

Review Article

Distribution of High Risk Human Pappiloma Virus Genotypes Among Women with Cervical Cancer in East Africa: Systematic Review

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Abstract: High- risk human papilloma viruses are the major etiological agent of cervical cancer, which is one of the leading cancers among women in sub-Saharan Africa. The aim of the present systematic review is to identify type distribution of high risk human Pappiloma viruses among women with cervical cancer in East Africa. The present systematic review was performed using published articles, which was accessed from electronic databases such as MEDLINE/PubMed, Google Scholar, EMBASE, CINAHL and Cochrane Central library. Eligible research articles were selected based on predetermined inclusion and exclusion criteria. Four studies, which fulfilled the inclusion criteria, were included in the present systematic review. The finding of the present systematic review revealed that the totals of 15 HR-HPV associated with invasive cervical cancer were identified from the current study setting. These HR-HPV genotypes include HPV 16, HPV 18, HPV 56, HPV 45, HPV 39, HPV 52, HPV 31, HPV 35, HPV 58, HPV 33, HPV 59, HPV 68, HPV 66, HPV 82 and HPV 73. According to the current systematic review the major genotype associated with cervical cancer in east Africa were HVP 16 followed by HPV 18 and HPV 45 respectively.

Keywords: High-risk Human Pappiloma Virus, Cervical Cancer, Genotype, East Africa

1. Introduction

Human Papilloma virus (HPV) is non-enveloped, double-stranded DNA viruses in the family *Papillomaviridae* with a genome of approximately 8000 base pairs. The virus has been identified as the etiologic agent of several different diseases in men and women worldwide [1]. The Centers for Disease Control estimates that at least half of all sexually active individuals will acquire HPV at some point in their lives, whereas at least 80% of women will acquire an HPV infection by age 50 [2].

It is widely accepted that certain oncogenic types of Human papilloma virus are necessary causes of cervical cancer development [3]. Different epidemiological, clinical and experimental evidence demonstrated that the high-risk human

papilloma virus (HR-HPV) infection plays a central role in causing cervical cancer [4]. Among many human papilloma virus (HPV) genotypes identified to date, around 50 genotypes are capable of infecting the cervical epithelium and HR-HPV including HPV16, HPV 18, HPV 31, HPV 33, HPV 34, HPV 35, HPV 39, HPV45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, HPV 68 and HPV 70 are explicitly associated with cervical cancer [5]. HPV 16 and HPV 18 are the most virulent HR-HPV genotypes causing about 70% of all invasive cervical cancer (ICC) in the world [6].

Worldwide, cervical cancer is among the most common cancer causing death in women, with an estimated 570,000 cases and 311,000 deaths in 2018 [7]. This disease ranks as the fourth most frequently diagnosed cancer in women. Cervical cancer ranks second in incidence and mortality

behind breast cancer in developing countries with the vast majority are in Sub-Saharan Africa and South- Eastern Asia [8, 9]. The highest regional incidence and mortality rates are seen in Africa, with the elevated rate (40.1) in Eastern Africa and the highest mortality rate in Malawi with rate of 30 [8]. According to the 2017 World Health Organization (WHO) report, the age-standardized incidence rate of cervical cancer in Djibouti, Eritrea, Ethiopia, South Sudan, Somalia and Kenya are 17.3; 17.4; 26.4; 30.4; 33.4 and 40.1 per 100,000 patients (estimated for 2012) [10].

Three prophylactic HPV vaccines, directed against high-risk HPV types, are currently available and marketed in many countries worldwide for the prevention of HPV-related disease. These are a bivalent vaccine, quadrivalent vaccine and nonavalent HPV vaccine. The bivalent vaccine contains non-infectious protein antigens for HPV 16 and 18, the quadrivalent contains non-infectious protein antigens for HPV 6, 11, 16, and 18 and the nonavalent has non-infectious protein antigens for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 [11, 12]. Understanding of the distribution of high risk HPV genotypes present in current study setting is important for good managements of cervical cancer and for effective vaccination program. The aim of the present systematic review was to review the type distribution of high risk Human Papillomavirus (HR-HPV) in east Africa.

2. Methods

2.1. Article Searching Strategy

This systemic review was conducted to identify the more prevalent high-risk Human Pappiloma Virus genotypes (HR-HPV) associated with cervical cancer in east African countries including Eretria, Ethiopia, Djibouti, Somalia, Kenya, South Sudan and Sudan. Electronic databases (MEDLINE/PubMed, Google Scholar, EMBASE, CINAHL and Cochrane Central library) were systematically searched from February 1st to 28, 2019. Research articles written in English language and published in peer reviewed journals were accessed from the above databases by using the following key words or terms/mesh terms either singly or in combination: distribution/prevalence, high risk Human Pappiloma Virus/HR-HPV, genotypes, women, cervical cancer, cervical carcinoma, cervical neoplasia, east Africa, Ethiopia, Kenya, Sudan, South Sudan, Eritrea, Djibouti and Somalia. (((Distribution[tw] OR Prevalence[tw]) OR ((High[All Fields] AND ("risk"[MeSH Terms] OR "risk"[All Fields]) AND Human Pappilomavirus[tw]) OR HR-HPV[tw])) OR (Genotypes[tw] OR ("Genotype"[Mesh] OR "Genetic Profile"[Mesh]))) AND (Women[tw] AND (((Cervical cancer[tw] OR "Uterine Cervical Neoplasms"[Mesh]) OR Cervical carcinoma[tw]) OR (Cervical neoplasia[tw] OR "Uterine Cervical Neoplasms"[Mesh])))) AND (((((East Africa[tw] OR Ethiopia[tw]) OR Kenya[tw]) OR Sudan[tw]) OR South Sudan[tw]) OR Eritrea[tw]) OR Djibouti[tw]) OR Somalia[tw]) was the query used to search records.

Preliminary search was conducted to identify key terms

used during the main search for records from the indicated databases. This systematic review used the CoCoPop (Condition, Context and Population) framework to determine the eligibility of the articles included. The study Condition (Co) was distribution of high risk Human Pappiloma Virus genotypes, the Context (Co) was east Africa and the Population (Pop) were women with cervical cancer.

2.2. Selection Criteria

Eligible research articles for this systematic review were selected in three stages: titles alone, abstracts, and then full-text articles, based on inclusion and exclusion criteria. All studies reported in English language, published in peer-reviewed journals, and revealed the distribution of HR-HPV genotype associated with cervical cancer in east Africa were included.

However, studies which do not report HR-HPV genotype association with cervical cancer [13-16], and that report association between HR-HPV and other microorganisms in inducing non-cancerous cervical lesions [17] were excluded. In addition, articles which were not fully accessible, review articles, commentary, and editorials were excluded from analysis.

2.3. Data Abstraction and Quality Assessment of the Studies

Eligible articles were identified by two reviewers, Matifan Dereje (MD) and Gemechis Tesso (GT), through independent reading of the titles and abstracts, which were searched and accessed broadly. The full texts of potential articles were accessed, and independent assessment was done for eligibility based on the predetermined inclusion and exclusion criteria. The two reviewers were independently extracted the data and controversies between the reviewers were resolved through discussion and common understanding among the reviewers. The data extraction was performed using the following template: first author, study setting, sample size, genotyping methodology, and number, type and prevalence of HPV genotype detected. The Joanna Briggs institute (JBI) critical appraisal tools for systemic review of prevalence study [18] were used to assess the quality of the current studies.

2.4. Method of HR-HPV Detection and Genotyping

Different techniques and assays were used for detection and genotyping of HR-HPV. Polymerase Chain Reaction (PCR) using generic or consensus primers and Hybrid capture 2 (HC2, Qiagen, Hilden, Germany) were used in majority of studies to detect HPV DNA. Line-probe assay (Inno-LiPA) and Southern Blot technique were used for detecting HR-HPV genotypes.

3. Result

3.1. Accessed Articles

The finding of the current systematic review was presented based on the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) guideline [19]. A total of 128 articles related to the review title were accessed in our initial literature search. After duplicate retrievals removed, 81 articles were remained. Based on title based screening, 62 articles were excluded. Of the remaining 19 articles, abstracts were screened and 10 articles were excluded because study setting was other than the east African countries and HR-HPV genotype was not reported rather than detection. For the

remaining 9, full-text articles were evaluated for eligibility based on predetermined inclusion and exclusion criteria and 5 studies were excluded. This was due to some of the articles do not report HR-HPV genotype association with cervical whereas, some of the studies report association between HR-HPV and other microorganisms in inducing non-cancerous cervical lesions. Finally, 4 studies were included in the present systematic review (Figure 1).

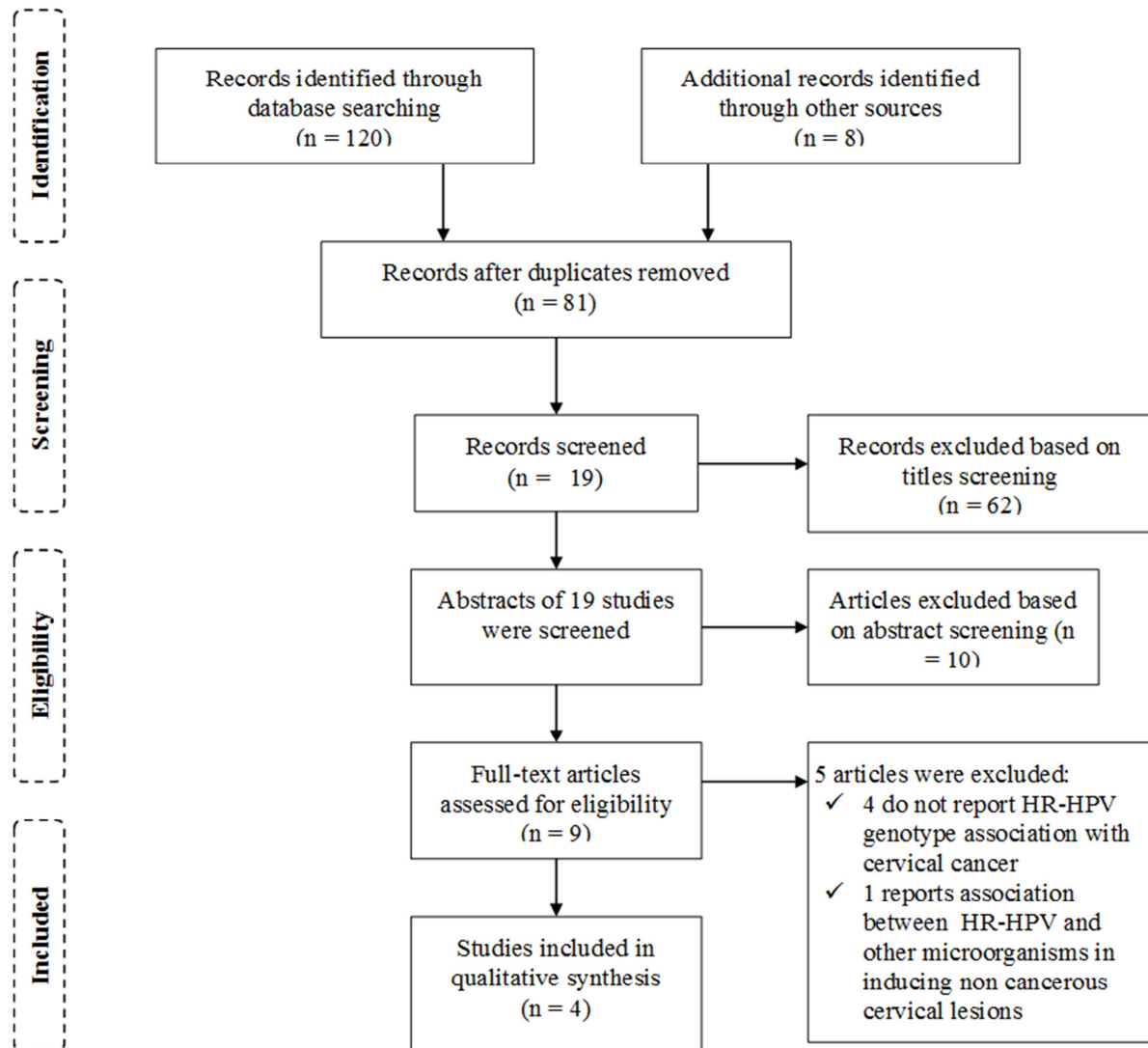


Figure 1. Flow chart, which reveals the procedures of study selection for the current systematic review.

3.2. Description of Study Setting and Sample Size

The current systematic review was aimed to review the genotype distribution of high risk human pappiloma virus associated with cervical cancer by including the studies from east African countries (Eretria, Ethiopia, Djibouti, Somalia, Kenya, South Sudan and Sudan). However, among the accessed research articles, only those conducted in Ethiopia, Kenya and Sudan were eligible to include in the present systematic review. No single study related to the current systematic review was accessed from Eretria, Djibouti, Somalia, and South Sudan. Of the four studies included, two

studies were from Ethiopia [20, 21] and one from Kenya [22]. While, one study was investigated the genotyping of human papilloma virus in paraffin embedded cervical tissue samples from women in Ethiopia and the Sudan [23], this particular study, therefore, was selected for the current review as for Ethiopia and Sudan. In the present systematic review a total; 228 women were from Ethiopia, 145 were from Kenya and 79 were from Sudan (table 1). The findings from the studies conducted to identify genotype distribution of HR-HPV associated with cervical cancer across east Africa are summarized in tables 1 and 2.

Table 1. Overall information of studies included in the systematic review of distribution of high risk human papilloma virus genotype associated with cervical cancer in east Africa.

Author	Study setting	Genotyping methodology	Number of woman with ICC and HR-HPV infection	Total number of genotype detected	Number of HR-HPV type detected	List of genotype identified
Bekele A et al., 2010 [20]	Ethiopia	GP5+/6+ HPV PCR	81	104	11	16, 18, 56, 45, 39, 52, 31, 35, 58, 33, 59
Abate et al., 2013 [23]	Ethiopia	SPF10 primers and Line probe assay	127	255	11	16, 18, 31, 33, 35, 39, 45, 52, 58, 66, 68
Wolday et al., 2018 [21]	Ethiopia	(MY09/MY11 and GP5/GP6 primers)	20	20	5	16, 45, 52, 56, 35
Ermel et al., 2016 [22]	Kenya	Roche Linear array assay	145	168	11	16, 18, 31, 33, 35, 39, 45, 58, 59, 73, 82
Abate et al., 2013 [23]	Sudan	SPF10 primers and Line probe assay	79	154	11	16, 18, 31, 33, 35, 39, 45, 52, 58, 59, 68

3.3. HR-HPV Genotype Distribution

A total of 15 HR-HPV associated with invasive cervical cancer were identified from east Africa. 13 HR-HPV were reported from Ethiopia; 11 from Kenya and 11 from Sudan. These HR-HPV genotypes include HPV 16, HPV 18, HPV 56, HPV 45, HPV 39, HPV 52, HPV 31, HPV 35, HPV 58, HPV 33, HPV 59, HPV 68, HPV 66, HPV 82 and HPV 73. HPV 56 and HPV 66 were reported only from Ethiopia, while HPV 82 and HPV 73 were exclusively reported from Kenya (table 2 and table 3).

Table 2. Prevalence of HR-HPV genotypes identified in women with invasive cervical carcinoma in East Africa.

Author	Genotype identified	Prevalence	Study setting
Abate E et al., 2013 [23]	HPV 16	65 (42.2%)	Sudan
	HPV 18	16 (10.4%)	
	HPV 45	14 (9.1%)	
	HPV 52	12 (7.8%)	
	HPV 58	12 (7.8%)	
	HPV 33	10 (6.5%)	
	HPV 35	8 (5.2%)	
	HPV 68	8 (5.2%)	
	HPV 31	5 (3.2%)	
	HPV 39	3 (1.9%)	
	HPV 59	1 (0.6%)	
Wolday D et al., 2018 [21]	HPV16	13 (65%)	Ethiopia
	HPV 45	3 (15%)	
	HPV 52	2 (10%)	
	HPV 56	1 (5%)	
	HPV 35	1 (5%)	
Abate E et al., 2013 [23]	HPV 16	117 (45.8%)	Ethiopia
	HPV 52	31 (12.2%)	
	HPV 58	28 (10.9%)	
	HPV 18	26 (10.2%)	
	HPV 45	16 (6.3%)	
	HPV 68	9 (3.5%)	
	HPV 31	8 (3.1%)	
	HPV 33	8 (3.1%)	
	HPV 35	6 (2.4%)	
	HPV 39	5 (1.9%)	
	HPV 66	1 (0.4%)	
	HPV 16	67 (64.4%)	
	HPV 18	10 (9.6%)	
	HPV 56	10 (9.6%)	
Bekele A et al., 2010 [20]	HPV 45	5 (4.8%)	Ethiopia
	HPV 39	3 (2.9%)	
	HPV 52	2 (1.9%)	
	HPV 31	2 (1.9%)	
	HPV 35	2 (1.9%)	
	HPV 58	1 (0.9%)	
	HPV 33	1 (0.9%)	
Ermel A et al., 2016 [22]	HPV 59	1 (0.9%)	Kenya
	HPV 16	118 (70.2%)	

Author	Genotype identified	Prevalence	Study setting
	HPV 18	28 (16.6%)	
	HPV 45	9 (5.4%)	
	HPV 31	2 (1.2%)	
	HPV 33	2 (1.2%)	
	HPV 58	2 (1.2%)	
	HPV 59	2 (1.2%)	
	HPV 82	2 (1.2%)	
	HPV 35	1 (0.6%)	
	HPV 39	1 (0.6%)	
	HPV 73	1 (0.6%)	

Among the 13 HR-HPV reported from Ethiopia, two genotypes (HPV 16 and HPV 52) were reported by all studies conducted in Ethiopia which included in the present systematic review. Of the 15 total HR-HPV genotypes identified by the present systematic review, 9 genotypes (HPV 16, HPV 18, HPV 45, HPV 39, HPV 31, HPV 35, HPV 58, HPV 33 and HPV 59) were reported from Ethiopia, Kenya and Sudan (table 3).

Table 3. List and type distribution of HR-HPV genotype identified in east Africa.

HR-HPV genotype	Country, percentage	Author
HPV 16	Ethiopia (58.4%), Kenya (70.2%), Sudan (42.2%)	Abate E et al., 2013; Bekele A et al., 2010; Wolday D et al., 2018; Ermel A et al., 2016
HPV 18	Ethiopia (9.9%), Kenya (16.6%), Sudan (10.4%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 56	Ethiopia (7.3%)	Bekele A et al., 2010; Wolday D et al., 2018
HPV 45	Ethiopia (8.7%), Kenya (5.5%), Sudan (9.1%)	Abate E et al., 2013; Wolday D et al., 2018; Ermel A et al., 2016
HPV 39	Ethiopia (2.4%), Kenya (0.9%), Sudan (1.9%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 52	Ethiopia (8%), Sudan (7.8%)	Abate E et al., 2013; Bekele A et al., 2010; Wolday D et al., 2018
HPV 31	Ethiopia (2.5%), Kenya (1.2%), Sudan (3.2%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 35	Ethiopia (2%), Kenya (0.6%) Sudan (5.2%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 58	Ethiopia (5.9%), Kenya (1.2%), Sudan (7.8%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 33	Ethiopia (2%), Kenya (1.2%), Sudan (6.5%)	Abate E et al., 2013; Bekele A et al., 2010; Ermel A et al., 2016
HPV 59	Ethiopia (0.9%), Kenya (1.2%), Sudan (0.6%)	Abate E et al., 2013; Ermel A et al., 2016
HPV 68	Ethiopia (3.5%), Sudan (5.2%)	Abate E et al., 2013
HPV 66	Ethiopia (0.4%)	Abate E et al., 2013
HPV 82	Kenya (1.2%)	Ermel A et al., 2016
HPV 73	Kenya (0.6%)	Ermel A et al., 2016

4. Discussion

Infection of cervix by the HR-HPV is the most important risk factor for cervical cancer [24]. Molecular epidemiologic evidence clearly indicates that certain types of human papilloma virus (HPV) are the principal cause of invasive cervical cancer [25]. The current systematic review is perhaps the first of its kind to be conducted in east Africa to identify the HR-HPV genotypes distribution in women with invasive cervical carcinoma. The findings of this study will have important implications for cervical cancer prevention programs run by governmental and non-governmental organizations.

Findings of this systematic review revealed that HPV 16 (58.4%), HPV 18 (9.9%), HPV 45 (8.7%), HPV 52 (8%) and HPV 56 (7.3%) are the top five HR-HPV causing cervical cancer in Ethiopia (table 3). Whereas, HPV 16 (70.2%), HPV 18 (16.6%) and HPV 45 (5.5%) are the top three HR-HPV reported from Kenya (table 2). Similarly, HPV 16 (42.2%), HPV 18 (10.4%), HPV 45 (9.1%), HPV 52 (7.8%) and HPV 58 (7.8%) are the top five HR-HPV associated with invasive cervical cancer reported from Sudan (table 2).

As revealed by the present systematic review, HPV 16 (56.9%) and HPV 18 (12.3%) are the most prevalent, top two,

HR-HPV genotype associated with ICC in east Africa (table 3). This is in line with HR-HPV genotype distribution report in Sub-Saharan Africa [26], China [27] and India [28]. Whereas HPV 45 is identified as the third most prevalent HR-HPV genotype in east Africa (table 3).

5. Limitations

Only English articles or reports were considered to conduct this review. Furthermore, in this systematic review, the studies included were reported from three east African countries. Research report in line with the present systematic review question, conducted in South Sudan, Somalia, Djibouti and Eritrea, were not found until database searching was completed. Therefore, the result may only be representative of Ethiopia, Kenya and Sudan.

6. Conclusions

The review demonstrated a high burden of HR-HPV genotypes in the women with ICC in east Africa (Ethiopia, Kenya and Sudan). HPV 16, HPV 18 and HPV 45 are the most prevalent HR-HPV genotypes in east Africa. HPV 16, HPV 18, HPV 45, HPV 52 and HPV 56 are the top five; HPV 16, HPV 18 and HPV 45 are top three, and HPV 16, HPV 18, HPV 45,

HPV 52 and HPV 58 are the top five HR-HPV associated with invasive cervical cancer in Ethiopia, Kenya and Sudan, respectively. Accordingly, nonavalent HPV vaccine which has non-infectious protein antigens for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 is recommended for Ethiopia, Kenya and Sudan.

Authors' Contributions

All authors equally contributed to the present systematic review.

Conflicts of Interest

The authors declare that they have no competing interests.

Abbreviations

DNA: Deoxyribonucleic acid

HPV: Human Papilloma virus

HR-HPV: High-risk human Papilloma virus

ICC: Invasive cervical cancer

PCR: Polymerase chain reaction

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

WHO: World Health Organization

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