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Genetic Susceptibility for Cervical Cancer in African Populations: What Are the Host Genetic Drivers?

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Abstract

Human papillomavirus (HPV) is an essential but not a sufficient cervical cancer etiological factor. Cancer promoters, such as host genetic mutations, significantly modulate therapeutic responses and susceptibility. In cervical cancer, of interest have been viral clearing genes and HPV oncoprotein targets, for which conflicting data have been reported among different populations. This expert analysis evaluates cervical cancer genetic susceptibility biomarkers studied in African populations. Notably, the past decade has seen Africa as a hotbed of biomarker and precision medicine innovations, thus potentially informing worldwide biomarker development strategies. We conducted a critical literature search in PubMed/MEDLINE, Google Scholar, and Scopus databases for case–control studies reporting on cervical cancer genetic polymorphisms among Africans. We found that seven African countries conducted cervical cancer molecular epidemiology studies in one of *Casp8*, *p53, CCR2, FASL, HLA, IL10, TGF-beta,* and *TNF-alpha* genes. This analysis reveals a remarkable gap in cervical cancer molecular epidemiology among Africans, whereas cervical cancer continues to disproportionately have an impact on African populations. Genome-wide association, whole exome- and whole-genome sequencing studies confirmed the contribution of candidate genes in cervical cancer. With such advances and omics technologies, the role of genetic susceptibility biomarkers can be exploited to develop novel interventions to improve current screening, diagnostic and prognostic methods worldwide. Exploring these genetic variations is crucial because African populations are genetically diverse and some variants or their combined effects are yet to be discovered and translated into tangible clinical applications. Thus, translational medicine and flourishing system sciences in Africa warrant further emphasis in the coming decade.

Keywords: Africa, translational medicine, cervical cancer, genetic susceptibility, genetic variation

Introduction

Cervical cancer is the second most commonly diagnosed cancer among women world-wide. The world population for women over 15 years is 2278 billion, and these women are at a very high risk of developing cervical cancer (Bruni et al., 2017). In 2012, the estimated global burden of cervical cancer was over 500,000, whereas the annual death toll as a result of the disease was nearly 266,000 (Bruni et al., 2017). The incidence and mortality rate of cervical cancer is much lower in developed countries because of readily available preventive, diagnostic, and screening tools, including human papillomavirus (HPV) vaccination programs that enable early diagnosis resulting in better prognosis (Chung et al., 2017).

In developed countries, the healthcare systems are robust and efficient, thus, drastically reducing cervical cancer-related deaths (Mbouba-Bouassa et al., 2017). However, in low- and middle-income countries (LMICs), the healthcare systems are overburdened by infectious diseases, which take most of the resources, leaving very little for noncommunicable diseases such as cancer and the requisite screening programs.

In addition, most patients are often diagnosed late leading to high mortality (Mbouba-Bouassa et al., 2017). Eighty-five percent of the global cervical cancer cases are detected in

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LMICs. Of the 98 countries that the World Bank considers to be LMICs, 41 countries are in Africa, translating to 72% of all African countries (World Bank, 2017). The country with the highest cervical cancer incidence is Malawi (46.5%), followed by Mozambique (44.8%), Comoros (39.4%), Zimbabwe (34.5%), and Zambia (33.7%). Table 1 illustrates the incidences of cervical cancer in African countries, where it is disproportionately high.

Etiology of cervical cancer

Cervical cancer is a complex multifactorial disease with etiological factors that can be subdivided into extrinsic and intrinsic factors. The risk of developing cervical cancer is centered mostly on sexual behavior. For example, the age of sexual debut, number of sexual partners, and history of sexually transmitted infections are key contributors to cervical cancer development (Brinton et al., 1989). Additionally, other extrinsic factors, such as hormone-regulating circumstances, including multiparity, age at first pregnancy, and prolonged use of oral contraceptives have also been shown to increase susceptibility to cervical cancer (Castellsague and Munoz, 2003; Louie et al., 2009).

While these other factors increase the risk of developing cervical cancer, high-risk HPV (hr-HPV) subtypes have been identified as the only definitive etiological factor for cervical intraepithelial neoplasia (CIN) and cervical cancer (Martínez-Nava et al., 2016). HPV deoxyribonucleic acid (DNA) encodes three oncoproteins E5, E6, and E7 that deregulate the function of major histocompatibility complex I, p53, and retinoblastoma (Di Maio and Petti, 2013; Tomaic, 2016).

Table 1. Proportion of Female Cancers Attributed to Cervical Cancer

Cancer incidence (%)	*Country (specific cervical cancer incidence)*
<7.9	Egypt (2.1), Sudan (4.5), Niger (4.8), Tunisia (4.9), Algeria (7.1), Libya (7.4)
8–13.6	Gambia (10.6), Chad (10.9), Namibia (11.1), Djibouti (11.9) Burkina Faso (13.1), Mauritius (13.6)
13.7–20.6	Togo (13.7), Congo (14.7), Gabon (15.1), Ethiopia (16.3), Liberia (17.3), Benin (16.5), Nigeria (17.1), Mauritania (18.2), Mauritius (18.5), Equatorial Guinea (18.3), Guinea Bissau (18.7), Cameroon (19.4), Somalia (19.6), Angola (20.4)
20.7–30.2	Uganda (22), Kenya (22.4), Senegal (22.4), Mali (22.8), Rwanda (23.8), Lesotho (27.8), Ghana (24.3), Botswana (24.6), Cape Verde (26.7), Madagascar (29), Tanzania (30.6), South Africa (30.2)
>30.3	Burundi (32.1), Zambia (33.7), Zimbabwe (34.5), Swaziland (36), Comoros (39.4), Mozambique (44.8), Malawi (46.5)
No cervical cancer data available	Central African Republic, Guinea, Sao Tome and Principe, Sierra Leone, Western Sahara

Table 2. Classification of Human Papillomavirus Subtypes

Classification by risk level	*HPV subtypes*
Low	6, 11, 26, 40, 42, 43, 44, 61, 54, 55, 57, 70, 71, 72, 84
Medium/moderate	53, 73, 81, 82
High	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

HPV, human papillomavirus.

Collectively, these oncoproteins enable the virus to evade the immune system while promoting uncontrolled cell proliferation, all of which are hallmarks of cancer (Hanahan and Weinberg, 2011). Under normal physiological circumstances, 90% of HPV infections resolve naturally within 24 months, dependent on the HPV subtype, and the remaining 10% spontaneously persist to invasive cancer (Bodily and Laimonis, 2011; Cubie, 2013; Miranda et al., 2013).

There are over 150 HPV subtypes that are generally classified into low, medium, and high risk (Table 2). Low- and medium-risk HPV subtypes have negligible carcinogenic potential, presenting as skin or external genital condylomas, which manifest as precancerous lesions named CIN (D'Ottaviano et al., 2013). Low-grade CIN (stages 1 and 2) has a high regression rate (≥50%), whereas CIN3 occurs as a result of inability to resolve the HPV infection, giving up to 4% risk of transforming to cervical cancer within 12 months (Goldie et al., 2004; Motamedi et al., 2015).

The hr-HPV subtypes (Table 2) have a high oncogenic potential and represent a necessary but not sufficient cause of cervical cancer. Thus, the persistence of hr-HPV occurs as a result of synergistic interaction with other HPV-related risk factors, such as early onset of sexual activity, alcohol, smoking, malnutrition, sexually transmitted infection, as well as HIV infection (Miranda et al., 2013). The most virulent subtypes are *HPV 16* and *18*, which collectively account for 80% of invasive cervical cancer cases (De Villiers et al., 2004).

Prevention of cervical cancer

As a preventative mechanism, HPV vaccines consisting of dead, noninfectious, and recombinant viral fragments are available. These vaccines target for hr-HPV subtypes 16/18 mostly (e.g., Cervarix); the quadrivalent vaccine against HPV 6, 11, 16, and 18 (Gardasil); and the novel nanovalent Gardasil 9, which targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Draper et al., 2013; Petrosky et al., 2015). The coverage of HPV vaccines has been extended to include both the hr-HPV and the most commonly diagnosed low-risk subtypes (HPV 6, 11). It is important to also target the low-risk HPV types as these produce irritating lesions in the form of condylomata acuminata (warts) often requiring invasive and cytodestructive techniques such as chemical/electrical ablation, and sometimes surgical excision (Ambuhl et al., 2016).

These benign lesions, in cases of viral persistence, often resurge after treatment (Yuan et al., 2016). Thus, for effective prevention, these vaccines are administered pre-HPV exposure

(which is assumed to be preadolescence or before sexual onset) so as to expose individuals to HPV and activate a memory response against secondary infections (Martins et al., 2016). In 2017, 36% of countries in the world had implemented national preventive HPV vaccination programs, whereas the remaining 64% were in pilot or prepilot phases (WHO, 2017).

In addition, HIV-induced immunosuppression has been shown to interfere with normal physiological HPV clearance by impeding the immunoprotective effects of HPV vaccines Gardasil and Cervarix (Ghebre et al., 2017). As a result, Gardasil and Cervarix vaccines may not offer HIV-positive women sufficient and effective protection against HPV infection and cervical cancer.

Genetics and cervical cancer

While infection with HPV is necessary, it is not sufficient for cervical cancer to develop since 70–90% of infected individuals can eliminate the virus (Ho et al., 1998). In addition to HPV infection, host inherent factors create a conducive environment for cervical cancer development, therefore showing great potential for utility as diagnostic and prognostic factors. Intrinsic factors that have been shown as key cervical cancer etiological factors include compromised immune system and genetic variation. Genetic susceptibility markers to cervical cancer are sometimes difficult to distinguish from pharmacogenes that lead to variable response to HPV treatment as well as immune-mediated conditions. For example, autoimmune diseases may impact and interfere with the body's ability to effectively clear HPV infections.

Studies conducted on familial aggregation in cervical cancer incidence illustrate that heritability can also confer risk to cervical cancer (Magnusson and Gyllensten, 2000). Cervical cancer risk was highest among full relatives, lower for half siblings, and lowest in distant relatives (Magnusson and Gyllensten, 2000). Given the role that p53, pRb, and the major histocompatibility complex I genes play in the pathogenesis of HPV, these genes have been of particular interest as possible susceptibility markers for cervical cancer. Of great relevance is *p53*, a gene encoding a tumor suppressor, which has been extensively studied in relation to cervical cancer susceptibility (Alsbeih et al., 2013).

The *p53 codon 72* mutation was described as a risk factor for cervical cancer by Storey et al. (1998), and these findings have been corroborated in different ethnicities by various researchers (Andersson et al., 2001; Bhattacharya et al., 2002; Dokianakis and Spandidos, 2000; Humbey et al., 2002; Kucera et al., 2000). However, conflicting findings suggest an interplay of secondary factors, such as environmental exposures that can directly enhance or downregulate the role of this mutation in cervical cancer risk (Ngan et al., 1999; Nishikawa et al., 2000; Rosenthal et al., 1998; Wang et al., 1999).

Molecular studies on cervical cancer have identified single nucleotide polymorphisms (SNPs) and copy number variations associated with increased risk of developing cervical cancer. Current reports show the involvement of *Caspase 8*, CCR2, *CTLA4*, *CYP1A1*, *EXO1*, *FASLG*, FASR, HOTAIR, *IFN gamma*, *PARP1*, *XRCC1*, *MDM2*, *IL10*, *IL12*, *HLA B/C*, *MTHFR*, *Tap2*, *TNF-a*, *TLR9, p16*, PIK3CA, and *p21* in cervical susceptibility (Alanazi et al., 2013; Barbisan et al., 2012; Chang et al., 2015; Jin et al., 2017; Ma et al., 2013; Martínez-Nava et al., 2016; Mehta et al., 2015; Mei et al., 2014; Piccolo and Crispi, 2012; Roszack et al., 2014; Dos Santos et al., 2016; Sousa et al., 2011; Tsakogiannis et al., 2017; Wang et al., 2017; and Zhuo et al., 2014). However, these findings have mostly been corroborated in Caucasian and Asian populations, and only a few have been reported on African populations.

Given the high burden of cervical cancer in Africa and the competing burden of infectious diseases, molecular epidemiological investigations can be useful in identifying target populations that require screening and are more likely to benefit from vaccination programs. Currently, there are ongoing molecular epidemiology studies across Africa, aiming to identify genetic susceptibility markers for infectious diseases through various consortia, including the Human Heredity and Health for Africa Consortium (H3Africa).

It is anticipated that the genetic characterization will also be useful in identifying molecular targets that are associated with the risk of developing cervical cancer. An example of such an initiative is the African Collaborative Center for Microbiome and Genomics research (ACCME), which has aimed to recruit 10,000 women to research on epidemiology of persistent hr-HPV, host germline and somatic genomics, epigenomics, vaginal microbiome, and susceptibility in relation to cervical cancer (Adebamowo et al., 2017).

Such efforts are geared toward improving understanding of the underlying biological mechanisms of cervical cancer, the development of diagnostic methods and the application of targeted and effective therapies in African patients. In this study, we review the current status of knowledge and molecular data on cervical cancer among Africans, to understand the role of host genetic polymorphisms in cervical cancer susceptibility among Africans as well as research gaps that need attention.

Literature Methodology

A literature search in the PubMed/MEDLINE (NCBI), Scopus, Google Scholar, and African Journals' online databases was performed. The keywords used individually or in combination in this search were: ''Cervical cancer AND susceptibility AND Africa, Cervical Cancer risks AND genes, Genetic variants AND cervical cancer, cervical cancer susceptibility AND SNPs'' ''Africa.'' A total of 1095 articles (785 from online databases and 310 from Google Scholar) was retrieved from the search and the studies were filtered down using the study selection criteria illustrated in Figure 1. After identification and screening, 20 studies were eligible for review.

Selection criteria

Selected studies were based on the following inclusion criteria: (i) studies evaluating an association between genetic polymorphisms and cervical cancer, (ii) studies based on African populations domiciled in Africa, (iii) studies that described control cases and cervical cancer cases, and (iv) articles published in English. Studies excluded were evaluating only precancerous (CIN) lesions.

Allele frequency retrieval

The NCBI Variation Resources Single Nucleotide Polymorphism Database (dbSNP) was used to access peer-reviewed journals that studied the different allele variants

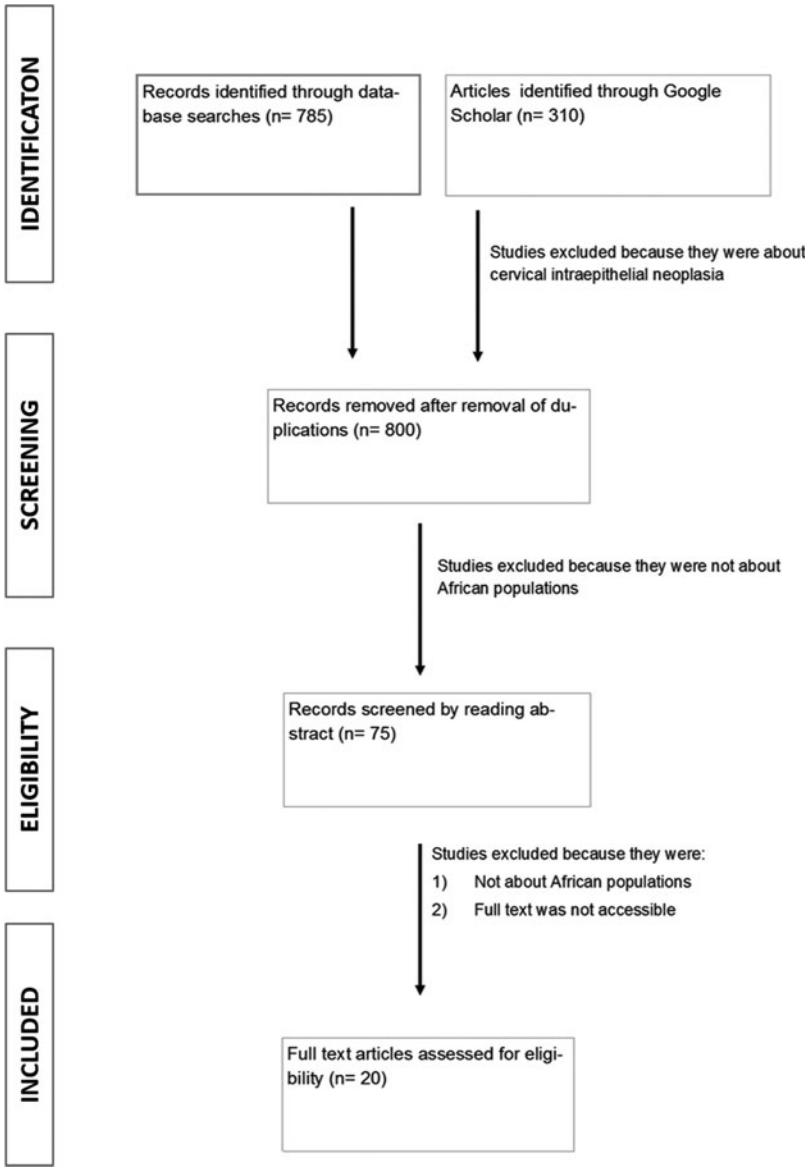

FIG. 1. Prisma flow diagram of the study selection process.

that were focused on in this review. Upon entering the SNP identification for the genetic polymorphisms studied here, data on the SNP were reviewed, and the Citation link was selected to access journal articles used to formulate the dbSNP datasets.

Results

A total of 20 studies were eligible for the purpose of this review (Fig. 1). Within the African continent, there have been 20 studies to investigate genetic polymorphisms that can be associated with risk of developing cervical cancer. From our findings, South Africa, Tunisia, Zimbabwe, Gabon, Senegal, Morocco, and Sudan are the African countries that have explored cervical cancer susceptibility markers at the molecular level (Table 3). The genes studied include *Casp8, CCR2, FasR, HLA, IL10, IFN-g, TNF-a, TGFb,* and *p53*. The most studied genetic polymorphisms include *p53 codon 72 mutation*, *Caspase 8 -652 6N ins/del, HLA II DRB1*13, TNF-alpha-308G≥A*, *CCR2-V64L, FasR -1377G*, *IFN-g 874T≥A*, and *IL10-1082G/A* (Table 3).

Out of the 57 countries in Africa, cervical cancer susceptibility studies were conducted in 7 countries (12%), whereas 45 countries (79%) have not conducted any molecular epidemiology studies on cervical cancer (Fig. 2). There is no molecular and nonmolecular cervical cancer data available for five countries (9%)—Central African Republic, Guinea, Sao Tome and Principe, Sierra Leone, and Western Sahara. Of the seven African countries that have conducted molecular epidemiology studies for cervical cancer, only two have established national HPV vaccination programs (Table 4) (Senegal and South Africa), and the third, Zimbabwe, has completed the pilot phase with prospects to implement in 2018 (Table 4). The programs have largely utilized Cervarix and Gardasil, and no African country has implemented the nanovalent Gardasil 9.

Table 3. Genetic Variations Evaluated in African Populations Reporting on Cervical Cancer

Gene polymorphism	Population	Sample size		Association		HPV	Reference
		Cervical cancer	Control	Increase	None	Yes (Y)/ No (N)	
Caspase 8 -652 6N ins/del; 652 6N del/del	South African	445	1221[a]		✓	Y	Chatterjee et al. (2011)
Caspase 8 -652 + Fas R -670A	South African	442	278[a]		✓	Y	Chattopadhyay et al. (2015)[a]
CCR2-V64L	South African	446	1432	✓		Y	Chatterjee et al. (2010)
Fas R 1377G/A, FasR 670A/G, FasL844T/C	South African	447	424		✓	Y	Chatterjee et al. (2009)
FasR -1377G	South African	442	278[a]	✓		Y	Chattopadhyay et al. (2015)[a]
HLA II DRB1	Tunisian	—	—	✓		N	Ben et al. (2012)
*HLA II DQB1*03, DRB1*1101, DQB1*0301*	Senegalese	55	107[a]		✓	Y	Lin et al. (2001)
IFN-g 874T>A	South African	458	587		✓	N	Govan et al. (2003)
IL10-1082G/A	Zimbabwean	77	69	✓		Y	Stanczuk et al. (2001)
	Tunisian	86	126	✓		N	Zidi et al. (2015a)
	South Africa				✓	N	Govan et al. (2003)
TNF-alpha-308G>A	Tunisian	130	260	✓		N	Zidi et al. (2015b)
	South African	244	228		✓	N	Govan et al. (2006)
	Zimbabwean	103	101		✓	N	Stanczuk et al. (2003)
TGF beta1 10C and C-509T	Zimbabwean	97	73		✓	Y	Stanczuk et al. (2002)
P53 codon 72	South African	100	251		✓	Y	Pegoraro et al. (2000)
	South African	281	340	✓		Y	Pegoraro et al. (2002)
	South African	111	143		✓	Y	Govan et al. (2007)
	Gabonese	31	71		✓	Y	Assoumou et al. (2015)
	Moroccan	113	100		✓	Y	Meftah El khair et al. (2009)
	Senegalese	30	93		✓	N	Ndiaye et al. (2014)
	Sudanese	78	235		✓	N	Eltahir et al. (2012)
	Zimbabwean	73	62		✓	N	Kouamou et al. (2016)

[a]Represents studies that investigated more than one SNP and obtained conflicting results; ✓means affirmative in relation to correlation. SNP, single nucleotide polymorphism.

The genes studied with respect to cervical cancer play a crucial role in cell cycle regulation (37.5%) or in immune response/inflammation pathways (62.5%) (Fig. 3). The immune response genes *CCR2V6L, HLA DRB1, IL10-1082G/A, TGFBT10C,* and *C-509T* as well as apoptotic gene *FasR -1377G* polymorphisms were associated with increased susceptibility to cervical cancer among South African, Tunisian, and Zimbabwean women (Table 3). There was no association between cervical cancer risk and *Casp 8 -652 6N ins/del, Casp8 -6526n del/del*, *FasR670 A/G, FasL844T/C, HLAII-DQB1*03, HLAII-DRB1*1101, HLAII-DQB1*0301, IFN-g 874T≥A,* and *TGFb- 10C* and *C-509T* genetic polymorphisms in the studies conducted on African populations.

Conflicting findings were observed between the different populations, particularly, for *TNF-a-308G≥A* and *p53 codon 72* SNPs (Table 3). A positive correlation was found between *TNF-a-308G≥A* and cervical cancer risk in Tunisian women, which is different from data obtained among Zimbabwean and South African women (Table 3). In relation to *p53 codon 72*, there is strong evidence pointing toward association with cervical cancer risk in South African women (Table 3). The allelic frequencies of the different polymorphisms studied in African populations are summarized in Table 5.

Discussion

Cancer is caused by both genetic and environmental factors (Gov et al., 2017). Successful management of cancer could benefit from identifying polymorphisms that play a role in gene expression and cell cycle regulation as well as genome–environment interactions (Advani et al., 2017). A plethora of genomic studies have been conducted to identify these functional genetic polymorphisms responsible for susceptibility and response to cervical cancer treatment. Elucidating the role of genetic polymorphisms in cervical cancer is an important first step toward precision medicine, which incorporates personal genomic information into electronic health records so as to tailor drug therapy (Tsimberidou et al., 2017).

To date, over 30 genes have been studied for their role in cervical cancer risk and these include, *Bid*, *BRIP1*, *Caspase 8*, *CCR2, CTLA4*, *CYP1A1*, *EXO1*, *FASLG*, FASR, HOTAIR, *IFN gamma*, *PARP1*, *XRCC1*, *MDM2*, *IL10*, *IL12*, *HLA B/C*, *MTHFR*, *Tap2*, *TNF-α*, *TLR9*, *p16*, *PIK3CA*, *p21*, and *p53* (Jin et al., 2017; Martínez-Nava et al., 2016; Mehta et al., 2015; Mei et al., 2014; Dos Santos et al., 2016; Sousa et al., 2011; Tsakogiannis et al., 2017; and Wang et al., 2017). Of these, genes only nine have been researched in African

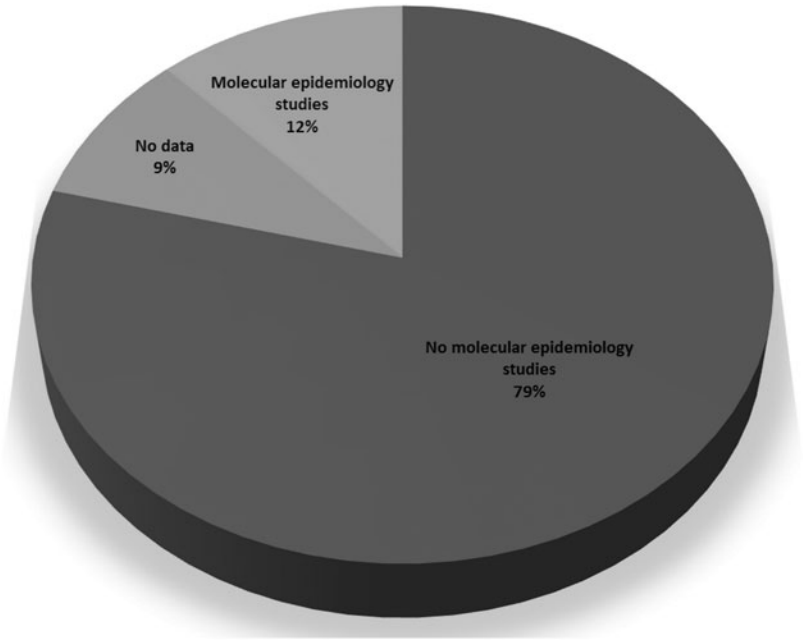

FIG. 2. The status of molecular epidemiology studies on cervical cancer in African countries.

populations, highlighting a big gap in cervical cancer molecular epidemiology studies in a continent where 90% of the cervical cancer-related deaths are predicted (Mbouba-Bouassa et al., 2017).

Caspase 8

Caspase 8 is an apical caspase that plays a crucial role in the extrinsic apoptotic pathway (Kominami et al., 2012). The *CASP8* gene is located on 2q33.1 and it encodes various caspase 8 isoforms, for which the most common are procaspase 8a and procaspase 8b (Borhani et al., 2015). Caspases exist in an inactive zymogen form, procaspase, which is activated by proteolytic signals during apoptosis (Pu et al., 2017). The absence or deregulation of proapoptotic genes, such as *CASP8*, can cause resistance to apoptosis which is associated with different diseases.

One of the hallmarks of cancer is uncontrolled proliferation (Hanahan and Weinberg, 2011), and in cervical cancer, *CASP8* is upregulated thus promoting carcinogenesis and influencing susceptibility to cancer (Stupack, 2013). Mutations in *CASP8* have been associated with autoimmune lymphoproliferative syndrome (Salvesen and Walsh, 2014), as well as missense mutations that are linked to immunodeficiency (Chun et al., 2002). The HPV early protein E6, has also been shown to interact with key apoptotic signals, such as tumor necrosis factor R1 and caspase 8 (Yuan et al., 2016).

When HPV E6 binds *CASP8*, there is an induction of aberrant functionality to promote HPV-positive cells to evade apoptosis-related clearance, and promote carcinogenesis (Yuan et al., 2016). Thus, it is plausible that *CASP8* mutations can also be a substantial alternative mechanism for HPV persistence.

There are two main *CASP8* polymorphisms that have been studied in relation to cancer, namely *CASP8* D302H and *CASP8* -652 6N ins/del. The latter has been associated with breast, prostate, cutaneous melanoma, and cervical cancer susceptibility (Sergentanis and Economopoulous, 2009). The role of *CASP8 -652 6N ins/del* in cervical cancer susceptibility has been studied in Chinese women (Sun et al., 2007), and data show decreased risk.

Table 4. Roll Out of National Human Papillomavirus Vaccine Programs in African Countries That Have Conducted Molecular Epidemiology Studies on Cervical Cancer

Country	*National HPV vaccine program status*	*Implementation year*	*Vaccine*	*Reference*
Gabon	No known program	—	—	Bruni et al. (2017)
Morocco	No known program	—	—	Bruni et al. (2017)
Senegal	Pilot completed	2017[a]	Gardasil Cervarix	Montagne et al. (2017)
South Africa	Implemented	2014	Gardasil Cervarix	Gallagher et al. (2017)
Sudan	No known program	—	—	Bruni et al. (2017)
Tunisia	No known program	—	—	Bruni et al. (2017)
Zimbabwe	Implemented	2018	Gardasil Cervarix	Ministry of Health and Child Care of Zimbabwe (2018)

[a]The vaccination program was set to be implemented end of 2017, but there is no available data as yet to confirm implementation.

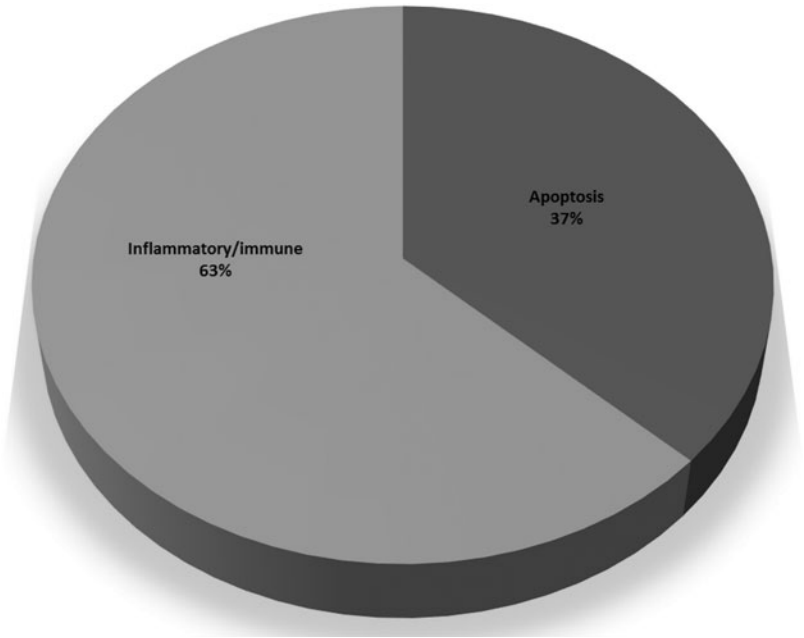

FIG. 3. Genetic variants associated with cervical cancer interrogated in studies on African populations.

These findings correspond with Chatterjee et al. (2011) who did not find an association between *CASP8 -652 6N del/del* or *ins/del* with hr-HPV infection and cervical cancer risk in black and mixed ancestry South African populations. However, *Casp8 -652 6N del/del* was found to increase susceptibility to esophageal cancer (another HPV-related cancer) in Chinese, Indian, and South African women (Bye et al., 2011; Umar et al., 2011; Yin et al., 2014).

The frequencies of genetic polymorphisms vary significantly between ethnic groups (Maples et al., 2013). The frequency of the *Casp8 -652 6N del* is lowest in Asian populations and highest in Africans (Table 5). Therefore, given the role of *Casp8* in HPV persistence, it is important for the different African subpopulations to be extensively investigated for the role of *Casp8* SNPs in cervical cancer and other HPV-related cancers (esophageal, anogenital).

Chemokine receptor 2

Chemokine receptor 2 (CCR2) is a major receptor that binds to chemokine ligands, basophils, monocytes, dendritic cells, and T cells playing a crucial role in inflammation (Vicari and Caux, 2002; Zheng et al., 2006). Inflammation is a self-regulating process that involves extensive gene–gene interaction so as to maintain homeostasis. The *CCR2* alleles that promote a homeostatic imbalance have the ability to increase disease risk, such as cancer, by promoting angiogenesis.

CCR2 is located on 3p21 and through alternative splicing is expressed as two isoforms—*CCR2A* and *CCR2B* (Mantovani and Sinca, 2010). A G190A substitution SNP results in a replacement of valine by isoleucine (*CCR2V64I*). In South African women, the CCR2 c.190A allele was associated with increased cervical cancer risk (Chatterjee et al., 2010). The allelic frequency in Africans is 10% compared with 23.5% and 30% in Caucasians and Asians, respectively (Coelho et al., 2007; Su et al., 2000; Zheng et al., 2006). It was also reported that *CCR2 V64I* conferred a protective effect in the instance of HPV 16 infection in Brazilian women, therefore, it is feasible that the prevalence of HPV 16 plays a significant role in relation to the role of *CCR2 V64I* as a cervical cancer susceptibility marker (Dos Santos et al., 2016).

HPV is a necessary initiator of cervical cancer, but in immunocompetent individuals, secondary factors, especially in the immune system, are also needed to facilitate malignant

Table 5. Allelic Frequencies of the Genetic Polymorphisms of Interest in This Review

	Allele frequency			
Polymorphism	*African (%)*	*Caucasian (%)*	*Asian (%)*	*Reference*
Casp8 -652 6N	56	48	12	Cai et al. (2017)
CCR2 V64I	—	30	23.5	Coelho et al. (2007)
FasR-1377G>A	—	13	37	Lai et al. (2003)
IFN gamma 874T>A	22	51	12.1	Gonzalez-Galarza et al. (2015)
IL10	57.1	49	36.8	Gonzalez-Galarza et al. (2015)
P53 codon 72	19	78	60	Sucheston et al. (2011)

transformation. HPV has an intrinsic immune evasion course of action, which is to suppress MHC-1; however, there are alternative proposed mechanisms by which HPV can manipulate inflammatory signals to sustain the tumor microenvironment. One mechanism is by HPV E2 protein interacting and stimulating NF-kB, which in turn upregulates the activity of inflammatory responses, such as CCR2, thereby providing a conducive microenvironment for tumor progression (Prabhavathay et al., 2014). Alternatively, CCR2 may also decrease macrophage recruitment during the establishment of the tumor microenvironment, therefore decreasing viral clearance (Wallin et al., 1999).

Another plausible mechanism is that the *CCR2* genetic variants increase macrophage affinity through MCP-1, thus evading immune response (Chatterjee et al., 2010). In general, there is limited evidence to support the role of *CCR2 V64I* as a direct cervical cancer susceptibility marker. However, it is evident that *CCR2* promotes HPV infection and persistence, therefore, more studies need to be conducted using powerful genomic tools such as GWAS and WGS to further investigate and determine the definitive role of the functional SNPs in *CCR2* and cervical cancer.

Fas cell death receptor

The Fas receptor (FasR) also known as CD95 is a tumor necrosis factor that activates downstream apoptotic activity through interaction with Fas ligand (FasL) (Du et al., 2013). Viral infection mediates an immune transactivation of the caspase cascade, thus inducing activation induced cell death (Siegel, 2006; Ueda et al., 2006). The caspase 8 plays a pivotal role in the Fas-mediated pathway (Hougardy et al., 2005). There are three functional polymorphisms in Fas that have been reported in relation to cervical carcinogenesis, namely *FasR-1377G≥A*, *FasR 670A≥G*, and *FasL 844T≥C* (Lai et al., 2003; Shen and Sun, 2013).

All three Fas polymorphisms have been reported to confer risk to cervical cancer susceptibility in Asians (Chinese and Malaysian women) (Lai et al., 2003, 2005; Nunobiki et al., 2011; Tan et al., 2017; Ueda et al., 2006). In addition, Zoodsma et al. (2005) showed a relationship between *FasR 670A≥G* and increased risk of adenocarcinoma and not squamous cell carcinoma of the cervix. However, in another study conducted in Chinese women, as well as in Caucasian populations, there was no association between Fas SNPs and cervical cancer susceptibility (Chen et al., 2013; Du et al., 2013; Engelmark et al., 2004b; Pavlidou et al., 2016; Sun et al., 2005) resonating with the findings from African populations (Table 3).

A meta-analysis of 12 studies that encompassed 2798 cases and 3039 controls showed increased risk associated with homozygous genotype (Tan et al., 2017). The *FasR 670G Allele* is correlated with high-grade squamous intraepithelial lesions. The impact of the 670A≥G change in the FASR gene decreases FAS expression, thus, abolishing gamma interferon signal transduction, leading to decreased apoptotic activity (Pavlidou et al., 2016). The *FasR 670A* allele is more common in Caucasians (51%) compared with Africans (29.5%) (Dybikowska et al., 2004; Lai et al., 2003; Pinti et al., 2002).

Therefore, more studies are needed to determine the role of *FasR 670A≥G* in African populations, given the high frequency of the G Allele (70.5%). The *FasR-1377A allele frequency* is 13% in Caucasians, 9% in black Africans, and 19% in mixed African women. In Chinese and Taiwanese, the frequency is 43% and 31%, respectively (Lai et al., 2003; Sun et al., 2005).

Human leukocyte antigen

The human leukocyte antigen (HLA) is an important variable in determining the overall cellular immune response to infections, such as HPV. The primary role of HLA molecules is to recognize and bind to nonself peptides (Chen et al., 2014). These nonself peptides are then presented to cytotoxic and natural killer T cells for destruction (Shi et al., 2013). Genome-wide association studies have reported strong association between cervical cancer and the various genes on the 6p21.3 loci, where the *HLA* gene is located (Shi et al., 2013). HLA class II molecules are expressed on antigen-presenting cells and contain alpha (DRA) and beta (DRB) chains (Greenstone et al., 1998; Nawa et al., 1995). In particular, the *HLA II- DQA1*, *DQB1*, and *DRB1* alleles have been associated with cervical cancer risk across different populations (Madeleine et al., 2008; Montoya et al., 1998).

A study conducted on siblings showed a significant relationship between familial aggregation and predisposition to cervical cancer and the strongest association was reported for *DQB1*, *DRB1*, and *DPB1* alleles (Dilthey et al., 2016; Engelmark et al., 2004a). These findings were consistent in both squamous cell cervical carcinoma and cervical adenocarcinoma. Of great significance, are the *DRB1* alleles, which have been extensively studied, and were associated with cervical cancer risk (Cuzick et al., 2000). In Tunisian women, the *DRB1** alleles increased the risk of cervical cancer. Similar findings were reported in Caucasian women (Apple et al., 1994; Gregoire et al., 1994; Safaeian et al., 2014).

In contrast, among Senegalese women, there was no relationship between *HLA II DQB1*03* and *DQB1*01* with cervical cancer and this is similar to observations in Asians, African Americans, and Brazilians (Duggan-Keen et al., 1996; Krul et al., 1999; Yang et al., 2006). There is compelling evidence that particular variants of the immunological factor HLA II increase the risk of cervical cancer, yet they also decrease the risk of HPV-related lesions in different populations (Chen and Gyllensten, 2014; Greenstone et al., 1998).

The class II *HLA DRB1*, *DQA1*, and *DQB1* variants showed reduced risk of developing cervical cancer in Caucasians (Chen and Gyllensten, 2014), and this is suggested to be due to the T haplotype carriers having higher HPV specificity and affinity, which can activate the HPV immune response (Chen and Gyllensten, 2014). Data generated from African populations interrogate small sample sizes, therefore, the frequency of these alleles as well as their impact is not thoroughly investigated. Thus, more data have to be generated in African populations to determine the effect.

Interferon gamma

Interferon gamma (IFN-g) is a cytokine that is secreted by T-helper cells, cytotoxic T cells, and cytotoxic $CD8^+$ cells (Schroder et al., 2004). IFN-g directly exerts antiproliferative and antimetabolic effect and can inhibit angiogenesis. The *IFN-g 874 T/A* polymorphism has been reported to result in upregulated IFN-g production, thus, increasing the risk of developing diseases, such as cervical cancer (Liu et al., 2015).

As a result of evolution and natural selection, the frequency distribution of such SNPs vary significantly between populations and the respective *IFN-g 874A* allelic frequency Caucasians, Asians, Hispanics, Arabs, and Africans are, 51%, 12.1%, 46.9%, 39.2%, and 22%, respectively (Gonzalez-Galarza et al., 2015; Govan et al., 2003). In Asian populations, the *IFN-g 874A* frequency that has been associated with increased risk of cervical cancer was observed (Liu et al., 2015), whereas in Africans and Caucasians no association was found (Ivansson et al., 2007; Tuguz et al., 2015).

Interleukin 10

Interleukin 10 (IL10) is a multifactorial cytokine that plays key roles in activating and mediating inflammatory responses and immune responses, both of which are important in cancer biology (Zhang et al., 2014). The *IL10-1082G≥A* SNP affects cytokine production (Barbisan et al., 2012). The frequency of the *IL10-1082A* allele differs by ethnicity as follows: Arabian (45%), Asian (36.8%), Caucasian (49%), African American (47.9%), and Africans (57.1%) (Gonzalez-Galarza et al., 2015). Among South African black and mixed ancestry (Govan et al., 2003), no association between IL10 production and risk of developing cervical cancer was observed. These findings were corroborated in Korean, Dutch, British, Chinese, and Argentinian populations (Barbisan et al., 2012; Farzaneh et al., 2006; Roh et al., 2002; Wang et al., 2011; Yu et al., 2011; Zoodsma et al., 2005).

Conversely, data generated from Zimbabwean women showed that homozygous AA and heterozygous GA carriers presented with increased susceptibility to cervical cancer (Stanczuk et al., 2001), similar to observations among Japanese women (Matsumoto et al., 2010). These conflicting data within the same African population can be due to underrepresentation of either the alleles within the studies or due to small sample sizes. Therefore, a larger sample size is needed to confirm the role of these findings.

Tumor protein 53

P53 is a tumor suppressor gene with a salient role in cellular function to regulate cellular processes, such as proliferation, senescence, apoptosis, metabolism, and DNA damage response pathways (Levine and Oren, 2009). P53 has a short half-life; however, in the presence of stimuli, such as DNA damaging agents or oxidative stress, its production levels are increased to maintain a homeostatic balance (Levine and Oren, 2009; Vousden and Lu, 2002). As a result of this central role in cellular function, *p53* mutations can increase disease risk as well as mediate drug response.

The *p53 codon 72* is the most commonly known and studied mutation with respect to many diseases, including cervical cancer. The *p53 codon 72* results from base substitution from C to G, which results in a change from arginine to proline (Beckman et al., 1994). The arginine allele has been described to be a more aggressive apoptotic inducer compared with the proline variant (Murphy, 2006). Discordant findings have been reported on the role of p53 codon 72 polymorphism in cervical cancer susceptibility (Pillai et al., 2002; Sousa et al., 2011; Storey et al., 1998; Zhou et al., 2012). In this review, only one study out of the eight reported an association between p53 codon 72 and increased risk of cervical cancer (Table 3).

In light of the conflicting reports, it is essential to understand the role of p53 codon 72 mutation in different patients from different population groups. Latitude, ecological adaptation, and distance from the equator are all significant selective pressures that have been reported to affect the frequency of *p53 codon 72* in different ethnic groups (Beckman et al., 1994; Hancock et al., 2008; Sjalander et al., 1994). The frequency of *p53 codon 72 (Arg)* is highest in Caucasians (78%), Asians (60%), and Africans (19%) and low in Hispanics (14%) (Sucheston et al., 2011). Therefore, the low frequency of the Arg allele in African populations, may account for the discordance in findings in most of the studies conducted in Africa.

Furthermore, of three studies conducted in South Africa, only one showed an increased risk of cervical cancer, indicating possibility of intraethnic variation, since ethnicity was only stratified in one of the studies (Pegoraro et al., 2002). This study was conducted among women with a high Arg homozygosity rate (55%) in cervical cancer compared with the control (34%). Further investigations on larger population size will result in a better representation of the role of the p53 codon 72 mutation in the different African populations.

Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNF-a) is a pleiotropic cytokine with function in the immune homeostasis, inflammation, and host defense mechanisms against infectious agents, including HPV (Rotar et al., 2014). When TNF-a is deregulated, it acts as a cancer promoter by stimulating invasion, migration, and metastasis (Wang et al., 2015). As a result, cytokines, such as TNF-a, are considered as candidate genetic susceptibility markers. Common SNPs in the TNF-a promoter region have the ability to regulate the transcriptional activity. Such functional polymorphisms include *TNF-a 308* and *TNF-a -238G/A*, and these have been associated with cervical cancer (Duarte et al., 2005; Li et al., 2013, 2016; Liu et al., 2012; Rotar et al., 2014).

No differences have been reported in genotype and allele frequencies between the cases and controls for the *TNF-a -238G/A* in Asians (Chinese, Japanese), Hispanics, and Caucasians (Calhoun et al., 2002; Deshpande et al., 2005; Jang et al., 2001; Li et al., 2016; Wang et al., 2009). However, in Argentinian women, the *TNF-a -238G/A* was associated with decreased cervical cancer risk (Barbisan et al., 2012). The *TNF-a 308* was reportedly associated with increased cervical cancer risk in Caucasian populations (Liu et al., 2012), but had no effect on cervical risk among Argentinian, South African, Zimbabwean, Chinese, and Tunisian women (Barbisan et al., 2012; Govan et al., 2006; Li et al., 2016; Stanczuk et al., 2003; Zidi et al., 2015b).

Transforming growth factor-beta 1

Transforming growth factor-beta 1 (TGF-B1) is a conserved peptide with pleiotropic cellular effect, such as regulating cell proliferation, differentiation, and matrix production (Iancu et al., 2010). TGF-B1 also has the ability to inhibit the HPV E6/E7-induced transformation thus inducing apoptosis of HPV-infected cells (Wei et al., 2012). Deregulation of TGF-B1 means HPV-infected cells can persist, favoring development of cancer (Lin and Karin, 2007). Glick

et al. (1993) illustrated that some squamous cell carcinomas do not express the *TGF-B* gene, thus suggesting the crucial role of this gene in oncogenesis, such as squamous cell cervical carcinoma (Cox et al., 2007).

Variations within the host have been observed in that, there are individuals that express higher or lower levels of TGF-B1, resulting in increased risk of developing cervical cancer. Two genetic polymorphisms have been described, T10C and *C-509T*, which confer increased TGF-B1 overexpression (Al-Harbi et al., 2017). In Zimbabwean populations, there was no association between *TGF-B1* genetic polymorphisms with cervical cancer (Stanczuk et al., 2002). Allele frequencies were reported in Arabic women to be 64%, Asian (55%), African American (47%), Caucasian (51%), and Hispanic (56%) (Gonzalez-Galarza et al., 2015).

Insight

HPV has been established as a causative agent for cervical cancer, with the administration of the HPV vaccines Cervarix, Gardasil, and Gardasil 9 being considered as preventive measures against cervical cancer (Gallagher et al., 2018; White, 2014). The national HPV vaccines were first implemented in 2006 in the United States of America (Bruni et al., 2016) and Rwanda was the first African country to implement a national HPV vaccination program in 2011, followed by Lesotho and Uganda in 2012 (Bruni et al., 2016). As of 2014, 1.2% of girls in all LMICs between 10 and 20 years, had received at least one dose of the HPV, and with the current extensive coverage and expansion of the HPV programs, the vaccination rate is expected to have significantly increased (Bruni et al., 2016).

There is possibility of potential vaccine–gene interference in the host that occurs post-HPV vaccine exposure, opening other interesting areas for future studies. For all the molecular epidemiology studies on cervical cancer conducted in African populations so far, none was done after HPV vaccination programs had been implemented, thus, there is no likely bias of the gene variants' association with cervical cancer being biased due to prior HPV vaccination.

Generally, the oncogenic genes of HPV have often been described to be E5, E6, and E7; however, studies show that the other early proteins E1, E2, and E4 encoded by HPV also play a lucid role in viral replication and potentially carcinogenesis. Specifically, the E2 protein plays a primary role in viral replication, and has been shown to activate and repress transcriptional activity (Graham, 2016). HPV E2 induces elevated levels of IL10, which is a cervical cancer susceptibility marker by facilitating virus persistency (Bermuda-Morales et al., 2011).

Likewise, HPV E2 also regulates the expression of host genes, such as matrix metalloproteinase 9, hTERT, beta 4-integrin, and splicing factor 4, thus it would be of great relevance to study these genes as cervical cancer susceptibility markers in African populations (Bermuda-Morales et al., 2011; McBride, 2013; McBride and Warburton, 2017).

Genome-wide association studies identified single nucleotide polymorphisms in DNA damage repair pathway genes, such as *IRF3*, *EXO1*, *FANCA*, and *CYBA* to increase the risk of persistence to CIN3 and cervical cancer, whereas genes, such as *TLR-2* and *XRCC1*, played a protective role against cervical cancer (Wang et al., 2009, 2010).

Conclusion

Cervical cancer is one of the most common causes of mortality in women in Africa, despite being preventable through early screening and HPV vaccination programs. The national HPV vaccination program is important in reducing the burden of hr-HPV and concurrently cervical cancer incidence. The statistics for the HPV vaccine coverage in Africa is worrying; a great proportion of African countries are yet to reach the pilot phase of national vaccination programs, whereas implementation is ongoing in only a few countries.

In addition, because the HPV vaccine is prophylactic, it does not benefit individuals that are already infected, thus, it is important that HPV vaccination programs need to be urgently implemented across Africa. It is expected that the impact of HPV vaccine programs in Africa will only be apparent in ≥20 years. Thus, it is paramount that alternative precautionary measures with potential for expeditious turnaround be explored and put in place for cervical cancer high-risk settings.

Genomic studies with objectives such as ACCME, are crucial pioneers for large-scale molecular studies and genomics in Africa, and should provide a model for molecular epidemiology studies that other countries in similar incomes can adopt. This would be a first step toward using genomic applications for personalized cervical cancer therapy by applying molecular epidemiology data to develop genetic-based molecular markers. Such molecular markers can be coupled with the currently available screening methods (pap smears, visual inspection tests, or HPV testing) to identify high-risk individuals from a molecular perspective.

This model can help to advocate for high-risk individuals to be aware and modify their respective behavioral, lifestyle, and occupational habits since the microbiome and metabolome have been shown to have a relationship with cervical cancer risk and response to therapy.

There seems to be a distinct ethnic heterogeneity in allelic frequencies as shown by inconsistencies reported in most genes studied in relation to cervical cancer risk. This study highlights relevant population-specific dissimilarities in genetic etiology of cervical cancer, which can be attributed to ethnic differences in mutation frequency profiles and differences in study methodologies. For each of the susceptibility markers studied, there are either limited or no studies conducted in African populations, in a limited sample size, therefore, the allelic distributions per population may be different.

Studies employing high-throughput methods for wider genome coverage using genome-wide panels and sequencing data are lacking in African populations. Thus, genome-wide association studies, whole exome sequences, as well as whole-genome sequencing technologies need to be employed in larger African cohorts for improved association studies. Large-scale association studies are essential to elucidate the specific role of cervical cancer susceptibility markers, which can be utilized to improve diagnosis and prognosis.

Given the current omics-centric approach to research, it is important to conduct studies on the microbiome, proteome, and metabolomes in relation to cervical cancer. These studies have provided insight on essential biomarkers that can be useful to predict the risk of developing disease and as predictors for response to therapy.

Limitations

This innovation analysis article has several limitations in that there were small sample sizes associated with the primary studies reported in the literature and thus might provide limiting statistical power of the data.

Second, all of the studies considered for this review enrolled both patients and controls from a hospital setting, therefore, data reported only represents a population of ailing individuals thus underrepresenting the general population.

Third, there is also poor subgroup analysis for other cervical cancer-related risk factors such as HPV status, smoking, and history of contraceptives within the primary studies. As a result, further analyses and research on other cervical cancer-related susceptibility factors, including the genome–environment interactions in cancer are called for as noted earlier (Nam, 2017). Cervical cancer remains an important and potentially treatable condition for which biomarkers are much needed.

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Abbreviations Used

Casp8 = caspase 8
CCR2 = chemokine receptor 2
CIN = cervical intraepithelial neoplasia
DNA = deoxyribonucleic acid
FasL = Fas ligand
FasR = Fas receptor
GWAS = Genome Wide Association Studies
HLA = human leukocyte antigen
HPV = human papillomavirus
hr-HPV = high-risk HPV
H3A = Human Health and Hereditary Africa
IFN = interferon
LMIC = low- and middle-income country
MCP-1 = monocyte chemoattractant protein-1
MHC-1 = major histocompatibility complex 1
P53 = tumor protein 53
Rb = retinoblastoma
SNP = single nucleotide polymorphism
TGF = transforming growth factor
TNF = tumor necrosis factor
WGS = whole genome sequencing