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REVIEW

Global Variation of Human Papillomavirus Genotypes and Selected Genes Involved in Cervical Malignancies

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Abstract

BACKGROUND Carcinoma of the cervix is ranked second among the top 5 cancers affecting women globally. Parallel to other cancers, it is also a complex disease involving numerous factors such as human papillomavirus (HPV) infection followed by the activity of oncogenes and environmental factors. The incidence rate of the disease remains high in developing countries due to lack of awareness, followed by mass screening programs, various socioeconomic issues, and low usage of preventive vaccines. Over the past 3 decades, extensive research has taken place in cervical malignancy to elucidate the role of host genes in the pathogenesis of the disease, yet it remains one of the most prevalent diseases. It is imperative that recent genome-wide techniques be used to determine whether carcinogenesis of oncogenes is associated with cervical cancer at the molecular level and to translate that knowledge into developing diagnostic and therapeutic tools.

OBJECTIVE The aim of this study was to discuss HPV predominance with their genotype distribution worldwide, and in India, as well as to discuss the newly identified oncogenes related to cervical cancer in current scenario.

FINDINGS Using data from various databases and robust technologies, oncogenes associated with cervical malignancies were identified and are explained in concise manner.

CONCLUSION Due to the advent of recent technologies, new candidate genes are explored and can be used as precise biomarkers for screening and developing drug targets.

KEY WORDS cervical cancer, HPV vaccines, human papillomavirus, mutation, oncogene

INTRODUCTION

Cervical neoplasia is the second most familiar malignancy threatening women and leading to death at final stage. Although there are various recent medical advances in diagnosis, treatment, and research, the disease mortality remains high in developing countries. Worldwide 529,000 new cases of and 275,000 deaths from cervical cancer were reported in 2008.[1]

Human papillomavirus (HPV) has been determined as one of the prime etiologic agents in development of cervical neoplasia. In the 1970s, Harold zur Hausen hypothesized a correlation between cervical neoplasia with infection caused by HPV, which belong to the family *Papillomaviridae*. These viruses are extremely specific and primarily tissue tropic, and they undergo entire cycle in fully differentiated squamous epithelial cells. The viral genome is constituted by circular double-stranded DNA containing

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6000 to 8000 base pairs, which constitutes 8 genes totally, such as early (*E*) and late (*L*) genes. There are more than 100 HPV genotypes and they are classified into high- and low-risk groups. The high-risk group is oncogenic in nature and causes persistent infection in the human system.[2] The low-risk group is responsible for genital warts or generates mild dysplasia on the cervix. The oncogenic potential of HPV infection depends on the activity of viral oncogenes such as *E6* and *E7*. HPV types 16 and 18 are considered as most prevalent "high-risk" types, whereas the 6 and 11 are "low-risk" types.[3]

The risk for cervical cancer is still high in developing countries. There is lack of awareness in women regarding the disease and the preventive measures that should be taken. It has been estimated that 132,000 newly reported cases and 74,000 deaths occur every year in India due to cervical neoplasia. As with all developing countries, organized cervical cancer screening programs have not been feasible in India due to various reasons. In India, 2 types of cancer registries are available, the population-based cancer registries and the hospital-based cancer registries collectively come under National Cancer Registry Programme.[4] Information on cancer patterns across India can be collected from the 18 population-based cancer registries.

Cervical malignancies are divided into 2 types, adenocarcinoma and squamous cell carcinoma. Tumors developing from the ectocervix region are called squamous cell carcinomas, and they represent 80% to 90% of cervical cancers in India. Tumors developing from the endocervix are adenocarcinomas.

The top 5 cancers of women worldwide are breast, cervix uteri, colorectal, ovarian, and lip-oral cavity. Among these, cervical cancer is next to breast cancer in incidence and prevalence affecting women.[5] Figure 1 illustrates the incidence age-standardized rate of cervical malignancy worldwide. This data was retrieved from the International Agency for Research on Cancer (IARC) Globocan 2012 database.

RISK FACTORS

There are various epidemiological studies that have identified risk factors for cervical cancer. These factors, which increase the frequency of the disease, include low socioeconomic status, marriage at a

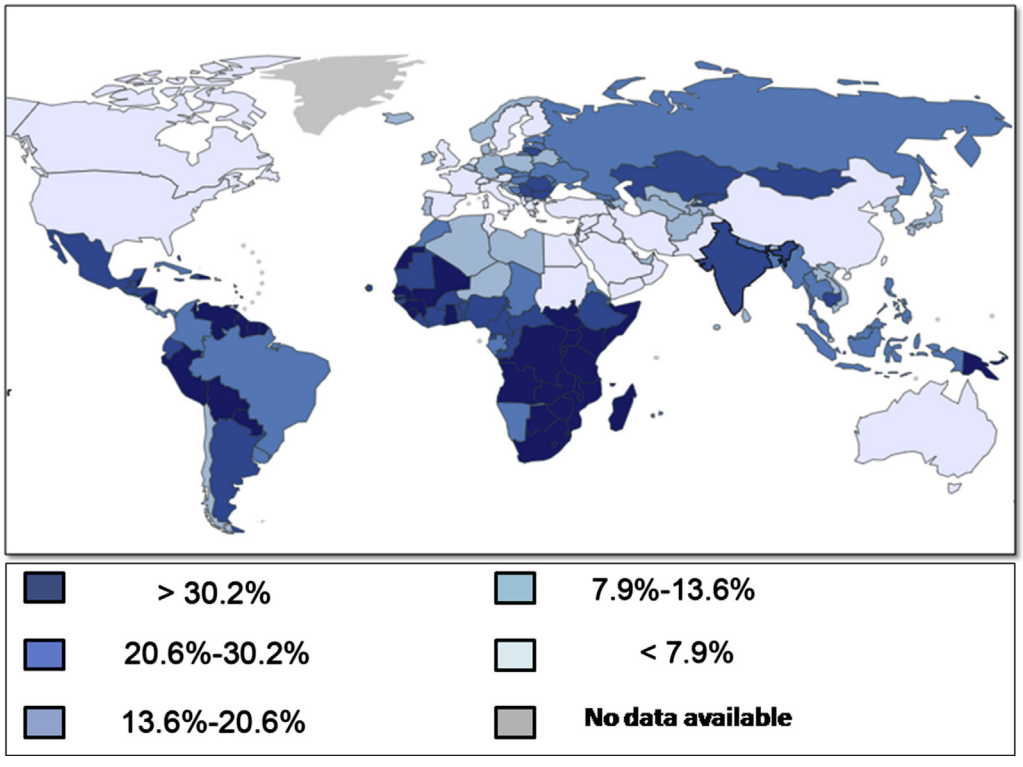

Figure 1. World map showing incidence (age—standardized rate) of cervical cancer.[5]

very early age, multiple sexual partners, long-term use of oral contraceptives, nutrient insufficiency, genetic factors such as active oncogenes and tumor suppressor genes, tobacco use, poor personal hygiene, and viral infections such as HPV, HIV, herpes simplex virus (HSV) type II, and bacterial infections caused by Chlamydia trachamatis.[6,7] Other significant factors that also contribute to the disease are an increase in the population, an increase in the number of elderly people, and urbanization. Figure 2 explains the risk factors leading to cervical malignancy.

HPV: WORLDWIDE DISTRIBUTION

Globally, the burden of HPV infection causing cervical neoplasia is high in developing countries. The oncogenic nature of the genotypes differs in each region of the world. A study published in 2013 from Brazil identified that 170 of 172 samples (99%) were found to be positive for HPV. The most frequent HPV genotypes observed were *HPV16* (77.6%), *HPV18* (12.3%), *HPV35* (5.9%), *HPV31* (8.8%), and *HPV33* (7.1%). Most of these infections (75%) were caused by individual HPV genotypes in Brazilian women.[8]

A study of high-risk HPV genotypes from Malaysia identified that of 200 samples collected from an ethnic group of Malay, Indians, and Chinese in a health screening program, 84 (46.7%) showed the existence of HPV DNA. In those samples, the most frequent HPV genotype found was high-risk oncogenic type *HPV16* (40%), followed by *HPV18* (3.3%), *HPV31* (0.6%), *HPV33* (1.7%), and low-risk *HPV87* (0.6%).[9] In a study conducted in the northeastern part of Brazil, where the cervical cancer incidence is high, results showed that 32 patients with abnormal colposcopic/cytologic changes had 30% positivity for HPV DNA.[10]

In East Asia and Latin America, genotype *HPV58* represents a prominent proportion of cervical neoplasia, but it is limited elsewhere. The rationale for this variation is not yet identified clearly but may be due to ethnogeographical distribution. In all, 401 *HPV58* samples were examined from 15 different cities or countries across 4 continents. Results demonstrated that there were specific variations in the *E7* gene that may have led to greater risk for cervical cancer.[11]

High-risk *HPV45* genotype constitutes about 5% of all cervical malignancies globally. It is more commonly found in adenocarcinoma than in squamous cell carcinoma. Three hundred samples of known *HPV45* collected from 36 countries throughout the world have been examined. The complete regions of *E7* and *E6* open reading frames of those samples have been analyzed and 43 *HPV45* variants were identified from 5 different phylogenetic sublineages. This may be one of the possible reasons for cervical malignancy caused by *HPV45*.[12]

The prevalence of HPV was identified in cervical cancer patients in Saudi Arabia in 2013. The study included 100 patients. HPV infection was observed in 82%. The most widespread genotypes were

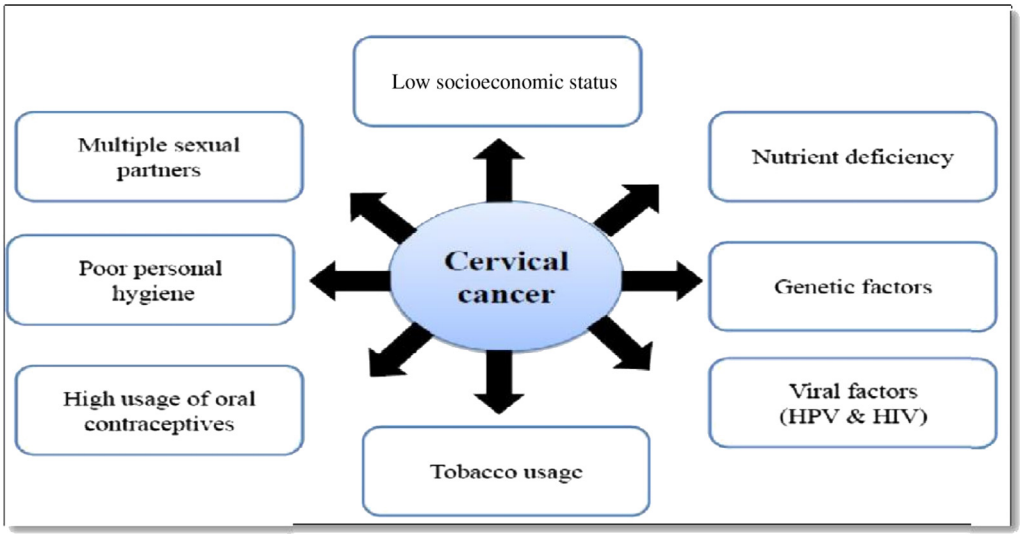

Figure 2. Multiple risk factors leading to cervical cancer.

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HPV16 (71%), *HPV18*, *HPV73*, *HPV45* (4% each), and *HPV31* (7%).[13] The characterization of HPV genotype was carried out in Sub-Saharan Africa in 2013, where researchers concentrated on 3 regions (ie, Nigeria, South Africa, and Ghana) for 3 years. The study population included 659 women, of which 579 cases were confirmed as invasive cervical cancer. The HPV-positivity rate observed was 90.4% (515 of 570). The most frequently detected genotypes were *HPV16* (51.2%), *HPV45* (7.4%), *HPV18* (17.2%), *HPV33* (4%), *HPV35* (8.7%), and *HPV52* (2.2%).[14]

A study published in 2014 from the Gurage zone of rural Ethiopia with 537 women aged 15 to 64 years identified various high- and low-risk groups. Of the high-risk positive infections (n = 86), the most widespread genotype identified was *HPV16* (24.4%), followed by *HPV52* (11.6%), *HPV56* (10.5%), and *HPV31* (10.5%).[15] The differences in HPV genotypes observed between young and old patients affected by cervical neoplasia were identified in 2014 in the Mexico City. The study population was consisted of 462 patients; of these 456 tested positive for HPV. Of those patients, 418 (90.5%) had single infections, and 38 (8.2%) had dual HPV infections. Genotypes *HPVI* (46.5%), *HPV45* (6.7%), *HPV18* (10.4%), and *HPV31* (4.1%) were the most frequent viral types in single-infected patients. These data indicate that most of the cervical malignancies in young women depend on the presence of high-risk oncogenic HPVs.[16]

HPV: INDIAN SCENARIO

According to a 2010 report from the World Health Organization, India has a population size of 366.58 million women aged 15 years and older who have the possibility of developing cervical cancer. In India, *HPV16* alone has been observed in 70% to 90% of women with cervical cancer, whereas the occurrence of *HPV18* varies from 3% to 20%.[17] India is a rapidly developing country with 17.2% of the world's total population (ie, one-sixth). Approximately 134,420 women were diagnosed with cervical malignancies in 2010, and 72,825 died of cervical cancer.[18]

The occurrence and oncopotency of specific HPV subtypes in cervical malignancies may diverge with the geographic origin of the specimen. *HPV16* was identified as the most ubiquitous type causing cervical lesions in several areas including Chennai, a major metropolitan city of India and capital for the Tamil Nadu. It has been determined that *HPV18* is more oncopotent and has the ability to cause invasive cancer from precancerous lesions within a shorter time frame than *HPV16*.[19]

In the southern side of the Tamil Nadu region, a comparatively high incidence of *HPV56* and *HPV42* has been reported in previous IARC surveys.[20] But *HPV42* is classified as low risk, whereas *HPV56* is high risk. Findings from a report from the eastern part of India showed that in rural regions of West Bengal the prevalence of HPV with the genotypes *HPV18* and *HPV16* in 534 Hindu and 478 Muslim women were 9.6% and 7.5%, respectively.[21]

In 2011, the government of India initiated a countrywide program, National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke, which covers nearly 100 districts of 21 states. However, cervical malignancy screening and prevention has been neglected compared with other higher incidence problems such as diabetes and stroke in this ongoing program.[22]

It has been estimated that the life expectancy of the Indian population will rapidly increase from 68 years in 2011-2015 to 71 years 2021-2025. The total population of India, as of March 2011 was 1.21 billion, according to the provisional population total provided by Census of India, 2011. In 2001, the total population was 1.028 billion. The incidence of cancer in India is expected to increase in the future as a result of increased in life expectancy and population, in addition to a lack of mass cervical cancer screening programs throughout the country. It has been predicted that the Indian population aged over 40 years is more prone to cervical cancer and disease frequency will increase from 28% in 2011 to 35.7% by 2026.[23]

The estimated 5-year prevalence of cancer in the adult female population for all cancers throughout India is 1,125,960, of which cervical cancer constitutes 308,901 (27.4%), as of 2012 from (IARC), Globocan database.[24] Tables 1 and 2 explain the incidence and prevalence rates (Table 1) and the incidence by age (Table 2) of the leading cancers in Indian women.

SPECIFIC GENES RELATED TO CERVICAL CANCER

Cervical cancer, as mentioned earlier, is a complex disease due to genetic and other general risk factors that lead to the progression of malignant cells. In general, all types of malignancies can be correlated with 3 types of genes; namely, oncogenes, DNA repair genes, and tumor suppressor genes. These genes play major roles in the development and

Table 1. Incidence and Prevalence Rate of Leading Cancers in India[5]

S. No	Cancer Type	Incidence Rate	Prevalence rate		
			1-y (prop.)	3-y (prop.)	5-y (prop.)
1	Breast	146,607	113,525 (26.4)	281,642 (65.5)	402,623 (93.6)
2	Cervix uteri	123,110	92,022 (21.4)	220,828 (51.3)	309,627 (72)
3	Colorectal	27,802	15,065 (3.5)	30,156 (7)	37,728 (8.8)
4	Ovarian	26,656	18,248 (4.2)	41,320 (9.6)	55,676 (12.9)
5	Lip, oral cavity	23,134	12,748 (3.0)	26,985 (6.3)	35,263 (8.2)

S. No, serial number; prop, propotion.

progression of the disease. In this section, we discuss the genes that are related to several stages of cervical neoplasia. The Cervical Cancer Gene Database, with a compilation of 537 genes is exclusively maintained for genes involved in cervical malignancies.[25] The genes listed here are identified from published literature over the past 10 years from PubMed and several other databases such as National Human Genome Research Institute, the National Cancer Institute, and the COSMIC Database.[26] The identified genes have variable gene expression profiles and genetic variations such as mutations in both exonic and intronic regions, and numerous single nucleotide polymorphisms. The following is a list of oncogenes and tumor suppressor genes and a description of their mechanisms that are closely linked to cervical malignancies.

Tumor Protein 53 (*TP53*). *TP53* encodes for tumor suppressor proteins that function predominantly to inhibit cell cycle progression, promote DNA repair, and apoptosis. It is located on chromosome 17, is constantly mutated in all types of cancers, and a single mutation of this gene is adequate to cause loss of normal *p53* function. Most of the genetic variations in this gene occur in the 5 to 8 exonic regions and this is believed to be a highly conserved region in the DNA-binding domain in this gene.[27] Various studies have determined the involvement of *p53* gene in cervical malignancies. *HPVE6* gene-stimulated degradation interferes with the function of *p53*, which in turn contributes to virus-induced mutations in cervical cancer.[28,29]

Phospha-tidyl inositol-4, 5-bisphosphate 3-kinase (*PIK3CA*). *PIK3CA* is an oncogene that plays a major role in the PI-K/AKT signaling pathway. This gene takes part in the regulation of cell growth, apoptosis, and vesicular trafficking and has 2 domains; namely, the helical and kinase domains. *PIK3CA* is present on the third chromosome and the mutation in 20th exon encodes for the kinase domain. The variations in ninth exon encode for the helical domain. These 2 regions have mutational hotspots all of which are somatic rather than germ line in origin. Several studies have identified diverse genetic variations such as mutations, and deletions and epigenetic alterations have been seen in patients affected with cervical cancer. The mutations in *PIK3CA* play a significant role in the development of this cancer from preinvasive to invasive.[30,31]

Serine/Threonine Kinase 11 (*STK11*). *STK11* acts as a tumor suppressor gene (also called *LKB1*) that is located on chromosome 19. These genes govern the activity of AMP-activated protein kinases and also control a variety of processes such as cell metabolism, apoptosis, and DNA damage response. Somatically acquired mutations in the *LKB1* gene are linked with Peutz-Jeghers syndrome and in gynecologic malignancies. After viral infection, additional mutations in genes including *LKB1* are essential to promote invasive carcinomas.[32]

Table 2. Estimation of Cancer Incidence by Age in Indian Women[5]

S. No	Cancer Type	Total	0-14 y	15-39 y	40-44 y	45-49 y	50-54 y	55-59 y	60-64 y	65-69 y	70-74 y	75+ y
1	Breast	14,4937	34	23,917	19,543	24,214	24,008	19,989	13,540	8629	5583	5480
2	Cervix uteri	122,844	6	18,841	15,513	19,635	20,863	19,062	13,367	8191	4543	2823
3	Colorectal	27,415	73	3315	1808	2460	3180	3615	3361	2976	2728	3899
4	Ovarian	26,834	371	4016	2452	3371	3968	4070	3143	2223	1570	1650
5	Lip, oral cavity	23,161	76	2158	1536	2279	3034	3589	3386	2709	2077	2317

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Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*). *KRAS* is an oncogene encoding for a small guanosine triphosphate (GTP) transducer protein located on chromosome 12. *KRAS* is mainly involved in the regulation of cell division. There are 150 *RAS*-like genes recognized in mammalian genomes and the oncogenic forms of the RAS protein have a reflective effect on the downstream effector pathways. Mutations resulting in the substitution of amino acids diminish the nucleotide affinity of the KRAS protein, thereby troubling the rate of GTP/guanosine diphosphate exchange. There are 2 main factors responsible for oncogenicity of RAS protein—carboxy-methylation and post-translational franesylation.[33] *KRAS* mutations are associated with *PIK3CA* gene mutations and have been found in various types of malignancies.[34]

Epidermal Growth Factor Receptor (*EGFR*). An oncogene, *EGFR* has been recognized as first tyrosine kinase transmembrane receptor directly correlated with human malignancies. The somatic mutations concerning *EGFR* lead to its constant activation, producing uncontrolled cell division of normal cells to form tumors. This gene is located on chromosome 7 and contains 3 protein-coding domains—the tyrosine kinase domain, the extracellular ligand-binding domain, and a transmembrane domain.[35] HPV proteins play a vital role in *EGFR* expression, and the E5 oncoprotein of HPV suppresses the activity of this gene.[36]

Nucleolar Protein 7 (*NOL7*). *NOL7* is a tumor suppressor gene observed on chromosome 6. It has recurrent loss of heterozygosity (LOH) in various types of malignancies such as retinoblastoma, lymphoma, nasopharyngeal carcinoma, breast cancer, and cervical cancer. *NOL7* genes play a major role in suppression of tumor growth. Diverse types of mutations both in exonic and intronic regions, splice junctions, and promoter methylation have been identified in cervical cancers. The first nonviral mechanisms contributing to cervical malignancies are mainly LOH and chromosomal instability.[37,38]

Cyclin-dependent Kinase Inhibitor 2A (*CDKN2A*). The *CDKN2A* gene encodes for tumor suppressor protein and plays a significant role in the regulation of cell cycle. Cyclin-dependent kinases such as 4 and 6 are mainly inhibited by *CDKN2A*. Mutations in the *CDKN2A* gene are mainly associated with increased risk for disease in a wide range of malignancies and numerous studies have reported the inconsistent expression profile of this gene in cancers. *CDKN2A* genes are being used as precise and reliable biomarkers for cervical cancer diagnostics. This gene is located on chromosome 9 and because HPVE7 protein inactivates the Rb protein, *CDKN2A* overexpression has been demonstrated in cervical cancer.[39]

Phosphatase and Tensin Homolog (*PTEN*). *PTEN* is a tumor suppressor gene that regulates the cell cycle and prevents rapid growth of cells. It has been found mutated in various types of cancers, particularly in endometrial carcinoma. *PTEN* and *PIK3CA* have been shown to harbor mutations in several carcinomas such as glioblastoma and breast cancer. It is present on the 10th chromosome.[40]

Binding Protein p300 (*EP300*). *EP300* plays a major role in regulating the cell growth and division, allowing the cells to mature and assume their specialized functions, thereby preventing the growth of tumors. This gene is located on chromosome 22 and on the basis of its function; it is called a transcriptional coactivator. *EP300* genes have 2 types of domains—the bromo-domain and histone acetyl-transferase—required for binding activity. Recent evidence suggested that somatic mutations identified in this gene are associated with head and neck, cervical, and endometrial cancers. In cervical malignancies especially, multiple new mutations have been reported for this gene.[30] Table 3 provides the list of genes, their chromosomal locations, coding exons, and precise functions.

VACCINES FOR HPV-ASSOCIATED CERVICAL CANCER

Vaccines are used widely to prevent infections that are caused by various types of viruses. The major HPV genotypes such as *HPV16* and *HPV18* are observed in cervical malignancies. Prophylactic vaccines are available by targeting these 2 types of genes and are known as bivalent or quadrivalent vaccines. The quadrivalent vaccine protects individuals from HPV in both the high- and low-risk group. These vaccines are not only found protective for cervical cancer but also effective against vaginal and vulvar cancer and genital warts. The vaccine should be administered before an individual becomes sexually active so that it can offer enhanced protection. In 2006, the FDA recommended preventive HPV vaccine for males and females in the 9- to 26-year age group.[41] Likewise, the Advisory Committee on Immunization Practices also recommended prophylactic vaccination to prevent precancers and cervical malignancies. These vaccines aim at a small proportion of HPV genotypes only; further research is needed to target a wider spectrum of HPV types.

Table 3. Major Genes Involved in Cervical Malignancies

S. No	Genes	Chromosome Location	Total Exons	Protein (Amino Acids)	Function	References
1.	Tumor protein 53 (*TP53*)	17p13.1	11	393	Controls the activity of cell cycle progression and apoptosis	26,27,45
2.	Phosphatidyl inositol-4, 5-bisphosphate 3-kinase (*PIK3CA*)	3q26.3	21	1068	An oncogene that plays major role in the PIK-AKT signaling pathway	29,30,45
3.	Serine/ Threonine Kinase 11 (*STK11*)	19p13.3	10	433	Controls the cell and DNA damage response	31,45
4.	Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*)	12p12.1	05	188	An oncogene involved in regulation of cell division	32,33,45
5.	Epidermal Growth Factor Receptor (*EGFR*)	7p11.2	28	1210	An oncogene involved in regulation of cell division	34,45
6.	Nucleolar Protein 7 (*NOL7*)	6p21.3	08	257	A tumor suppressor gene that plays a role in the cell cycle	37,45
7.	Cyclin- dependent Kinase Inhibitor 2A (*CDKN2A*)	9p21.3	03	156	Encode for tumor suppressor protein; plays a significant role in the regulation of the cell cycle	38,45
8.	Phosphatase and Tensin Homolog (*PTEN*)	10q23.3	09	403	Main function is to regulate the cell cycle	39,45
9.	Binding Protein p300(*EP300*)	7p11.2	31	2414	Regulates cell growth, assumes specialized functions	29,45

S. No, serial number.

Similarly, therapeutic vaccines are under clinical trial and should be made available for individuals with HPV-associated cancers.[42,43] The cost of these vaccines should be made affordable to those in low socioeconomic groups because they are more prone to risk for cervical malignancy[44]. Effective steps should be taken to conduct massive HPV vaccination programs to affect a decrease in the morbidity of the disease in developing countries worldwide.

CONCLUSION

The present study discussed the current picture of cervical malignancy both worldwide and in India, and the data interpret global burden of the disease. Both factors such as HPV infection and activity of oncogenes should be given more importance to reduce the mortality of the cervical neoplasia. Due to advent of recent "omics" technologies such as whole-exome sequencing, transcriptome profiling, and whole-genome sequencing, new candidate genes are being identified; those novel genes can be used as predictive biomarkers for screening. The positional drug targets that are being elucidated can be used for treating the disease in a more efficient manner. These technologies together can lead to specific targets and personalized therapies; ultimately meeting the clinical needs of late-stage cancers in future. Every person in the community should be made aware of the disease and the preventive strategies for it.

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