УДК 633.826:615.322.015.4.03 doi:10.25298/2221-8785-2022-20-2-137-143

ROLE OF HUMAN PAPILLOMAVIRUS GENOTYPE 16 IN PATHOLOGY OF CERVICAL CANCER

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Cervical cancer is the fourth most common malignant neoplasm in women worldwide and the third in Iraq. One of the reasons accounting for this is the human papillomavirus (HPV), which is found in 70% of Iraqis. The present study is aimed at finding the mechanism of pathogenesis which the HPV16 genotype possesses in this disease.

Keywords: *HPV16, genotype, cervical cancer, pathology*

For citation: *Jalil AT, Karevskiy AE. Role of Human Papillomavirus Virus 16 Genotype in Pathology of Cervical Cancer. Journal of the Grodno State Medical University. 2022;20(2):137-143. https://doi.org/10.25298/2221-8785-2022-20-2-137-143.*

Introduction

Cervical cancer (CC) is the third most frequent cancer in women worldwide (15%), and the second most common in developing countries [1]. According to the World Wellbeing Association, around 530000 women are diagnosed with CC each year, with 275000 dying as a result [2]. The major cause of CC is the human papillomavirus, which has been related to the diagnosis of illnesses ranging from benign warts to aggressive malignancy [3]. Despite the fact that more than 80% of women have HPV before the age of 50, only approximately 1% of persistent infections progress to severe cervical cancer. It is uncertain why only certain uterine cervical lesions associated with high-risk genes progress to invasive carcinoma [4].

Despite the well-established association between various HPV types and cancer development, data shows that genetic differences within the same viral genotype may boost infection potential, viral persistence, the formation of precursor lesions, and the progression to invasive carcinoma [5, 6]. Because HPV16 is so common in CC cases, the association between HPV16 and cancer has been explored at the intra-type variation level, and numerous lines of study have connected specific HPV 16 strains to an elevated risk of invasive cervical cancer. HPV variants have been examined to better understand their association with compulsive and carcinogenic characteristics of cervical injuries [7, 8]. Although the factors influencing HPV disease in cervical malignant growth are not completely understood, it is accepted that HPV16 variants play an important role in cervical carcinogenesis and are currently regarded as a significant marker for research on viral transmission, persistence, and cancer-causing nature [8,10]. Variety in these perspectives might add to variations in cervical disease frequency [9]. In general, studies dealing with the role of the HPV16 genotype in the pathogenesis of cancer are insufficient, especially at a genetic and epigenetic level. Therefore, we believe it is necessary to shed more light on HPV16 genotype and the mechanism that makes it more related to CC, and to explore the qualifications it possesses as virulence factors and a replication mechanism that makes it more virulent compared to other types.

Virulence factors of HPV16

The high-risk varieties HPV 16 and 18 are implicated in 70% of cervical cancer cases, according to the well-classified 80 kinds. HPV pathogenicity is predominantly shown by oncoproteins encoded by the E5, E6, and E7 genes, which cause low to high-grade cervical lesions (CIN-1, 2, 3), resulting in 99.68% squamous cell and 88.9% adenocarcinomas cervical cancer worldwide [11, 12]. Furthermore, HPV16 possesses additional virulence factors such L1, L2, E1, E2, and E4 that are linked to the pathogenesis of CC. Furthermore, the sequence of nucleotide alterations, such as single-nucleotide polymorphisms or genetic mutations, inside the L1, LCR, E6, and E7 sections of HPV may determine the HPV type's families, relatedness, and phylogeny [13, 14].

The E1 protein is a viral protein of 73 kDa that is required for viral replication. This protein binds to a particular DNA sequence and forms hexametric complexes with the help of the E2 protein. The helicase activity required for oligomerization is present in the resulting complex [15]. Viruses' E2 protein is also involved in viral DNA replication. It forms a complex with the E1 protein and connects to specific destinations near to the replication origin. The affinity of E1 binding to the replication origin is increased by the adhesion between E2 and E1. E2 binds to mitotic chromosomes as well, and is thought to aid in the precise separation of viral genomes between the two daughter cells [16].

The E4 is derived from the area containing the E1 and E4 ORFs entangled. This protein is mostly produced during the late stages of viral replication. In developing cells, it interacts with the cytoskeleton and replicates. keratinocytes, which is therefore thought to have a role in the collapse of the keratinocyte's cytokeratin filament [17, 19].

The E5 protein appears to have an effect on the epidermal growth factor (EGF) signaling pathway. Internalization of the EGF receptor into endosomes results in the return of a few particles to the cell surface. The E5 binds to the EGF receptor and increases the amount of particles that return to the cell surface, therefore increasing the receptor's intensity on the cell surface. The result is an increase in the number of infected cells [18, 19].

The E6 protein's primary function is to stall and corrupt the tumor suppressor protein p53 via the

protein ligase E6 associated protein. This activity leads in transcriptional suppression of p53's activity and apoptosis inhibition. Nevertheless, E6 induces telomerase, a critical enzyme for maintaining the telomere length of chromosome, which is required for cell escape and long-term cell growth. E6 may cause the death of infected cells to be prolonged [20]. When the early protein E7 attaches to the tumor suppressor protein p105Rb, the tumor suppressor protein's ability to regulate E2F transcription factors is compromised. E7 is also associated with the proteins p107 and p130.These collaborations have the potential to make the world a better place cells are immortalized, and typical, normal reactions to DNA are no longer their damage [21]. E7 also has the capacity to alter the immune system. This capacity begins when E7 binds to the interferon regulatory factor 9 (IRF-9) protein, which is linked to the interferon- (IFN-) signaling pathway, and continues when E7 binds to the interferon regulatory factor 9 (IRF-9) protein. As a result of blocking IRF-9 nuclear translocation, it obstructs the IFN- that has antiviral properties [22]. The two capsid proteins L1 and L2, which are encoded by HPV during the late stages of the virus' life cycle, are essential for viral survival. The genes that code for these two proteins account for approximately 40% of the virus's genome [23, 24] The L1 protein of the Papillomavirus is the most important constructional protein, and it is highly immunogenic, allowing it to insert conformational virus-neutralizing epitopes. Furthermore, it has the potential to be used to detect HPV antibodies in the sera of cancer patients. The L2 protein of HPVs is a small capsid protein that plays a role in the contact of the virus with the cell surface [24], as shown in figure (1).

Effect of HPV16 Genotype Infection on Cervical Intraepithelial Lesions

The vast majority of HPV infections are transitory and go unnoticed for 12–24 months [25, 26]. Furthermore, certain women with persistent infections have a significant risk of developing precancerous cases. According to multiple studies [27, 28], persistent infection with an oncogenic HPV 16 type is the leading risk factor for cervical intraepithelial neoplasia (CIN) ranging from CIN1 to CIN3 and cancer. HPV16 was connected to the greatest risk of CIN formation in the VIVIANE study, followed by HPV18, HPV33, HPV31, and HPV45 [29].

The natural course of CIN lesions varies based on their severity. CIN1 is a squamous intraepithelial lesion of low grade (LSIL). According to research [30], more than 70–80 percent of CIN1 lesions spontaneously shrink or become undetectable without treatment. As a result, CIN1 signifies an infection rather than a stage of disease development. As a result, the appearance of CIN1 after HPV16 infection does not always imply disease progression. Furthermore, obvious clearing may be connected to a failure to detect the sickness. As a result, clearance rates must be regarded with caution [31].

Although both CIN2 and CIN3 are classified as high-grade dysplasia or high-grade squamous intraepithelial lesion (HSIL), CIN2 has a reduced probability of evolving into cancer. In adult women, the yearly regression rate of CIN2 is projected to range from 15% to 23%, with up to 55 percent regressing by 4–6 years [32], whereas about 2% of CIN2 lesions develop to CIN3 during the same time period. CIN3 is a true precancer, with a 0.2 percent to 4% chance of progressing to invasive cancer within a year [33]. During a 30-year period, untreated CIN3 has a 30% probability of becoming invasive cancer, but appropriately treated CIN3 has a 1% chance of becoming invasive cancer [27, 33, 34]. Cervical adenocarcinoma is distinct from squamous cell carcinoma in that it arises from the glandular epithelium of the endocervical canal, with adenocarcinoma in situ as its immediate predecessor (Figure 2). Cervical cancers seldom progress fast since it takes around 20 years from HPV16 infection to the beginning of cervical cancer [35].

The discovery of a link between high-risk HPV strains and the development of cervical cancer aided the acceptance of new screening systems. The WHO and the European Guidelines for Quality Assurance in Cervical Cancer Screening both advocate testing for the presence of high-risk HPV as a screening approach [36]. HPV testing has been demonstrated to be effective in detecting precancerous cervical lesions in population-based cervical screening programs [37]. As a result of the discovery of a causative association between HPV and cervical cancer, as well as a better understanding of the epidemiology and natural history of HPV infection, a new model for cervical carcinogenesis has emerged: HPV acquisition, HPV persistence, precancer progression, and invasion are all aspects that can aid in the development of age-appropriate preventive measures [31, 38].

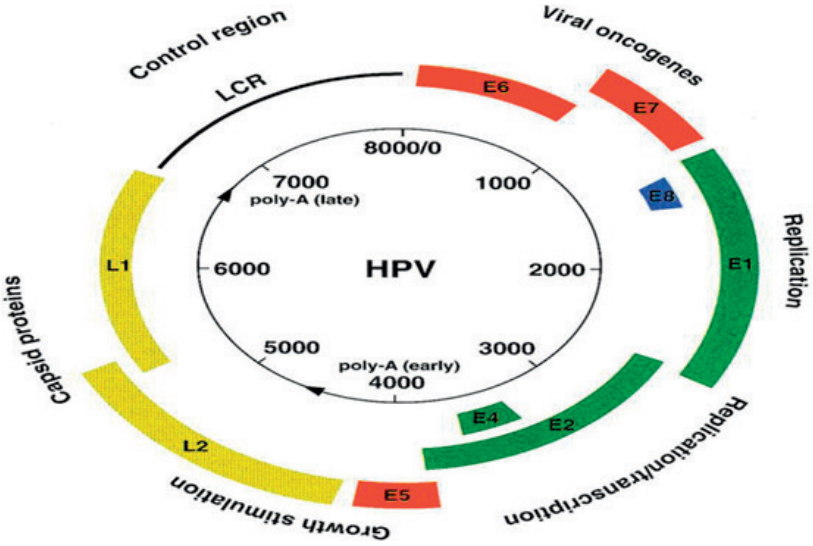

Figure 1. – Genetic map of HPV16 genotype [52]

Following HPV16 Infection, the Pathogenesis of Cervical Cancer Development

Cervical cancerogenesis is a complicated process of uncontrolled cell proliferation that includes HPV gene integration as well as other cellular alterations and epigenetic variables. Under cellular and other environmental circumstances, HPV-infected DNA can be altered, resulting in viral DNA integration and interaction with the host DNA synthesis machinery. Viruses can therefore evade cellular and immune defenses while encouraging cell proliferation and inhibiting apoptosis [31, 39].

The control of viral transcriptional factors determines HPV16's carcinogenic potential. The HPV16 genome may emerge as an unintegrated small DNA molecule known as an episome at the start of a viral infection, resulting in benign and precancerous cervix lesions. In contrast, HPV16 has the potential to integrate its genome into the host genome, which can lead to cervical cancer and cervical intraepithelial neoplasia grade III [40]. The carcinogenic process is aided by viral genome integration in conjunction with dysregulation of the E2 protein, an oncoprotein regulator. These activities cause overexpression of E6 and E7 proteins, which contribute to viral carcinogenesis by altering the cellular apoptotic pathway. E6 and E7 viral genes are found to be integrated into the host genome and expressed in HPV16-positive cells (Figure 2), while E6/E7 overexpression may be lacking in some HPV16-infected cells [40, 41]. According to transgenic mouse model cervical cancer studies, E7 increased proliferation and centrosome copy number, causing the progression of multifocal microinvasive cervical cancers, whereas E6 increased centrosome copy number and eliminated detectable p53 protein, but did not cause neoplasia or cancer. Importantly, combining both oncoproteins resulted in bigger, more invasive tumors and a higher number of centrosomes [42]. Overexpression of E6 and E7 is insufficient to contribute to cancerogenesis since other genetic and epigenetic factors must be generated. E6 interacts with E6-associated binding protein (E6AP), a ubiquitin ligase, causing E6 to change structurally, allowing it to connect to p53, the cell cycle control tumor suppressor protein, to create the E6/E6AP/p53 trimeric complex. This binding causes p53 to be degraded, which leads to cell growth [43].

TP53 gene polymorphisms and HPV16

The P53 protein is known as the genome's guardian and plays an important role in the cellular response to genotoxic stress. This protein also suppresses tumors through a variety of mechanisms, including cell cycle arrest, apoptosis induction, and cellular senescence (Figure 3) [44]. The expression of the p53 protein in cervical intraepithelial lesions and invasive carcinomas has been studied previously. Throughout the cell cycle, the TP53 gene product works as a tumor suppressor, halting it in G1 so that DNA damage may be repaired before DNA replication. [45]. The presence of high-risk HPV16 during the transition from preinvasive lesions to cervical cancer is expected to affect the link between the TP53 Arg72Pro polymorphism and cervical cancer [47]. The HPV16 E6 protein interacts to the p53 tumor suppressor, causing it to be degraded by the 26S proteasome, inactivating it and impairing p53-induced cellular death [44]. The most prevalent P53 genotype in HPV16-associated malignancies, according to Habbous et al., is homozygosis arginine/arginine [47]. This homozygosis was shown to be a risk factor for cervix cancer by the authors, showing that arginine ity especially vulnerable to HPV16 E6-mediated degradation [46]. However, many single-nucleotide polymorphisms in the TP53 gene have been discovered, which are likely to cause different HPV16 E6 sensitivities. Exon 4 codon 72, where arginine is swapped for proline, is the most

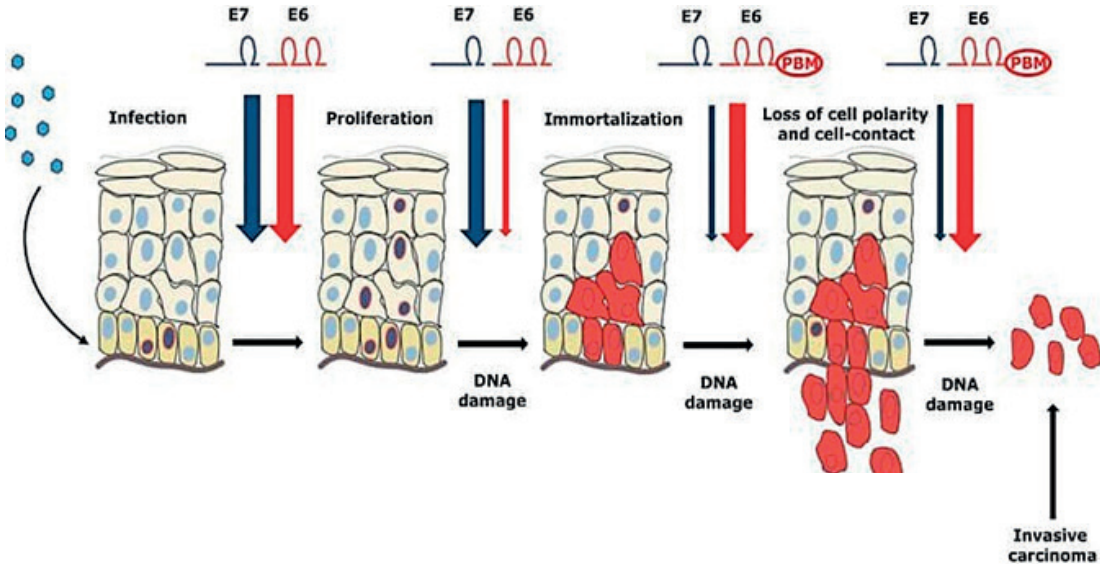

Figure 2. – The interaction of the oncoproteins HPV E6 and E7 is required for HPV-induced malignancy. By targeting pRb, E7 promotes tumor growth and contributes to the early phases of HPV-driven malignancy. E6 is hypothesized to have a role in the latter stages of cancer due to its capacity to target PDZ-domain containing cellular substrates via its C-terminal PDZ-binding motif (PBM) [15].

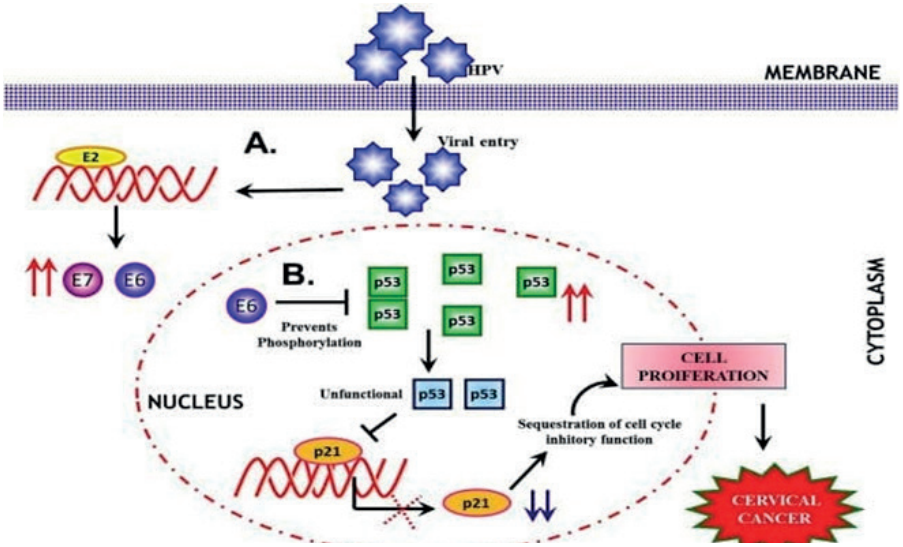

Figure 3. – In cervical cancer, a schematic representation of the interaction of HPV16-E6 with p53 and p21 is shown: A. HPV viruses infect host cervix cells and transcriptionally activate E6 and E7 oncoproteins. B. HPV-E6 oncoprotein then prevents P53 protein phosphorylation, inhibiting its normal function in p21 transactivation. This results in the sequestration of p53's cell cycle inhibitory function, abnormal cell proliferation and initiation, and cervical cancer progression [53]

common polymorphism, resulting in the "Arg72Pro" genotype. Proline-containing variants were shown to be less likely to be degraded by the HPV16 E6 protein than arginine-only variants [47].

IGFIR receptor and HPV16

In a number of malignancies, the insulin-like growth factor 1 receptor (IGF1R) is a tyrosine-kinase receptor that promotes mitogenic, metastatic, and antiapoptotic chara-cteristics. IGF1R has previously been reported as a hypoxia-mediated prognostic biomarker of tumor aggressiveness in cervical cancer [48, 49]. In preneoplastic (1986) and invasive cancer (2002), the proportion of IGFIR expression was greater than in controls. IGF1R may have an early and crucial role in the development of invasive cancer, as evidenced by the enhanced expression reported between preneoplastic and neoplastic tissues [46]. In preneoplastic tissues, it promoted stealthy cell growth and aberrant survival, and it intensified the impact in neoplastic tissues [48]. Furthermore, Zacapala-Gómez et al. claimed that IGF1R overexpression was caused by the expression of E6 mutations AA-c and E-G350 [49]. As a result, the persistent HPV16 coinfection in this case might have had a direct role in the IGF1R dysregulation. IGF1R has previously been linked to cellular radio-resistance in cervical carcinoma; Moreno-Acosta et al., 2012 discovered that IGF1R overexpression is a predictive marker for patients undergoing radiotherapy who have HPV16 (+), with overexpression conferring a 28.6-fold increased risk of treatment failure [50].

hTERT expression and HPV16

In preneoplastic lesions and cervical cancer, human telomerase reverse transcriptase (hTERT) was discovered to be expressed in both the nucleus and the cytoplasm. The expression of the hTERT protein has been studied in chronic cervicitis, intraepithelial neoplasms, and invasive cervical cancer in several publications. The expression of hTERT increases as cervical illness advances [51]. HPV16 E6 causes the cellular tumor suppressor protein p53 to be degraded, hTERT activity to be activated, and cervical carcinogenesis to occur. Apoptosis prevention, gene transcription, and cell proliferation are all regulated by non-regular activities. This increase might play a significant role in the HPV16 viral life cycle, as well as cell immortalization and malignant transformation [48, 52].

Conclusion

The current study showed a clear association between HPV16 and cervical cancer because it has many virulence factors, the most important of which are E6 and E7. This virus has an elaborate mechanism of inhibiting anti-cancer genes and stimulating cancer-promoting genes by entering and linking with cell genes. On the other hand, we noticed through our review of previous studies that HPV16 is the most virulent, adding to its stimulus to the development of cancer with a shorter period than the rest of the HPV genotypes. Moreover, despite the attempts of studies to reach the pathological mechanism possessed by this virus, many reasons remain vague, meaning that HPV16 may have other mechanisms that make it more virulent.

References

1. International Collaboration of Epidemiological Studies of Cervical Cancer; Appleby P, Beral V, Berrington de González A, Colin D, Franceschi S, Goodhill A, Green J, Peto J, Plummer M, Sweetland S. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet.* 2007;370(9599):1609-1621. doi: 10.1016/S0140-6736(07)61684-5.
2. Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, Ferlay J. Worldwide burden of cervical cancer in 2008. *Ann Oncol.* 2011;22(12):2675-2686. doi: 10.1093/annonc/mdr015.
3. Saxena U, Sauvaget C, Sankaranarayanan R. Evidence-based screening, early diagnosis and treatment strategy of cervical cancer for national policy in low-resource countries: example of India. *Asian Pac J Cancer Prev.* 2012;13(4):1699-1703. doi: 10.7314/apjcp.2012.13.4.1699.

4. Hang D, Yin Y, Han J, Jiang J, Ma H, Xie S, Feng X, Zhang K, Hu Z, Shen H, Clifford GM, Dai M, Li N. Analysis of human papillomavirus 16 variants and risk for cervical cancer in Chinese population. *Virology*. 2016;488:156-161. doi: 10.1016/j.virol.2015.11.016.
5. da Silva RL, da Silva Batista Z, Bastos GR, Cunha APA, Figueiredo FV, de Castro LO, Dos Anjos Pereira L, da Silva MACN, Vidal FCB, Barros MC, da Costa Fraga E, Brito LMO, do Carmo Lacerda Barbosa M, Moreira MÂM, do Desterro Soares Brandão Nascimento M. Role of HPV 16 variants among cervical carcinoma samples from Northeastern Brazil. *BMC Womens Health*. 2020;20(1):162. doi: 10.1186/s12905-020-01035-0.
6. Vidal JP, Felix SP, Chaves CB, Patury P, Franco VF, de Morais EA, de Carvalho NA, Carvalho AC, Almeida Neto OF, Vieira LM, Correa FM, Martins LF, Negrão A, de Almeida LM, Moreira MA. Genetic diversity of HPV16 and HPV18 in Brazilian patients with invasive cervical cancer. *J Med Virol*. 2016;88(7):1279-1287. doi: 10.1002/jmv.24458.
7. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. *Rev Med Virol*. 2015;25(Suppl 1):2-23. doi: 10.1002/rmv.1822.
8. Borbély ÁA, Murvai M, Kónya J, Beck Z, Gergely L, Li F, Veress G. Effects of human papillomavirus Type 16 oncoproteins on survivin gene expression. *J Gen Virol*. 2006;87(Pt 2):287-294. doi: 10.1099/vir.0.81067-0.
9. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Mäenpää J, Andrijono A, Purwoto G, Maheshwari A, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynecol Obstet*. 2019;145(1):129-135. doi: 10.1002/ijgo.12749.
10. Burk RD, Harari A, Chen Z. Human papillomavirus genome variants. *Virology*. 2013;445(1-2):232-243. doi: 10.1016/j.virol.2013.07.018.
11. Volpini LPB, Boldrini NAT, de Freitas LB, Miranda AE, Spano LC. The high prevalence of HPV and HPV16 European variants in cervical and anal samples of HIV-seropositive women with normal pap test results. *PLoS One* 2017;12(4):e0176422. doi: 10.1371/journal.pone.0176422.
12. Tan G, Duan M, Li Y, Zhang N, Zhang W, Li B, Qu P. Distribution of HPV 16 E6 gene variants in screening women and its associations with cervical lesions progression. *Virus Res*. 2019;273:197740. doi: 10.1016/j.virusres.2019.197740.
13. Altekruse SF, Lacey JV Jr, Brinton LA, Gravitt PE, Silverberg SG, Barnes WA Jr, Greenberg MD, Hadjimichael OC, McGowan L, Mortel R, Schwartz PE, Hildesheim A. Comparison of human papillomavirus genotypes, sexual, and reproductive risk factors of cervical adenocarcinoma and squamous cell carcinoma: Northeastern United States. *Am J Obstet Gynecol*. 2003;188(3):657-663. doi: 10.1067/mob.2003.132.
14. Rogers A, Waltke M, Angeletti PC. Evolutionary variation of papillomavirus E2 protein and E2 binding sites. *Virol J.* 2011;8:379. doi: 10.1186/1743-422X-8-379.
15. Thomas M, Narayan N, Pim D, Tomaić V, Massimi P, Nagasaka K, Kranjec C, Gammoh N, Banks L. Human papillomaviruses, cervical cancer and cell polarity. *Oncogene*. 2008;27(55):7018-7030. doi: 10.1038/onc.2008.351.
16. Chin MT, Hirochika R, Hirochika H, Broker TR, Chow LT. Regulation of human papillomavirus type 11 enhancer and E6 promoter by activating and repressing proteins from the E2 open reading frame: functional and biochemical studies. *J Virol*. 1988;62(8):2994-3002. doi: 10.1128/JVI.62.8.2994-3002.1988.
17. Lakspere T, Tynell J, Kaloinen M, Vanlede M, Parsons A, Ikonen N, Kallio-Kokko H, Kantele A, Mattila P, Almusa H, Julkunen I. Full-genome sequences of influenza A (H1N1) pdm09 viruses isolated from Finnish patients from 2009 to 2013. *Genome Announcs*. 2014;2(1):e01004-01013. doi: 10.1128/genomeA.01004-13.
18. Howie HL, Katzenellenbogen RA, Galloway DA. Papillomavirus E6 proteins. *Virology*. 2009;384(2):324-334. doi: 10.1016/j.virol.2008.11.017.
19. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus res*. 2002;89(2):213-228. doi: 10.1016/s0168-1702(02)00190-9.
20. Galloway DA, Laimins LA. Human papillomaviruses: Shared and distinct pathways for pathogenesis. *Curr Opin Virol*. 2015;14:87-92. doi: 10.1016/j.coviro.2015.09.001.
21. Comparetto C, Borruto F. Human Papillomavirus Infection: Overview. In: Smith HB, ed. *Handbook on human papillomavirus: prevalence, detection and management*. New York: Nova Science Publishers; 2013. Ch. 1; p. 1-137.
22. Chowdhury SM. *Graphene nanoribbons elicit cell specific uptake and drug delivery via activation of epidermal growth factor receptors* [doctoral dissertation]. New York: State University of New York at Stony Brook; 2014.
23. Wold WS, Ison MG. Adenovirus. In: Knipe DM, Howley P. *Fields Virology*. 6th ed. Lippincott, Williams & Wilkins; 2013. p. 1732-1767.
24. Fiorucci G, Chiantore MV, Mangino G, Romeo G. MicroRNAs in virus-induced tumorigenesis and IFN system. *Cytokine Growth Factor Rev*. 2015;26(2):183-194. doi: 10.1016/j.cytogfr.2014.11.002.
25. Insinga RP, Dasbach EJ, Elbasha EH, Liaw K-L, Barr E. Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women. *Infect Agent Cancer*. 2007;2:15. doi: 10.1186/1750-9378-2-15.
26. Brianti P, De Flammineis E, Mercuri SR. Review of HPV-related diseases and cancers. *New Microbiol*. 2017;40(2):80-85.
27. Stanley M. Pathology and epidemiology of HPV infection in females. *Gynecol Oncol*. 2010;117(2 Suppl):S5-10. doi: 10.1016/j.ygyno.2010.01.024.
28. Mirabello L, Clarke MA, Nelson CW, Dean M, Wentzensen N, Yeager M, Cullen M, Boland JF, Schiffman M, Burk RD; NCI HPV Workshop. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. *Viruses.* 2018;10(2):80. doi: 10.3390/v10020080.
29. Skinner SR, Wheeler CM, Romanowski B, Castellsagué X, Lazcano-Ponce E, Del Rosario-Raymundo MR, Vallejos C, Minkina G, Pereira Da Silva D, McNeil S, Prilepskaya V, Gogotadze I, Money D, Garland SM, Romanenko V, Harper DM, Levin MJ, Chatterjee A, Geeraerts B, Struyf F, Dubin G, Bozonnat MC, Rosillon D, Baril L; VIVIANE Study Group. Progression of HPV infection to detectable cervical lesions or clearance in adult women: analysis of the control arm of the VIVIANE study. *Int J Cancer*. 2016;138(10):2428-2438. doi: 10.1002/ijc.29971.
30. Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infect Dis*. 2009;9:119.

doi: 10.1186/1471-2334-9-119.
31. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination – Review of Current Perspectives. *J Oncol*. 2019;2019:3257939. doi: 10.1155/2019/3257939.
32. Rositch AF, Burke AE, Viscidi RP, Silver MI, Chang K, Gravitt PE. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. *Cancer Res*. 2012;72(23):6183-6190. doi: 10.1158/0008-5472.CAN-12-2635.
33. Gravitt PE, Rositch AF, Silver MI, Marks MA, Chang K, Burke AE, Viscidi RP. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. *J Infect Dis*. 2013;207(2):272-280. doi: 10.1093/infdis/jis660.
34. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, Skegg DC. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9(5):425-434. doi: 10.1016/S1470-2045(08)70103-7.
35. Rodríguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, Solomon D, Burk R; Proyecto Epidemiológico Guanacaste Group. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst*. 2008;100(7):513-517. doi: 10.1093/jnci/djn044.
36. World Health Organization. *Comprehensive Cervical Cancer Control: A Guide to Essential Practice*. 2nd ed. Geneva, Switzerland; 2014. 364 p.
37. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ; International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383(9916):524-532. doi: 10.1016/S0140-6736(13)62218-7.
38. Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst*. 2010;102(19):1478-1488. doi: 10.1093/jnci/djq356.
39. Hong D, Ye F, Lu W, Hu Y, Wan X, Chen Y, Xie X. Methylation status of the long control region of HPV 16 in clinical cervical specimens. *Mol Med Rep*. 2008;1(4):555-560.
40. Lehoux M, D'Abramo CM, Archambault J. Molecular mechanisms of human papillomavirus-induced carcinogenesis. *Public Health Genomics*. 2009;12(5-6):268-280. doi: 10.1159/000214918.
41. Jing Y, Wang T, Chen Z, Ding X, Xu J, Mu X, Cao M, Chen H. Phylogeny and polymorphism in the long control regions E6, E7, and L1 of HPV Type 56 in women from southwest China. *Mol Med Rep*. 2018;17(5):7131-7141. doi: 10.3892/mmr.2018.8743.
42. Thomas MC, Chiang C-M. E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. *Mol Cell*. 2005;17(2):251-264. doi: 10.1016/j.molcel.2004.12.016.
43. Riley RR, Duensing S, Brake T, Münger K, Lambert PF, Arbeit JM. Dissection of human papillomavirus E6 and E7 function in transgenic mouse models of cervical carcinogenesis. *Cancer Res*. 2003;63(16):4862-4871.
44. Hoste G, Vossaert K, Poppe WA. The Clinical Role of HPV Testing in Primary and Secondary Cervical Cancer Screening. *Obstet Gynecol Int*. 2013;2013:610373. doi: 10.1155/2013/610373.
45. Tjalma WA, Van Waes TR, Van den Eeden LE, Bogers JJ. Role of human papillomavirus in the carcinogenesis of squamous cell carcinoma and adenocarcinoma of the cervix. *Best Pract Res Clin Obstet Gynaecol*. 2005;19(4):469-483. doi: 10.1016/j.bpobgyn.2005.02.002.
46. Moreno-Acosta P, Romero-Rojas A, Vial N, Huertas A, Acosta J, Mayorga D, Carrillo S, Molano M, Gamboa O, Cotes M, Casadiego C, Vallard A, Magne N. Persistent High-Risk HPV Infection and Molecular Changes Related to the Development of Cervical Cancer. *Case Rep Obstet Gynecol*. 2020;2020:6806857. doi: 10.1155/2020/6806857.
47. Habbous S, Pang V, Eng L, Xu W, Kurtz G, Liu FF, Mackay H, Amir E, Liu G. P53 Arg72Pro polymorphism, HPV status and initiation, progression, and development of cervical cancer: a systematic review and meta-analysis. *Clin Cancer Res*. 2012;18(23):6407-6415. doi: 10.1158/1078-0432.CCR-12-1983.
48. Huang Y-F, Shen M-R, Hsu K-F, Cheng Y-M, Chou C-Y. Clinical implications of insulin-like growth factor 1 system in early-stage cervical cancer. *Br J Cancer*. 2008;99(7):1096-1102. doi: 10.1038/sj.bjc.6604661.
49. Zacapala-Gómez AE, Del Moral-Hernández O, Villegas-Sepúlveda N, Hidalgo-Miranda A, Romero-Córdoba SL, Beltrán-Anaya FO, Leyva-Vázquez MA, Alarcón-Romero Ldel C, Illades-Aguiar B. Changes in global gene expression profiles induced by HPV 16 E6 oncoprotein variants in cervical carcinoma C33-A cells. *Virology*. 2016;488:187-195. doi: 10.1016/j.virol.2015.11.017.
50. Moreno-Acosta P, Gamboa O, Sanchez de Gomez M, Cendales R, Diaz GD, Romero A, Balart Serra J, Conrado Z, Levy A, Chargari C, Magné N. IGF1R gene expression as a predictive marker of response to ionizing radiation for patients with locally advanced HPV16-positive cervical cancer. *Anticancer Res*. 2012;32(10):4319-4325.
51. Cheah PL, Looi LM, Ng MH, Sivanesaratnam V. Telomerase activation and human papillomavirus infection in invasive uterine cervical carcinoma in a set of Malaysian patients. *J Clin Pathol*. 2002;55(1):22-26. doi: 10.1136/jcp.55.1.22.
52. Jawanjal P, Salhan S, Dhawan I, Rath G. Comparative analysis of p53 and p21 proteins in normal cervix and HPV associated precancerous and cancerous lesions of cervix. *J Anat Soc India*. 2015;64(1):3-11. https://doi.org/10.1016/j.jasi.2015.05.001.
53. Sağnıç, S. Human Papillomavirus and Cervical Cancer. In: Rajkumar, R., editor. Cervical Cancer - A Global Public Health Treatise [Internet]. London: IntechOpen; 2021 [cited 2022 Mar 30]. Available from: https://www.intechopen.com/chapters/77729 doi: 10.5772/intechopen.98490.

РОЛЬ ГЕНОТИПА ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА 16 В ПАТОЛОГИИ РАКА ШЕЙКИ МАТКИ

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Рак шейки матки является четвертым по частоте злокачественным новообразованием у женщин во всем мире и третьим в Ираке. Одной из причин этого является вирус папилломы человека (ВПЧ), который обнаруживается у 70% жителей Ирака. Настоящее исследование направлено на поиск механизма патогенеза, которым обладает генотип ВПЧ16, при данном заболевании.

***Ключевые слова**: ВПЧ16, генотип, рак шейки матки, патология.*

***Для цитирования:** Джалил, А. Т. Роль генотипа вируса папилломы человека 16 в патологии рака шейки матки / А. Т. Джалил, А. Е. Каревский // Журнал Гродненского государственного медицинского университета. 2022. Т. 20, № 2. С. 137-143. https://doi.org/10.25298/2221-8785-2022-20-2-137-143.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Conflict of interest. The authors declare no conflict of interest.

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Поступила / Received: 04.01.2022 *Принята к публикации / Accepted for publication: 22.03.2022*

Королева, Елена Григорьевна. Психические расстройства при соматических заболеваниях : пособие для студентов учреждений высшего образования, обучающихся по специальности 1-79 01 05 "Медико-психологическое дело" : рекомендовано учебно-методическим объединением по высшему медицинскому, фармацевтическому образованию / Е. Г. Королёва ; Министерство здравоохранения Республики Беларусь, Учреждение образования "Гродненский государственный медицинский университет", Кафедра медицинской психологии и психотерапии. – Гродно : ГрГМУ, 2021. – 175 с. – ISBN 978-985-595-604-5.

В данном пособии освещаются виды психических расстройств, которые могут иметь место при различных соматических заболеваниях, описывается их патогенез и основные терапевтические подходы при них. Дана постановка диагнозов по МКБ-10 при различных психических расстройствах при соматических заболеваниях.

Пособие предназначено для студентов медико-психологического факультета (специальность 1-79 01 05 "Медико-психологическое дело").