Cervical cancer in low and middle-income countries (Review)

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Abstract. Cervical cancer is a malignant tumour that occurs in the cervix and is classified into two histological types, adenocarcinoma and squamous cell carcinoma (SCC); SCC is more common and accounts for 70% of all cases. In 2018 there were ~569,000 new cases of cervical cancer diagnosed worldwide and ~311,000 deaths were attributed to cervical cancer. Of these, between 84 and 90% occurred in low- and middle-income countries (LMICs) such as South Africa, India, China and Brazil. The most common cause of cervical cancer is persistent infection caused by the sexually transmitted human papilloma virus. Other factors that contribute to the incidence of cervical cancer include geography, traditional practices and beliefs, the screening levels, socioeconomic status, healthcare access, public awareness, use of oral contraceptives, smoking and co-infection with HIV. An estimated 11 million women from LMICs will be diagnosed with cervical cancer in the next 10-20 years. The aim of this review was to explore various types of genetic and epigenetic factors that influence the development, progression or suppression of cervical cancer.

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1. Introduction

Cervical cancer is a malignant tumour of the cervix that can be divided into two histological types, adenocarcinoma (AC) and squamous cell carcinoma (SCC) (1). SCC is more common and has an occurrence rate of 70% (2). AC originates from glandular cells that line the cervical canal (the endocervix), whereas SCC originates from squamous cells lining the outer part of the cervix that opens to the ectocervix. The region in which the squamous and the thin, flat glandular cells are located is termed the transformation zone, and the majority of tumours originate from this zone (3).

The most common cause for the occurrence of cervical cancer is a persisting infection with the sexually transmitted human papilloma virus (HPV) (4). HPV is accountable for 90-100% of cervical cancer cases amongst women, especially those <35 years old (5). The types of HPV can be classified as either high-risk (HR) or low-risk in terms of their association with precancerous, benign or cancer lesions (6). HR HPV 16 and 18 subtypes are the most prevalent subtypes of HPV, which are responsible for 70% of cervical cancer cases (1,4). In addition, previous studies have identified an association

between the HPV 16 and 18 subtypes and malignant tumours of the penis, vulva and anus (1,7).

Globally, cervical cancer is the fourth most commonly diagnosed cancer amongst women, and it is especially common in low- and middle-income countries (LMICs) such as South Africa (SA), India, China and Brazil (8-10). A total of ~569,000 new cases of cervical cancer and 311,000 deaths linked to cervical cancer were reported worldwide in 2018 (1,8). In total, 84% of the new cases and between 87 and 90% of the deaths occur in LMICs (1,8). However, HPV infections and associated malignancies are also common in regions of high socioeconomic status. In 2008, 80 million individuals were estimated to be infected with HPV in the USA (11). Despite this, thousands more women from LMICs die prematurely from cervical cancer compared with women from developed countries (2,12).

The aim of the current review was to discuss the types of genetic and epigenetic factors as well as socio-economic factors that influence the occurrence, progression or suppression of cervical cancer. These factors may assist in identifying potential prognostic and diagnostic tools (e.g. biomarkers) for the treatment of cervical cancer.

2. Cervical cancer incidence in low- to middle-income countries

In 2010, Bruni *et al* (5) reported a 4-fold higher prevalence of cervical cancer in LMICs compared with that in developed countries. In countries ranked low in the Human Development Index, cervical cancer is ranked as the second most common type of cancer and the second highest cause of cancer-related mortality amongst women after breast cancer. In Africa, cervical cancer is the most commonly diagnosed type of cancer and the leading cause of cancer-related death among women (13). Table I and Fig. 1 (14-16) present data from the GLOBOCAN 2018 report (15) and show the rate of cervical cancer in LMICs compared with that in developed countries. In Sub-Saharan Africa, the highest incidence of cervical cancer since 2012 was observed in women aged between 15 and 44 years (15,17,18).

Gonidia and Sartorius (18) used three mathematical models to predict the prevalence of HPV in Swaziland by applying age-specific cervical cancer incidence rates from GLOBOCAN 2012 to the Swazi female population in 2014 (13,18,19). The results revealed that the published incidence rates were a gross underestimation of the actual number of cervical cancer cases (18). Another model was used to regress age-standardised cervical cancer incidence (20) in Sub-Saharan African countries against HR HPV prevalence among women with normal cervical cytology (21). The model estimated that, among women with normal cervical cytology, the age-standardised cervical cancer incidence rate was 62.6 per 100,000 women; the prevalence of HPV-HIV among women with normal cytology exhibited a higher estimated age-standardised incidence of 101.1 per 100,000 women (21). South Africa has the highest age-standardised incidence of cervical cancer globally, with 32 cases per 100,000 women (22), whereas Paraguay (a middle-income country) has the highest incidence (34.2 per 100,000 women) and a mortality rate of 15.7 per 100,000 women (21,23). These results indicated that women infected with HIV may be at a higher risk of developing HPV infection, pre-invasive cervical disease and invasive cervical cancer (ICC) (18,24,25). Currently, South Africa has the highest incidence of HIV infection worldwide, with ~7.2 million cases in a population of 58 million (26); an estimated 13 million women are infected with HIV in sub-Saharan Africa (25,27). The treatment of cervical cancer in women infected with HIV presents with great difficulties. For example HIV infection increases the likelihood of the patient having a persistent HPV infection resulting in cervical abnormalities and cervical cancer (7). A compromised immune system and increased risk of HPV infection lowers the number of individuals that have been successfully treated in this population (25). The cancer burden in developing countries such as Swaziland is increased due to late diagnosis, advanced stages of HIV and HPV infections when the cancer is diagnosed, lack or inaccessibility of treatment, lack of treatment facilities, and logistic and cultural obstacles to treatment (28), which result in poor prognosis (14).

These factors, which are common to the majority of developing countries, resulted in the identification of an association between cervical cancer and the level of development (i.e. the socioeconomic status) of a country and its individuals. Cervical cancer is significantly associated with the geographical area; the highest incidence rates are prevalent in low-income countries (10). The incidence in 2013 was 24% in sub-Saharan Africa, 21% in Eastern Europe and 16% in Latin America (29). A prevalence of >30% was also reported in Eastern Africa and the Caribbean (30). Southern Africa has the highest prevalence of HIV (19.9% out of a population of 66,401,000), and the second highest cervical cancer incidence (18.4% out of a total population of 668,319 women with cancer) after Asia and the Pacific (53.1%) (27). This suggested that Southern Africa might have a leading number of HIV-associated cervical cancer cases.

Countries representing specific areas. As previously stated, areas where cervical cancer is the leading cause of death amongst women include Sub-Saharan Africa, Melanesia (Western Pacific), South Central and South East Asia, the Caribbean and Latin America (31). In wealthier developed countries, it is recommended that screening for cervical cancer with the Papanicolaou (Pap) smear is initiated at 21 years and repeated every year until the patient is 65 years old (32). Pap smears should be performed in conjunction with HPV screening; if the test reveals no signs of cervical cancer but presence of HPV, genotyping of the HPV should be performed, which may either be followed by a colposcopy, or HPV and cytology must be repeated at a later stage (33). Table II presents the age-standardised rate (ASR) which is the number per 100,000 people diagnosed with cervical cancer in the four countries, which will be discussed below. These four LMICs (South Africa, Tanzania, India and Brazil) are also compared against China Despite its large number of new cervical cancer cases, cervical cancer only comprises 2.5% of all cancer cases (15).

South Africa. The United Nations defines South Africa as an upper middle-income country with unequal distribution of wealth and a high rate of poverty (34). The 2014 South African National Cancer Registry statistics (35) for cervical cancer

Table I. Region-specific incidence and mortality ASRs for cancers of the cervix in 2018.

Region	Incidence	Mortality
Southern Africa	43.1	20.0
Eastern Africa	40.1	30.0
Western Africa	29.6	23.0
Melanesia	27.7	19.0
Middle Africa	26.8	21.1
South-Eastern Asia	17.2	10.0
Eastern Europe	16.0	6.1
Caribbean	15.5	8.5
South America	15.2	7.1
Micronesia/Polynesia	14.2	6.3
Central America	13.0	7.0
South Central Asia	13.0	8.2
Eastern Asia	10.9	4.1
Northern Europe	9.5	2.1
Southern Europe	7.8	2.2
Northern Africa	7.2	5.1
Western Europe	6.8	2.1
Northern America	6.4	1.9
Australia/New Zealand	6.0	1.7
West Asia	4.1	2.5

ASR per 100,000 women. Rates are shown in descending order of the world Age Standardised incidence Rate (ASR), The ASRs for incidence and mortality are given for each region (15). ASR, age-standardised rate.

Table II. Cervical cancer statistics.

Country	New cases (no.)	All cancers (%)	ASR per 100,000 women	(Refs.)
South Africa	5,735	15.17	22.56	(31)
Brazil	16,370	8.1	12.2	(32)
India	96,922	17	14.7	(26)
Tanzania	9,772	37,9	59.1	(26)
China	106,430	2.5	10.7	(26)

ASR, age-standardised rate.

Table III. Cervical cancer statistics in different population groups in South Africa (35).

Group	New cases (no.)	All cancers (%)	ASR per 100,000 women
Asian	81	6.89	9.98
Black	4,870	30.46	27.01
White	407	3.45	13.10
Other	340	8.36	13.72

ASR, age-standardised rate.

cases and deaths reported that the number of new observed cases in South African women was 5,735 in 2014, accounting for 16.17% of all cancers diagnosed in South African women; the ASR was 22.56 per 100,000 women (35). Analysis of the ASR and new cases by ethnic group revealed that the black population was more affected than any other group (Table III). The 'white' and 'other' population groups, which includes those of mixed ancestry, had <10% of the number of cases and an ASR <50% compared with the black population. The Asian population had the lowest number of cases and the lowest ASR. This population group is also the most economically disadvantaged and has poor access to healthcare (36). Since South Africa has the highest infection rate of HIV and the largest anti-retroviral program in the world (37), it is important to consider the influence of these two factors on cervical cancer. The total levels of HIV-related cancers have decreased following the introduction of anti-retroviral therapy; despite this, the mortality due to Acquired Immune Deficiency Syndrome (AIDS)-related illnesses is still high and has contributed to a lower life expectancy in South Africa (38). HIV is associated with abnormal cervical cytology and higher levels of HPV or numerous HPV types (34). The high prevalence of HIV in South Africa was predicted to lead to a marked increase in the incidence of cervical cancer, as it is one of the AIDS-defining illnesses, but such an increase has not occurred. Initially, prior to the introduction of anti-retroviral treatment, this was due to women succumbing to HIV/AIDS before they could develop cervical cancer; following the introduction of retroviral therapy, a decrease in the rates of all AIDS-defining cancers affected the numbers of cervical cancer cases (36).

The screening policy for cervical cancer in South Africa was established in 2000 and involves three Pap smears per lifetime starting at 30 years of age and occurring at 10-year intervals. The smear is repeated after 12 months if any abnormality is observed. If the abnormality persists or if a high-grade lesion is identified, the patient is referred for a colposcopy (39).

HPV is common among young, sexually active individuals; the infection normally clears without treatment, but recurrence is also common. Persistent infection with HR HPV genotypes leads to precancerous lesions and ultimately cervical carcinoma (39). Due to the high prevalence of transient HPV infection in young women among certain population groups, the usefulness of HPV screening as a tool for identifying those at risk of cervical cancer is limited (34). One preventive strategy for HPV infection used in South Africa is the introduction of the HPV vaccine. In 2014, a national school-based program for the HPV bivalent vaccine was introduced in all public schools, targeting girls in grade 4 (aged ≥9 years old) with a two-dose (6 months apart) schedule (40). Although a high vaccination rate was achieved in these school based programs, the effect on HPV infection rates is yet to be elucidated.

Tanzania. Cervical cancer accounts for 40% of all cancer cases diagnosed in women in East Africa, with the highest ASR

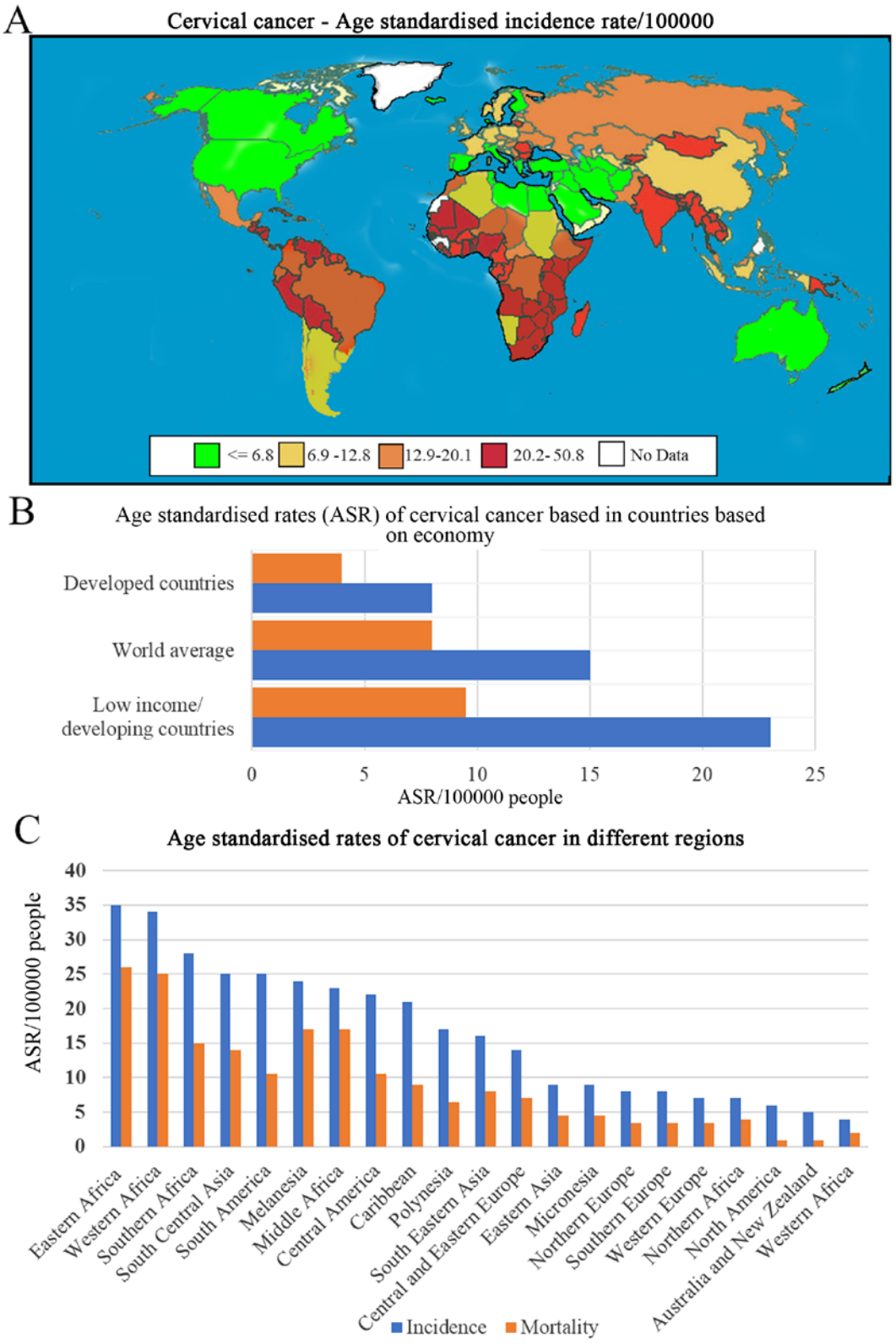

Figure 1. Incidence of cervical cancer. (A) Worldwide incidence by country. (B) The difference in incidence and mortality rates based on economic development compared with the global average. (C) Incidence and mortality rates based on geographic location.

(50.6 per 100,000 women) in Tanzania. Tanzania also ranks 13th on prevalence of HIV infection worldwide (15). Since women infected with HIV are at an increased risk of developing cervical cancer, it is important that they are screened early and often (23,41). To combat cervical cancer, Tanzania has introduced a 'screen and treat' policy; the most common form of screening is visual inspection of the cervix with the naked eye following the application of acetic acid, abbreviated as visual inspection with acetic acid (VIA) (42). The acetic acid solution swabbed on the surface of the cervix (cervical epithelium) turns pre-cancerous

lesions white (43). Following a positive diagnosis, the lesions are immediately treated by cryotherapy (41). Similarly to other low-income, developing countries, the rates of HPV infection are high in Tanzania; this has led to the Tanzanian Ministry of Health to initiate a school-based HPV vaccination program (44). Other factors that contribute to the high incidence of cervical cancer in Tanzania include; resource allocation (in term of distribution of trained personnel, funds and equipment in urban and rural areas nationwide), lack of resources to fulfil the needs of the entire population, sociocultural influence and a lack of political will (where leaders do not prioritise healthcare programmes and choose to divert funds and resources from screening and treatment programmes) (45). Sociocultural factors such as folklore and myths around cervical cancer screening influence the willingness of people to undergo screening (41).

India. In 2015, cervical cancer was the second most common cancer amongst women in India; an estimated 132,314 new cases were diagnosed and 73,337 patients succumbed to cervical cancer (46). Due to India's large population of 1.2 billion, this accounted for nearly one-fifth of all cervical cancer cases worldwide (47). It is difficult to determine an accurate ASR for India, as different cancer registries cover different areas, and ASRs vary between 9 and 40 per 100,000 women, depending on the region (47). India spends 0.9% of its gross domestic product (GDP) on healthcare, and no organised cervical cancer screening programs are available (48). Risk factors associated with cervical cancer in India include illiteracy, lack of toilets or running water inside the house, not washing genitals after sexual intercourse, age at first sexual intercourse <15 years, multiple lifetime sexual partners, widowhood and HPV (49). The prevalence of HR HPV in India ranges between 7 and 13%, and HPV 16 and 18 are the most common types of HPV in India (50). This varies by region and is also possibly influenced by culture; however, unlike in developed countries, the number of young women diagnosed with HPV is not higher than that of older women (47), suggesting that the infection is equally distributed across all age groups.

HPV testing is cheap, objective and reproducible in rural areas in India (50). However, the use of HPV testing in a 'screen and treat strategy' can cause problems, as the majority of HPV infections in young women do not result in cervical cancer (47). HPV cytology-based cervical cancer screening is not possible for the entire population of India due to its large size, as well as a lack of resources, trained staff and facilities. This has led to the adoption of other low-cost, easy-to-perform screening methods; VIA is a popular option. Variants of this method include VIA with magnification or with Lugol's iodine. These tests have been demonstrated to be sensitive but not specific (46). The HPV vaccine is not widely available in India at present, mainly due to its cost. A study of the willingness of parents to vaccinate their daughters was performed in Eastern India and reported that, initially, only 40% of parents agreed to vaccinate their children; this increased to 80% following a short education session about the vaccine (50). The most common reason stated for refusing the vaccine was the safety of the vaccine, followed by the perception of the vaccine as permission to engage in sexual activity (51). Effective vaccination against HPV 16 and 18 in India is expected to result in a 75% decrease in the number of cervical cancer cases (47).

Brazil. The poorest regions of Latin America with the lowest resources have high rates of cervical cancer, possibly due to economic, social, educational and geographical factors that limit access to cervical cancer screening (52). Brazil is one of the few countries that have implemented an organised screening program (52). It is predicted that >8,079 women die every year in Brazil from cervical cancer (15). HPV infections have been estimated to affect >5.7% of women in Brazil and account for 68% of cervical cancer cases (53). Brazil has a long history of cervical cancer screening programs, the first of which was initiated in 1956 (54). The screening strategy for preventing cervical cancer in Brazil targets women between 25 and 64 years of age. Pap smears are recommended to be repeated every 3 years (55). However, similarly to other developing nations, there is a shortage of resources, especially in trained healthcare professionals, that limits the coverage of the population using cytology-based pap-smear screening. The physical size of the country is another factor limiting screening coverage, which is further complicated by the large population, as there are >64 million women aged >15 years in Brazil (55). To lower HPV infection rates and control the rates of cervical cancer, the National Health System of Brazil has adopted the quadrivalent HPV vaccine as part of the national vaccination program; the vaccine was adopted in 2014 and is offered to girls between 9 and 13 years of age, and to women infected with HIV between the ages of 9 and 26 years.

3. Factors that contribute to the development of cervical cancer

Epigenetic factors. Several factors other than persistent HPV infection contribute to the development and/or progression of cervical cancer, including smoking tobacco (including cigarettes, cigars, pipes, hookah and shisha), high parity, continuous use of oral hormonal contraceptives, promiscuity and co-infection with HIV (Fig. 2) (1,16,56). Of those, high parity and tobacco smoking are the most important contributing factors, as they mediate HR HPV infection progression, which results in high rates of cervical pre-cancer and cancer (57-59). Chatzistamatiou *et al* (58) identified a significant association between smoking and HR HPV DNA positivity, but not between smoking and the viral HPV 16 E7 oncoprotein in HPV-associated carcinogenesis (58). In addition, the study displayed a higher odds ratio for smokers and ex-smokers compared with that for non-smokers (58). In contrast to non-smokers, continuous cigarette smokers have previously been reported to exhibit higher risk of developing SCC; among women with an increased smoking intensity, those who start smoking at a young age are at higher risk of developing SCC but not AC (60,61). However, Haverkos (62) observed no significant association between cervical cancer and smoking. Therefore, the influence of smoking on increasing the risk of developing cervical cancer remains controversial. However, previous studies have provided evidence of cigarette smoking derivatives acting as causative agents of cervical and lung cancer (61,63).

Co-infection with *Chlamydia trachomatis* and herpes simplex virus type-2, immunosuppression, and nutritional challenges have also been demonstrated to contribute to cervical cancer development and progression (1,16). Several

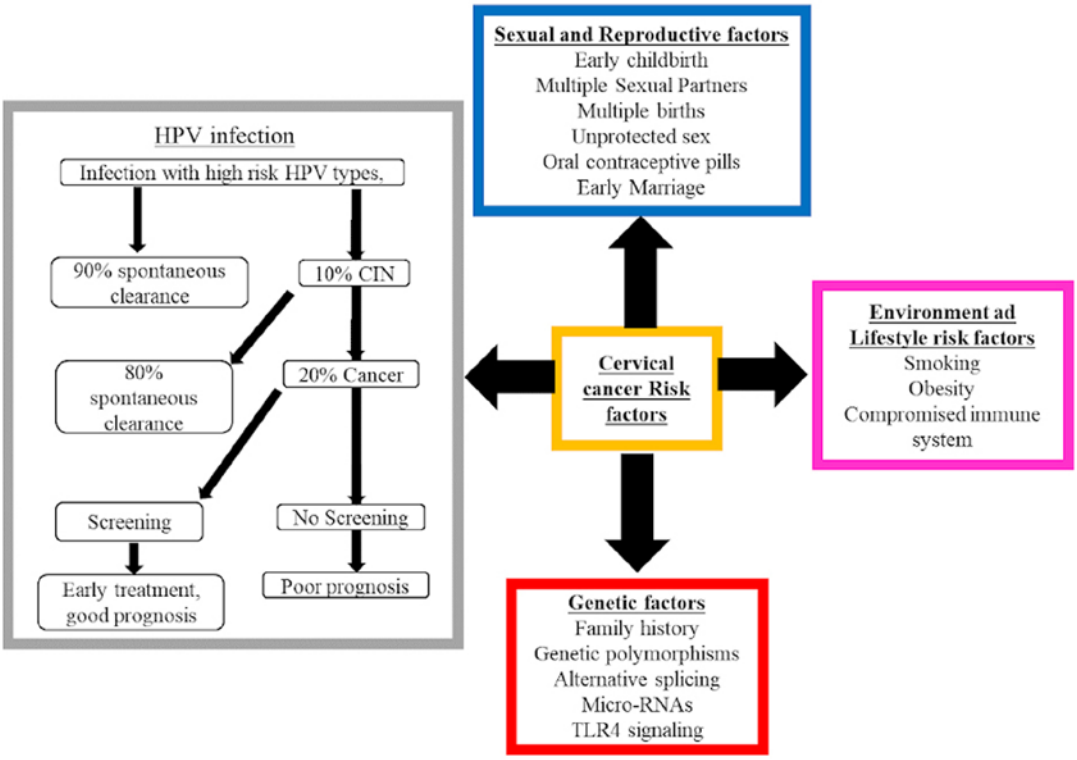

Figure 2. Risk factors associated with the development of cervical cancer. HPV infection is the most important risk factor associated with the development of cervical cancer. The risk of infection with HPV is associated with various sexual and reproductive factors, which further increase the risk of developing cervical cancer. HPV, human papilloma virus; CIN, cervical intraepithelial neoplasia; TLR, toll-like receptor.

genetic and immunological host and viral factors are also predicted as contributing factors (64). Goodson *et al* (65) identified >80 environmental chemicals that serve roles in dysregulating host pathways in carcinogenesis. Environmental risk factors for cervical cancer also include compounds associated with cigarette smoke, such as coal tar derivatives, tar-based vaginal sanitary products and smoke inhaled from biomass-burning stoves (62). These environmental factors can activate signalling pathways responsible for the carcinogenesis of HPV-related cancers, including SCC, in low-income countries (62). These pathways are similar to those known as the hallmarks of cancer, and include hyperproliferative signalling, insensitivity to growth-factor signals, evasion of apoptosis, continuous angiogenesis, genomic unsteadiness, mutation, advanced inflammation and the disruption of normal metabolic functions (65).

In the past decade, the World Health Organization (WHO) reported that billions of individuals from developing regions such as Africa still utilize coal, crop residue, dung and wood for heating and cooking purposes. This is unfortunate because biomass-burning stoves are universally known as a vital source of bio-carcinogens (65). Therefore, women exposed to excessive smoke from these stoves are at greater risk of developing cervical cancer (16,66). This was further verified by Bennett *et al* (67), who identified an association between the use of solid fuel and cervical cancer.

Coaltar derivatives, such as Lysol, are sometimes used in vaginal sanitary products. The first evidence to associate Lysol usage with cervical cancer was in 1931 when it was noted that the majority of a group of New York women with cervical cancer were continuous users of Lysol sanitizers (62). Lysol is a tar-based derivative, which was initially used in animal research for carcinogenesis (68). A later study amongst Californian women found a significant association between the use of Lysol and cervical cancer (69). Goodson *et al* (65) also reported that chemical constituents of tobacco (e.g. benzyl pyrenes, polycyclic aromatics and tobacco-based nitrosamines) and tar-based vaginal sanitizers could affect the development of cancer, including cervical cancer, since they penetrate cells and tissues, and stimulate vital carcinogenic pathways. The precise understanding of these pathways may lead to more effective immunotherapeutic strategies and control measures of HPV-related tumours that are usually induced in HR populations exposed to multiple carcinogens due to a low socioeconomic background.

Role of genetic polymorphisms in cervical cancer. Genetic polymorphisms are single nucleotide base changes that occur between two genomes as a deletion, insertion or a substitution of a single nucleotide. These alterations can either be insignificant due to being silent, or they can be highly significant, as they can lead to different types of disorders, such as cervical cancer (70). HPV is considered to be the primary contributory factor to cervical cancer tumour angiogenesis, although a review of previous studies (71) reported additional contributors, including the regulation of long non-coding RNAs (lncRNAs) and/or their gene polymorphisms, such as polymorphisms in toll-like receptor (TLR) genes (72).

LncRNA LINC00673 has been implicated in the development and prognosis of multiple tumours, including SCC (73).

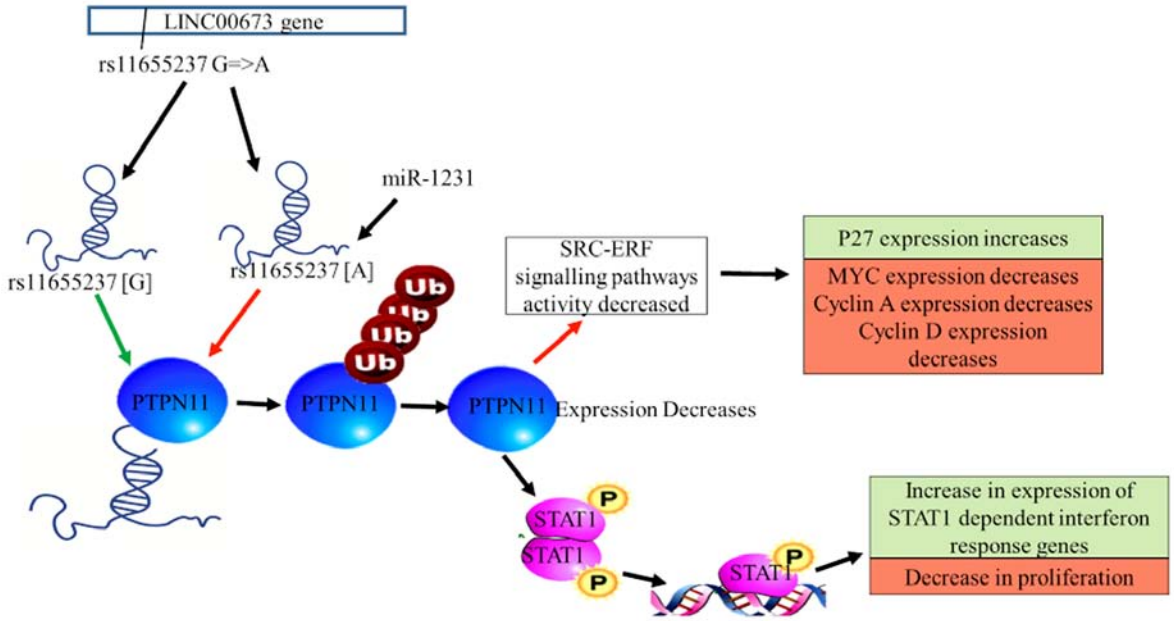

Figure 3. Long non-coding RNA LINC00673 serves an anti-tumour function by controlling PTPN11 degradation. The figure demonstrates how mutations due to SNPs in LINC00673 can promote the development of squamous cell carcinoma. An SNP at position rs11655237 in LINC00673 can increase the risk of developing cervical cancer. A decrease in the level of the normal wild type and an increase in the level of a variant known as LINC00673A that contains a G-to-A nucleotide substitution at rs11655237 may cause dysregulated transcription and result in an increase in the risk of developing cervical cancer. PTPN11, tyrosine-protein phosphatase non-receptor type 11; SRC-ERF, proto-oncogene tyrosine protein kinase-ETS domain-containing transcription factor; STAT, signal transducer and activation of transcription.

In 2018, Wang and Luo (72) demonstrated that the genetic variant of LINC00673 rs11655237 increases vulnerability to cervical cancer in the Chinese population, suggesting that this gene variant is associated with the risk of cervical cancer The study further suggested that downregulation of the transcription levels of LINC00673 rs11655237 in cervical tissues may be the main reason for the association between the genetic variant rs11655237 and the risk of cervical cancer. In addition, a G-to-A nucleotide substitution in the rs11655237 gene variant of LINC00673 may be the cause of dysregulated transcription, as it generates a target locus for microRNA (miRNA or miR)-1231 attachment, which in turn inhibits LINC00673 (60,74). The A allele and the AA/AG genotype of the rs11655237 gene variant have been demonstrated to be associated with the risk of developing cervical cancer, since the gene variant alters the transcription of LINC00673, which is vital for tumour suppression (Fig. 3) (72).

In 2018, Weng *et al* (75) investigated the association between the lncRNA HOX transcript antisense intergenic RNA (HOTAIR) genetic polymorphisms and the recurrence of cancer, as well as the survival rates of patients with cervical cancer. Although no significant association was observed between HOTAIR gene polymorphisms and patient clinicopathological characteristics, the study revealed that GG-genotype carriers in the HOTAIR rs920778 gene variant exhibited high risk of cervical cancer recurrence, low predicted survival due to stomal and pelvic lymph node metastasis, and increased mortality compared with carriers of the AA/AG genotype (74-76). Although the AA genotype is not associated with cervical cancer, it is significantly associated with gastric and oesophageal squamous cancer in Chinese populations (77). Therefore, the prognosis of a patient may depend on the impact of HOTAIR expression on the rs920778 gene variant. In addition, since the HOTAIR gene polymorphism rs920778 has insignificant associations with cervical cancer carcinogenesis, it cannot be described as a potential predictive factor for patient prognosis (75).

A previous meta-analysis conducted by Yang *et al* (78) identified an association between TLR gene polymorphisms and the risk of cervical cancer. The results revealed that white populations carrying the C allele of the TLR 9 1486 T/C gene polymorphism and the A allele of the TLR 9 G2848A gene polymorphism were significantly associated with an increased risk of developing cervical cancer (78,79). TLR 9 has been previously reported to promote cervical intraepithelial neoplasia (CIN) progression in women from Tunisia (80). These results suggested that TLR 9 may represent a potential biomarker for the malignant transformation of cervical squamous cells. The ability of genes and epigenetic factors to act as contributors of cervical cancer carcinogenesis, and the identification of these factors indicate their potential use in diagnosis and treatment.

Role of alternative splicing in cervical cancer

Alternative splicing mechanisms. Alternative splicing is a process by which introns are excised (i.e. 'spliced') from pre-mRNA to allow the assembly of exons for translation into a protein (81). The alternative splicing process is imperative to all eukaryotic organisms for the production of multiple alternative isoforms, which are needed for the functional diversity of proteins (82,83). Alternative splicing can undergo several interruptions, such as disturbances associated with miRNA expression, which may lead to several human disorders, including cancer (84,85). In addition, Skotheim and

Nees (86) have reported that cellular activities such as cell proliferation, motility and drug responsiveness can be negatively affected by the expression of alternative splice variants and tumour-specific variants.

Alternative splicing abnormalities. Abnormalities in alternative splicing have been demonstrated to lead to the development of multiple human diseases such as cancer, heart disease, and age-associated diseases, HIV-associated nephropathy and autoimmune disorders (87). Aberrant alternative splicing is usually a result of genomic point mutations that occur in splicing factors or elements that result in transcriptome alterations such as exon alteration, intron retention and gene expression changes (Fig. 4) (83). These mutations and alterations normally affect multiple protein pathways and mRNA expression (83,88). The influence of aberrant alternative splicing in the majority of cancer types results from splicing factor mutations in cancer genes or transcripts of non-mutated genes (89). Genome-wide associated studies have demonstrated the association of the splicing factor 3A subunit 1 (SF3A1) gene (which is located on 22q12.3) with several diseases, including lung and breast cancer, as well as inflammatory bowel disease (90,91). Mutations in the SF3A1 coding region are associated with susceptibility to multiple types of cancer, including oesophageal AC, osteosarcoma, myxoid liposarcoma, synovial sarcoma, ovarian carcinoma, glioblastoma, endometrial, lung, breast and gastric cancer (92).

Expression studies by Liu *et al* (93) demonstrated the ability of HR HPV oncoproteins E6 and E7 to induce the expression of serine- and arginine-rich splicing factor 10 (SRSF10), which is crucial for HPV 16- and 18-positive cervical carcinogenesis. Increased levels of SRSF10 were induced by E2F transcription factor 1 (93). The synthesis of the membrane form of interleukin-1-receptor accessory protein (mIL1RAP) is controlled by SRSF10 through the modulation of alternative splicing of the IL1RAP exon 13. This gives rise to the interleukin 1β isoform, which induced NF-κB transcription of the CD47 receptor. This cell surface molecule signals cells to escape macrophage phagocytosis (Fig. 5) (93). The study further revealed a significant association amongst SRSF10, mIL1RAP and CD47 expression in tissues of the uterus (93). This revealed that alternative splicing, inflammatory molecules and immune scrutiny served crucial roles in HPV 16/18-positive carcinogenesis (93,94). These results suggested that proteins associated with cervical cancer need to be researched for splice site abnormalities, since this method can also be used as a screening tool for the disease.

TLR mechanisms that lead to cervical cancer. TLRs are pattern recognition receptors that function in innate immune responses by identifying conserved components of microorganisms known as pathogen-associated molecular patterns. Previous studies have indicated that TLRs are expressed in tumour cells and in the tumour microenvironment of various types of cancer (95). TLR 3 (96), TLR 4 (96), TLR 5 and TLR 9 (96) have been identified in cervical cancer tissues, indicating that they may be involved in the occurrence of the disease. TLRs are activated by ligands such as lipids, and have been demonstrated to serve an important role in the development and progression of cervical cancer (97). These protein receptors are also expressed in other tumours (98), indicating that they may bind different ligands (Table IV). TLRs are highly expressed in immune and cancerous cells (80,99). Persisting HPV infection is the major cause of cervical cancer; however, alterations in expression levels of TLRs are suspected to also serve a significant role in HPV infection-induced cervical cancer (80). In support of this, Fehri *et al* (80) analysed the expression of TLR 9 in 53 samples from Sian women with ICC, CIN, condyloma and normal cervical tissues; the results revealed statistically significant differences in CIN and ICC between condyloma and normal healthy tissues. Almost all patients with ICC exhibited a higher level of TLR 9 expression in tumour epithelial cells, whereas between 50-80% of patients with CIN and condyloma exhibited weaker TLR expression (80). These results supported previous studies on Korean, Chinese and Canadian populations, which also revealed low TLR 9 expression in CIN and high TLR 9 expression in ICC (100,101). High expression levels of TLR 9 were mainly observed in the absence of HPV and/or its clearance (102). Hasan *et al* (103,104) reported that HPV subtype 16 proteins E6 and E7 dysregulated TLR 9 expression and functions. This suggested that HPV may use TLR 9 dysregulation to suppresses its function of viral DNA recognition, as TLR 9 is a crucial recognition receptor for DNA-introducing pathogens, particularly DNA viruses; in addition, it promotes inflammatory and immune responses (99,105). The results indicated the potential role of TLR 9 in CIN progression among women from various populations, suggesting that it may be used as a biomarker for SCC transformation.

Table IV. TLR expression in different types of cancer (97).

Cancer type	TLRs
Cervical	TLR 3, TLR 4, TLR 5, TLR 9
Gastric	TLR 2, TLR 4, TLR 5, TLR 9
Colorectal	TLR 2, TLR 3, TLR 4, TLR 5, TLR 9
Ovarian	TLR 2, TLR 3, TLR 4, TLR 5
Lung	TLR 2, TLR 3, TLR 4, TLR 9
Prostate	TLR 4, TLR 9
Breast	TLR 2, TLR 3, TLR 4, TLR 9
Liver	TLR 2, TLR 3, TLR 4, TLR 6, TLR 9
Pancreatic	TLR 2, TLR 4, TLR 9

TLR, toll-like receptor.

TLR 9 signalling induces tumour progression, survival and immune evasion in various cancer types, including cervical cancer (106). However, whether TLR 9 promotes or suppresses tumour growth remains unknown. Better understanding of the TLR 9 signalling pathway in cervical cancer may aid in the development of new immunotherapeutic strategies (80).

The combination of TLR 4 and the ligand lipopolysaccharide may trigger lipid raft flow that leads to the alteration of the lipid raft space conformation (Fig. 6A) (107). The change in the conformation of lipid rafts results in the aggregation of NADH oxidase subunits on lipid rafts, inducing a redox reaction of

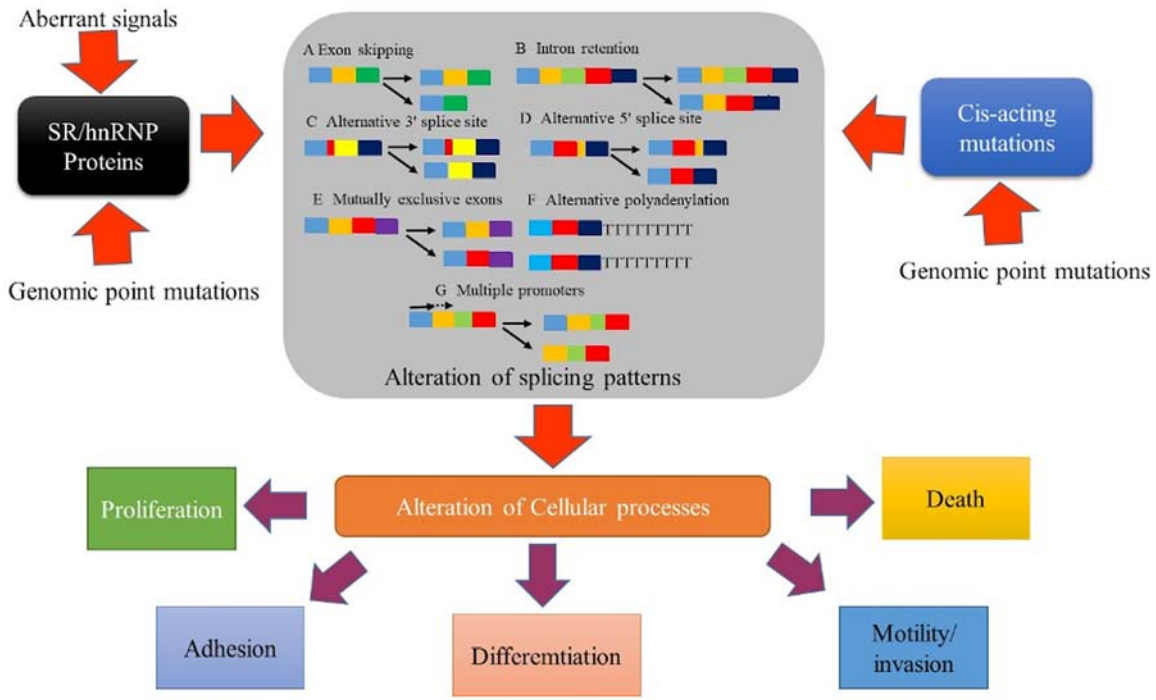

Figure 4. Pathways of aberrant alternative splicing resulting in diseases such as cervical cancer. The flow chart depicts the causes, mechanisms and results of aberrant alternative splicing. Aberrant alternative splicing is caused by genomic point mutations in splicing factors or elements. These lead to changes in splicing and different populations of splice variants, such as exon alteration, intron retention, alteration in 3' and 5' splicing, mutually exclusive introns, alteration in polyA tail length or occurrence of multiple promoters. Aberrant alternative splicing can contribute to a variety of pathologies. SR protein, serine arginine domain splicing factors; hnRNP, Heterogeneous nuclear ribonucleoproteins.

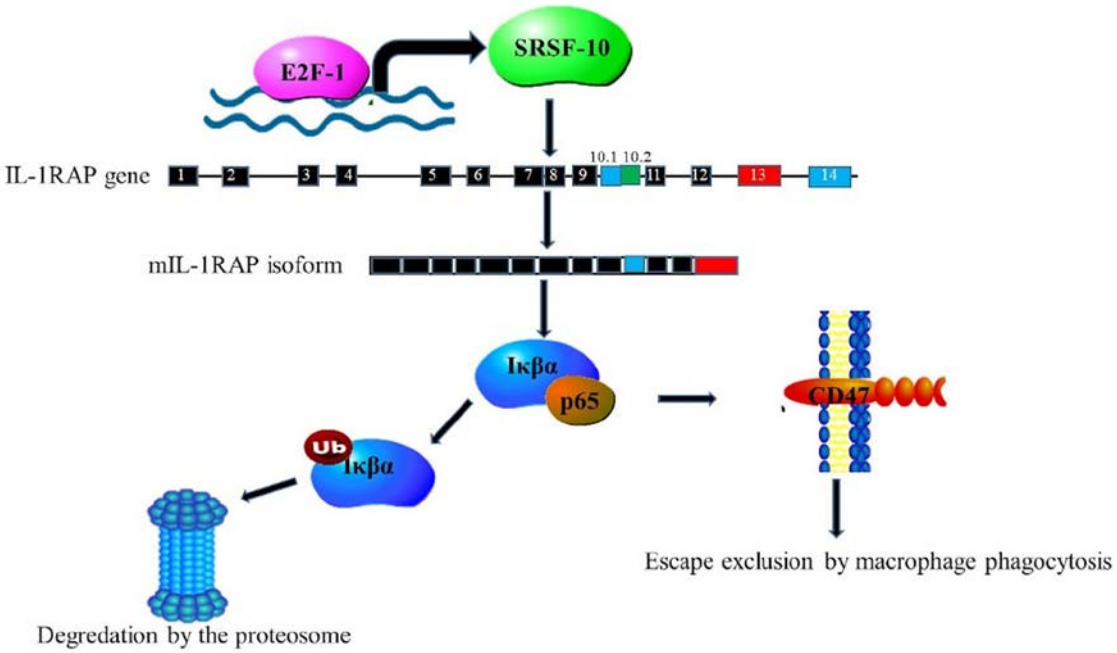

Figure 5. Aberrant alternative splicing of the IL1RAP gene leads to immune evasion and development of cervical cancer. The synthesis of mIL1RAP is controlled by the SRSF10 splicing factor. This allows the alternative splicing of the *iLIl1rap* exon 13 to form the mRNA corresponding to the membrane-bound isoform. This stimulates the IL-1β-induced NF-κB-mediated transcription of CD47, allowing the tumour cells to avoid phagocytosis by macrophages. CD47, CD antigen 47; E2F1, E2 Transcription factor 1; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL1RAP, interleukin-1-receptor accessory protein; mIL1RAP, membrane form of interleukin-1-receptor accessory protein; p65, transcription factor 65; SRSF10, serine- and arginine-rich splicing factor 10.

lipid rafts to produce reactive oxygen species and the inhibition of hypoxia-inducible factor 1α degradation, which may lead to the induction of cervical cancer (Fig. 6B) (97).

miRNA in cervical cancer. miRNAs are a group of small non-coding RNAs of 18-25 nucleotides in length that regulate gene expression at the post-transcriptional level (108). miRNAs

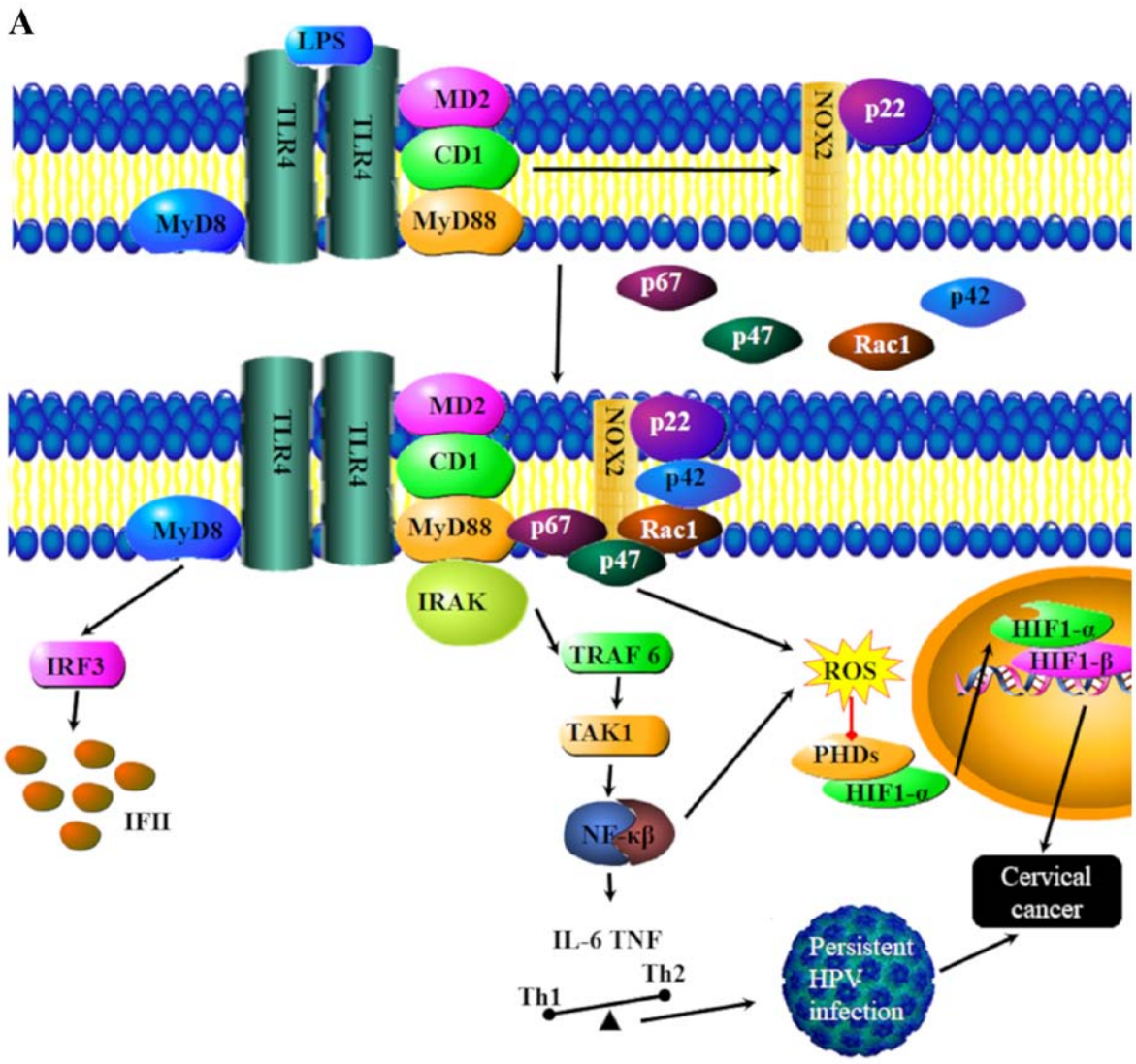

Figure 6. TLR4 signaling pathways in cervical cancer. (A) Binding of LPS to TLR4 leads to the transmission of signals via MyD88, At the same time the activation of TLR5 leads to increased Nox1 signaling.

also serve crucial functions in cell proliferation, differentiation, migration, invasion and drug resistance (78,109-111). The translation of mRNA can be suppressed or degraded when their 3'-untranslated regions (3'-UTRs) are targeted by miRNAs (93,112-114). Abnormal miRNA expression has been reported to contribute to the progression of multiple types of cancer, including breast, lung, oesophageal and ovarian cancer (115-120).

Expression of miR-214 in cervical cancer. Several miRNAs serve significant roles in the development of cancer, such as miR-98 (121), miR-98 (121), miR-146b-5p (122) and miR-214 (122). miR-214 has been demonstrated to be associated with both the inhibition and progression of multiple types of cancer, including cervical cancer (78). Yang *et al* (78) analysed the expression levels of miR-214 in cervical cancer and non-cancerous tissues. The results revealed that the inhibition of miR-214 expression in cancerous tissue stimulated cervical cancer proliferation, whereas excessive expression of miR-214 inhibited cancer progression (78). MTT assays were performed on cervical cancer cells revealed a significant inversely proportional association between the expression levels of miR-214 and enhancer of zeste homolog 2 (EZH2); increased expression levels of miR-214 and reduced expression levels of EZH2 resulted in reduced cervical cancer cell proliferation, whereas low expression of miR-214 combined with high EZH2 expression resulted in increased cervical cancer cell proliferation *in vitro* (78). Thus, the differential expression levels of miR-214 suggest that it may be a potential biomarker for prognosis and diagnosis of cervical cancer, or a tool for treatment of this disease. Statistical analysis determined an association between miR-214 expression levels and the survival rates of patients with cervical cancer (78). Patients expressing low levels of of miR-214 exhibited enhanced levels of cervical cancer proliferation. Moreover, patients with higher expression levels of miR-214 exhibited improved survival rates. A decrease in the EZH2 expression levels was significantly associated with the inhibition of cervical cancer proliferation (78).

Expression of miR-217 in cervical cancer. Previous studies have revealed that miRNAs act as tumour suppressors in

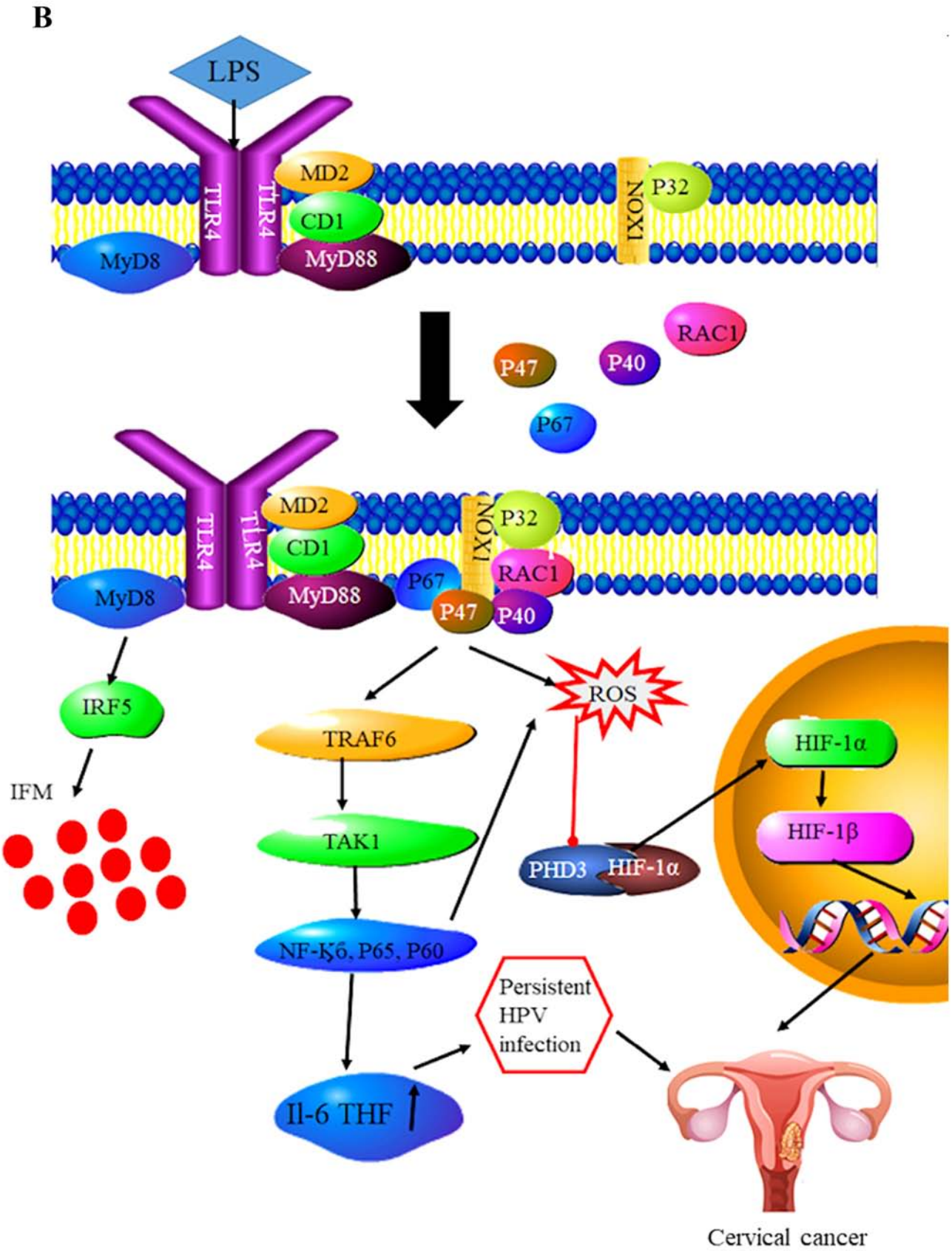

Figure 6. Continued. (B) The primary role of NOX1 is to generate ROS. NOX1 signaling also leads to the inhibition of HIF-1α degradation, which increases the possibly of developing cervical cancer MyD88 signaling in conjunction with NOX1 leads to the activation of transcription factors and Interfrons (IFN), leading to a pro-inflammatory and antiviral response. This pathway demonstrates how inflammation can lead to cancer progression. CD1, cluster differentiation 1; HIF-1α, hypoxia inducible factor 1α; IL-6, interleukin 6; IFN, interferon; IRAK, interleukin-1 receptor-associated kinase; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharides; MyD8, myeloid differentiation primary response 8; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nox1, NADPH oxidase 1; PHDs, propyl hydroxylases; Rac1, ras-related C3 botulinum toxin substrate 1; TAK1, transforming growth factor beta-activated kinase 1; TLR, toll-like receptor; Traf6, tumor necrosis factor receptor (TNFR)-associated factor 6; NADH, nicotinamide adenine dinucleotide hydrogen.

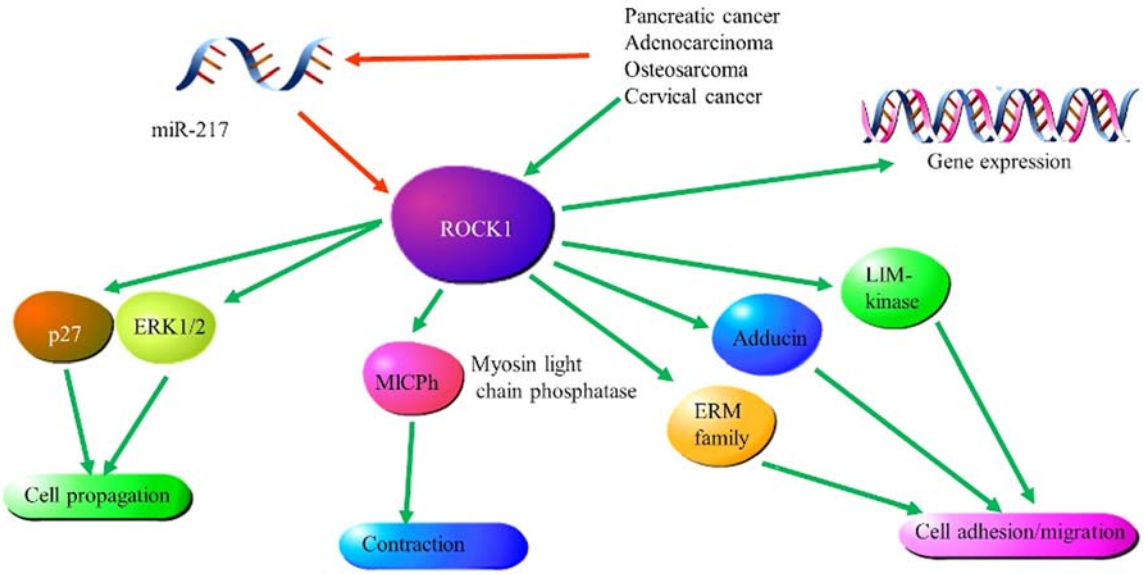

Figure 7. Increased expression of ROCK1 in cancer may be due to decreased levels of miR-217. ROCK1 expression is regulated by miR-217. Lower transcript levels of this miRNA are associated with metastatic and non-metastatic cervical cancer. Overexpression of miR-217 significantly inhibits cell growth. ROCK1 leads to increased invasion and metastasis. ERK, extracellular signal-regulated kinases; ERM, ezrin, radixin and moesin; LIM kinase, Lin11, Isl-1 and Mec-3 kinase; miR, microRNA; MLC phosphatase, myosin light-chain phosphatase; ROCK1, rho-associated coiled-coil containing protein kinase 1.

cervical cancer cells by regulating specific target genes. For example, Dong *et al* (123) compared Rho-associated coiled-coil containing protein kinase 1 (ROCK1) expression levels in cervical cancer and non-cancerous tissues and cell lines. Significantly lower expression levels of miR-217 were observed in metastatic and non-metastatic cervical cancer tissues and cell lines compared with those in non-cancerous tissues and cell lines (123). Reduced invasive capabilities of SiHa and HeLa cell lines, as well as reduced colony formation, was demonstrated when miR-217 was highly expressed; in addition, the effect of high miR-217 expression on apoptosis in SiHa and HeLa cell lines was analysed by flow cytometry. The flow cytometry indicated that increased transcription of miR-217 in cells resulted in a greater proportion of these cells undergoing apoptosis (123). Overexpression of miR-217 significantly inhibited cell growth, whereas overexpression of ROCK1 increased cell invasive abilities in the SiHa cell line due to decreased miR-217 expression (123). Therefore, the ability of miR-217 to suppress cervical cancer may be modulated through ROCK1. This was further supported by suppressed luciferase activity of pmirGLO-ROCK1-3'UTR-1 and pmirGLO-ROCK1-3'UTR-2 following overexpression of miR-217 (123). Lastly, western blot analysis revealed that overexpression of miR-217 significantly lowered ROCK1 expression levels, whereas reduced levels of miR-217 expression resulted in increased ROCK1 expression levels (Fig. 7) (120). Therefore, miR-217 may target ROCK1 to inhibit cervical cancer proliferation (123). The level of miRNA transcription serves an important role in cervical cancer progression, which in turn highlights the importance of broadening our knowledge on potential miRNA target genes, as well as the potential mechanisms of migration and invasion for the identification of potential prognostic and diagnostic tools, and for the development of novel immunotherapeutic strategies for cervical cancer.

4. Prevention and diagnosis of cervical cancer

Geographic variation in cervical cancer incidence is based in part on differences in the availability of screening to allow for the early identification and removal of precancerous lesions. The diagnosis of HPV should also be considered as an important and challenging causative factor for cervical cancer that varies geographically (124).

Cervical cancer prevention: HPV vaccination. In 2013, Adesina *et al* (125) estimated that 11 million women in Sub-Saharan Africa would be diagnosed with cervical cancer within the next 10-20 years, with ~1.7 million cases diagnosed in 2010 (126). Prevention of cervical cancer is regarded as the best control method; however, treatment is also an important intervention (127). A cost-effective HPV vaccine has been reported as lifesaving amongst girls between 9 and 12 years of age (50). The number of cervical cancer cases are predicted to effectively decrease after five decades of comprehensive vaccination (128). There are two types of HPV vaccines used for targeting the predominant subtypes of HPV: The bivalent vaccine, which targets the HPV 16 and 18 subtypes, and the quadrivalent vaccine, which targets the HPV 6, 11, 16 and 18 subtypes (2,129). HPV vaccines have been reported to effectively assist in preventing HPV infection, and result in the prevention of CIN (130,131) HPV vaccination first became popular in high-income countries but remained unpopular in low income countries due to the high price of the vaccine. Since 2011, HPV vaccinations have gained popularity in middle-income countries due to a decrease in cost (2); since 2012, increased financial support for HPV vaccination projects in low-income countries has enabled such countries to adopt vaccination programs (2,132). HPV vaccination for women in South Africa was first introduced in 2014 through the National HPV Immunization Program. The primary target age for HPV vaccination in South Africa is 9 years

(pupils in grades 3 and 4) (6,17). According to the European Medicines Agency, the standard dose for girls <14 years of age is two doses at 0 and <6 months depending on whether they are receiving the Cervarix or Gardasil vaccine (21). Herrero *et al* (2,7) clinically demonstrated that three doses of HPV vaccine can provide total protection against persisting HPV infection and associated precancerous lesions in women aged between 15 and 26 years old, provided that they have not been previously exposed to the virus (7). Therefore, treatment (or vaccination) and screening is crucial for lowering the incidence, burden and mortality rates of cervical cancer (7).

Cervical cancer screening. It is of great global interest to eliminate or decrease the number of new cases and high mortality of cervical cancer caused by persistent HPV infection. Therefore, Pap smear screening for cervical cancer is highly encouraged during the HIV diagnosis process. This procedure should be repeated every 3 years for women who have been previously screened and diagnosed as negative (50). Regular screening for cervical cancer amongst women is predicted to lower the lifetime risk of developing the disease (133). Population screening for cervical cancer in regions of low socioeconomic status and low-resource settings remains elusive; the cervical cancer screening coverage in Southern Africa ranges between 4.1 and 38.0%. A study of 642 females in urban areas found that 17.3% had been screened, while of 580 females in rural areas 9.6% had been screened for HPV (130,134,135). This low coverage is due to factors such as inaccessibility (due to areas being remote), lack of funding, community awareness and cost-effectiveness, complications of Pap smear, a lack of public policy attention, or the implementation of ineffective public policies (128,130,136).

HIV-associated cervical cancer incidence is predicted to gradually increase in LMICs for the next 10 years (137). Despite the incidence of cervical cancer in many LMICs being lower than in many developed countries, the cancer burden in LMICs is increasing due to the advanced stage at diagnosis and inaccessible treatment (28). Thus, immediate action in the public and global health sectors is advised (2,138). Effective precancerous lesion detection using the PapilloCheck® microarray and the HPV restriction fragment length polymorphism (RFLP) PCR assay was achieved with 62.5 and 25.0% HPV co-infection detection, respectively (4). The RFLP PCR assay is suggested as a primary HPV test for screening in LMICs, as it is cost-effective, while the PapilloCheck® microarray assay is considered a more sensitive and descriptive test (4). However, widespread access to screening at the population level in LMICs remains challenging. For example, in Uganda, cervical cancer is the leading type of cancer amongst women, with 3,915 new cases and 2,275 deaths per year (21); however, <10% of Ugandan women have ever been screened (139).

Several studies have reported multiple compounding factors that contribute to non-participation of women in cervical cancer screening, such as unemployment, lack of or low education level, poor language proficiency (for example, the information and education campaigns not being provided in the native language of the women the programs are aimed at), being unmarried, lack of knowledge of screening, previous negative experiences of screening, cultural and traditional beliefs, and multiple other determinants (140-142). Thus, the WHO and the European Commission have recognised that equal access and equal utilization of healthcare is essential to deal with inequity issues in healthcare (143). This may improve healthcare service practices such as screening and treatment (144,145). In conclusion, appropriate cervical cancer screening programs and good-quality cytological testing can assist in lowering the incidence and mortality rates of cervical cancer. The effectiveness of prevention and treatment programs is dependent on equity in healthcare and good healthcare service practices. A lack of cervical cancer screening is not the sole cause for the high burden of cervical cancer in LMICs. Another important consideration is the decision on whether to treat a patient based on a positive result for an HPV test. Since most HPV infections clear spontaneously, especially in younger women, if a patient is treated without further screening, it may contribute to unnecessary treatment costs (146).

5. Conclusions

Globally, Southern Africa displays the largest HIV burden amongst women, contributing to it being a HR region for developing an HPV infection, pre-invasive cervical disease and ICC. Poor prognosis and diagnosis are common in low-income settings, where women experience advanced stages of HPV infection and lack treatment.

Control methods, including Pap smear screening and HPV vaccines, have been used to help reducing the exponential increase in new cervical cancer cases, although the low coverage for screening remains a challenge in a number of LMICs. However, these control methods were initially only available in developed countries and have only recently become available in middle-income countries, leaving women from low socioeconomic backgrounds vulnerable. This is caused by the lack of funding and accessibility to cost-effective treatment. Thus, the present review highlights the importance of equity in the access and utilization of healthcare services and products.

Although HPV vaccines have been introduced in multiple LMICs, their prophylactic efficacy is only beneficial to women who have not been exposed to the virus; therefore, this identifies a need for further research into other possible interventions, particularly for those already infected. The effect of aberrant alternative splicing on cervical cancer requires further research and may be a promising tool for treatment of the disease. Similarly, TLRs and miRNAs may be explored further as potential immunotherapeutic interventions.

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Availability of data and materials

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Authors' contributions

ZD was responsible for the Acquisition of funding. RH, MM, RM and ZMK were responsible for the collection of data. RH, MM, TM, RM and ZMK were responsible for writing the manuscript. RH, TM, RM, ZMK, CH, SMW, RMR, GK and DOB were responsible for editing/revising the manuscript. ZD is responsible for supervising the research group. The review was written by RH, MM, TM, RM, ZMK and ZD. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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