagnosed after long time periods leading to advanced stages at diagnosis. Measures to raise awareness about cervical cancer, to increase screening and to shorten the time interval from recognition of symptoms to diagnosis are urgently needed.

Keywords: Cervical cancer, Sub-Saharan Africa, Patient interval, Ethiopia, HIV

Introduction

Cervical cancer incidence and mortality has been drastically reduced in high resource countries during the last decades. This can be largely attributed to the implementation of screening programs for the detection of precancerous lesions and HPV and improved therapy [1, 2]. Yet in low- and middle income countries where access to such measures is limited, cervical cancer remains a significant health problem. The vast majority of an estimated number of 311.000 cervical cancer deaths worldwide occur in less developed regions [3]. In Ethiopia, where almost 6.300 new cases are diagnosed annually,

about 4.884 women die from cervical cancer each year. This makes cervical cancer the second-most common cancer in the country, and the second-most deadly cancer among Ethiopian women [4].

One of the most important prognostic factors is stage at diagnosis, linking early-stage diagnosis with better chances of survival [5]; still most cervical cancer patients present at advanced stages in Ethiopia [6]. Studies examining predictors of late and advanced stage presentation of cervical cancer patients in low- and middle-income countries have been scarce [7]. The relationship between HIV-infection and cervical cancer and the question of whether HIV-infection leads to more advanced cancer stages is discussed controversially [8–10]. The timespan between symptom onset and diagnosis has been associated with stage at diagnosis [11], but other studies could not confirm this [12, 13]. However, these studies were

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conducted in high-income countries where time to diagnosis is considerably shorter. It is unclear whether these results likewise apply to low-income countries such as Ethiopia, where time to diagnosis is long and patients present at advanced stages. Tragically, in a previous study of a hospital cohort of 1.059 cervical cancer patients receiving oncologic treatment in Addis Ababa, Ethiopia, we found long periods of time between diagnosis and the beginning of cancer treatment. This led to stage-migration and thus decreased chances of survival [6].

In this study, using the same cohort (with the addition of patients who were diagnosed with cervical cancer but never received therapy) we focused on the time between patient reported onset of symptoms and pathological diagnosis (patient interval). The aim of this study was to find predictors for cancer stage at pathological diagnosis and longer patient intervals in Ethiopia. We further hypothesized that longer patient intervals lead to more advanced stages at diagnosis.

Methods

Setting

We conducted a retrospective cohort study among cervical cancer patients who registered at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia between September 2008 and September 2012 as described earlier [6, 14, 15]. TASH is the largest hospital in Ethiopia and the only hospital in the country currently offering radiotherapy – thus, people from all parts of the country were referred there for therapy. Early tumor stages from FIGO Ia - IIa were treated with radical hysterectomy with curative intentions. More advanced tumor stages and cases of unclear surgical margins were treated with external beam radiotherapy. At the time of the study, brachytherapy as recommended according to international guidelines was not available in Ethiopia.

Study population

Ethiopian woman who presented at TASH between September 2008 until September 2012 with a primary diagnosis of invasive cervical cancer were eligible for this study. Of 1655 collected patient files, we used 1575 cases for further analysis. Of these 80 patients were excluded: 42 patients presenting with recurrent disease; two asymptomatic patients who were incidentally diagnosed with cervical cancer; 35 with missing dates regarding pathological diagnosis or symptom onset; one with non-invasive cancer. Since there was no nationwide cervical cancer screening program in place, all women included presented with symptomatic disease. Information regarding patient characteristics, clinical characteristics such as histology, FIGO-Stage, symptoms and waiting times were retrieved from patient files from the oncology and gynecology ward.

Predictor variables

The patients' residency was classified as urban or rural. Patients living in one of the 10 largest cities in Ethiopia were classified as 'urban', while the remaining patients living in smaller cities and villages were classified as 'rural'. HIV-status was subdivided into two groups: positive HIV-status, and negative or unknown HIV-status. Comprehensive HIV-screening at TASH was routinely introduced after September 2011; before this time, only clinically-suspicious patients or patients with a high risk profile (e.g. those with an HIV-positive partner) were screened for HIV. The predictor variables in both models were preselected using variables that were coherent with similar studies [16–18]. Other risk factors commonly examined in regards to both late and advanced stage presentation include socioeconomic status variables such as low education and illiteracy [16–22]. These were not recorded in the patient files at TASH, and thus could not be assessed in this analysis.

Staging

Tumors were staged according to guidelines set by the International Federation of Gynecology and Obstetrics (FIGO) [23]. Stage at primary diagnosis when first seen by a physician was used for further analysis in this study. FIGO-stages were assessed around the date of pathology report. In most cases, a chest X-Ray and abdominal ultrasound followed. If there was an upstaging within 4 weeks after the first staging due to distant metastasis findings or hydronephrosis, the higher FIGO-stage was used. FIGO-stages were later grouped for statistical analysis into stage of FIGO I - IIa (patients receiving primary surgery), FIGO IIb, FIGO III (FIGO IIIa and IIIb) and stage of FIGO IV (IVa and IVb).

Time intervals

Patient interval was defined as the time interval between the date the patient noticed the first symptom and the date of the biopsy report. This interval was used because the date of the first symptom and the date of pathologic diagnosis were widely available, whereas the date of first presentation – i.e. when the patient was first seen by a clinician – was not documented for most patients. Data on symptom onset were abstracted from handwritten documents in the patient files. Patient interval was used as a continuous variable in weeks to avoid loss of power and bias [24, 25].

Statistical analysis

Data were analyzed using SPSS Version 23. A cumulative odds ordinal logistic regression with proportional

odds was conducted to examine the effect of time to diagnosis, HIV-status, place of residence and age on stage at diagnosis. The proportional odds assumption was assessed by a full likelihood ratio test. Odds ratios are presented with their corresponding 95% confidence intervals.

Cox proportional hazards regression was used to evaluate the association between predictors and the patient interval and to calculate hazard ratios (HRs) with 95% confidence intervals. Simple regression analysis was conducted using the predictor variables age, place of residence and HIV-status. For multiple regression analysis, we included all three variables into the model.

Results

Patient characteristics

Mean age was 49 years (SD ±11.6 years). Known HIV-seropositive women presented at a mean age of 39 years, while patients with a negative or unknown HIV-status presented at a mean age of 50 years. One hundred thirty-five of the patients were tested HIV-seropositive

(8.6%). Out of the 494 women screened for HIV, 135 women were screened positive and 359 were screened negative. The rest of the women where not screened. Of the HIV-seropositive women, 86.3% were on antiretroviral medication. Close to two thirds of the women came from rural areas. Most woman presented with advanced stages (55.2% stage IIIb or higher). Only 12.1% presented with an early FIGO-stage of I-IIa, making them eligible for surgery (Table 1).

Predictors for longer patient interval

Median patient interval was 30 weeks (range 0–526 weeks). It was shorter for HIV-positive women (25 weeks) compared to women with a negative or unknown HIV-status (30 weeks). Rural women received their pathologic diagnosis after a median time of 32 weeks whereas women from one of the 10 largest cities in Ethiopia were diagnosed after a median time interval of 25 weeks.

Univariate analysis indicated a higher risk for longer patient intervals for women from rural areas compared

Table 1 Demographic and clinical characteristics of the study population according to FIGO Stage at diagnosis (*n* = 1575)

Patient Characteristics	FIGO Stage				
	All Stages	I-IIa	IIb	III	IV
	N	N (%)	N (%)	N (%)	N (%)
All Patients	1575	191 (12.1)	497 (31.6)	731 (46.4)	156 (9.9)
Age (years) (mean + SD) Range 21–93	48,9 ± 11,5	47.9 ± 11.4	49.6 ± 11.9	48.4 ± 11.3	50.9 ± 11.5
Menopausal status					
Premenopausal	344	41 (11.9)	102 (29.7)	175 (50.9)	26 (7.6)
Postmenopausal	1212	148 (12.2)	386 (31.8)	548 (45.2)	130 (10.7)
Unknown	19	2 (10.5)	9 (47.4)	8 (42.1)	0 (0)
Residence					
Rural	976	114 (11.7)	303 (31.0)	465 (47.6)	94 (9.6)
Urban (Biggest 10 Cities)	599	77 (12.9)	194 (32.4)	266 (44.2)	62 (10.4)
HIV Status					
HIV-positive	135	11 (8.1)	37 (27.4)	74 (54.8)	13 (9.6)
negative / unknown	1440	180 (12.5)	460 (31.9)	657 (45.6)	143 (9.9)
Parity (mean + SD) Range 0–17	6.1 ± 3.0	5.6 ± 2.9	6.6 ± 3.1	6.0 ± 3.0	6.5 ± 3.0
Marital Status					
Unmarried	12	2 (6.7)	4 (33.3)	5 (41.7)	1 (8.3)
Early marriage (< 18 years)	1187	146 (12.3)	380 (32.0)	550 (46.3)	111 (9.4)
> 18 years / unknown age	94	20 (21.3)	30 (31.9)	38 (40.4)	6 (6.4)
Unknown Martial Status	282	23 (8.2)	83 (29.4)	138 (48.9)	38 (13.5)
Histology					
Squamous cell carcinoma	1488	170 (11.4)	462 (31.1)	711 (47.8)	145 (9.8)
Adenocarcinoma	66	17 (25.8)	29 (43.9)	12 (18.2)	8 (12.1)
Other	21	4 (19.0)	6 (28.6)	8 (38.1)	3 (14.3)

FIGO International Federation of Gynecology and Obstetrics, *SD* Standard deviation, *HIV* Human immunodeficiency virus
% as proportion among stages

with woman coming from one of the 10 largest cities (HR 1.23; CI 1.11–1.36) (Table 2). Also more likely to be diagnosed later in univariate analysis were younger patients (HR 0.99) and women with a negative or unknown HIV-status (HR 1.19, (CI 1.004–1.43)). After entering all three variables (age, place of residence, HIV-status) in the multiple Cox-Model, the adjusted Hazard Ratio for HIV-status was 1.1 (CI 0.91–1.32) and for age 0.99 (CI 0.99–1). The adjusted Hazard Ratio for place of residence remained 1.23 (CI 1.11–1.36).

Predictors for more advanced stage at diagnosis

We found longer patient intervals associated with more advanced FIGO-stages at diagnosis in the proportional odds model (OR 1.004 (CI 1.002–1.006) p: < 0.001) (Table 3). This means that the odds of being diagnosed in a more advanced stage group increased by 0,004 every week. Patient interval was shortest for early stages (24 weeks for FIGO I-IIa) and longest for advanced stages (35 weeks for FIGO IV) (Fig. 1).

Known HIV-infection was associated with an almost 1.5-fold risk of diagnosis at a more advanced stage compared to those patients with a negative or unknown HIV-status (95% CI 1.05–2.1 *p* = 0.025). Our data suggested no association between place of residence, age and stage at diagnosis.

Symptoms at diagnosis

All patients presented with symptoms related to cervical cancer, with the most common symptoms being abnormal vaginal bleeding, abdominal pain and vaginal discharge (Table 4). Even in early stages I-IIa, 91.1% of patients presented with abnormal vaginal bleeding. Constipation was suggestive of late stage disease: 64% of the patients presenting with constipation were staged IIIb and higher.

Discussion

We found that longer patient intervals increased the risk of advanced stage cervical cancer diagnosis. Previous studies on the effect of longer patient intervals on outcomes like advanced stage and impaired survival

Table 3 Predictors for more advanced stage at diagnosis

Predictors	Odds Ratio (95% CI)	*p*-value
Waiting time (weeks)	1.004 (1.002–1.006)	< 0.001
Age (years)	1.004 (0.99–1.01)	0.31
Place of residence		
rural	1.08 (0.89–1.31)	0.42
urban	1	
HIV-Status		
positive	1.48 (1.05–2.1)	0.025
Negative / unknown		

CI Confidence interval, *HIV* Human immunodeficiency virus

presented conflicting results. Consistent with our findings, in the 1980s Fruchter et al. reported an increased risk for presentation at advanced stages of cervical cancer after long patient intervals [11]. In contrast, Tokuda et al. in Japan found no association between patient interval and stage of cervical cancer in the 1990s. However, Japan is a high-resource country and median patient interval was only 30 days [12], differing substantially from the long patient intervals observed in Ethiopia.

We also found that HIV-infection was associated with more advanced cancer stages at time of diagnosis compared to patients with a negative or unknown HIV-status. The association of HIV and HPV is well-known, and previous studies repeatedly linked HIV-infection with a higher prevalence, incidence and persistence of HPV-infection and its progression into precancerous lesions (especially for patients with low CD4 cell counts) [26, 27]. However, the association between HIV and invasive cervical cancer is less clear. Published data indicate a 1.6 to 2.4 increased risk of developing invasive cervical cancer for HIV-positive women [28, 29]. The effect of seroprevalence of HIV on cancer stage at time of diagnosis in comparable settings is similarly hard to establish.

In South-Africa, Lomalisa et al. found that HIV-positive patients with a CD4 count of below 200/mm3 had significantly more advanced tumor stages than HIV-negative women [9]. Fruchter et al. found HIV-positive

Table 2 Predictors for longer patient interval (time between symptom onset and pathologic diagnosis)

Predictor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p*-value
Age (years)	0.99 (0.99–1)	0.99 (0.99–1)	0.7
Place of residence			
Rural	1.23 (1.11–1.36)	1.23 (1.11–1.36)	< 0.001
Urban			
HIV-Status			
positive	1.19 (1.004–1.43)	1.1 (0.91–1.32)	0.29
Negative/unknown	1	1	

HR Hazard ratio, *CI* Confidence interval, *HIV* Human immunodeficiency virus
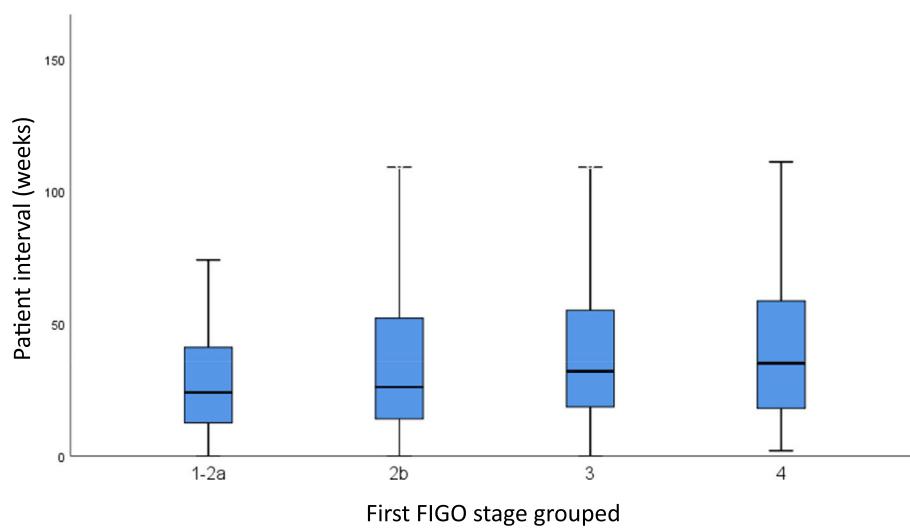
Fig. 1 Box-plot showing median patient interval (time between symptom onset and pathologic diagnosis in weeks) with 25th and 75th percentile by FIGO stage group

patients to be at elevated risk for advanced cervical cancer diagnoses in univariate analysis. That said, their observed study group was small and statistical significance ceased after adjusting their model for other variables [8]. Moodley et al. found advanced stages among both HIV-positive and -negative patients with no association between HIV-status and stage [10]. On average HIV-seropositive women in our study presented 11 years younger than patients with a negative or unknown HIV-status [14]; this is consistent with the previous scientific literature where HIV-positive women presented 10–15 years earlier than HIV-negative women [10, 30]. The association of HIV-infection and advanced stage presentation of cervical cancer could potentially be explained by the HIV-associated immunodeficiency leading to a more rapid cancer growth, although other authors attribute this to molecular interactions between HIV and HPV [31–33]. Ibrahim et al. in Sudan identified high age and rural residence as predictors for advanced stage presentation [16]. Findings from similar studies in Morocco and South India include socioeconomic factors such as low education and illiteracy [17, 19].

In our study, women from rural areas tended to have longer patient intervals. This may be attributable to a low awareness of cervical cancer and its associated symptoms or the lack of health facilities and skilled personnel in rural parts of the country. Macleod et al. reported a lack of awareness and a misinterpretation of the seriousness of symptoms as the main risk factor for long patient intervals [20]. Fear of finding cancer and socioeconomic factors like illiteracy were other common themes among comparable studies [11, 17, 21].

In multivariate analysis, rural origin was associated but both age and HIV-status were not associated with long patient intervals in our study. Other factors that presumably influence the length of the patient interval include financial and logistic factors including delays in health care service.

We observed long time periods of median 25 to 35 weeks between women noticing the first symptom and pathological diagnosis among all stages, increasing with FIGO-stage. A comparable study in Nepal found shorter patient intervals of median 22 weeks [18]. Even in early stages, women were often diagnosed after many weeks or months of experiencing symptoms of cervical cancer such as abnormal vaginal bleeding, pain and vaginal discharge. After pathological diagnosis, patients often had to wait months until radiotherapy started, which further increased the risk of cancer progression [6].

Table 4 Intensity of common symptoms when first seen by a physician among cervical cancer patients (*n* = 1575)

Symptoms	Intensity of symptoms									
	None		Mild		Moderate		Severe		Unknown	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Vaginal bleeding	115	(7.3)	404	(25.7)	977	(62.0)	74	(4.7)	5	(0.3)
Pelvic pain	442	(28.1)	213	(13.5)	858	(54.5)	57	(3.6)	5	(0.3)
Vaginal discharge	424	(26.9)	331	(21.0)	814	(51.7)	–		6	(0.4)
Constipation	1267	(80.4)	101	(6.4)	197	(12.5)	5	(0.3)	5	(0.3)

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The key strength of this study is the large sample size with patients coming from all over Ethiopia. There are, however, certain limitations we need to acknowledge. Data regarding patient and tumor characteristics and dates used for the calculation of patient interval were extracted from handwritten medical records. These dates relied on self-reporting from patients who might have been subjected to recall bias. We do not know how well women remembered the date of symptom onset and how meticulously it was documented. Secondly, women who were symptomatic for a long time but never presented to a health care professional may have died at advanced stages without ever being diagnosed at TASH and thus did not appear in our study. Hence, such a selection bias might falsely result in favorable data, particularly for patients with advanced cancer stages. Since the date of first presentation to a health care professional was not available for many patients, it was not possible to identify precisely at which stages of the diagnostic pathway these delays occur. Some patients may have been clinically diagnosed earlier and then had to wait until referral for pathological diagnosis – yet for the patients for whom all data were available, this interval did not vary substantially between tumor stages and residence. Qualitative research is needed to identify the impediments to diagnosis which lead to long patient intervals and more advanced stage presentation.

Previous studies found that efforts in down-staging helped to significantly increase overall survival. A three-year program in rural Tanzania with the aim of down-staging cancer through proactive visits from trained health aides into people's homes showed favorable results [34]. One study conducted in rural India found that a cervical cancer education group effectively reduced the ratio of advanced stage diagnoses and increased the number of women diagnosed at early tumor stages [35]. However, awareness of cervical cancer and knowledge of risk factors, signs and symptoms are still low among women in Ethiopia and other African countries [36–38]. In Malaysia, advanced cervical cancer presentation (stages III and IV) dropped from 60 to 26% within 4 years after a program was introduced, focusing on training health staff and strengthening public awareness through the use of pamphlets and posters in clinics and hospitals [39].

Prevention and down-staging programs could be integrated in HIV/AIDS care programs and other preexisting healthcare infrastructures like it has been successfully implemented in Zambia [40, 41]. Alongside an increased coverage of HPV vaccination and screening, such initiatives could help reduce cervical cancer mortality and incidence worldwide.

Conclusion
Our results support the hypothesis that long patient intervals lead to more advanced cervical cancer stages at pathologic diagnosis. Especially rural women tended to be diagnosed late and need to be addressed through awareness programs. HIV-postive women were at elevated risk of advanced tumor presentation; this should encourage efforts of the government to implement specific screening programs for HIV positive women. In addition to the current government efforts to implement nationwide screening programs, information about signs and symptoms of the disease should be spread.

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Publisher's Note

3. Discussion

In this section, an attempt was made to link the major findings of studies included in this document to the current national and global direction in cervical cancer screening, as part of the goal of cervical cancer elimination. In addition, the strength and limitations of the studies were elaborated so that future research can further consider the gaps identified. Finally, this chapter points out key conclusion remarks with recommendations for better implementation of cervical cancer screening in Ethiopia. Therefore, I will discuss the results of each study by comparing it with other similar studies conducted elsewhere. Chronologically, I preferred to first discuss studies related to cervical cancer screening as it is the main interest of this Ph.D. work. Secondly, I will discuss studies that focused on cervical cancer patients' presentations and their survival, which were conducted to understand the impact due to the lack of organized cervical cancer screening in Ethiopia; this calls again for the need for effective and acceptable methods of preventive and controlling interventions.

3.1 Uptake of Self-Sampled HPV Testing for Cervical Cancer Screening in Ethiopia

Screening is a cornerstone of cervical cancer prevention and control. It has been stated that most developed countries are able to prevent up to 90% of cervical cancer incidence and death through organized early detection and treatment of precancerous lesions. Accordingly, developing countries, where the burden of the disease is very high, and only limited resources are available, should invest in disease prevention aspects through HPV vaccination as the primary prevention and screening as the secondary prevention. In addition, attaining the high coverage of these preventive interventions can only be achieved by appropriate technology that fits the need of a large population. As part of this effort, we have conducted a first-in-kind population-based randomized trial to investigate whether self-sampled HPV testing would result in higher acceptability and uptake by the Ethiopian population compared to the standard care of screening, in our case that of VIA.

The population-based uptake of self-sampled HPV testing in the Ethiopian setting was significantly higher compared with VIA. In this population, the uptake for self-sampled HPV testing was 1020 (84.1%) compared with the VIA, where 575 (50.5%) visited the screening point for VIA (P <0.0001). In addition, self-sampled HPV showed a higher adherence to procedures, including the follow-up tests and treatment compared with VIA (65.4% vs 40%). These findings are supported by studies conducted in the region and elsewhere worldwide. A study from Uganda reported >99% uptake of self-sampled HPV testing vs 48.4% for VIA

(Moses et al., 2015); an underserved rural population in Greece (100% vs 17.1%) (Chatzistamatiou et al., 2017); and 93% of women preferred self-sampled HPV testing among the indigenous community in Guatemala (Gottschlich et al., 2017).

Currently, as part of the global cervical cancer elimination plan, the WHO and key stakeholders have recommended highly precise HPV testing for cervical cancer screening for all settings, including resource-limited settings (WHO, 2019). For the successful implementation of any intervention, the acceptability or preference of the end-user has paramount importance. In this regard, women's preference for self-sampled HPV testing has positively influenced the uptake of the method to attain the expected outcome.

Prior to this trial, we conducted a community-based survey to assess women's knowledge, attitude, and practice of cervical cancer and its screening in the same study setting. Accordingly, we found that 33% of the women were aware of the screening service was available, but only 2.3% of the community in the study area had previously been screened for cervical cancer. Moreover, only 4.7% of women knew one or more symptom of the disease, and none of the women named HPV as a risk factor. Therefore, in countries including Ethiopia, where the coverage of cervical cancer screening is very low (Kasa et al., 2018; Ruddies et al., 2020), self-sampled HPV testing could be a potential solution as the method avoids several barriers associated with VIA, such as taboo related to medical vaginal examination, fear of pain, long travel to the point of care, and long waiting time at health facilities (Gupta et al., 2018; Gizaw et al., 2019).

Despite all these benefits, the costs related to the lab-based HPV testing are considerably high, including its logistic requirements, compared with the VIA. Therefore, as the development of a point of care test is not yet ensured, it is difficult to recommend it for general practice due to its feasibility in Ethiopia. However, there are attempts by several companies to develop a point of care test, and the cost is expected to become lower than the current price for developing countries. In Ethiopia, there is a vision to nationally enroll the self-sampled HPV testing once a low-cost point of care is available in the global market.

In addition to increasing women's uptake of screening, HPV self-sampling also improves the adherence for the follow-up tests and treatment. In this study, 85% of women who were tested positive for one of the high-risk HPV underwent the follow up VIA screening and colposcopy examination. Moreover, all women who were referred for cancer treatment have visited the appropriate health facility as per the request. These findings are comparable with studies done

in Chile and Australia, where 85% and 76% of women attended a follow-up colposcopy examination, respectively (Gupta et al., 2018).

3.2 Reasons For Not Attending Cervical Cancer Screening in Rural Ethiopia

Since there were women who did not attend VIA and also some who did not attend the HPV self-sampling, we explored the actual reasons for not attending the cervical cancer screening from both arms. A direct comparison was done between those who attended the screening and those who did not show up for cervical cancer screening after receiving similar education and sensitization.

The findings suggested that 83% of women who did not participate in either of the screening approaches had assumed themselves to not be at risk of developing the disease in their lifetime (Gizaw et al., 2020). This result is consistent with studies from our baseline study, and those in Ghana and Saudi Arabia, where the majority of study participants claimed the same misconception (Ebu et al., 2015; Salem et al., 2017; Ruddies et al., 2020). Additionally, personal reasons for not attending the offered screening were being busy with other competing livelihood activities (72.5%), self-assertion of being healthy (13.6%), husband influence (20.3%), fear of positive results, and the feeling of shame as screening involved their genitalia being touched. These findings reaffirm that personal beliefs and perceptions, societal influence, and health service-related barriers have an impact on the attendance of women for cervical cancer screening. (Ebu et al., 2015; Salem et al., 2017).

In developing countries where the majority of women live in rural settings with very limited education and service access, assuring or resolving inbuilt individual and societal barriers is very difficult. Therefore, it is highly important to understand the community perception and potential difficulties that prevent women's participation in screening. At the same time, community engagement and involvement of key actors or influential's such as elders, religious leaders, community leaders, leaders of informal arrangements, and women association frontiers must come on board in all aspects of screening activities. In our screening activities, we worked with all levels of community arrangements, from the first rapid assessment study which aimed to understand the situation, up to the end of screening activities. In general, to improve the participation of women in cervical cancer screening, the interventions must be culturally sound and uphold an individual's perception and customs. Moreover, the screening strategy should also be accustomed in a way to meet societal expectations.

"Lack of time" or "being busy" with other routine activities was singled out as a key hindering factor for cervical cancer screening. It was found to be difficult for women to get a good time to visit a health facility, especially for many women from rural settings. In Ethiopia, about more than 80% live in rural parts of the country, in difficult situations coping with poverty. So, it seems harder for them to pursue the offer, especially when they feel healthy and asymptomatic. So far, in Ethiopia, access to cervical cancer education and screening is only confined to a few hospitals, with most of them in the urban parts of the country. Therefore, making the screening service available at their "door step" would resolve difficulties related to time. As a result of this, self-sampled HPV testing could be used as a means to mitigate such barriers, as it can be offered in women's vicinity or at home in less time and with higher uptake.

3.3 Cervical Cancer Patients´ Presentations and Survival

The International Federation of Gynecology and Obstetrics (FIGO) stage at presentation for 80% of cervical cancer patients from the main tertiary referral hospital in Addis Ababa was above IIB, and therefore associated with a higher mortality rate. In this population, only 14% of the women presented at an early stage when treatment is more effective. These proportions are comparable to studies from the neighboring countries, where 72% of the women were diagnosed IIIA and above at presentation in Lagos (Anorlu et al., 2004), 73% in Kenya (Wamburu et al., 2016), and 72% in Sudan (Ibrahim et al., 2011). This late presentation at diagnosis, specifically in developing countries like our settings, is mainly associated with poor or no access to preventing and controlling services for cervical cancer such as availability of HPV vaccination and screening for early detection. Moreover, knowledge and educational levels were also identified as a key hindering factor for poor health-seeking behavior.

In our study, the median survival of cervical cancer patients was only 38 months; this is comparable with women from Uganda, where the absolute 5 years survival was 16%. However, it was 60% even in the underserved African-American population residing in the USA (Denny and Anorlu, 2012). It has been well noted that HIV infection increases the susceptibility for cervical cancer and fastens the progression of full-blown cervical cancer (Denslow et al., 2014). In Africa, where the HIV prevalence is high, the treatment of cervical cancer is becoming challenging since HIV infection is related to the advanced stage of the disease and a very low CD4 count (Begoihn et al., 2019). However, in our study, the survival of CC patients with positive HIV status was similar to those with negative or asymptomatic with unknown HIV status (Gizaw et al., 2017). The absence of a significant difference in survival in our study could

be due to a lack of data on the cause of death and widespread use of antiretroviral therapy (ART) that reduces HIV related deaths and fast progression of cervical cancer.

In developing countries like Ethiopia, longer patient intervals are a major problem to provide appropriate treatment as it directly associated with the late presentation at diagnosis and ends up with poor patient prognosis. The median patient interval reported was 30 weeks, where the majority of rural residents appeared to seek health care (Begoihn et al., 2019).

Cervical cancer is disproportionally affecting women from the region with lower Human Developmental Index (HDI); more than 80% of new cervical cancer and 90% of death due to cervical cancer are being reported from these regions. However, despite the presence of effective preventive interventions, a considerable number of women are left behind from accessing the service in developing countries (Ginsburg et al., 2017; Bray et al., 2018). Therefore, the high burden of late-stage diagnosis of cervical cancer in African settings warranted appropriate interventions for the general population, and special attention should be rendered for women residing in rural settings and HIV patients. To meet the desired goal, cervical cancer prevention and control interventions such as HPV vaccination, screening, and timely appropriate treatment should target underserved women in developing countries, including Ethiopia.

3.4 Strengths and Limitations

The key strength of the trial was the findings generated using the robust study design, which employed a cluster-randomized trial. The study was also unique in the country, as the comparison of screenings was made at the population level using the HDSS. In addition, the reasons for not attending the screening were collected from the direct interview of the study participants who did not show up for the screening. On the other hand, self-sampled HPV testing was first introduced in the study area for cervical cancer screening. In addition, the baseline survey had good external validity as it was conducted at a community level with an adequate sample size.

One of the strengths of the studies on cervical cancer patients' presentations and survival was maintaining the larger sample size with a good representation of cervical cancer patients throughout the country, as the data was generated from the only referral hospital for cancer care during the study period. Moreover, all registered patients for cervical cancer care were included in the study irrespective of their treatment status.

The first limitation of the randomized trial to optimize cervical cancer screening was that clusters were randomized either to Butajira Hospital for VIA screening, where the service was available or to the primary health care center in their vicinity for self-sampling for HPV testing. In this regard, women from the VIA arm had to travel longer and incurring additional charges to reach the service point. So, the availability of the VIA service in women's proximity would have increased the uptake of VIA screening. However, the uptake of VIA was still found to be lower than the self-sampled HPV testing in clusters were both screening methods were rendered similarly at their "door step". Moreover, to avoid the high influence of travel costs, study participants were compensated for any study associated costs during the sensitization events.

The first limitation while assessing reasons for non-attending cervical cancer screening was the inability to assess all women who did not attend both screening strategies. In this study, data were collected for 390 women of the total 761 non-attendants. Even though we assumed that a considerable number of women accessed compared well to the other studies and most of the missing data were probably random, it was more likely to miss certain groups of women who were working outside their home, and their opinion may have therefore been underestimated. The second limitation was that the main reasons for not attending the screening were explored by open-ended questions without considering qualitative in-depth interviews. Hence, it would have been better to explore the reasons for not attending the screening by a supplemental qualitative research component to better understand the situations of women. However, we assume explored reasons for not attending screening could be similar to qualitative findings as the identified reasons were supported by other studies conducted elsewhere.

One of the limitations of the baseline survey was the lack of standardized tools to assess knowledge, attitude, and practice pertaining to cervical cancer and its prevention; therefore, this may have affected the comparability with other studies. Furthermore, social desirability bias may have affected the response of the study participants.

The first limitation from the two studies focusing on cervical cancer patients presentation and survival and the predictors of the advanced stage, was that about 20% of women who were symptomatic for a long time but never presented to a health care professional may have died in the advanced stages without ever being diagnosed at Tikur Anibessa Specialized Hospital(TASH) and thus did not appear in our study. Therefore, this study might underestimate the level of late presentations and cannot accurately identify the stages of the diagnostic pathway on which the delay occurred. In addition, these studies were based on secondary data;

as a result, important information was missing, such as HIV status. Moreover, the accuracy of data could not be verified as the information was captured from handwritten medical charts and some of the charts were damaged. Recall bias also could not be ruled out as information on survival was obtained by self-reporting.

3.5 Conclusions

In conclusion, as part of the efforts to improve cervical cancer screening uptake in Ethiopia, self-sampled HPV testing could resolve the challenges associated with the standard care of screening currently being implemented. The findings suggested that self-sampled HPV based screening has superior uptake by the targeted women compared to the VIA. Moreover, the self-sampled HPV testing has improved the uptake of a follow-up screening and adherence to required procedures. However, the scale-up of the HPV-based screening in Ethiopia could be challenged with the current lab-based testing as this method requires trained personnel, more logistics, and other resource mobilization. As a result, the development of a point of care will have a significant impact on resolving all the odds associated with the current sample processing practice.

On the other hand, to increase the women's participation in cervical cancer screening, special consideration must be given for women who reside in rural settings and engaged in small scale outdoor jobs for a living. The perception of women about their health was also associated with poor awareness and knowledge about cervical cancer and its prevention, which in turn contributed to women not attending the screening. Therefore, culturally acceptable behavioral education to resolve the perception and misconception related to disease and screening should be emplaced. Besides, to increase women's attendance for screening a swift and convenient screening service should be offered, which can be done at the women's "door step". Finally, community engagement by including all relevant actors, could have an impact on the better outcome of cervical cancer prevention interventions, especially for the rural settings in Ethiopia.

Late presentation at diagnosis is a critical concern of cervical cancer care in Ethiopia. The advanced stage of cervical cancer at the presentation is associated with the poor survival of the disease. Studies have identified older age, rural residence, HIV status, and extended patient interval as significant predictors of advanced tumor presentation. Consequently, community awareness creation about the disease and its signs and symptoms to improve the health-seeking practice should be done nationwide with due emphasis for rural settings. The current government and non-government organizations' efforts to achieve nationwide cervical cancer

screening should be strengthened. Moreover, adequate attention should be given on creating awareness among health care providers, including primary care workers on cervical cancer and its screening, since they are the primary source of information among the population in the study area.

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5. Thesis:

1. Self-sampled HPV testing for cervical cancer screening has superior uptake compared to the conventional VIA screening at the population level in Ethiopia (84.1% vs 50.5%).

2. Self-sampled HPV testing has significantly improved the adherence of women for follow up tests and treatment in Ethiopia. 85% of women followed the subsequent tests after the HPV testing result is being positive.

3. The majority of women in the study area (83%) considered that they were not at risk of developing cervical cancer in their lifetime without being vaccinated and screening practice.

4. Only 2.3% of the women in the study area had been screened for cervical cancer before the screening trial was rolled out.

5. Cervical cancer prevention and control must be widely implemented in Ethiopia as the awareness of women towards the disease, the access of treatment, and palliative care service is very limited.

6. Being busy with other routine activities (72.5%), assumption that their spouse would not allow screening (20.3%), self-assertion of being healthy (13.6%), and fear of positive results after screening were the commonest reasons reported for withholding cervical cancer screening.

7. Being assigned to VIA screening (AOR 3.51, 95% CI, 2.56–4.82), Women residing in rural settings (AOR 1.99, 95% CI, 1.13–3.48), and women engaged in some form of outdoor work (AOR 1.64, 95% CI, 1.13–2.39) had higher odds of deferring participation in cervical cancer screening.

8. More than 80% of cervical cancer patients are diagnosed at FIGO stage of IIB and above with stage IA being very unlikely.

9. Only 13.5% of cervical cancer patients in Ethiopia received curative radiotherapy doses due to their late stage presentation and longer waiting time to get the treatment, as the service is only available at Tikur Anibessa Specialized Hospital in Addis Ababa.

10. The median patient interval for cervical cancer patients is 30 weeks in Ethiopia. The median survival of cervical cancer patients is 38 months. The survival was not different according to HIV status (Log rank $p = 0.06$)). An increased risk of advanced-stage diagnosis was higher among rural residents and HIV positive women.

Declaration of Independence (Selbstständigkeitserklärung):

I hereby declare that I have written this work independently and have never used any sources or tools other than those specified.

Addis Ababa, 04.08.2020_____

    Place and date   Signature

Explanation of Previous dissertation attempt (Erklärung über frühere Dissertationsversuche):

I hereby declare that this work is the first attempt of writing a dissertation. I also declare that this work is exclusively submitted as a dissertation for the Medical Faculty of the Martin Luther University Halle Wittenberg.

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Top ten Peer-reviewed Publications

1. **Gizaw M,** Teka B, Ruddies F, Abebe T, Kaufmann AM, Worku A et al. Reasons for not Attending Cervical Cancer Screening and Associated Factors in Rural Ethiopia: *Cancer Prev Res* 2020; Published OnlineFirst May 5, 2020
2. **Gizaw M,** Teka B, Ruddies F, Abebe T, Kaufmann AM, Worku A et al. Uptake of cervical cancer screening in Ethiopia by self-sampling HPV DNA compared to visual inspection with acetic acid: a cluster randomized trial. *Cancer Prev Res* 2019;12:609-616
3. Friederike R., **Muluken G**., Brhanu T. et al,: Cervical cancer screening in rural Ethiopia: a cross- sectional knowledge, attitude and practice study. BMC Cancer (2020) 20:563
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