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Optimierung des Zervixkarzinom Screenings im ländlichen Äthiopien: Wissensstand, Einstellung und Teilnahme

Dissertation zur Erlangung des akademischen Grades

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Referat

Die vorliegende Arbeit beruht auf den Ergebnissen vierer quantitativer populationsbasierter Studien mit dem Ziel die Zervixkarzinom Prävention im ländlichen Äthiopien zu optimieren. Die erste Studie „Knowledge, Attitude and Practice“ (KAP) Studie untersucht Wissen, Haltung und Praxis bezüglich des Zervixkarzinoms und dessen Prävention in der ländlichen Bevölkerung in Äthiopien. Die zweite „Screening“ Studie vergleicht die populationsbezogenen Teilnahmeraten an zwei verschiedenen Screeningmethoden: Humane Papillom Viren (HPV)-Selbstabnahme und visuelle Inspektion mit Essigsäure (VIA), sowie die Adhärenz zu Therapieempfehlungen. Im Anschluss wurden die Gründe bei Nichtteilnahme („non-Attendance“ Studie) erfragt. Von den Proben der HPV-Selbstabnahme wurden die populationsbezogene Prävalenz und Verteilung der HPV-Geotypen erfasst („HPV-Studie“).

Im Rahmen der KAP-Studie wurden 350 Frauen befragt. Die meisten Frauen hatten ein fehlendes Bewusstsein für das Zervixkarzinom und hielten sich nicht für gefährdet. Kommunale Krankenschwestern waren die meist genannte Informationsquelle zum Thema Zervixkarzinom. Acht Frauen (2,3%) hatten zu Beginn der Studie bereits an einem Screening teilgenommen. Höhere Schulbildung, die Angabe von Informationsquellen und die Verwendung von Verhütungsmitteln waren assoziiert mit einem besseren Wissenstand und einer positiveren Haltung zur Prävention des Zervixkarzinoms. Die cluster- randomisierte „Screening“ Studie wurde 2018 in Butajira, Äthiopien durchgeführt. 2356 Frauen wurden zum Screening mittels HPV DNA-Nachweis oder VIA eingeladen. Der HPV-Test war mit einer Teilnahmerate von 84,1% (1020/1213) und einer Adhärenz zu Therapieempfehlungen von 65,4% (794/1213) der VIA mit einer Teilnahmerate von 50,5% (575/1143) und einer Adhärenz zu Therapieempfehlungen von 40% (458/1143) überlegen. Zeitmangel, ein subjektives Gesundheitsgefühl und Angst vor dem Testergebnis waren Gründe für die Nichtteilnahme. 764 der 893 HPV-Proben wurden untersucht, um die HPV Prävalenz in Butajira zu bestimmen und eine Genotypisierung vorzunehmen. Die Prävalenz für Hochrisiko HPV in Butajira lag bei 20,5 % (157/764). HPV 16 (101/764, 13,2%), HPV 35 (36/764, 4,7%), HPV 52 (28/764, 3,7%), HPV 31 (25/764, 3,3%) HPV 45 (17/764, 2,2%) und HPV 18 (16/764, 2,1%) waren die häufigsten Genotypen.

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Summary Report

This dissertation report is based on the results of four quantitative population- based studies aiming to optimise cervical cancer screening in rural Ethiopia. The first Knowledge, attitude, and practice study (KAP Study) assesses knowledge, attitude and practice of cervical cancer and its prevention as well as barriers towards cervical cancer screening in a rural population cohort in Butajira, Ethiopia. The second study (Screening study) compares uptake rates and adherence to therapy recommendations of two different cervical cancer screening methods among the same population: Human papilloma virus (HPV)- self sampling and nurse conducted visual inspection with acidic acid (VIA). Afterwards, reasons for refusal to participate were evaluated ("non-attendance study"). The HPV samples were used to assess the HPV prevalence as well as genotype distribution ("HPV-study").

For the KAP study 350 women were selected randomly. Awareness of cervical cancer was low among women in Butajira and most believed not to be susceptible to developing cervical cancer. Only 8 women (2.3%) had previously participated in cervical cancer screening. Community nurses were the most named source of information regarding cervical cancer. A higher level of formal education, naming community nurses as source of information and the use of contraceptives were positively associated to a better outcome in the comprised knowledge, attitude, and practice score. The cluster randomised screening study was conducted in Butajira, Ethiopia in 2018. 2356 women were invited to participate in the screening using either VIA or HPV based tests. With a participation rate of 84.1% (1020/1213) and an adherence to therapy recommendations of 65.4% (794/1213) the HPV test proved to be superior to the VIA with a participation rate of 50.5% (575/1143) and an adherence to therapy of 40% (458/1143). Reasons for non-attendance were feeling healthy, a lack of time and fear of the result. 764 of the 893 HPV samples were used to assess the prevalence and genotype distribution in Butajira, Ethiopia. The high-risk HPV prevalence was 20.5% (157/764). HPV 16 (101/764, 13,2%), HPV 35 (36/764, 4,7%), HPV 52 (28/764, 3,7%), HPV 31 (25/764, 3,3%), HPV 45 (17/764, 2,2%) and HPV 18 (16/764, 2,1%) were the most common genotypes.

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Abkürzungen und Akronyme

DNA	Desoxyribonucleid acid
FIGO	The International Federation of Gynecology and Obstetrics
HDI	Human development Index
HDSS	Health and demographic surveillance site
HIV	Human immune deficiency virus
HPV	Human papilloma virus
IARC	International Agency for Research on Cancer
KAP	Knowledge attitude and practice
KI	Konfidenzintervall
LMIC	Low- and middle-income countries
NCDs	Non communicable diseases
OR	Odds Ratio
SSA	Sub-Sahara Africa
UICC	Union for International Cancer Control
VIA	Visual inspection with acetic acid
WHO	World Health Organisation

1.Einleitung und Zielsetzung

Das Zervixkarzinom ist noch immer die vierthäufigste Krebserkrankung der Frau weltweit, obwohl die Entstehung eines Zervixkarzinoms durch adäquate Prävention verhindert werden kann (1) (2). Weltweit unterscheiden sich Inzidenz und Mortalität erheblich (siehe Abbildung 1) (3) .

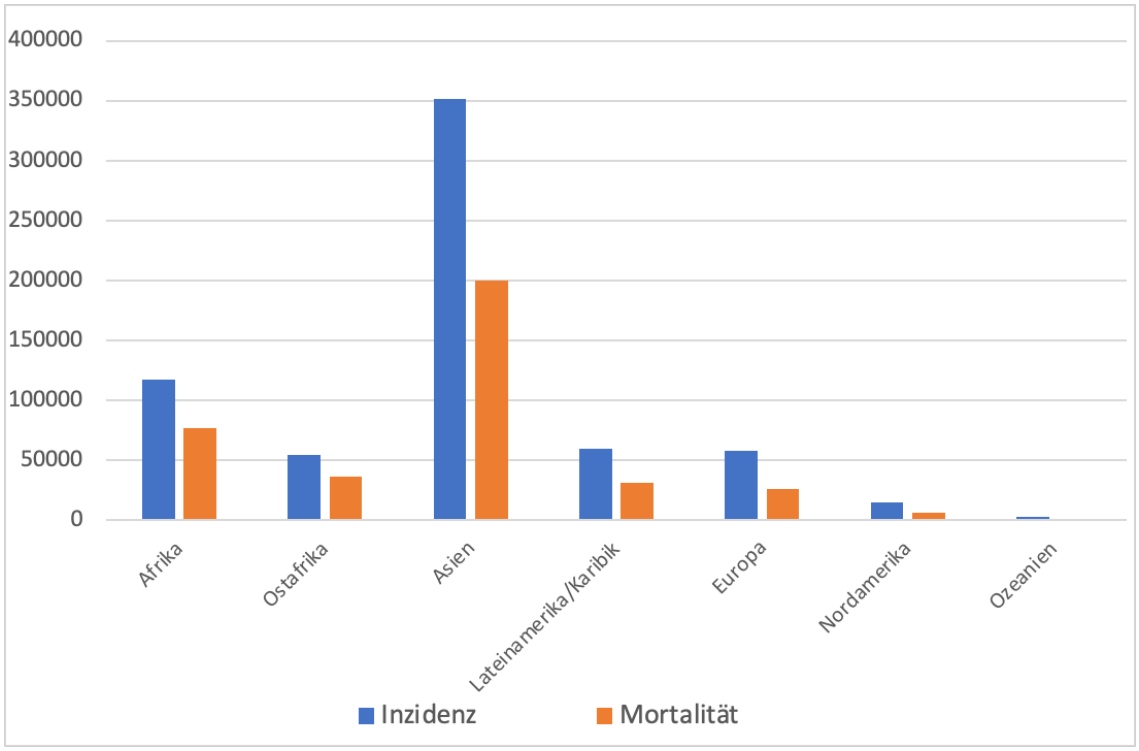

Abbildung 1: Inzidenz und Mortalität des Zervixkarzinoms

Die GLOBOCAN Studie von 2018 schätzte, dass es weltweit 569,847 Neuerkrankungen gab, davon traten 180,877 in Ländern mit mittleren oder niedrigen Einkommen (LMICs) auf (4). Sub Sahara Afrika (SSA) hat eine der höchsten altersstandardisierten Inzidenzen und Mortalitätsraten (5). In Äthiopien gab es im Jahr 2018 geschätzt 7,100 neu am Zervixkarzinom erkrankte Frauen und 4,700 durch ein Zervixkarzinom verursachte Todesfälle (6). Im August 2020 veröffentlichte die Weltgesundheitsorganisation (WHO) eine globale Strategie zur Elimination des Zervixkarzinoms. Die Zielsetzung der globalen Strategie ist die Absenkung der Mortalität auf unter 4 pro 100.000 Frauenjahre (7). Bis 2030 sollen laut dieser Strategie 90% der Mädchen im Alter unter 15 Jahren mindestens eine HPV-Impfung und 70% der Frauen im Alter von 35 Jahren eine Screeninguntersuchung erhalten haben, sowie 90% aller an einem Zervixkarzinom erkrankten Frauen adäquat behandelt werden (7).

Das Zervixkarzinom entwickelt sich langsam im Laufe von 10-20 Jahren (2). Die Hauptursache des Zervixkarzinoms ist eine chronische Infektion mit humanen

Papillomaviren (HPV) (2). HPV sind Doppelstrang-DNA-Viren, deren DNA 6 frühe regulative Proteine (E1, E2, E4, E5, E6, E7) und 2 späte strukturelle Proteine (L1, L2) kodiert (8). Die Klassifizierung der Viren in ihre Genotypen erfolgt anhand des L1 Proteins, das für das Anbinden an die Epithelien und die daraus resultierende Infektion von Bedeutung ist. Infektionen, die von dem Immunsystem nicht eliminiert werden, verursachen vorwiegend durch das Onkoprotein E6 und E7, das regulativ in den Zellzyklus der Wirtszellen eingreift, Mutationen und konsekutiv präkanzeröse Läsionen (8). HPV werden in „Hochrisiko“ und „Niedrigrisiko“ Genotypen unterschieden. Die Hochrisiko Genotypen HPV 16 und 18 sind zusammen für 70% aller Zervixkarzinom Erkrankungen verantwortlich (2). Weitere Hochrisiko HPV Genotypen sind unter anderem 31, 33, 35, 39, 45, 51, 52, 56, 58, 68 und 59 (9). Andere Risikofaktoren für die Entstehung des Zervixkarzinoms sind Rauchen, ein geschwächtes Immunsystem, eine HIV-Infektion, frühe sexuelle Aktivität und Multiparität, sowie Ko-Infektionen mit Chlamydien (9).

Präventive Maßnahmen gegen das Zervixkarzinom umfassen Impfungen gegen die high-risk HPV-Typen und Früherkennung von Krebsvorstufen durch regelmäßiges Screening (1). Als Optionen für das Screening stehen die zytologische Untersuchung mittels PAP-Abstriches, die visuelle Inspektion nach Applikation von Essigsäure (VIA) oder der HPV DNA-Nachweis zur Verfügung (7, 10).

Der PAP Abstrich ist eine Zytologie- basierte Untersuchung, bei der entnommene Abstriche pathologisch untersucht werden (10). Die WHO empfiehlt PAP-Abstrich basierte Screeninguntersuchungen nur für Länder mit einem bereits etablierten Screeninguntersuchungsprogramm und einer hohen Partizipationsrate (11). 2016 ergab eine systematische Literaturrecherche, dass nur ein kleiner Anteil aller Frauen in SSA jemals an einer gynäkologischen Untersuchung mit einem PAP-Abstrich teilgenommen habe, in Äthiopien nur 1% der Frauen (12).

Um auch in LMICs ein möglichst flächendeckendes Zervixkarzinom-Screening zu gewährleisten, hat die WHO bis zur Veröffentlichung der neuen Leitlinien im Jahr 2021 die VIA empfohlen (1, 13). Präkanzeröse Läsionen verfärben sich in der Transformationszone aufgrund der Proteindenaturierung in den Krebszellen weiß. Diese Läsionen können mit einer guten Lichtquelle mit dem bloßen Auge erkannt werden (14). Die Vorstufen des Zervixkarzinoms können lokal mit einer Kryo- oder Lasertherapie behandelt werden. Die WHO empfiehlt die Kryotherapie mit Kohlendioxid- oder Stickstoffgas als kostengünstige Behandlungsoption für LMICs (15). 2015 wurde in Äthiopien mit der VIA als Screeninguntersuchung begonnen, bisher gibt es aber kein flächendeckendes lokal verfügbares Screening für das Zervixkarzinom in Äthiopien (16) (17). Aktuell wird die VIA von der WHO nur noch als primäre

Screeninguntersuchung empfohlen, wenn Länder keine Ressourcen für das HPV-basierte Screening haben (18).

Eine weitere Screeningmethode ist der Nachweis von HPV-DNA (7). In den 2021 von der WHO veröffentlichten Richtlinien für das Screening und die Therapie des Zervixkarzinoms wurde der HPV-DNA Test aufgrund seiner höheren Spezifität und des höheren negativen prädiktiven Wertes als primäre Screeninguntersuchung weltweit empfohlen (18). Ein weiterer Vorteil des HPV DNA-Tests gegenüber der VIA ist, dass die Frauen die Probe selbst abnehmen können, (19), was den Zugang zu Screeninguntersuchungen erheblich erleichtert (20). Viele Länder nutzen die Zytologie weiterhin im Anschluss an einen positiven HPV-Test als Triage Untersuchung (21) (22). Der HPV-Test erwies sich als kosteneffektive Screeninguntersuchung (23, 24). In einer Studie aus Nicaragua wurden die Alternativen PAP-Abstrich alle 3 Jahre, HPV-Test plus gegebenenfalls konsekutive Kryotherapie, HPV-Test und VIA und HPV-Test und PAP miteinander verglichen, mit dem Ergebnis, dass HPV-Test plus konsekutive Kryotherapie am wenigsten kostenintensiv und am effektivsten war (23). Neuere HPV-basierte Testverfahren, die das Ergebnis innerhalb von wenigen Stunden ermitteln, ermöglichen eine single-visit Strategie (24). Ein Beispiel ist der Xpert-Test, der in Malawi in einer ländlichen Kohorte getestet wurde (25).

Die Impfung gegen HPV- Hochrisiko Stämme, wie HPV 16 und HPV 18, ist eine weitere effektive Strategie zur Eradikation des Zervixkarzinoms (22). Die WHO empfiehlt die HPV Impfung für Mädchen im Alter 9-14 Jahren vor Beginn der sexuellen Aktivität mit 2 Impfdosen (7). HPV-Impfstoffe bestehen aus L1-Kapsid Proteinen verschiedener HPV-Genotypen und enthalten keine HPV-DNA (26). Es stehen bivaltente, quadrivalente und nonavalente Impfstoffe zur Verfügung, je nach Anzahl der enthaltenen HPV-Genotypen (26). Alle Impfstoffe enthalten HPV 16 und 18, quadrivalente zusätzlich die Niedrigrisiko Genotypen HPV 6 und HPV 11 und nonavalente außerdem HPV 31, 33, 45,52, und 58 (26). 2017 hatten 65 Länder erfolgreich ein 2 Dosen Regime für 9-14-jährige Mädchen implementiert (26). Studien zur Effektivität zeigten eine Serokonversion bei 98% der Kohorten nach einer 2-maligen Impfung mit dem nonavalenten Impfstoff, der im April 2016 in einem 2 Dosen Impfregime zugelassen wurde (27). Der zusätzliche Vorteil der nonavalenten Impfung im Gegensatz zu der quadrivalenten Impfung für die Prävention des Zervixkarzinoms wird auf 14,7-20% geschätzt (28). Die Seropositivität für Antikörper gegen HPV wurde bis zu 9,4 Jahre nach 3-maliger Impfung nachgewiesen (29). Ein mathematisches Modell belegte die Reduktion der Zervixkarzinom Inzidenz um 89,4% bei einmaliger Impfung und einer 90% Partizipationsrate innerhalb einer Bevölkerung (22). Zwischen 2006 und 2017 wurden weltweit 100 Millionen Mädchen und junge Frauen gegen HPV geimpft, von denen 95% aus ressourcenstarken Ländern stammen. Im Jahr 2020

haben nur 25% der LMICS die HPV Impfung in das nationale Impfprogramm aufgenommen (7).

Alleinige Impfung führt allerdings auch bei einer 90% Partizipationsrate in allen 78 LMICS bis 2030 zu keiner deutlichen Senkung der Mortalität (30). Diese wird kumulativ mit 13,2 Todesfällen pro 100.000 Frauen angegeben, lässt sich aber durch die Implementierung von 2 Screeninguntersuchungen im Alter 35 und 45 mittels HPV Tests auf 8,5 pro 100.000 Frauenjahren absenken (7).

In den von der WHO 2020 herausgegebenen Rahmenrichtlinien zur Verbesserung der Behandlung des invasiven Zervixkarzinoms wird der Fokus auf eine flächendeckende adäquate Behandlung gelegt, die Radiotherapie, eine operative Versorgung und Chemotherapie umfasst (31). Die WHO NCD cancer capacity survey ergab aber, dass 60% der LMICs eine Screeninguntersuchung für das Zervixkarzinom anbieten ohne über die Ressourcen für die konsekutive Diagnostik, Therapie und palliative Versorgung zu verfügen (31, 32). Die Dezentralisierung der kurativen und palliativen Behandlung des Zervixkarzinoms ist für die erfolgreiche Implementierung des WHO Plans von Bedeutung (33), da sonst insbesondere in ländlichen Regionen der LMICs der Zugang zu Diagnostik und Therapie erschwert wird (33, 34). Frauen aus ländlichen Regionen Äthiopiens hatten ein längeres Zeitintervall zwischen Beginn der Symptome bis zur pathologischen Diagnose des Zervixkarzinoms, was möglicherweise an einem Mangel an Gesundheitseinrichtungen und Fachpersonal in den ländlichen Regionen liegt (6). Die meisten der Zervixkarzinom Erkrankungen in SSA, so auch in Äthiopien, werden in einem fortgeschrittenen Stadium diagnostiziert (35). 2014 waren in einer in Addis Ababa durchgeführten Studie 46,7% der Patientinnen im FIGO Stadium IIb- IIIa (36) und in einer retrospektiven Studie aus dem Jahr 2019 waren 65,1% der Patientinnen in Addis Ababa im Stadium III oder IV (37). Besonders für das fortgeschrittene Zervixkarzinom ist die Radiotherapie mit externer Bestrahlung und Brachytherapie eine wichtige kurative oder palliative Behandlungsoption (31). Radiotherapie ist nur in 16% der LMICS flächendeckend verfügbar (31). Eine Studie aus Äthiopien belegte eine mediane Wartezeit bis zum Beginn der Radiotherapie von 3,8 Monaten (36). Radiotherapie wird aufgrund der niedrigen Personalkosten als eine kosteneffektive Therapieoption beschrieben (38). Aufgrund der qualitativen Unterschiede in der Therapie, maßgeblich bestimmt durch das Vorhandensein von Radiotherapie, schwankt die 5-Jahres Überlebensrate aller Stadien des Zervixkarzinoms weltweit zwischen 20-80% (31). So wurde die 5-Jahresüberlebensrate in einer retrospektiven Studie, die 2019 in Addis Ababa, Äthiopien durchgeführt wurde mit 38,6% angegeben (37).

Für die kurative Therapie früher Stadien des Zervixkarzinoms ist die operative Therapie eine wichtige Therapieoption, aber Studien ergaben, dass in SSA ein Mangel an gynäkologisch-onkologisch subspezialisierten Ärzten besteht (25).

Die WHO Studie zum Management von NCDs aus dem Jahr 2020 ergab, dass in 68% der Länder die Palliativversorgung am wenigsten finanzielle Mittel erhielt, sodass ein Jahr nach der Erstdiagnose 48% der Zervixkarzinom Patientinnen finanzielle Katastrophen erleiden (39). Eine 2018 in Äthiopien durchgeführte Studie zur Palliativversorgung weiblicher Patientinnen ergab, dass die meisten Patientinnen nicht adäquat mit Schmerzmitteln versorgt waren und unter Nausea, Anorexie, Schmerzen und Schlaflosigkeit litten (40). Für Äthiopien gibt es nationale Leitlinien für die Palliativtherapie, diese sind aber noch nicht flächendeckend umgesetzt und das Konzept der Palliativversorgung ist in Äthiopien wenig bekannt (40). Aufgrund der insgesamt schlechten therapeutischen Situation ist die Prävention des Zervixkarzinoms in Äthiopien von großer Bedeutung.

Screeninguntersuchungen und HPV- Impfprogramme haben die Inzidenz und Prävalenz des Zervixkarzinoms in ressourcenstarken Ländern effizient gesenkt, aber strukturelle und soziokulturelle Barrieren erschweren die Implementierung präventiver Maßnahmen in LMICs (5, 17). Viele LMICs haben bisher keine für den lokalen Kontext adaptierte Leitlinie für die Screeninguntersuchung, Diagnostik und Behandlung des Zervixkarzinoms, sodass regionale strukturelle und soziokulturelle Barrieren nicht berücksichtigt werden (33). Strukturelle Barrieren zur Teilnahme an Screeninguntersuchungen umfassen Kosten, Anfahrtswege, und fehlende lokal verfügbare Impfungen und Screeninguntersuchungen durch Mangel an geschultem Personal, Technik, oder Materialien (41). Soziokulturelle Barrieren sind unter anderem die Scham vor dem Entkleiden, das für die gynäkologische Untersuchung nötig ist und das Stigma des positiven Testergebnisses (19). Zusätzlich ist das Konzept der Prävention zur Früherkennung von Krankheiten vor dem Auftreten von Symptomen in vielen LMICs nicht bekannt, sodass Screeninguntersuchungen und Diagnostik oft miteinander verwechselt werden (42). In vielen afrikanischen Ländern wird ein Arzt oft erst aufgesucht, wenn die Erkrankung alltagsrelevant symptomatisch wird (43). Zudem gilt eine Krebserkrankung in LMICs oft noch immer als ein Todesurteil, da lokal kaum Behandlungsoptionen zur Verfügung stehen (44, 45).

Auch ein fehlendes Bewusstsein für das Zervixkarzinom, Wissenslücken über die Ursachen der Erkrankung und die Fehleinschätzung der eigenen Suszeptibilität sind häufig Barrieren zur Teilhabe (43, 46). Der Zusammenhang zwischen der Infektion mit HPV und der Entstehung eines Zervixkarzinoms ist in LMICs oft nicht bekannt (42). Frauen nannten in einer qualitativen Studie, die 2017 in Äthiopien durchgeführt wurde, kulturelle und religiöse Überzeugungen als Ursache (43). Aufgrund der 2018 in

Äthiopien begonnenen Implementierung von HPV Impfungen und HPV basierenden Screeninguntersuchungen wird der Mangel an Wissen über HPV in der Bevölkerung zunehmend problematisch (43) .

Die vorliegenden Studien zur Optimierung des Zervixkarzinom Screenings wurden 2018 in Butajira durchgeführt, einer Stadt mit circa 40.000 Einwohnern, die 130 km südwestlich der äthiopischen Hauptstadt Addis Ababa in Zentraläthiopien gelegen ist. Dort unterhält die Universität Addis Ababa eine „Health and Demographic Surveillance Site“ (HDSS) zur Erfassung der Geburts- und Sterberate, sowie der Migration in einem urbanen und 9 ländlichen administrativen Bezirken in und um Butajira. Die Daten der HDSS wurden im Rahmen dieser Studie zur Identifizierung der Haushalte genutzt. Die 10 administrativen Bezirke der HDSS in Butajira, Äthiopien wurden in 22 Cluster mit je 80 Frauen aufgeteilt. 350 Frauen aus dieser Stichprobe wurden für die zuerst durchgeführte „KAP Studie“ gezogen, um den aktuellen Wissensstand und die Haltung zum Zervixkarzinom und dessen Prävention zu erfassen (47). KAP Studien werden oft genutzt, um quantitative Information bezüglich bestehender Wissenslücken, kultureller Überzeugungen und Barrieren zu präventiven Maßnahmen zu erheben (48). KAP Studien evaluieren den Wissensstand und das Bewusstsein (Knowledge), sowie die Einstellung (Attitude), einschließlich bestehender Gefühle, Vorlieben, Abneigungen und Barrieren zur Prävention (49). Dem Abschnitt zur Einstellung liegt das Konzept des Health belief Modells zugrunde, welches unter anderem die Dimensionen Suszeptibilität, Selbstwirksamkeit, und Barrieren zur Teilhabe an der Prävention untersucht (49). Die Fragen zum Verhalten (Practice) befassen sich mit der Teilnahme an präventiven Maßnahmen wie dem Zervixkarzinomscreening (siehe Tabelle 1) (48).

Tabelle 1: Knowlegde, Attitude and Practice: Abschnitte und Themen des Fragebogens in Butajira, Äthiopien

Abschnitt	Thema
Knowledge (Wissen)	Bewusstsein
	Symptome
	Prävention
	Behndlungsoptionen
	Risikofaktoren
Attitude (Einstellung)	Bedrohlichkeit der Erkrankung
	Suszeptibilität
	Soziale Akzeptanz
	Handlungsmotivation
	Barrieren
	Zugang (zu Practice verschoben)
	Selbstwirksamkeit
Practice (Ausüben)	Screening in der Vergangenheit
	Intention zur Teilnahme am Screening
	Zugang

Aus den 22 Clustern in Butajira, Äthiopien, wurden im Anschluss an die „KAP Studie“ zufällig 2356 Frauen zur Screeninguntersuchung mittels HPV DNA-Nachweis oder VIA eingeladen („Screening Studie“) (50). Frauen aus den Clustern, die an keiner der Screeninguntersuchungen teilnahmen, wurden zu den Gründen ihrer Nichtteilnahme befragt („Non-Attendance“ Studie) (51). Die HPV-DNA Abstriche wurden im Labor der Universität Addis Ababa untersucht und zur Qualitätssicherung mit den Ergebnissen der Charité, Berlin verglichen. Ergebnisse der HPV-DNA Abstriche wurden zur Erhebung einer populationsbasierten HPV-Prävalenz und Genotypisierung genutzt („HPV-Studie“) (52). Daraus ergeben sich die folgenden Fragestellungen:

1. Was wissen Frauen in Butajira, Äthiopien über das Zervixkarzinom und dessen Prävention?

2. Welche Einstellung haben Frauen in Butajira, Äthiopien zu der Prävention des Zervixkarzinoms?

3. Welcher Anteil der Frauen in Butajira, Äthiopien hat bereits an einer Screeninguntersuchung teilgenommen?

4. Welche soziodemographischen Faktoren beeinflussen den Wissensstand und die Einstellung zum Zervixkarzinom und dessen Prävention, sowie die Teilnahme am Screening in Butajira, Äthiopien?

5. Welche Informationsquellen haben Frauen in Butajira, Äthiopien zu dem Thema Zervixkarzinom und dessen Prävention?

6. Welche Screeningmethode (VIA versus HPV) bevorzugen Frauen in Butajira, Äthiopien?

7. Welche soziodemographischen, kulturellen und strukturellen Vor- und Nachteile bieten die VIA- und die HPV-DNA basierte Untersuchung im Kontext der Provinz Butajira im ländlichen Äthiopien?

8. Was sind Gründe für die Nichtteilnahme am Screening für das Zervixkarzinom in Butajira, Äthiopien?

9. Wie hoch ist die populationsbasierte high risk HPV- Prävalenz in Butajira, Äthiopien?

10. Wie ist die Verteilung der HPV- Genotypen in Butajira, Äthiopien?

Die vorliegende Dissertation basiert auf vier als Anlage beigefügten Veröffentlichungen. Ziel der Studien ist ein Beitrag zur Optimierung des Zervixkarzinom Screenings im ländlichen Äthiopien. Im Rahmen der Dissertation war ich zusammen mit äthiopischen Kollegen der School of Public Health der Universität Addis Ababa an der Gestaltung, Anpassung und Testung der Fragebögen für die „KAP-Studie“ und die „non-attendance Studie“ beteiligt. Ich habe im Rahmen der „KAP-Studie“ die Datensammler, die vor Ort die Interviews durchgeführt haben, eingewiesen und beaufsichtigt. Ferner habe ich an der Erstellung des Informationsmaterials für die Aufklärungskampagne für die „Screening Studie“ mitgewirkt. Ich habe für die „Screening Studie“ den VIA- Arm betreut und war für die „HPV- Studie“ an der Probenentnahme beteiligt.

2. Diskussion

2.1 KAP Studie

2.1.1 Wissensstand und lokale Evidenz zu Wissen

Frauen in der Region um Butajira, im südlichen Äthiopien, wussten wenig über das Zervixkarzinom, dessen Symptome und Risikofaktoren. Nur 36% (125/341) der Frauen hatten ein Bewusstsein für das Zervixkarzinom (47). In einer anderen Studie, die im Norden Äthiopiens durchgeführt wurde, gaben 31% (196/633) der Frauen an, vom Zervixkarzinom gehört zu haben (53) und auch in einer Studie aus Burkina Faso wurde ein vergleichbarer Mangel an Bewusstsein für das Zervixkarzinom genannt (54). Keine der Probandinnen in Butajira nannte eine HPV-Infektion als Risikofaktor für die Entstehung des Zervixkarzinoms (47). Zu ähnlichen Ergebnissen kam auch eine 2019 in der Amhara Region Äthiopiens durchgeführte Studie, in der 88,7% der 337 Probandinnen angaben, niemals von HPV gehört zu haben (55). 2017 nannten in Kenia 15,1% (68/451) der Probandinnen HPV als Risikofaktor für die Entstehung eines Zervixkarzinoms (56). Zwar gaben Probandinnen in einer 2017 in Äthiopien durchgeführten qualitativen Studie an, vom Zervixkarzinom gehört zu haben, konnten aber wenig konkrete Symptome benennen, verwechselten es mit einem Prolaps oder Hämorrhoiden und gaben als Ursache den Kontakt zur Sonne oder heißen Oberflächen an (42). In Butajira wurden Blutungen nur von 4,1% (14/341) der Probandinnen als Symptom des Zervixkarzinoms genannt (47), aber in einer quantitativen Studie aus Jimma, Äthiopien, nannten 33,2% (244/737) der Probandinnen postkoitale Blutungen als ein Symptom des Zervixkarzinoms (57). Wie auch in Butajira hielten sich viele junge Frauen, die an einer Studie in Zimbabwe teilnahmen, selbst häufig für nicht gefährdet, ein Zervixkarzinom zu entwickeln (58).

In der vorliegenden Studie aus Butajira wurden die Probandinnen gefragt, woher sie Informationen bezüglich des Zervixkarzinoms und dessen Prävention hatten. Kommunale Krankenschwestern wurden mit 32% (109/341) als häufigste Informationsquelle zum Thema Zervixkarzinom angegeben (47). Auch eine in Hossana, Äthiopien durchgeführte Studie ergab, dass Frauen die meisten Informationen bezüglich des Zervixkarzinoms von kommunalen Krankenschwestern erhielten (17), in Jimma nannten 35,7% (263/737) der Probandinnen Gesundheitsfachkräfte als Informationsquelle (57). Die Absicht, am Screening teilzunehmen war in einer in Uganda durchgeführten Studie mit dem Kontakt zu kommunalen Gesundheitsarbeitern und der Diskussion über das Zervixkarzinom assoziiert (59). In einer Studie aus Gondar, Äthiopien hatten nur 68,6% (269/392) der teilnehmenden Krankenschwestern einen exzellenten Wissenstand zum Thema Zervixkarzinom (60). Eine qualitative Studie in Uganda belegte ebenfalls, dass Krankenschwestern oft wenig Detailwissen

über das Zervixkarzinom hatten (61). Ursachen, Prävention und Therapie des Zervixkarzinoms sollten daher in das Curriculum der Krankenschwestern integriert werden (62). In Uganda (62) und in einer Studie aus dem Kongo (63) gaben Probandinnen an, die meisten Informationen von der Familie und Bekannten zu bekommen. In Butajira nannten nur 5 % (17/341) der befragten Frauen die Nachbarn, oder Freunde als Informationsquelle (47).

2.1.2 Haltung und Einstellung und dessen lokale Evidenz

In Butajira hielten sich 13,5% (46/341) Frauen für gefährdet, an einem Zervixkarzinom zu erkranken (47). Eine Studie, die in Ghana durchgeführt wurde, konnte einen signifikanten Zusammenhang zwischen der wahrgenommenen Suszeptibilität für das Zervixkarzinom und der Teilnahme an einer Screeninguntersuchung nachweisen (64). 61,5% (210/341) der Frauen in Butajira hielten das Zervixkarzinom für eine tödliche Erkrankung (47). In Uganda wies eine populationsbasierte Studie auf einen Zusammenhang zwischen der wahrgenommenen Schwere der Erkrankung und der Absicht, an einer Screeninguntersuchung teilzunehmen, hin (65).

Im Gegensatz zu anderen Studien aus Kenia (56) und Äthiopien (43) gaben Frauen in Butajira, Äthiopien an, dass ihre Männer der Screeninguntersuchung und- Behandlung des Zervixkarzinoms gegenüber meist positiv eingestellt seien (47). In Zimbabwe zeigte sich, dass junge Männer, die zu dem Thema Zervixkarzinom befragt wurden, oft wenig über die Erkrankung wussten und generell keine positive Einstellung zur Zervixkarzinom-Screeninguntersuchung hatten (58). Ein Teilnehmer sprach zum Beispiel von sexuellen Problemen und konsekutiver Infertilität durch Zervixkarzinom als einem Anlass zur Trennung (58). Angst vor Konflikten in der Ehe und dem Missfallen der Ehemänner gegenüber der Untersuchung wird oft als Hindernis für die Zervixkarzinom Prävention empfunden (66), weil das Zervixkarzinom durch den Zusammenhang mit HPV als sexuell übertragbare Krankheit mit einem Stigma versehen ist (66, 67). Männer haben besonders im oft patriarchal geprägten Kontext vieler afrikanischer Länder einen wichtigen Einfluss auf das Gesundheitsverhalten der Frauen, da sie häufig die finanziellen Mittel bereitstellen und sich viele Frauen auch die Erlaubnis zur Teilnahme an einer Screeninguntersuchung einholen müssen (68). Die WHO empfiehlt daher, Männer in die Aufklärung und in die Durchführung von Gesundheitsinitiativen zu integrieren (10).

2.1.3 Ausübung und Teilnahme am Screening und lokale Evidenz

In Butajira haben nur 2,3% (8/341) der Frauen bereits an einem Zervixkarzinom Screening teilgenommen (47). In Hossana, Äthiopien hatten 9,9% (58/583) der Frauen an einem Zervixkarzinom Screening teilgenommen (17) und in Yirgalem, Äthiopien waren es 9,3% (36/402) (69). In Debre Berhan, einer Stadt im Norden Äthiopiens, gaben 2017 2,9% (24/821) der Frauen an, in den letzten 5 Jahren an einem Screening für das Zervixkarzinom teilgenommen zu haben (70). Insgesamt ist die Rate der Frauen, die an einem Screening teilgenommen haben, in Butajira aber höher als im nationalen Durchschnitt für Äthiopien, der in Jahr 2012 bei 0,6% liegt (68).

In Butajira gaben 70,4% (240/341) der Frauen an, die Absicht zu haben, an einem Screening teilzunehmen (47). Obwohl es zum Zeitpunkt der Datenerhebung in Butajira kein existierendes Screeningprogramm gab, sagten 31,4 % (107/341), dass sie Zugang zum Zervixkarzinomscreening hatten (47), was die Frage nach Missverständnissen eröffnet. In Debre Berhan gab es zum Zeitpunkt der Datenerhebung ein Zervixkarzinomscreeningprogramm und 45,3% (361/821) der Frauen gaben an, an einem Zervixkarzinomscreening teilnehmen zu wollen (70). Es ist wichtig, das Angebot für das Zervixkarzinomscreening im ländlichen Raum auszubauen, sodass Frauen, die am Screening teilnehmen wollen, dies ohne lange Anfahrtswege tun können.

2.1.4 Soziodemographische Einflussfaktoren auf KAP

Frauen, mit einer höheren formellen Schulbildung hatten eine 2,4 fach erhöhte Wahrscheinlichkeit, einen guten Wissenstand zum Zervixkarzinom zu haben, als Frauen ohne formelle Schulbildung (Odds Ratio OR 2,4; 95% Konfidenzintervall 95% KI 1,3-4,3) (47). Auch in einer Studie, die 2018 in Addis Ababa mit HIV positiven Frauen durchgeführt wurde, war eine höhere Bildung mit einem besseren Wissensstand bezüglich des Zervixkarzinoms assoziiert (71). Frauen, die eine Informationsquelle bezüglich des Zervixkarzinoms angaben, hatten einen besseren Wissensstand in Butajira, Äthiopien (OR 9,1, 95% KI 4,0-20,6) (47). Die Angabe einer Informationsquelle war auch in der in Addis Ababa durchgeführten Studie (71), sowie in einer Studie aus Hossana, Äthiopien aus dem Jahr 2015 mit einem besseren Wissensstand assoziiert (17). Frauen in Butajira, die ein Verhütungsmittel verwendeten, hatten einen besseren Wissensstand und eine positivere Haltung zu der Screeninguntersuchung des Zervixkarzinoms als Frauen, die nie ein Verhütungsmittel verwendet haben (OR 2,3, 95% KI 1,3-4,1) (47). In Jimma, Äthiopien war die Verwendung von Kontrazeption ebenfalls mit einem besseren Wissensstand assoziiert (57). Auch in Kenia ergab eine quantitative Studie eine positive Assoziation zwischen dem Bewusstsein für das Zervixkarzinom und der Verwendung von Kontrazeptiva (72). Der intensivere Kontakt zum Gesundheitssystem ist hierfür eine mögliche Erklärung. Eine andere Erklärung ist ein Selektionsbias, weil Frauen, die eine Verhütung verwenden, ein besseres Gesundheitsverhalten an den Tag legen. Ein höheres Einkommen, gemessen in USD, war ebenfalls mit einem besseren Wissenstand zum Zervixkarzinom assoziiert (OR=1,009, 95% KI: 1,00-1,01).

In einer 2020 durchgeführten Metaanalyse über die Teilhabe äthiopischer HIV-positiver Frauen an der Screeninguntersuchung des Zervixkarzinoms wurden als Einflussfaktoren zur Teilnahme ebenfalls das Bildungsniveau der Frauen, ihr Wissensstand bezüglich des Zervixkarzinoms und wahrgenommene Suszeptibilität gegenüber der Erkrankung genannt (73).

2.1.5 Aufklärung und Implementierung

Eine Barriere zur Teilnahme an Screeninguntersuchung, die in vielen Studien beschrieben wird, ist ein Mangel an Bewusstsein für das Zervixkarzinom, wie eine systematische Literaturrecherche ergab (33). Studien belegen eine höhere Teilnahmerate an Screeninguntersuchungen nach Aufklärungsinterventionen (74). Nach der Durchführung der KAP Studie und vor Beginn der Studie zur Teilnahme und Adhärenz in Butajira, Äthiopien wurde eine Aufklärungskampagne in allen Clustern separat für den VIA-Arm und den HPV-Arm der Studie durchgeführt (50). Eine 2018 in Addis Ababa durchgeführte Studie wies ebenfalls auf den positiven Effekt von Gesundheitsaufklärung auf die Teilnahmerate an Screeninguntersuchungen des Zervixkarzinoms hin (75). Das Einbinden der Screeninguntersuchung in kommunale Interventionen mit kulturell adäquater Gesundheitsaufklärung kann das Wahrnehmen von Screeninguntersuchungen verbessern (12), wie es auch die in Butajira durchgeführte Studie zeigt (50). Eine in Ghana durchgeführte Studie belegte ebenfalls den positiven Effekt von Aufklärungskampagnen auf die Bereitschaft, an Screeninguntersuchungen teilzunehmen (76). Eine Metaanalyse aus SSA ergab allerdings, dass Aufklärungskampagnen die Teilnahmerate an Screeninguntersuchungen oft nicht effektiv steigern (77). Ausnahmen waren die Studien, die die Aufklärung durch kommunale Gesundheitsarbeiter oder Peer-on-Peer Kampagnen durchführen (77). Generell zeigt das Einbinden von kommunalen Gesundheitsarbeitern in die Aufklärungsarbeit, Rekrutierung und Durchführung von ZervixkarzinomScreeninguntersuchungen einen positiven Einfluss auf die Partizipationsrate (78). Der positive Effekt von Einladungsschreiben und Erinnerungsanrufen auf die Teilhabe an Screeninguntersuchungen wurde in vielen Studien untersucht und ließ sich generell belegen (74). In einer ländlichen Population, wie in Butajira, Äthiopien mit einem niedrigen Technisierungsgrad ist die Umsetzung von Erinnerungsanrufen und Erinnerungsschreiben aber oft erschwert (47). Besonders der niedrige Bildungsgrad der Frauen in Butajira, die im Durchschnitt 2 Jahre Schulbesuch absolviert haben und von denen ein Großteil nicht lesen und schreiben kann, erschwert den Zugang zu schriftlichen Aufklärungskampagnen (47). Zusammenfassend ist kulturell adäquate Aufklärungsarbeit wichtig, um soziokulturellen Barrieren abzubauen und dadurch die Partizipationsrate an der Screeninguntersuchung des Zervixkarzinoms zu erhöhen (33).

Aufgrund des niedrigen Bildungsniveaus im ländlichen Äthiopien sollten Aufklärungskampagnen vorwiegend mündlich und durch peer-groups stattfinden. Da kommunale Krankenschwestern als häufigste Informationsquelle für das Zervixkarzinom angegeben wurden, sollte ein Fokus auf deren Ausbildung liegen.

2.2 Teilnahmerate an zwei verschiedenen Screeningmethoden und Adhärenz zu Therapieempfehlungen in Butajira, Äthiopien (Screening Studie)

In Butajira, Äthiopien wurden die VIA- und die HPV basierte Screeninguntersuchung bezüglich der Teilnahme und der Adhärenz zu Therapieempfehlungen miteinander verglichen (50). 50,3% (575/1143) der eingeladenen Frauen nahmen an der Screeninguntersuchung mit VIA teil und 40% (458/1143) an allen weiteren Untersuchungs- und Behandlungsschritten, wie der VIA, gegebenenfalls Kolposkopie und Kryotherapie (50). 84,1% (1020/1213) der zum HPV-DNA Test eingeladenen Frauen nahmen an der Screeninguntersuchung teil und 65,4% (794/1213) an allen folgenden Untersuchungs- und Behandlungsschritten, wie der VIA und der Kryotherapie (50). In Uganda wurde die Partizipation bei VIA und HPV-Selbstabnahme gegeneinander verglichen und auch hier schnitt der HPV-DNA Test mit einer Teilnahmerate von 99,2% (248/250) deutlich besser ab als die VIA mit 48,4% (121/250) (79). Auch eine systematische Literaturrecherche ergab, dass im Durchschnitt die Partizipation am Screening mit dem selbstabgenommenen HPV- DNA basierten Test deutlich höher ist, als in den aus VIA oder PAP-Abstrich bestehenden Vergleichsgruppen (80).

VIA basierte Screeninguntersuchungen sind kostengünstig und besonders in strukturschwachen Regionen gut umsetzbar (10). Ein weiterer Vorteil ist, dass das Ergebnis direkt mitgeteilt werden kann und die Behandlung mit Kryotherapie bei positiver VIA direkt im Anschluss innerhalb eines Klinikbesuches stattfinden kann (1). Eine Barriere für die Kryotherapie ist allerdings die Versorgung mit dem für die Behandlung nötigen Kohlendioxid oder Nitrogen, die besonders in LMICs nicht immer gewährleistet ist (23). Die Untersucherabhängigkeit der Ergebnisse bei der VIA stellt ebenfalls oft ein Problem dar (41). In Butajira wurden in der nachträglich von einem Gynäkologen durchgeführten Kontrolluntersuchung nur 50% (11/22) der ursprünglich für positiv befundenen Frauen als tatsächlich VIA- positiv diagnostiziert (50). Eine Studie aus dem Kongo zeigte ebenfalls, dass Krankenschwestern mehr Frauen als VIA-positiv diagnostizierten als ausgebildete Gynäkologen (81). VIA ist außerdem, im Gegensatz zur HPV-DNA basierten Screeninguntersuchung mit Selbstabnahme der Proben, in der Durchführung an ein Krankenhaus gebunden (82), wodurch die Anfahrtswege und hiermit verbundene Kosten eine Barriere darstellen (19, 83). Das für die Untersuchung nötige Entkleiden in Gegenwart einer Krankenschwester oder eines Arztes/Ärztin ist eine mögliche soziokulturelle Barriere für die Teilnahme an der VIA (19).

Wie auch die Studie in Butajira zeigt (50), ermöglicht die Screeninguntersuchung mittels HPV-DNA Nachweis in selbstabgenommenen Proben die Teilnahme an der Screeninguntersuchung für Frauen in strukturschwachen Regionen (80, 84). In Butajira führten die Probandinnen in einer lokalen Gesundheitsstation die HPV- DNA Probenentnahme durch, was sich als praktikabler Ansatz erwies (50). Eine Krankenschwester war vor Ort als Ansprechpartner verfügbar (50). Die Partizipationsrate ist bei einem Tür-zu-Tür Ansatz hoch, bei dem kommunale Gesundheitsarbeiter das Test-Kit für die Selbstabnahme persönlich überbringen (85, 86). Frauen in einer qualitativen Studie in Kenia beschreiben die Probenentnahme als einfach und schmerzlos und berichten, dass so einige der empfundenen Barrieren, wie das Entkleiden vor einem Arzt oder einer Krankenschwester entfielen (19). In Adama, Äthiopien gaben 2015 87,9% (73/83) der Probandinnen an, dass sie die Probenentnahme als einfach empfanden und Vertrauen in die Qualität ihrer Probe haben (87). Allerdings zeigten sich Frauen in einer in Äthiopien durchgeführten Studie initial skeptisch, ob sie die Probe selbst korrekt abnehmen können (43). Auch Frauen in einer Studie aus Mexiko gaben an, sich die Probenentnahme nicht zuzutrauen (88). Die Sensitivität von selbstabgenommenen Proben ist oft niedriger als bei vom Gesundheitspersonal gesammelten Abstrichen (85, 89). Eine in der Amhara Region, Äthiopien, 2017 durchgeführte Studie ergab, dass in 18% der Fälle (94/523) die abgenommenen Proben ohne valides Testergebnis blieben, was die Akzeptanz des HPV Tests negativ beeinflusste (90). Auch in Butajira konnten 19,2% (171) der selbstabgenommenen Proben aufgrund einer zu niedrigen Zellzahl nicht analysiert werden (52). Problematisch für die HPV-DNA basierte Screeninguntersuchung ist außerdem der hohe technische Aufwand der Testung, der ein gut ausgestattetes Labor und eine hohe Anzahl von Proben pro Testdurchlauf voraussetzt (24). In einer 2017 in Äthiopien durchgeführten Studie wurden alle HPV-Proben erfolgreich im Labor der Universität Addis Ababa analysiert und zur Qualitätssicherung mit den Ergebnissen der parallel stattgefundenen Analyse an der Charité, Berlin verglichen (90). Bei der Analyse der Proben aus Butajira ergaben sich in dem Labor in Addis Ababa Schwierigkeiten, sodass die Proben final ausschließlich an der Charité, Berlin ausgewertet wurden (52). Durch die hieraus resultierende Zeitverzögerung kam es in Butajira zu Unzufriedenheit bei den Probandinnen (50). Ähnliche Probleme traten in einer Studie in Uganda auf, sodass 39 der 73 HPV- positiven Frauen nicht erreicht werden konnten, um das Ergebnis mitzuteilen (79). Im Anschluss an den HPV Test sind weitere Klinikbesuche zur Ergebnissicherung und Behandlung nötig, was sich in strukturschwachen Regionen oft nicht verwirklichen lässt (12, 64). In Madagaskar nahmen aufgrund des Zeitverzugs zwischen der Abnahme des HPV- Testes und der Ergebnismitteilung weniger Frauen an der konsekutiven VIA teil (91). In Butajira erschienen 15% (22/144) der HPV-DNA positiv getesteten Frauen nicht zur anschließenden VIA (50). Die Teilnahmerate an

weiteren Untersuchungen ist bei einer direkten Überweisung nach HPV-basierter Triage höher als bei zeitlich versetzter Überweisung (86). Frauen in Südafrika beschrieben in einer qualitativen Studie eine psychische Belastung in der Wartezeit bis zur Mitteilung des Testergebnisses (92). Ein weiteres Problem der HPV-basierten Screeninguntersuchung ist die hohe Rate an HPV-positiven Frauen, die in der konsekutiven Kolposkopie oder VIA ein negatives Ergebnis erhalten. Diese Frauen sind schwer in strukturierte Screeninguntersuchungen einzubinden (93). In einer im Norden Äthiopiens durchgeführten Studie wurden 14 der 53 HPV positiven Frauen in der konsekutiven VIA positiv auf präkanzeröse Läsionen getestet (90) und auch in Butajira waren nur 8,2% (10/122) der HPV-positiven Frauen in der konsekutiven VIA ebenfalls positiv (50). Die Notwendigkeit weiterer Untersuchungen nach einem positiven HPV-Test sind gerade in Ländern mit einem niedrigen Bildungsniveau schwer zu vermitteln (94).

Der HPV-Test kann trotz aller vorwiegend technischen und infrastrukturellen Schwierigkeiten zusammenfassend aufgrund der deutlich höheren Teilnehmerrate für Äthiopien als primäre Screeningmethode für das Zervixkarzinom empfohlen werden. Eine VIA oder Kolposkopie kann im Anschluss durchgeführt werden.

2.3 Gründe für die Nichtteilnahme (Non-Attendance Studie)

761 der 2356 Frauen aus den 22 Clustern in Butajira nahmen an keiner Screeninguntersuchung teil (51). 390 der 761 Frauen, die nicht am Screening teilgenommen hatten, konnten zu ihren Gründen, nicht am Screening teilzunehmen, befragt werden (51). Die soziodemographischen Daten der Nichtteilnehmerinnen wurden mit denen der Teilnehmerinnen verglichen (51). Assoziierte Faktoren für die Nichtteilnahme waren eine berufliche Tätigkeit, das Leben in einer ländlichen Gegend und ein niedriger Bildungsgrad (51). Als Gründe für die Nichtteilnahme wurde ein Mangel an Zeit, ein subjektives Gesundheitsgefühl und die Angst vor einem schlechten Ergebnis angegeben (51). 83% (324/390) der nichtteilnehmenden Frauen hielten sich für nicht gefährdet und 20.3% (79/390) gaben an, dass ihr Mann die Teilnahme an einer Screeninguntersuchung nicht billigen würde (51), was im Widerspruch zu den Aussagen in der “KAP-Studie” steht, wo die Frauen eher angaben, das ihre Männer dem Screening gegenüber positiv eingestellt seien (47). 15% (58/390) der Frauen nannten mangelndes Vertrauen in die Mitarbeiter des Gesundheit Systems als Grund für die Nichtteilnahme (51). In einer 2018 in Addis Ababa durchgeführten Studie zum Einfluss von Gesundheitsaufklärung auf die Teilnahme an Screeninguntersuchungen gaben die Probandinnen ebenfalls die Abwesenheit von Symptomen an (75). Weitere Gründe waren Zeitmangel und ein geringer Wissensstand bezüglich des Zervixkarzinoms und dessen Prävention (75). In einer qualitativen Studie, die 2008 in Schweden zum Thema Nichtteilnahme an Screeninguntersuchungen durchgeführt wurde, nannten die 14 Probandinnen ein subjektives Gesundheitsgefühl, Angst vor einem positiven Ergebnis und Angst vor der gynäkologischen Untersuchung, sowie ein Misstrauen in das Gesundheitssystem als Gründe, in den letzten 5 Jahren an keiner Screeninguntersuchung teilgenommen zu haben (95).

2.4 HPV Prävalenz und Genotypisierung in Butajira, Äthiopien und Ausblick auf eine HPV Impfung für Äthiopien (HPV-Studie)

893 der HPV- DNA Proben aus Butajira, Äthiopien wurden untersucht, um die Prävalenz von HPV Infektionen zu bestimmen und eine Genotypisierung vorzunehmen (52). 19,7% der Proben (176/893) wiesen initial für die PCR Testung zu wenig Zellmaterial auf, hiervon waren 47 nach einer erneuten Entnahme der Proben für die Testung geeignet, sodass insgesamt 764 Proben getestet wurden (52). 20.5 % (157/764) der Frauen in der Studie wurden positiv für mindestens einen Hochrisiko HPV Genotyp getestet (52). In einer in Adama, Äthiopien durchgeführten Studie waren 22.7% der 83 getesteten Frauen positiv für Hochrisiko-HPV Typen (87). Die Prävalenz für HPV 16 und HPV 18 war 7,1% in einer 2019 in der Amhara Region, Äthiopien durchgeführten Studie (55). Diese Prävalenz ist niedriger, als in Butajira, Äthiopien, allerdings wurden die Proben, anders als in Butajira, nur auf HPV 16 und 18 getestet (55). Für 2017 und 2018 wurde die Prävalenz für mindestens einen der Hochrisiko HPV in der Amhara Region, Äthiopien mit 13,5% (58/429) angegeben (90). HPV 16, 35, 52, 31, 45 und 18 waren die häufigsten HPV Typen in Butajira Äthiopien, HPV 11 der häufigste low risk HPV Typ (siehe Tabelle 2) (52).

Tabelle 2: Auswahl der häufigsten HVP Typen in Butajira, Äthiopien

HPV Typ	Absolute Häufigkeit (n=764)	Relative Häufigkeit (%)
HPV 16	101	13,2
HPV 35	36	4,7
HPV 52	28	3,7
HPV 31	25	3,3
HPV 45	17	2,2
HPV 18	16	2,1
HPV 51	13	1,7
HPV 26	12	1,6
HPV 56	10	1,3
HPV 53	10	1,3
HPV 58	5	0,7
HPV 33	3	0,4
HPV 11	50	6,5
HPV 6	11	1,4

In einer 2015 in Addis Ababa, Äthiopien, durchgeführten Studie lag die Prävalenz für HPV 16 bei 16% (8/50) und für HPV 18 bei 2% (1/50) (96). In einer 2015 in Adama, Äthiopien durchgeführten Studie war der prädominant nachgewiesene Genotyp HPV 51 (87). In einer systematischen Literaturrecherche waren HPV 16, HPV 52 und HPV 18 die 3 häufigsten Genotypen (97). Auch in Butajira waren die von der nonavalenten Impfung mit abgedeckten HPV Typen 52, 45 und 31 häufig, sodass die nonavalente Impfung hier einen Vorteil gegenüber der quadrivalenten Impfung für die Prävention des Zervixkarzinoms bieten würde (52). Der zweithäufigste Genotyp in Butajira war HPV 35, der bisher noch von keinem Impfstoff mit erfasst wird. Zusammenfassend zeigen viele der genannten Studien eine hohe Prävalenz für HPV 52, 56, 58 und 31 (97, 98). Diese HPV Genotypen werden von den zwei gängigsten Impfstoffen (bivalent und quadrivalent) jedoch nicht mit abgedeckt, weswegen die Entwicklung eines für den Markt der Subsahara Region passenden Impfstoffes eine wichtige Voraussetzung für den Impferfolg in der Region ist (98). Eine HPV- Impfung, die auch die Genotypen 52, 58, 31 und 45 beinhaltet, sollte aufgrund der HPV Genotypverteilung auch für Äthiopien priorisiert empfohlen werden (98).

2019 wurde in einer Modellstudie mit der Impfung von Mädchen gegen HPV 16 und 18 in der Amhara Region begonnen (55). Eine in Äthiopien durchgeführte Studie zur Impfbereitschaft ergab, dass 85,97% der teilnehmenden Frauen bereit war, für die Impfung zu zahlen und dass Einkommen und Bildung sowie der Wissensstand der Gesundheitsfacharbeiter wichtige Einflussfaktoren auf die Zahlungsbereitschaft waren (60). Eine 2019 in Gondar, Äthiopien, durchgeführte Studie zu Einflussfaktoren auf die Impfbereitschaft von Eltern für ihre Töchter ergab den höheren Einkommensstand, den besseren Wissensstand zu HPV und dem Zervixkarzinom, sowie die Einstellung zur HPV Impfung als wichtige Einflussfaktoren (99). Wichtige Barrieren zur Impfung in Äthiopien sind unter anderem die Kosten für die Impfung und Defizite in der Infrastruktur (99). Die HPV Impfung in Äthiopien sollte von einer Aufklärungskampagne begleitet werden und Barrieren wie die Kosten sollten abgebaut werden.

2.5 Grenzen und Stärken der Studien

Bisher gibt es keinen internationalen standardisierten Fragebogen zum Thema Zervixkarzinom Prävention. In dieser Studie wurde ein WHO Fragebogen zur Durchführung einer KAP Studie adaptiert, KAP Studien aus anderen Ländern thematisch gruppiert und daraus Fragen abgeleitet. Die Ergebnisse der Studie in Butajira sind denen aus anderen Studien ähnlich, dennoch ist die Vergleichbarkeit durch den fehlenden standardisierten Fragebogen limitiert. KAP Studien haben generell den Nachteil, dass Probanden dazu neigen, die von ihnen gesellschaftlich erwartete Antwort auf eine Frage zu geben. Um dem entgegenzuwirken, wurden die Frauen möglichst einzeln interviewt.

In Bezug auf die „Screening Studie“ ist als Limitation besonders zu nennen, dass nur die VIA- basierte Screeninguntersuchung mit einem Anfahrtsweg nach Butajira zu dem Kreiskrankenhaus verbunden war. Um diesen Verzerrungsfehler zu kompensieren, wurde den Frauen im VIA Arm eine finanzielle Entschädigung für die Anfahrtskosten angeboten.

Nur 48,7% (371/761) der Frauen, die an keiner der Screeninguntersuchungen teilgenommen haben, konnten erreicht werden, um sie nach ihren Gründen für die Nichtteilnahme zu befragen. Die Aussagekraft der Studie zu den Gründen für die Nichtteilnahme wird dadurch negativ beeinflusst.

In Bezug auf die “HPV-Studie” ist besonders zu nennen, dass 127 der HPV Proben ohne Ergebnis blieben, da die Qualität der Proben für die Analysen nicht ausreichend war. Zudem erfolgte die Analyse der Proben schlussendlich in Deutschland.

Die Stärken dieser Studie liegen in dem Tür-zu-Tür Ansatz, der eine repräsentative Stichprobe der ländlichen Bevölkerung in Äthiopien bietet. Zudem ist die HPV-Prävalenz populationsbasiert erhoben worden, im Gegensatz zu Studien, die Probandinnen krankenhausbasiert rekrutieren. Die Studie exploriert die Einstellungen der Probandinnen zum Thema Zervixkarzinom detailliert und strukturiert auf der Basis des Modells der Gesundheitsüberzeugungen (health belief model). Besonders die Befragung der nichtteilnehmenden Frauen nach ihren Gründen und der Vergleich der soziodemographischen Daten, zu denen der teilnehmenden Frauen ist zum Zeitpunkt der Erstellung dieser Dissertation nach unserem Wissen zuvor nicht untersucht worden.

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4. Thesen

1. Insgesamt hatten die Probandinnen in Butajira, Äthiopien einen niedrigen Wissensstand bezüglich des Zervixkarzinoms. Nur 36% (125/341) der Frauen waren sich des für Zervixkarzinoms bewusst und nur 4,1%(14/341) konnten Symptome benennen. Keine der Frauen identifizierte eine HPV-Infektion als Risikofaktor.

2. Die meisten Probandinnen hatten eine für die Teilnahme an Screeninguntersuchungen vorteilhafte Einstellung zum Zervixkarzinom und dessen Prävention. Allerdings hielten sich nur 13% (47/341) der Frauen in Butajira, Äthiopien für gefährdet, am Zervixkarzinom zu erkranken.

3. In Butajira hatten 2,3% (8/341) der Frauen zu Beginn der Studie an einem Screening für das Zervixkarzinom teilgenommen.

4. Ein höheres Einkommen (OR 1,009, KI 1,0-1,01), ein besserer Bildungsstand (OR 2,4, KI 1,3-4,3) und eine Informationsquelle bezüglich des Zervixkarzinoms (OR 9,1, KI 4,0-20,6), sowie die Verwendung von Verhütungsmitteln (OR 2,3 KI 1,3-4,1) waren assoziiert mit einem besseren Wissensstand über das Zervixkarzinom. Die Angabe von Krankenschwestern als Informationsquelle (OR 4,2, KI 2,4-7,4), die Angabe anderer Informationsquellen (OR 5,0, KI 2,4-10,3) und die Verwendung von Verhütungsmitteln (OR 2,2, KI 1,2-3,8) korrelierten positiv mit positiven Haltung gegenüber der Teilnahme am Zervixkarzinom-Screening.

5. Krankenschwestern waren mit 32% (109/341) die meist genannte Informationsquelle bezüglich des Zervixkarzinoms und dessen Prävention in Butajira, Äthiopien. Sie sollten daher als Multiplikatoren zum Thema Zervixkarzinom gut ausgebildet werden.

6. Die Teilnahmeraten der Cluster- randomisierten Studie unterschieden sich je nach Screeningmethode in Butajira, Äthiopien. Für das Screening mit HPV-Test war die Teilnahmerate bei 84,1% (1020/1213) und beim Screening mit VIA bei 50,5% (575/1143). Die Adhärenz zu Therapieempfehlungen war bei dem HPV Test bei 65,4% (794/1020) und bei der VIA bei 40% (458/1143). Die HPV-basierte Screeninguntersuchung kann daher in Bezug auf die Teilnahmerate für Äthiopien priorisiert empfohlen werden.

7. Vorteile der VIA in Butajira, Äthiopien war das zeitnahe Ergebnis und der „single-visit Approach“. Nachteile waren die geringe Teilnahmerate und die Anfahrtswege.

8. Ein Vorteil der HPV in Butajira, Äthiopien war die durch die Selbstabnahme der Proben bessere Akzeptanz der Screeningmethode. Zudem entfielen durch die Testung in lokalen Gesundheitszentren die langen Anfahrtswege. Nachteile waren der hohe technische Aufwand, die hieraus resultierende Verzögerung bis zur Ergebnismitteilung und die Notwendigkeit einer konsekutiven Zweituntersuchung mittels VIA/ Kolposkopie,

für die ein zweiter Besuch in einem Krankenhaus oder Gesundheitszentrum nötig wurde.

9. Die Rate an Hochrisiko HPV in Butajira war bei 20,5%. 13,2% der Frauen (101/764) waren positiv für HPV 16, 4,7% (36/764) positiv für HPV 35, 3,7% (28/764) positiv für HPV 52, 3,3% (25/764) positiv für HPV 31, 2,2% (17/764) positiv für HPV 45 und 2,1% 16/764) positiv für HPV 18. Aufgrund der HPV-Genotypverteilung in Butajira, Äthiopien, die auch in anderen Studien in Äthiopien nachgewiesen wurde, kann der nonavalente HPV-Impfstoff priorisiert für Äthiopien empfohlen werden.

Publikationsteil

Publikation 1:

Ruddies F, Gizaw M, Teka B, Thies S, Wienke A, Kaufmann AM, et al. Cervical cancer screening in rural Ethiopia: a cross- sectional knowledge, attitude and practice study. BMC Cancer. 2020;20(1):563.

Beitrag: Ich war hauptverantwortlich für die Konzeption, das Entwickeln und Formulieren der Fragestellung, des Entwurfs der Fragebögen und habe die Datenerhebung beaufsichtig. Weiterhin habe ich die Daten analysiert und die Ergebnisse formuliert und das Manuskript verfasst.

Publikation 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 (Phila). 2019;12(9):609-16.

Beitrag: Ich habe die Screeninguntersuchung mittels VIA betreut, war an der Auswertung der Daten und dem Verfassen des Manuskripts beteiligt und habe meine Zustimmung zur Publikation gegeben.

Publikation 3

Gizaw M, Teka B, Ruddies F, Kassahun K, Worku D, Worku A, Wienke A, Mikolajczyk R, Jemal A, Kaufmann AM, Abebe T, Addissie A, Kantelhardt EJ. Reasons for Not Attending Cervical Cancer Screening and Associated Factors in Rural Ethiopia. Cancer Prev Res (Phila). 2020 Jul;13(7):593-600. doi: 10.1158/1940-6207.CAPR-19-0485. Epub 2020 May 5. PMID: 32371553.

Beitrag: Ich war an der Konzeption und Entwicklung der Fragebögen beteiligt, habe das Manuskript Korrektur gelesen und der Veröffentlichung zugestimmt.

Publikation 4

Teka B, Gizaw M, Ruddies F, Addissie A, Chanyalew Z, Skof AS, Thies S, Mihret A, Kantelhardt EJ, Kaufmann AM, Abebe T. Population-based human papillomavirus infection and genotype distribution among women in rural areas of South Central Ethiopia. Int J Cancer. 2021 Feb 1;148(3):723-730. doi: 10.1002/ijc.33278. Epub 2020 Sep 8. PMID: 32875552.

Beitrag: Ich war an der Proben Gewinnung beteiligt und habe das Manuskript Korrektur gelesen, sowie meine Zustimmung zur Veröffentlichung gegeben.

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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

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

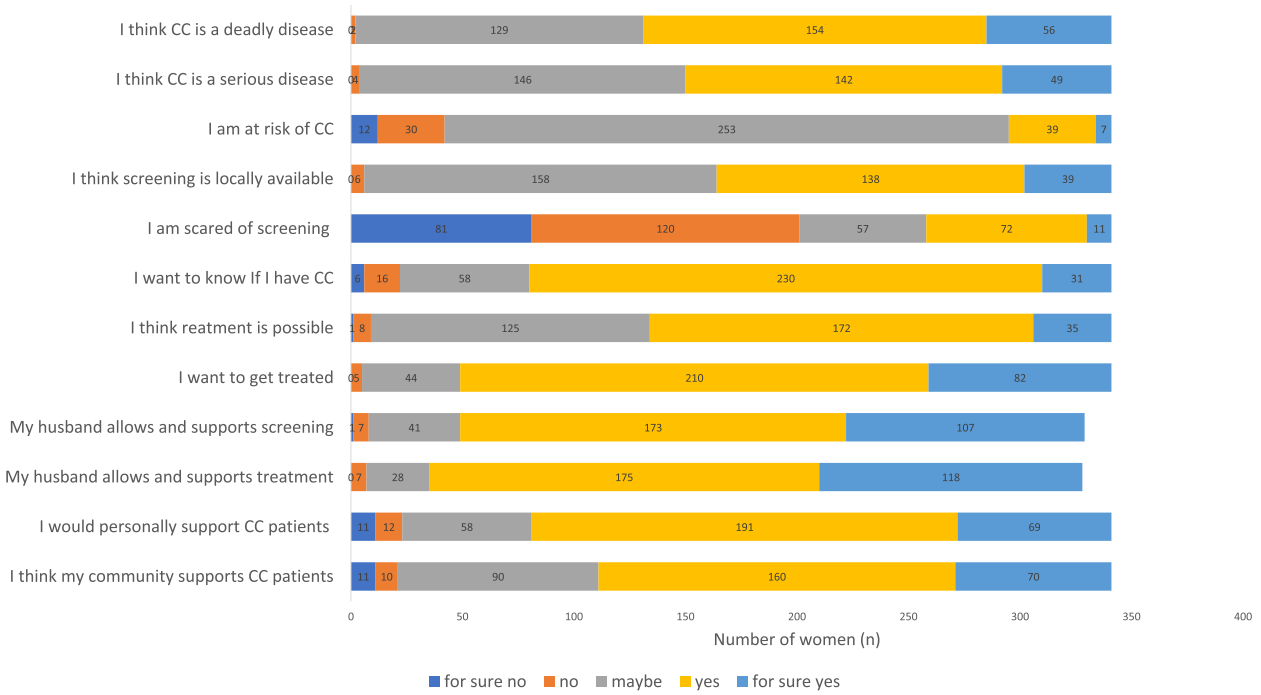

Fig. 1 Women's attitude towards cervical cancer and cervical cancer screening

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

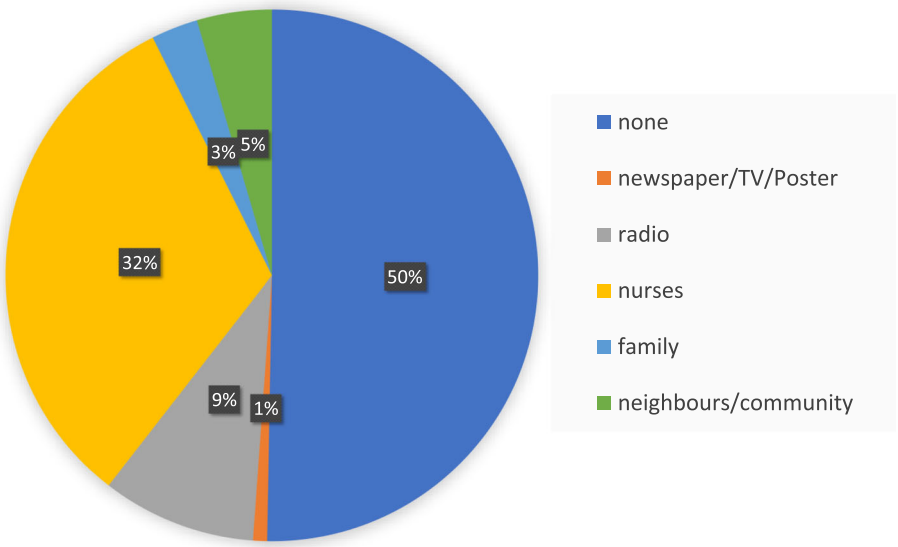

Fig. 2 Women's source of information concerning cervical cancer and cervical cancer screening

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.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12885-020-07060-4.

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

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Authors' contributions

FR made substantial contributions to the concept and design of the study, analyzed and interpreted the data and has drafted the manuscript. EK made substantial contributions to the concept and design of the study and has helped drafting, and critically revised the manuscript. AW made substantial contributions to the concept and design of the study, helped with statistical analysis and critically revised the manuscript. AA has acquired clinical data and critically revised the manuscript. MG made substantial contributions to the concept and design of the study and critically revised the manuscript. BT has critically revised the manuscript. TA has critically revised the manuscript. AMK has critically revised the manuscript. ST has critically revised the manuscript. All authors read and approved the final version of the manuscript for publication.

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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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Research Article

Cancer Prevention Research

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 post-screening 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

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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 ($P < 0.0001$).

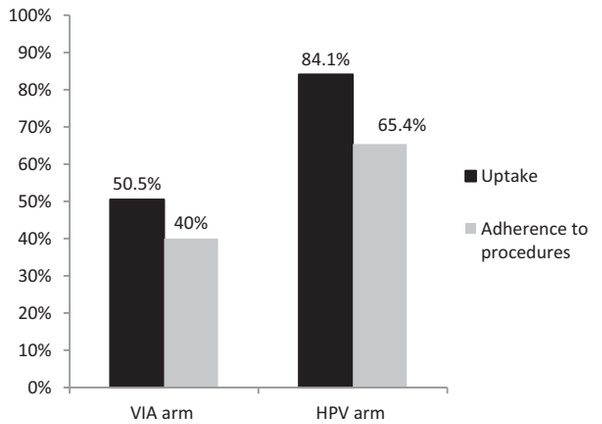

Figure 1.
Proportion of adherence to the uptake and procedures for women who participated in screening for cervical screening, Butajira, Ethiopia, 2018.

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

		Study arm	
Demographic characteristics	**Total (*N* = 1,299) *n* (%)**	**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 (± SD) age at first pregnancy of the HPV arm and VIA arm was 18.4 (±4.8) and 18.6 (±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

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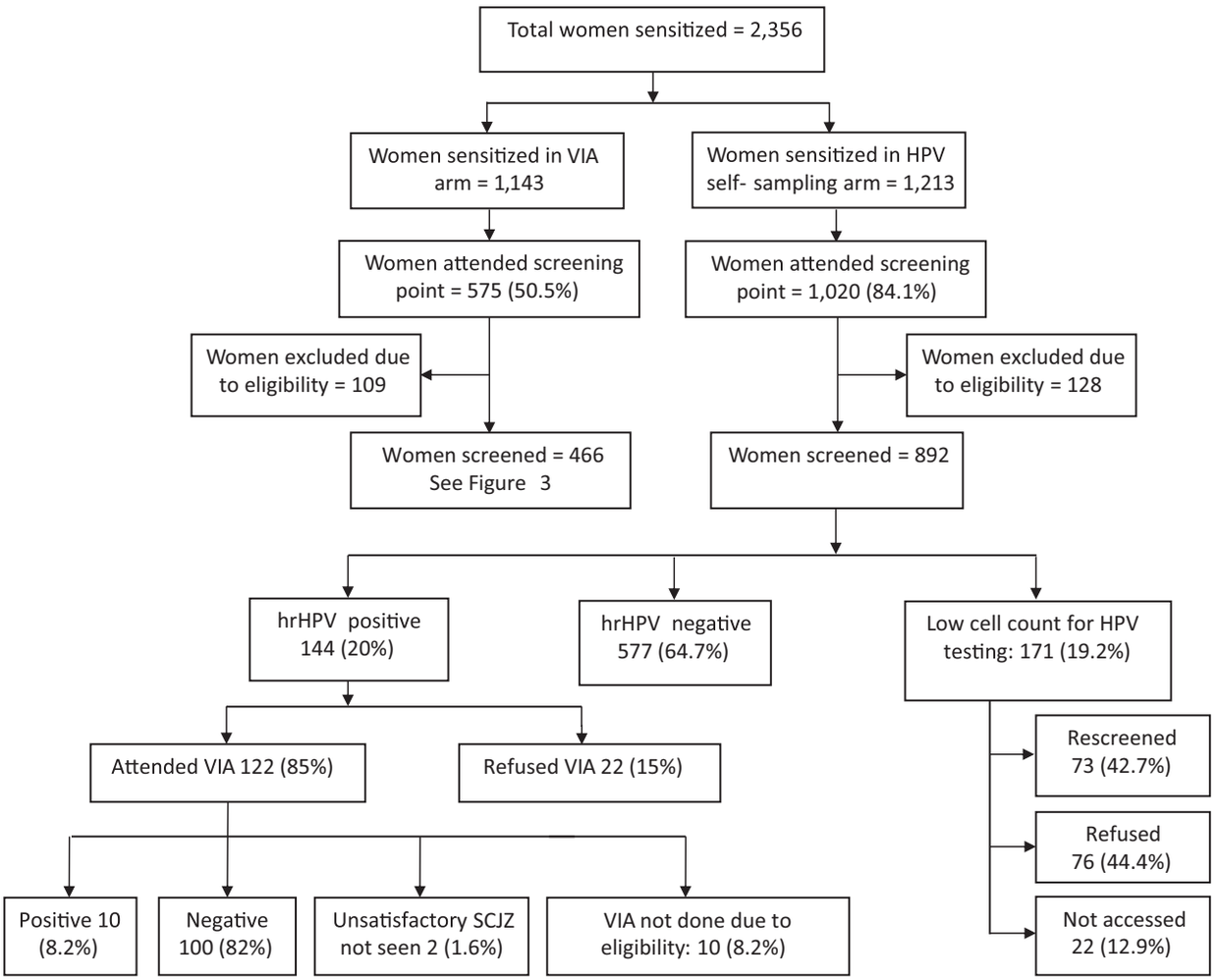

Figure 2.
Study trial flow chart and screening adherence outcomes for women who participated in HPV arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

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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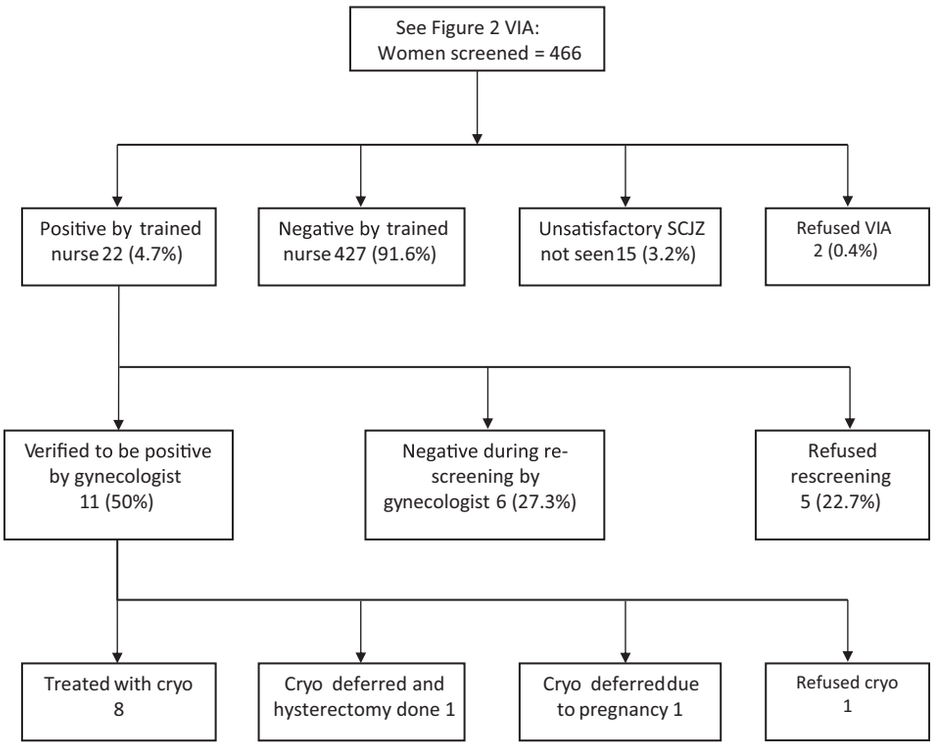

Figure 3.
Study trial flow chart and screening adherence outcomes for women who participated in VIA arm, Butajira, Ethiopia, 2018 (squamo-columnar junction zone SCJZ).

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.

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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

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Cancer Prevention Research

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

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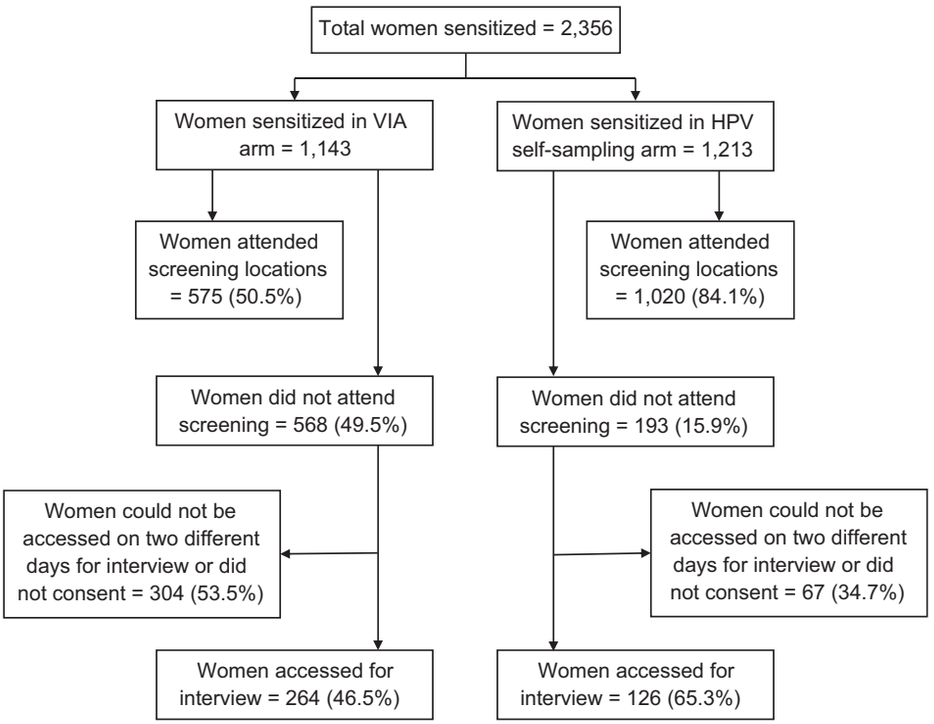

Figure 1.
Schematic flow of study participants in Butajira District, Ethiopia, 2018.

(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 education 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

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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**).

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)	—

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

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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

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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

A.M. Kaufmann reports a patent to EP 19 15 6203 pending. No potential conflicts of interest were disclosed by the other authors.

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

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INFECTIOUS CAUSES OF CANCER

Population-based human papillomavirus infection and genotype distribution among women in rural areas of South Central Ethiopia

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Abstract

In Ethiopia, cervical cancer is the second leading cause of morbidity and mortality from all cancers in women. Persistent infection with human papillomaviruses (HPV) plays a key role in the development of cervical intraepithelial neoplasia and invasive cervical cancer. To establish baseline data on the population-based prevalence of HPV infection and genotype distribution, we investigated cervical HPV epidemiology among rural women. This population-based study was conducted among rural women aged 30-49 years in Butajira, south-central Ethiopia. A total of 893 samples were tested from 1020 screened women. A self-sampling device (Evalyn Brush, Rovers, Oss, The Netherlands) was used and HPV presence and genotype was determined using multiplexed genotyping (MPG) by BSGP5+/6+ PCR with Luminex read out. The HPV positivity rate was 23.2% (95% CI: 23.54-22.86%) and 20.5% (95% CI = 20.79-20.21) and 10.3% (95% CI = 10.52-10.08) women were high-risk (hr- and low-risk (lr-) HPV positive, respectively. Fifty five (7.2%) of the women showed multiple hr-HPV infections. Age-specific hr-HPV infection peaked in the age-group 30- to 34 years old (58.6%) and decreased in 35-39, 40-44 and 45-49 years to 20.4%, 4.5% and 3.8% respectively. The top five prevalent hr-HPV genotypes were HPV16 (57.1%), 35 (20.3%), 52 (15.8%), 31 (14.1%), and 45 (9.6%) in the Butajira district. As a first population-based study in the country, our results can serve as valuable reference to guide nationwide cervical cancer screening and HPV vaccination programs in Ethiopia.

KEYWORDS

Butajira, cervical cancer, high-risk HPV, HPV based screening, HPV epidemiology

Abbreviations: CC, cervical cancer; CIN, cervical intraepithelial neoplasia; HDSS, Health and demographic Surveillance site; HEWs, Health extension workers; HPV, human papillomavirus; hr-HPV, high-risk human papillomavirus; ICC, invasive cervical cancer; lr-HPV, low-risk human papillomavirus; MPG, multiplex genotyping; NRERC, national research ethics review committee; ORF, open reading frame; PCR, polymerase chain reaction; SSA, sub-Saharan Africa; VIA, visual inspection with acetic acid; WHO, World Health Organization.

1 | INTRODUCTION

Cervical cancer (CC) is one of the infection-associated cancers and the fourth for both incidence and mortality among women.[1] There are

geographical differences in the prevalence of cervical cancer clearly associated with country income level[2] where more than 85% of these cases are occurring in developing countries.[3] In sub-Saharan Africa (SSA), more than 80 000 women die per year from cervical cancer.[4] The major cause for such disparity in incidence and mortality could be lack of functional/efficient primary and secondary prevention of cervical cancer in SSA regions. In Ethiopia, cervical cancer is the second most common female cancer in women aged 15 to 44 years. From the 2018 estimate, about 6294 new cervical cancer cases were diagnosed annually in Ethiopia.[4]

Infection with human papillomavirus (HPV) is the primary cause of cervical cancer.[2] More than 200 HPV genotypes have been characterized and among these 40 are known to infect the anogenital tract.[5] Persistent infection with HPVs is a necessary cause for the development of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC).[6] The higher the prevalence of cervical HPV infection, the higher the incidence of cervical cancer.[2]

Depending on their oncogenic potential, HPVs are classified as either high-risk (hr), which are frequently associated with invasive cervical cancer and precancerous lesions,[7] or low-risk HPVs (lr), which are often associated with genital warts. Although HPV16 and 18 genotypes contribute for more than 70% of cervical cancer cases worldwide,[8,9] genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are considered as carcinogenic or high-risk types, and types 26, 53, and 66 are considered as probably carcinogenic.[7]

Different observational studies have demonstrated that the prevalence and distribution of HPV genotypes is heterogeneous among women from different regions and populations.[10,11] Hence, the acquisition of population-based data is crucial to the development of new screening and management protocols for cervical neoplasms as well as to the assessment of the effect of HPV vaccination programs as primary methods for prevention of cervical cancer.[12,13]

In Ethiopia, there is scarcity of data on the rate of HPV infection or genotype distribution. Furthermore, the limited studies about HPV prevalence and genotypes conducted so far in Ethiopia are mainly facility-based studies focused on women with or without gynecological complaints. Among the few studies, Ruland et al and Leyh-Bannurah et al[14,15] determined HPV prevalence among women who attended outpatient department of Hospitals. The studies by Abate et al and Fanta[16,17] also investigated the HPV genotypes from women with cervical histological abnormalities. But these facility-based studies may not show the real picture of HPV infection and genotypes circulating in the community. As per our knowledge, this is the first population-based study in the country dealing with the prevalence of HPV and circulating genotypes in rural women believing that the knowledge of the molecular epidemiology of HPV diversity among women is crucial for nationwide cervical cancer screening and HPV vaccination programs in Ethiopia.

Hence, we investigated HPV infections by self-collected cervicovaginal samples among rural women who attended cervical cancer screening to determine the age-specific and genotype-specific prevalence of HPV in the rural area of Butajira, south-central Ethiopia.

What's new?

Infection with human papillomavirus (HPV) is the primary cause of cervical cancer, a disease that is most prevalent in developing countries. Population-based HPV data is crucial for cervical cancer screening and vaccination programs. This is the first population-based study in rural women in Ethiopia using self-sampling. The authors found a high-risk HPV positivity rate of 20.5% in the study area and a different list of top five prevalent high-risk HPV genotypes compared to other studies worldwide. The findings will help guide national cervical cancer screening and vaccination programs in Ethiopia.

2 | MATERIAL AND METHODS

2.1 | Study design

This population-based study is part of the ongoing cluster-randomized trial that has been registered in clinicaltrials.gov (NCT03281135) and was conducted in Butajira Health and Demographic Surveillance Site (HDSS) of Addis Ababa University, Ethiopia.[18] It was specifically designed to determine the circulating HPV genotypes in the community and to follow the same population after 16-18 months to evaluate the persistence, clearance, and reinfection rates of HPV genotypes. The study district is located 135 km south of the capital Addis Ababa. We here report the baseline findings.

2.2 | Study population

Women aged 30-49 years old (the WHO recommended age for screening) were recruited from 11 rural Kebeles (a smallest administrative unit in Ethiopia) of Butajira, south-central Ethiopia in the Gurage Zone of the Southern Nations, Nationalities and Peoples' Region of Ethiopia. The target population size for our study (women 30-49 years) is around 16.2% of the population. Women eligible for inclusion were those who reside permanently in the selected study area and had no plans to relocate for the duration of the study and those who were willing to participate in the study. Pregnant women and women at menstruation during the sample collection period were excluded from sample collection and invited for another sampling time.

2.3 | Collection device and training of health workers

Community sensitization and awareness creation were performed at health facilities and in communities at social gatherings, about cervical

cancer and its prevention for eligible women in the selected districts. Community health workers, in our case Health Extension Workers (HEWs) and Health Development Armies (HDAs) were pretrained about cervical cancer and cervical cancer prevention and the sample collection. Cervicovaginal samples were taken by self-collection using the Evalyn Brush device (Rovers Medical Devices, Oss, The Netherlands). Women were assisted by trained HEWs. Training consisted of local language translated video and a step-by-step demonstration of the self-collection device.

2.4 | Collection procedure

During the community screening campaign, women living in the predefined areas (Kebeles, lowest administrative unit) were sensitized and invited to undergo HPV self-sampling at nearby health posts with the Evalyn Brush. At the health post, an explanation was given by the trained HEW on how to collect the cervical self-sample. Then, the Evalyn brush was given to each eligible and willing woman and self-collection was carried out in a preset private room under supervision at the local health post.

2.5 | Sample storage and transportation

After self-collection, a six-digit alpha numeric sample identification ID was given for each sample and linked to the name in an excel sheet, placed in a plastic bag and stored in a dry and safe place in the health post for a maximum of 5 days. A batch of sample was transported every Friday from Butajira to the HPV laboratory of Department of Microbiology, Immunology and Parasitology, School of Medicine, Addis Ababa University, to process the sample and DNA extraction according to the predefined study protocol.

2.6 | Sample processing and HPV DNA extraction

The Evalyn brush was removed from the plastic bag, the tip pulled off and put into a 2 mL Eppendorf tube, and soaked in 1 mL PBS overnight to wash the cells out from the dry Evalyn brush. After centrifugation for 5 minutes at 2500 rpm and vortexing vigorously for 1 minute, an aliquot of 100 μL of the fluid was used to produce crude DNA lysates using bacteria lysis buffer method (AID/GenID GmbH, Strassberg, Germany). Prior validation of this protocol was done to compare crude DNA lysates and the DNA extracted using Maxwell 16 LEV Blood Kit (Promega GmbH, Mannheim, Germany) at Charité-Universitätsmedizin Berlin, Germany. The validation results showed that the crude DNA lysates have enough concentration and purity of DNA for the intended PCR use. Furthermore, for every batch of samples, a quality control (10% of the samples) for the DNA extraction was also done in Charité-Universitätsmedizin Berlin, Germany, using Maxwell 16 LEV Blood Kit and the results were comparable with the crude DNA lysates. All the sample processing and isolation of DNA lysate were performed in the HPV laboratory of Department of Microbiology, Immunology and Parasitology School of Medicine, Addis Ababa University, Ethiopia. The DNA lysate was stored at −20°C until shipment and further analyses.

2.7 | HPV genotyping

For the HPV genotyping, a 20 μL aliquot of the DNA lysate was shipped to the collaborators Laboratory for Gynecologic Tumor Immunology at Charité-Universitätsmedizin Berlin, Germany. HPV presence and its genotype were determined using the L1 primer system BSGP5+/6+ PCR with MPG-Luminex Assay read out .[19] This assay detects 18 high-risk genotypes (HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82) and 9 low risk genotypes (HPV6, 11, 42, 43, 54, 57, 70, 72 and 90). In this method, broad spectrum GP5+/6+ primers[19] were used to amplify approximately 150-nucleotide-long conserved target gene L1 ORF fragments.[19] The final PCR reaction mix was 25 μL with 20 μL master mix and 5 μL DNA templates. The analysis was exactly performed as described by Schmitt et al in 2008. The PCR products were stored at −20°C if not immediately used. PCR products were detected on a Bioplex 200 (Bio-Rad, Hercules, California).

2.8 | Result reporting and triage of hr-HPV DNA-positive women

A result notification format was prepared and all the HPV-negative women were notified at the nearby health post through the HEWs and HDAs with full information what this negative result meant in the context of cervical cancer screening. However, for those women who were hr-HPV positives, their result was notified by inviting them to come to the health post and discuss on the subsequent actions to be taken. During result notification, all hr-HPV DNA-positive women were invited to visit Butajira Hospital for visual inspection using acetic acid (VIA) and cryotherapy treatment according to the national screening algorithm.

2.9 | Statistical analysis

Prevalence of HPV infection and individual genotype distribution were presented using bar and line graphs. Women participated in the study were stratified by age (30-34 years, 35-39 years, 40-44 years, and 45-49 years), and we reported HPV infections and age-specific HPV prevalence.

3 | RESULTS

Out of the 1020 women aged 30 to 49 years (mean = 33 years) who attended the screening program sensitization at health posts,

893 (87.5%) provided cervical self-sampled specimen. The rest (n = 127) were excluded due to pregnancy, refusal to participate and being in active menses during sample collection time.

Among the 893 samples tested for HPV DNA, 717 (80.3%) had adequate cellularity to detect HPV in the sample while the remaining 176 (19.7%) were found with inadequate cellularity to detect HPV in the sample due to low internal control values for ß-globin PCR. All of the 176 women with low (inadequate) β-globin samples were invited for resampling and only 62 (35.2%) gave a repeat self-sample with 24.2% had again low ß-globin. Overall, 764 (85.6%) were found to have sufficient β-globin positivity for HPV analysis and were included in this analysis.

3.1 | Prevalence of HPV infection

Overall, 23.2% (95% CI: 23.54-22.86%) women were positive for HPV DNA. Of these, 20.5% (95% CI = 20.79-20.21) women were hr-HPV positives and 10.3% (95% CI = 10.52-10.08) had lr-HPV DNA. High-risk HPVs were detected more frequently than low-risk types. Among the women positive for hr-HPV, 13.4% had a single HPV infection and 7.2% had multiple HPV infections. Among the 55 women with multiple hr-HPV infections, 41.8% had dual high-risk infections, 29.1% had triple high-risk infections and 29.1% had four or more hr-HPV infections. The hr- and lr-HPV coinfection in our study is 7.7%. Furthermore, 3% of the tested women had non-typable lr-HPVs by the MPG-Luminex system used that genotypes 9 lr-HPVs. The combined prevalence of HPV16 and 18 infections among the total screened women and among the hr-HPV positive women was 13.5% and 65.7%, respectively.

3.2 | HPV genotype distribution

The positivity rate of the detected genotypes in our study among all of the tested samples and the distribution of each genotype in the HPV-positive women is shown in Figure 1. Of the identified HPV genotypes in our study population, HPV16 is the most prevalent genotype found (13.2%) followed by HPV11 (6.5%). From the hr-HPV genotypes identified in our study, HPV16, 35, 52, 31 and 45 were the five most prevalent genotypes in our study population, respectively (Figure 1). From the nine lr-HPV types detected in our study, HPV11 was found to be the most prevalent low- risk genotype followed by HPV42, 54, 43 and 6 (Figure 1).

Among the HPV-positive women, the proportion of the 9-valent vaccine preventable genotypes HPVs6, 11, 16, 18, 31, 33, 45, 52 and 58 was 6.2%, 28.2%, 57.1%, 9%, 14.1%, 1.7%, 9.6%, 15.8% and 2.8%, respectively. This amounts to 76.8% of all HPV infections present in our study population. The seven hr-HPV types that are included in the 9-valent vaccine preventable HPV types contributes to 79% of the total hr-HPV infection in our study (Figure 2).

3.3 | Age-specific prevalence of HPV infection

As HPV prevalence differs with age, we analyzed the proportion of hr-HPV infection in different age groups. The women were divided into four age groups (30-34 years, 35-39 years, 40-44 years and 45-49 years). The frequency of hr-HPV infection decreased with age (Figure 3). High-risk HPV infection was high (58.6%) in the young age group (30-34 years) followed by 35-39 years (20.4%) and steadily decreased to 4.5% and 3.8% in the age group 40-44 years and 45-49 years, respectively.

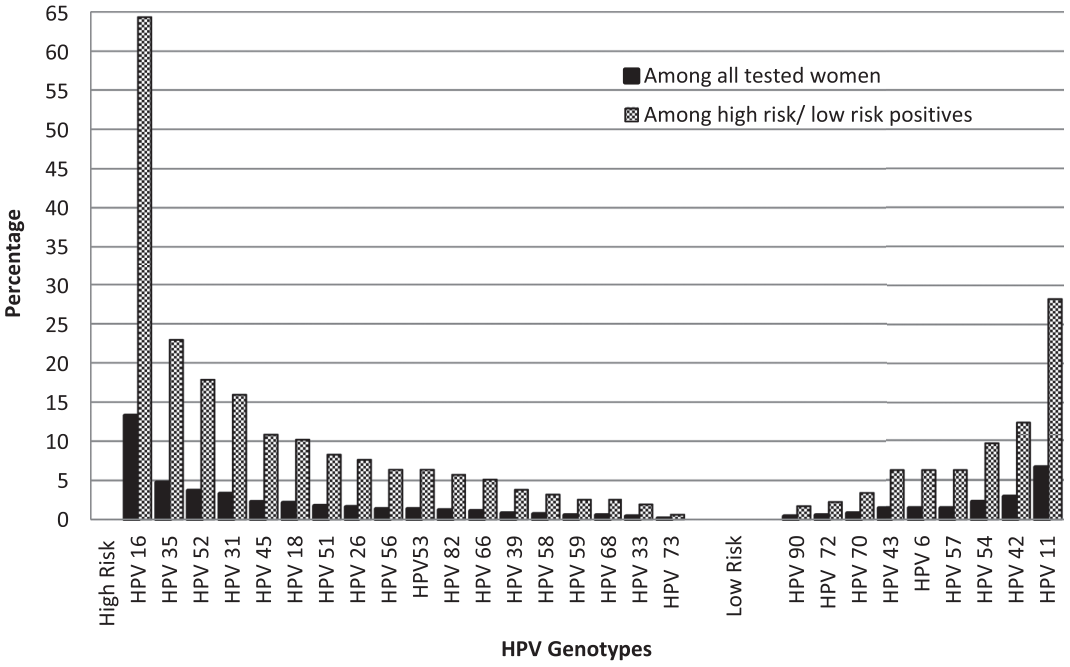

FIGURE 1 Prevalence and genotype distribution of hr- and lr-HPVs among Butajira women, South Central Ethiopia

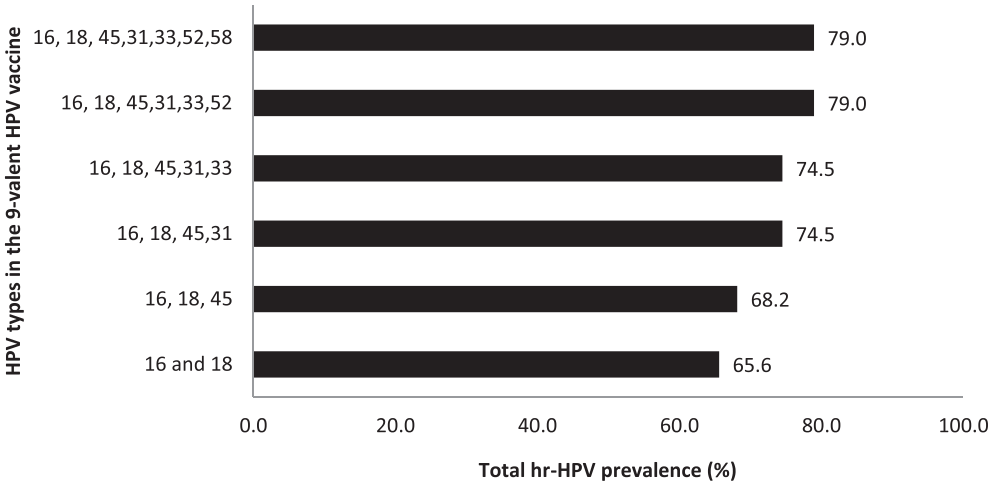

FIGURE 2 The contribution of the 9-valent vaccine preventable hr-HPV types to total hr-HPV prevalence in Butajira, South Central Ethiopia

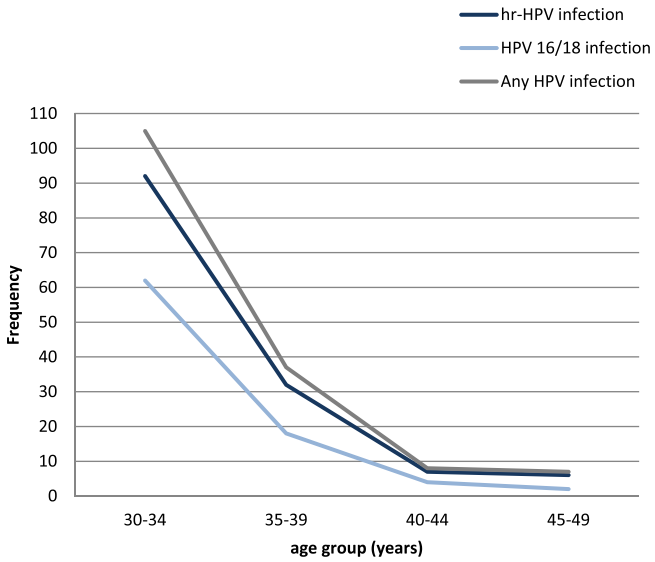

FIGURE 3 Age-specific prevalence of hr-HPV infection among Butajira women, South Central Ethiopia [Color figure can be viewed at wileyonlinelibrary.com]

In the women from Butajira among the hr-HPV positive, the age-specific prevalence of HPV 16 and 18 was higher (39.5%) in the age group 30-34 when compared to the other age groups. Only two women (33.3%) had HPV16 and 18 infections in the age group 45-49.

4 | DISCUSSION

The global strategy to eliminate cervical cancer as a public health problem calls for, screening 70% of women by the age 35 and 45 years with a high-precision test and. HPV testing is regarded as one of the most accurate and cost-effective method of primary screening.[20] Therefore, establishment of laboratories that perform HPV testing with the required quality and wider coverage is equally important in the effort to prevent cervical cancer.

This is the first population-based study aimed to determine overall HPV infection, genotypes of HPV circulating in the population and age-specific prevalence of HPV by using self-sampling in rural Ethiopia. About 85.6% of the collected specimens were adequate while 14.4% had inadequate DNA content for HPV analysis (low β-globin) according to our quality criteria. In our study, the problem of inadequate DNA content arose despite comprehensive demonstration of the self-sampling procedure and assistance by HEW when requested. It is in contrast to similar studies using a field approach and HEW supporting collection where less than 2% smears were inadequate.[21] Several factors could account for such higher rate of poor quality specimen. Cultural issues associated with inserting foreign body and the fear of the women she might hurt herself or may not be able to collect good samples as well as lack of experiences in self-sampling for other procedures will also account to some extent. We have reviewed literature to our capacity and very few had shown how much of the self-samples were analyzable.[22] However, Ingeborg et al's report was based on as few as 49 samples. Similar problems with the inadequacy of sample for HPV DNA test were observed in a study conducted in other part of Ethiopia[23] at which significant number of the collected samples were with poor quality. The other possible reason of why such amounts of samples were with inadequate DNA content might be due to the fact that most of the rural women in our study are illiterate (65.4%) and 30% only primary level education[24] and could not manage to understand the demonstration and the self-collection. Furthermore, the training given by the HEW might not be enough since the self-sampling device is used for the first time in the country. As far as what should be the case in Ethiopia in the future if self-sampling is the strategy for cervical cancer screening, we proposed to conduct a study to assess the challenges associated with this. Any problem associated with transportation of the samples from the field to the lab also needs to be addressed. However, from our study, it was possible to proof that a self-sampling device can be used to determine community-level prevalence and genotype distribution of HPV and employ HPV testing using self-sampling to screen for cervical (pre-) cancer in rural Ethiopia. Besides, HPV self-sampling increased the uptake of cervical cancer screening by approximately

20% in the study area, as compared to VIA invitation, which is the current practice, as we have shown in our previous publication.[18]

Even if it is hard to compare and draw conclusions with previous few studies conducted in Ethiopia[14,15] for a number of reasons, the observed population-based HPV prevalence in the study area was high (23.2%) and the hr-HPV infection was 20.5%. This prevalence was high not only compared to other studies in Ethiopia but also compared to the global HPV prevalence in women with normal cytology, which is in the range of 11% to 12%.[25] However, the figure is comparable to the estimated prevalence of HPV burden in sub-Saharan African regions (24.0%) as stated in a meta-analysis of about 1 million women with normal cytology.[26] Despite the established fact that the higher the prevalence of HPV infection the higher the incidence of cervical cancer, how many of these hr-HPV-positive women have persistent infection, progressive dysplasia, and/or invasive lesion is not known and requires triage tests and repeated longitudinal testing. A study from Ghana detected disease (CIN2+) predominantly in those women (6.7% of the investigated population) who had a genotype-specific persistence over >4 years.[21] One of the inherent disadvantage of HPV testing is its low specificity and thus only defines women at risk of invasive disease. The implication of this is important in terms of what triage tests to employ in the region where there is limited resources and facilities if HPV-based screening is to be rolled out in national screening programs.

Determining the genotype of HPV circulating in the population is important to assess the impact of the vaccination program in Ethiopia and further advice the program which vaccines to choose/use and HPV testing to implement in the national program of screening. In this first of its kind population-based study, we found that HPV 16, 35, 52, 31, 45, 18 and 51 are the seven dominant high-risk genotypes in decreasing order that accounted for 87.9% of the infections. The association of the hr-HPV infection with invasive cancer and precancerous lesion is variable. In our study, of the total hr-HPV infected women, 35% had multiple infections. The relative contribution of such multiple infections in the development of invasive cancer and CIN3+ lesions requires further investigation in our population. A study that involved a large number of women had shown that multiple hr-HPV infection was present in 11.9% of ICC and 15.8% CIN3 lesions.[27]

In our study, HPV18 was less common than HPV31, 35 and 52. Compared to HPV31, 33, 52 and 58, the prevalence of HPV 18 in CIN3 lesion was less as described elsewhere. In contrary, the absolute risk in causing CIN3+ and CIN2+ as well as the prevalence of HPV18 in cervical cancer is next to HPV16.[27-29] However, unlike in different studies worldwide, HPV35 and HPV45 were also found as the most relevant hr-HPV types for infection prevalence. Most importantly, HPV35 (the second most dominantly detected in our study) is not included in the current 9-valent HPV vaccine (Gardasil 9). HPV35 is among the top 10 CC causing HPV types and reported in 3.9% of CC cases in Ethiopia.[4] Similarly, HPV35 was detected in 9.7% histologically confirmed ICC cases with single HPV infection in a study done in Ghana, Nigeria and South Africa.[28] Thus, the role of HPV35 in causing invasive cervical cancer in Ethiopia requires further studies.

In our study, the overall prevalence of hr-HPV infection declined sharply with age, the highest (12.0%) being in the age group (30-34 years). This is in agreement with the global trend of high infection rate at younger age.[12,30,31] Even though the frequency of infection is lower, the infection identified in the older age group in our study could be a persistent infection and these women may require follow-ups more urgently. The prevalence of HPV infection at the younger age (30-34) is highest and one could conclude it will be more cost-effective to implement HPV-based screening only as of the age of 34+ as an initial phase of HPV-based screening in Ethiopia.

5 | CONCLUSION

In conclusion, our study provides new data on the overall prevalence of HPV infection and distribution of specific HPV types in rural Ethiopia. The overall prevalence of hr-HPV was high as expected for an unscreened population. This implies that the risk of developing cervical cancer could be high in Ethiopian women unless organized HPV-based screening and treatment programs are implemented in the country.

In our study population, HPV16, HPV35, HPV52, HPV31 and HPV45 were the most prevalent genotypes. Since our study is the first population-based study in the country, this result serves as a baseline data and is essential for the development of public health policy for cervical cancer prevention.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Raw data were generated at the laboratories of Department of Microbiology, Immunology and Parasitology, Addis Ababa University, Ethiopia and Clinic for Gynecology, Charité - Universitätsmedizin Berlin, Germany. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

Ethical approval was obtained from the Institutional Review Board of the College of Health Sciences, Addis Ababa University (057/17/SPH) and Martin Luther University, Halle Germany (2017-143). In addition, our study was also approved by the National Research Ethics Review Committee (NRERC) (SHE/RAAA/9.1/339/19/11) and a material

transfer agreement was signed by both institutions to transfer samples to Germany. Oral informed consent was obtained from all women who participated in the screening before data and biological sample collection. During sample collection, a sterile Evalyn brush was given to consenting participants and samples were collected at the place where privacy was assured.

The HPV-positive results were communicated for the client only and treatment was provided based on the national cervical cancer treatment guideline. A second sampling opportunity was given for women who were excluded by the exclusion criteria. Moreover, any participant-related data was collected in a way to ensure confidentiality of the women by pseudonomization of the sample and linkage to a password protected excel file.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Erklärungen

(1) Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

(2) Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

(3) Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Halle Saale, den 22. 11.2021

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