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Genetic Susceptibility of Cervical Cancer

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Abstract:

Fifteen human papillomaviruses (HPVs) cause cervical cancer with a high risk of infection. Although genital HPV infections are common in young women, the majority of infections resolve spontaneously. Variations in host genes involved in immune response pathways may affect the outcome of HPV infection and cervical cancer in high-risk individuals. The findings of preclinical studies have revealed associations between genetic variants in many susceptibility loci for cervical malignant transformation and the development of the disease. However, many of these accounts are contradictory. Since conflicting findings have been reported across populations, well-designed global collaborative research is necessary to establish the consistency of the connections, paving the way for a more precise definition of patients at high risk of developing cervical cancer.

Keywords **—Cervical cancer, genome-wide association studies, human papillomaviruses**

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I. INTRODUCTION

Cervical cancer has been one of the most frequent cancers in women. High-risk human papillomaviruses (HPVs) is the main requisite which causes cervical cancer (1). HPV consists of 2 types in total which is the low-risk and the high-risk types. HPVs that usually pose cervical cancer is the high risk one from an epidemiological survey it has 15 genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) (2). Among all of these genotypes the most found detected in cervical cancer patients is HV16 moreover according to a prospective cohort study it was also the most pertinacious HPV type during infection with HPVs. It might also be related to head and neck squamous cell carcinomas (3-5).The HPV16 structure is double-stranded 7,908 bp molecule and there are three regions: the early region consists of the E1 and E2 (6-8). The replication of viral protein also requires these proteins. The late region, including L1 and L2; and the long control region (LCR), that is consists of controlling transcription and replication sequences (9, 10). AT-rich sequence would be recognized and bonded by the protein E1 within the viral DNA origin of replication in cooperation with the E2 protein and the complex composed of the E1 and E2 proteins then binds to the viral origin of replication with high affinity and starting DNA replication via the E1 ATP-dependent helicase domain(11, 12). From the studies it indicated that different regions and ethnicities show different diffusion of HPV16 variants (13, 14). The aim of this review is to identify gene mutations that are involved in an increasing risk of cervical cancer. in order to detect it beforehand so it could help promoting therapeutic success of cervical cancer treatment.

II. CERVICAL CANCER

At least 200 HPV types have been identified, however, not many are genuinely carcinogenic and are listed as high-risk HPV types, consisting of the well-known HPV-16 and HPV-18, which are associated with squamous cell carcinomas (15-17). Moreover, E6 and E7 which are encoded by the HPV promote cellular proliferation, inhibit the death of cells, and inhibit cell cycle arrest

mechanisms which in result are involved in the formation of cancer(18, 19). These mechanisms either accelerate cell division or impair the normal regulation of the cell-cycle progression system, resulting in uncontrolled cell growth and, potentially, cancer (20). Despite the high prevalence of HPV infection in squamous cell carcinomas, study results indicate that infection with only HPV is insufficient to induce cancer (21, 22). Indeed, most HPV infections are asymptomatic and resolve spontaneously within a year, with 90 percent naturally resolving within two years (23, 24). Precancerous growths do not occur frequently: only a tiny percentage of cases show persistent viral infections, which result in the development of epithelial lesions and thus raise the risk of cancer but are not definite cancer indicators. HPV-positive cancers are found in younger patient populations and have been indicated to lead to a better survival rate (25-27). Numerous previous studies have linked improved the percentage of survival to younger ages and less tobacco and alcohol use, thereby discounting the importance of HPV as a prognostic factor (28-30). Nevertheless, some studies refute the mentioned method, demonstrating that prognosis differences persist even after adjusting for prognostic factors such as age, smoking, and alcohol consumption (31).

The method that HPV targets genes that are fatal in order to generate various cancers has been suggested by this study imitates which is similar to an effect from somatic driver mutations (32, 33). Because this group of genes might vary from the usual drivers in HPV-negative cases, be aware that the corresponding set of genes could be different (33). The hypothesis above implies that it must be associated with specific somatic driver mutations in order for an HPV infection to cause cancer (34, 35). On the other hand, an HPV infection by itself is insufficient, as HPV does not cause cancer through all the somatic driver mutations needed (36). Because HPV infection can serve as a long-term substitute for somatic mutation accumulation, it cuts down on the number of driver mutations required to induce cancer for HPV-positive patients (37-39). This also implies that the mimicking effect is weaker than the random set of somatic driver mutations effect on a carcinogenic effects necessary, which may help explain the observation that HPV-positive cancer patients usually have better prognosis.

III. MUTATION OF GENES

Unfortunately, the development of cervical cancer cannot always be attributed to HPV, as 70% to 90% of individuals can clear the virus from their bodies after twelve to twenty-four months of initial diagnosis, and intervention is not necessary (40-42). Familial aggregation in the occurrence of cervical cancer has been demonstrated to exist and involves strong, intermediate, and mild familial associations (43-45). Because of this, it's crucial to perform molecular epidemiological studies in order to find the host genetic elements and identify the patient subset that are associated with the increasing rate of carcinogenesis in cervical cancer, which will help maximise the overall effectiveness of cervical cancer prevention strategies (46).

A. Interleukin-1B gene (IL-1B)

This protein, which is known as IL-1β, is involved in the innate immune system's inflammatory response. Several studies have proven that IL-1β is essential in developing cervical cancer. [1, 2]. Cervical cancer incidence was shown to be elevated among patients whose plasma IL-1β rates were about 75% or more quartile in controls (1.74 times as common) (47-50). It appears that polymorphisms in the regulatory regions of the interleukin-1B gene contribute to variation in IL-1B levels between individuals, which appear to be dependent on functional variation (48, 51). In the case of C-511T (rs16944), multiple case-control studies were performed to determine whether the IL-1B promoter SNP C-511T (rs16944) is associated with the development of cervical cancer. It has been proved that cervical cancer susceptibility is increased because of the IL-1B-511T along with -31C alleles, especially in subjects with high levels of IL-1β(49**,** 52-54)**.**

B. Tumor necrosis factor A gene (TNFA)

Another potent pro-inflammatory cytokine known as TNF-, encoded by the *TNFA* gene and

produced by the TNFA protein is associated with the management of HPV infection (55). Many of the cervical cancer cell lines and patient washing fluid that were tested had elevated TNF-α levels. It is believed that TNF- controls HPV infection by induction of apoptosis in cells that have been infected with HPV, halting the growth of infected keratinocytes, and down-regulating HPV transcription in HPV-infected keratinocytes (56, 57). The TNF-α-308A variant in the promoter region has been one of the keys focuses of most published studies on *TNFA* polymorphisms (58-60). Others, however, found no evidence to support the hypothesis that individuals with the GA/AA genotype were at elevated risk of cervical cancer (58).

C. Human leukocyte antigen genes (HLA)

HLA is necessary for the presentation of viral antigens. The activity of the HLA molecule appears to be a crucial factor in the induction of an adaptive immune response (61). In the development of cervical cancer, HLA polymorphisms are believed to play a role in HPV control because of their function in the immune system (62, 63). A variety of case-control studies have found links between particular HLA alleles and the risk of cervical cancer (64-66). In a meta-analysis, Yang et al. found that seven alleles (HLA DRB1*0403, *0405, *0407, *0701, *1501, *1502, and *1503) were closely linked with cervical squamous cell carcinoma, while four additional alleles (HLA DRB1*0901, *1301, *1302, and *1602) were negatively related (67). A heterodimer composed of interleukin-12A (IL12A) and interleukin-12B (IL12B) is an inflammatory cytokine constructed between 35,000 p35 lights (known as IL12A) and 40,000 p40 heavy chains (known as IL12B), which stimulates interferon β (IFN-β) production (68). Aside from its antiviral properties, IL-12 is important for the person's resistance to carcinogenesis (68).

D. Interleukin-10 gene (IL-10)

Studies have documented a pattern of increased Th2 and decreased Th1 cytokine . Innate and Th2 immunity functions are stimulated by IL-10, but an immunological response by Th1 is suppressed (69, 70). Increased IL-10 serum levels have an effect on both the progression and chance of generating cervical cancer in women with CIN and cervical cancer and cervical cancer (71, 72). The IL-10 promoter has identified three polymorphisms, at positions -1082, -819 and -592. GG is associated with a high level of IL-10, and a single nucleotide polymorphism (SNP) (-1082) is significant in cytokine production (71).

E. Cytotoxic T-lymphocyte antigen-4 gene (CTLA-4)

A CTLA4 gene located on chromosome 2q33 encodes a receptor that is used by activated T cells (73). SNPs in CTLA4 have been shown to increase the risk of developing autoimmune disease and cancer. A polymorphism in the CTLA4 gene at position 49 caused by a single amino acid substitution at the end of the receptor's leading peptide results in a Thr to Ala change in the receptor's CTLA4 protein. Recombinant CTLA4-17Ala was found to inhibit T-cell proliferation and activation significantly better than CTLA4-17Thr in a recent study (74). A molecular epidemiological study found that CTLA4 G49A was significantly linked with the risk of developing a range of different types of cancer. Despite numerous studies which have looked into the connection between the CTLA4 G49A variant and the risk of cervical cancer, no significant associations have been found or were ever found risk of developing this disease (75-77).

F. p53

p53 protects the human genome's integrity by regulating cell cycle arrest, DNA repair, and apoptosis. HPV oncoprotein E6 is described as being able to degrade p53 in the ubicitin pathway leading to chromosomal instability and cellular malignancy (78, 79). Codon 72 of p53 is a well-known common SNP, with two alleles encrypting either arginine or proline (80). According to Storey et al. HPV-associated cervical carcinogenesis individuals homozygous to P53Arg are seven times more susceptible to heterozygotes, numerous groups examined the effect of p53 codon 72 polymorphism on cervical cancer risk (81).

Additional subgroup analyses revealed that only three of the eleven studies mentioned above reported excess risks (82, 83).

G. Breast cancer susceptibility gene 1 (BRCA1) and BRCA1-associated ring domain protein 1 (BARD1) gene

BRCA1 (also known as the E6 and E7 oncoproteins) was found to be related directly with and functionally antagonise E6 and E7 oncoproteins, indirectly inhibiting BRCA1-dependent p53 transcription (84). An established hypothesis about the formation of a BRCA1-BARD1 complex has been advanced, and it has been discovered that BRCA1 and BARD1 interact to form a stable BRCA1-BARD1 complex in the nucleus (85). BRCA1 and BARD1 have also been found to interact to cause E6 inactivation and to keep p53 in a steady state. We undertook a case-control study in which we typed the BRCA1 Pro871Leu (rs799917) and BARD1 Pro24Ser (rs1048108) and discovered in a recessive genetic model, people with the TT genotype of the BRCA1 SNP rs799917 had a 62% lower risk of developing cervical cancer (86-88).

H. ESR1

When other growth factors (such as estrogen) are present, ESR1 binds and activates itself as a transcription factor, and it associates with numerous other genes to produce a change in their expression levels (89). Many previous genome-wide breast cancer studies have discovered numerous ESR1 mutations in metastatic kinds of the disease (90). Echoing previous findings, subsequent studies confirmed and, in some cases, dramatically increased the resistance of ESR1-mutated samples to aromatase inhibitors (91). Endometrial and colorectal cancer have also been found to have rare variants in ESR1 (92). Cervical cancer shares genetic aberrations with breast cancer, including frequent mutations in the PIK3CA, TP53, PTEN, and ARID1A genes, and these aberrations are also connected to increased levels of oestrogen in the body. Moreover, increased levels of oestrogen can impact the development of both breast and cervical cancer (93). According to these similarities, it appears that cervical cancer may harbour the ESR1 mutations, as well (94). The preliminary investigation sought to verify the theory that distinct forms of cervical cancer display different frequencies of ESR1 mutations. The analysis of 207 cervical squamous cell carcinoma (CCa) samples showed the presence of three heterozygous missense ESR1 mutations, whereas no mutations were found in the 27 adenosquamous carcinomas (ACCa) or 26 adenocarcinomas (ACCa) samples (93, 94). The identified ESR1 mutations may prove to be of predictive value, and this may enable researchers to obtain insight into the diagnosis and molecular treatment of cervical cancer.

CONCLUSIONS

Cervical cancer is a condition in which malignant cells develop in the cervix's tissues. The vast majority of cases are caused by long-term infections with specific types of HPVs. Cervical cancer has been linked to genetic changes in several classes of genes. This new understanding gained from genetic susceptibility studies may pave the way for new methods of predicting whether a tumour will respond to targeted therapy and immunotherapy treatment.

REFERENCES

1. Yao Y, Yan Z, Dai S, Li C, Yang L, Liu S, et al. Human Papillomavirus Type 16 E1 Mutations Associated with Cervical Cancer in a Han Chinese Population. International journal of medical sciences. 2019;16(7):1042.
2. Muñoz N, Bosch FX, De Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. New England journal of medicine. 2003;348(6):518-27.
3. Jalil AT, Kadhum WR, Khan MUF, Karevskiy A, Hanan ZK, Suksatan W, et al. Cancer stages and demographical study of HPV16 in gene L2 isolated from cervical cancer in Dhi-Qar province, Iraq. Applied Nanoscience. 2021:1-7.
4. Cai H, Zhang P, Xu M, Yan L, Liu N, Wu X. Circular RNA hsa_circ_0000263 participates in cervical cancer development by regulating target gene of miR‐150‐5p. Journal of cellular physiology. 2019;234(7):11391-400.
5. Xu W, Xu M, Wang L, Zhou W, Xiang R, Shi Y, et al. Integrative analysis of DNA methylation and gene expression identified cervical cancer-specific diagnostic biomarkers. Signal transduction and targeted therapy. 2019;4(1):1-11.
6. Valencia-Reséndiz DG, Palomino-Vizcaino G, Tapia-Vieyra JV, Benítez-Hess ML, Leija-Montoya AG, Alvarez-Salas LM. Inhibition of human papillomavirus type 16 infection using an RNA aptamer. nucleic acid therapeutics. 2018;28(2):97-105.
7. Landaverde L, Wong W, Hernandez G, Fan A, Klapperich C. Method for the elucidation of LAMP products captured on lateral flow strips in a point of care test for HPV 16. Analytical and bioanalytical chemistry. 2020;412:6199-209.

8. Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, et al. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science. 2018;360(6387):436-9.
9. Hindmarsh PL, Laimins LA. Mechanisms regulating expression of the HPV 31 L1 and L2 capsid proteins and pseudovirion entry. Virology Journal. 2007;4(1):1-12.
10. Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. Virology. 1991;185(1):251-7.
11. Bergvall M, Melendy T, Archambault J. The E1 proteins. Virology. 2013;445(1-2):35-56.
12. McBride AA, Warburton A. The role of integration in oncogenic progression of HPV-associated cancers. PLoS pathogens. 2017;13(4):e1006211.
13. Piirsoo A, Piirsoo M, Kala M, Sankovski E, Lototskaja E, Levin V, et al. Activity of CK2α protein kinase is required for efficient replication of some HPV types. PLoS pathogens. 2019;15(5):e1007788.
14. Amaro-Filho SM, Chaves CBP, Felix SP, Basto DL, de Almeida LM, Moreira MAM. HPV DNA methylation at the early promoter and E1/E2 integrity: A comparison between HPV16, HPV18 and HPV45 in cervical cancer. Papillomavirus Research. 2018;5:172-9.
15. Parker KH, Kemp TJ, Pan Y, Yang Z, Giuliano AR, Pinto LA. Evaluation of HPV-16 and HPV-18 specific antibody measurements in saliva collected in oral rinses and merocel® sponges. Vaccine. 2018;36(19):2705-11.
16. Chen X, Zhang P, Chen S, Zhu H, Wang K, Ye L, et al. Better or Worse? The Independent Prognostic Role of HPV-16 or HPV-18 Positivity in Patients With Cervical Cancer: A Meta-Analysis and Systematic Review. Frontiers in oncology. 2020;10:1733.
17. Torres-Ibarra L, Cuzick J, Lorincz AT, Spiegelman D, Lazcano-Ponce E, Franco EL, et al. Comparison of HPV-16 and HPV-18 Genotyping and Cytological Testing as Triage Testing Within Human Papillomavirus–Based Screening in Mexico. JAMA network open. 2019;2(11):e1915781-e.
18. Yim E-K, Park J-S. The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis. Cancer research and treatment: official journal of Korean Cancer Association. 2005;37(6):319.
19. Almeida AM, Queiroz JA, Sousa F, Sousa Â. Cervical cancer and HPV infection: ongoing therapeutic research to counteract the action of E6 and E7 oncoproteins. Drug discovery today. 2019;24(10):2044-57.
20. Poirson J, Biquand E, Straub ML, Cassonnet P, Nominé Y, Jones L, et al. Mapping the interactome of HPV E6 and E7 oncoproteins with the ubiquitin‐proteasome system. Wiley Online Library; 2017.
21. Farsi NJ, Rousseau M-C, Schlecht N, Castonguay G, Allison P, Nguyen-Tan PF, et al. Aetiological heterogeneity of head and neck squamous cell carcinomas: the role of human papillomavirus infections, smoking and alcohol. Carcinogenesis. 2017;38(12):1188-95.
22. Franzen A, Vogt TJ, Müller T, Dietrich J, Schröck A, Golletz C, et al. PD-L1 (CD274) and PD-L2 (PDCD1LG2) promoter methylation is associated with HPV infection and transcriptional repression in head and neck squamous cell carcinomas. Oncotarget. 2018;9(1):641.
23. Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. EClinicalMedicine. 2020;22:100293.
24. Huber J, Mueller A, Sailer M, Regidor P-A. Human papillomavirus persistence or clearance after infection in reproductive age. What is the status? Review of the literature and new data of a vaginal gel containing silicate dioxide, citric acid, and selenite. Women's Health. 2021;17:17455065211020702.
25. Rakislova N, Alemany L, Clavero O, Del Pino M, Saco A, Quirós B, et al. Differentiated vulvar intraepithelial neoplasia-like and lichen sclerosus-like lesions in HPV-associated squamous cell carcinomas of the vulva. The American journal of surgical pathology. 2018;42(6):828-35.
26. Li W, Tian S, Wang P, Zang Y, Chen X, Yao Y, et al. The characteristics of HPV integration in cervical intraepithelial cells. Journal of Cancer. 2019;10(12):2783.
27. Miyagi Y, Takehara K, Nagayasu Y, Miyake T. Application of deep learning to the classification of uterine cervical squamous epithelial lesion from colposcopy images combined with HPV types. Oncology letters. 2020;19(2):1602-10.
28. De Cicco R, de Melo Menezes R, Nicolau UR, Pinto CAL, Villa LL, Kowalski LP. Impact of human papillomavirus status on survival and recurrence in a geographic region with a low prevalence of HPV‐related cancer: A retrospective cohort study. Head & neck. 2020;42(1):93-102.
29. Floberg JM, DeWees TA, Chin RI, Garsa AA, Dehdashti F, Nussenbaum B, et al. Pretreatment metabolic tumor volume as a prognostic factor in HPV‐associated oropharyngeal cancer in the context of AJCC 8th edition staging. Head & neck. 2018;40(10):2280-7.
30. Lafaurie GI, Perdomo SJ, Buenahora MR, Amaya S, Díaz‐Báez D. Human papilloma virus: an etiological and prognostic factor for oral cancer? Journal of investigative and clinical dentistry. 2018;9(2):e12313.
31. Mirghani H, Leroy C, Chekourry Y, Casiraghi O, Aupérin A, Tao Y, et al. Smoking impact on HPV driven head and neck cancer's oncological outcomes? Oral oncology. 2018;82:131-7.
32. Aghamiri S, Talaei S, Roshanzamiri S, Zandsalimi F, Fazeli E, Aliyu M, et al. Delivery of genome editing tools: A promising strategy for HPV-related cervical malignancy therapy. Expert opinion on drug delivery. 2020;17(6):753-66.
33. Gupta S, Kumar P, Das BC. HPV: Molecular pathways and targets. Current problems in cancer. 2018;42(2):161-74.
34. Wang Y, Springer S, Mulvey CL, Silliman N, Schaefer J, Sausen M, et al. Detection of somatic mutations and HPV in the saliva and plasma of patients with head and neck squamous cell carcinomas. Science translational medicine. 2015;7(293):293ra104-293ra104.
35. Litwin TR, Clarke MA, Dean M, Wentzensen N. Somatic host cell alterations in HPV carcinogenesis. Viruses. 2017;9(8):206.
36. Xing D, Zheng G, Schoolmeester JK, Li Z, Pallavajjala A, Haley L, et al. Next-generation sequencing reveals recurrent somatic mutations in small cell neuroendocrine carcinoma of the uterine cervix. The American journal of surgical pathology. 2018;42(6):750.
37. Banister CE, Liu C, Pirisi L, Creek KE, Buckhaults PJ. Identification and characterization of HPV-independent cervical cancers. Oncotarget. 2017;8(8):13375.
38. Zhang J, Zhang Y, Zhang Z. Prevalence of human papillomavirus and its prognostic value in vulvar cancer: A systematic review and meta-analysis. PLoS One. 2018;13(9):e0204162.
39. Kofler B, Laban S, Busch CJ, Lörincz B, Knecht R. New treatment strategies for HPV-positive head and neck cancer. European Archives of Oto-Rhino-Laryngology. 2014;271(7):1861-7.
40. Muñoz-Quiles C, Díez-Domingo J, Acedo L, Sánchez-Alonso V, Villanueva RJ. On the Elimination of Infections Related to Oncogenic Human Papillomavirus: An Approach Using a Computational Network Model. Viruses. 2021;13(5):906.
41. Gurmu ED, Koya PR. Sensitivity analysis and modeling the impact of screening on the transmission dynamics of Human Papilloma Virus (HPV). American journal of applied mathematics. 2019;7(3):70-9.
42. Tan N, Sharma M, Winer R, Galloway D, Rees H, Barnabas RV. Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa. Vaccine. 2018;36(32):4830-6.
43. Nickel B, Dodd RH, Turner RM, Waller J, Marlow L, Zimet G, et al. Factors associated with the human papillomavirus (HPV) vaccination across three countries following vaccination introduction. Preventive medicine reports. 2017;8:169-76.
44. Teteh DK, Dawkins-Moultin L, Robinson C, LaGroon V, Hooker S, Alexander K, et al. Use of community forums to increase knowledge of HPV and cervical cancer in African American communities. Journal of community health. 2019;44(3):492-9.
45. Bakheit A, Mansour M, Shomo A, Salih M, Elhassan M. Screening for Cervical Cancer and Its Association with Human Papilloma Virus (HPV) among Sudanese Women. 2019.
46. Mena Cervigón M, Lloveras Rubio B, Tous S, Bogers J, Maffini F, Gangane N, et al. Development and validation of a protocol for optimizing the use of paraffin blocks in molecular epidemiological studies: The example from the HPV-AHEAD study. PLos One, 2017, vol 12, num 10, p e0184520. 2017.
47. Leo PJ, Madeleine MM, Wang S, Schwartz SM, Newell F, Pettersson-Kymmer U, et al. Defining the genetic susceptibility to cervical neoplasia—A genome-wide association study. PLoS genetics. 2017;13(8):e1006866.

48. Carrero YN, Callejas DE, Mosquera JA. In situ immunopathological events in human cervical intraepithelial neoplasia and cervical cancer. Translational Oncology. 2021;14(5):101058.
49. de Moura EL, Dos Santos ACM, da Silva DM, Dos Santos BB, Figueredo DdS, Moura AWA, et al. Association of Polymorphisms in Cytokine genes with susceptibility to Precancerous Lesions and Cervical Cancer: A systematic review with meta-analysis. Immunological Investigations. 2021;50(5):492-526.
50. Qian N, Chen X, Han S, Qiang F, Jin G, Zhou X, et al. Circulating IL-1β levels, polymorphisms of IL-1B, and risk of cervical cancer in Chinese women. Journal of cancer research and clinical oncology. 2010;136(5):709-16.
51. Verma HK, Farran B, Bhaskar LVKS. Immune response, inflammation pathway gene polymorphisms, and the risk of cervical cancer. Overcoming Drug Resistance in Gynecologic Cancers: Elsevier; 2021. p. 207-23.
52. Dutta S, Chakraborty C, Mandal RK, Basu P, Biswas J, Roychoudhury S, et al. Persistent HPV16/18 infection in Indian women with the A-allele (rs6457617) of HLA-DQB1 and T-allele (rs16944) of IL-1β– 511 is associated with development of cervical carcinoma. Cancer immunology, immunotherapy. 2015;64(7):843-51.
53. Wang L, Zhao W, Hong J, Niu F, Li J, Zhang S, et al. Association between IL1B gene and cervical cancer susceptibility in Chinese Uygur Population: A Case–Control study. Molecular genetics & genomic medicine. 2019;7(8):e779.
54. Hadi AA. Interleukin IL1β-511C> T (rs16944) gene polymorphism and cervical cancer: Meta-analysis. Meta Gene. 2021:100940.
55. Cabeça TK, de Mello Abreu A, Andrette R, de Souza Lino V, Morale MG, Aguayo F, et al. HPV-Mediated resistance to TNF and TRAIL is characterized by global alterations in apoptosis regulatory factors, dysregulation of death receptors, and induction of ROS/RNS. International journal of molecular sciences. 2019;20(1):198.
56. Hong HS, Akhavan J, Lee SH, Kim RH, Kang MK, Park N-H, et al. Proinflammatory cytokine TNFα promotes HPV-associated oral carcinogenesis by increasing cancer stemness. International journal of oral science. 2020;12(1):1-10.
57. Du G-H, Wang J-K, Richards JR, Wang J-J. Genetic polymorphisms in tumor necrosis factor alpha and interleukin-10 are associated with an increased risk of cervical cancer. International immunopharmacology. 2019;66:154-61.
58. Traore IMA, Zohoncon TM, Djigma FW, Compaore TR, Traore Y, Simpore J. Association of TNF-α-308G/A and IL-18 Polymorphisms with risk of HPV infection among sexually active women in Burkina Faso. Biomolecular concepts. 2020;11(1):97-101.
59. Behboodi N, Farazestanian M, Rastgar-Moghadam A, Mehramiz M, Karimi E, Rajabian M, et al. Association of a variant in the tumor necrosis factor alpha gene with risk of cervical cancer. Molecular Biology Reports. 2021;48(2):1433-7.
60. Jin L, Sturgis EM, Zhang Y, Huang Z, Song X, Li C, et al. Association of tumor necrosis factor-alpha promoter variants with risk of HPV-associated oral squamous cell carcinoma. Molecular cancer. 2013;12(1):1-9.
61. Ou D, Adam J, Garberis I, Blanchard P, Nguyen F, Levy A, et al. Influence of tumor-associated macrophages and HLA class I expression according to HPV status in head and neck cancer patients receiving chemo/bioradiotherapy. Radiotherapy and Oncology. 2019;130:89-96.
62. Hu Y, Wu J-Z, Zhu H, Zhang S-H, Zhu Y-Y, Wu Y-Y, et al. Association of HLA-DRB1, HLA-DQB1 polymorphisms with HPV 16 E6 variants among young cervical cancer patients in China. Journal of Cancer. 2017;8(12):2401.
63. Chambuso R, Ramesar R, Kaambo E, Denny L, Passmore J-A, Williamson A-L, et al. Human Leukocyte Antigen (HLA) Class II-DRB1 and-DQB1 alleles and the association with cervical cancer in HIV/HPV co-infected women in South Africa. Journal of Cancer. 2019;10(10):2145.
64. Kamiza AB, Kamiza S, Mathew CG. HLA-DRB1 alleles and cervical cancer: A meta-analysis of 36 case-control studies. Cancer epidemiology. 2020;67:101748.
65. Helland Å, Olsen AO, Gjøen K, Akselsen HE, Sauer T, Magnus P, et al. An increased risk of cervical intra‐epithelial neoplasia grade II‐III among human papillomavirus positive patients with the HLA‐DQA1* 0102‐DQB1* 0602 haplotype: A population‐based case–control study of Norwegian women. International journal of cancer. 1998;76(1):19-24.
66. Chan PKS, Cheung JLK, Cheung T-H, Lin CK, Siu S-SN, May MY, et al. HLA-DQB1 polymorphisms and risk for cervical cancer: a case-control study in a southern Chinese population. Gynecologic oncology. 2007;105(3):736-41.
67. Yang Y-C, Chang T-Y, Lee Y-J, Su T-H, Dang C-W, Wu C-C, et al. HLA-DRB1 alleles and cervical squamous cell carcinoma: experimental study and meta-analysis. Human immunology. 2006;67(4-5):331-40.
68. Zheng Y, Wang M, Tian T, Liu K, Liu X, Zhai Y, et al. Role of interleukin-12 gene polymorphisms in the onset risk of cancer: a meta-analysis. Oncotarget. 2017;8(18):29795.
69. Zhang S, Kong Y-L, Li Y-L, Yin Y-W. Interleukin-10 gene–1082 G/a polymorphism in cervical cancer and cervical intraepithelial neoplasia: meta-analysis. Journal of international medical research. 2014;42(6):1193-201.
70. Matsumoto K, Oki A, Satoh T, Okada S, Minaguchi T, Onuki M, et al. Interleukin-10– 1082 gene polymorphism and susceptibility to cervical cancer among Japanese women. Japanese journal of clinical oncology. 2010;40(11):1113-6.
71. Guo C, Wen L, Song J-K, Zeng W-J, Dan C, Niu Y-M, et al. Significant association between interleukin-10 gene polymorphisms and cervical cancer risk: a meta-analysis. Oncotarget. 2018;9(15):12365.
72. Roh JW, Kim MH, Seo SS, Kim SH, Kim JW, Park NH, et al. Interleukin-10 promoter polymorphisms and cervical cancer risk in Korean women. Cancer letters. 2002;184(1):57-63.
73. Hu S, Pu D, Xia X, Guo B, Zhang C. CTLA-4 rs5742909 polymorphism and cervical cancer risk: A meta-analysis. Medicine. 2020;99(11).
74. Cao S, Zheng L. Impacts of CD152 polymorphisms on cervical cancer susceptibility. Pathology-Research and Practice. 2020;216(8):152918.
75. Kassardjian A, Shintaku PI, Moatamed NA. Expression of immune checkpoint regulators, cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), in female breast carcinomas. PloS one. 2018;13(4):e0195958.
76. Zhuo C, Yi T, Wei C, Wu X, Cen X, Feng S, et al. Association of cytotoxic T lymphocyte-associated protein 4 gene-1772T/C polymorphism with gastric cancer risk: A prisma-compliant meta-analysis. Medicine. 2020;99(50).
77. Fang M, Huang W, Mo D, Zhao W, Huang R. Association of five SNPs in cytotoxic T-lymphocyte antigen 4 and cancer susceptibility: evidence from 67 studies. Cellular Physiology and Biochemistry. 2018;47(1):414-27.
78. Kamiza AB, Kamiza S, Singini MG, Mathew CG. Association of TP53 rs1042522 with cervical cancer in the sub‐Saharan African population: a meta‐analysis. Tropical Medicine & International Health. 2020;25(6):666-72.
79. Khan MA, Tiwari D, Dongre A, Mustafa S, Das CR, Massey S, et al. Exploring the p53 connection of cervical cancer pathogenesis involving north-east Indian patients. PloS one. 2020;15(9):e0238500.
80. Ratre YK, Jain V, Amle D, Patra PK, Mishra PK. Association of TP53 gene codon 72 polymorphism with incidence of cervical cancer in Chhattisgarh. 2019.
81. Hayati L, Delvia S. Polymorphism of p53 Codon 72 Gene on Cervical Cancer Incidence in Malay Population. Archives of The Medicine and Case Reports. 2020;1(1):21-5.
82. Isakova J, Vinnikov D, Bukuev N, Talaibekova E, Aldasheva N. TP53 Codon 72 Polymorphism and Human Papilloma Virus-Associated Cervical Cancer in Kyrgyz Women. Asian Pacific journal of cancer prevention: APJCP. 2019;20(4):1057.
83. Guo H, Wen Z, Yang S, Qi H. Association of p73 G4C14-A4T14 and p53 codon 72 polymorphism with cervical cancer in Chinese population. Indian Journal of Cancer. 2021.
84. Landen C, Molinero L, Sehouli J, Miller A, Moore K, Taskiran C, et al. Association of BRCA1/2, homologous recombination deficiency, and PD-L1 with clinical outcomes in patients receiving atezolizumab versus placebo combined with carboplatin, paclitaxel, and bevacizumab for newly diagnosed ovarian cancer: exploratory analyses of IMagyn050/GOG3015/ENGOT-ov39. Gynecologic Oncology. 2021;162:S37-S8.

85. Xu G-P, Zhao Q, Wang D, Xie W-Y, Zhang L-J, Zhou H, et al. The association between BRCA1 gene polymorphism and cancer risk: a meta-analysis. Oncotarget. 2018;9(9):8681.
86. Paik ES, Lee JH, Kang M, Kang JH, Jeong SY, Kim MS, et al. EP376 BRCA1 immunohistochemistry expression and survival in cervical cancer. BMJ Specialist Journals; 2019.
87. Dang H, Zheng P, Liu Y, Wu X, Wu X. MicroRNA-543 acts as a prognostic marker and promotes the cell proliferation in cervical cancer by BRCA1-interacting protein 1. Tumor Biology. 2017;39(2):1010428317691187.
88. Wen X, Liu S, Cui M. Effect of BRCA1 on the concurrent chemoradiotherapy resistance of cervical squamous cell carcinoma based on transcriptome sequencing analysis. BioMed research international. 2020;2020.
89. Ma X, Liu J, Wang H, Jiang Y, Wan Y, Xia Y, et al. Identification of crucial aberrantly methylated and differentially expressed genes related to cervical cancer using an integrated bioinformatics analysis. Bioscience reports. 2020;40(5):BSR20194365.
90. Kumagai K, Takanashi M, Ohno S-i, Harada Y, Fujita K, Oikawa K, et al. WAPL induces cervical intraepithelial neoplasia modulated with estrogen signaling without HPV E6/E7. Oncogene. 2021;40(21):3695-706.
91. Yang XM, Wu ZM, Huang H, Chu XY, Lou J, Xu LX, et al. Estrogen receptor 1 mutations in 260 cervical cancer samples from Chinese patients. Oncology letters. 2019;18(3):2771-6.
92. Dai F, Chen G, Wang Y, Zhang L, Long Y, Yuan M, et al. Identification of candidate biomarkers correlated with the diagnosis and prognosis of cervical cancer via integrated bioinformatics analysis. OncoTargets and therapy. 2019;12:4517.
93. Chen Y, Gu Y, Gu Y, Wu J. Long Noncoding RNA LINC00899/miR-944/ESR1 Axis Regulates Cervical Cancer Cell Proliferation, Migration, and Invasion. Journal of Interferon & Cytokine Research. 2021;41(6):220-33.
94. Kirn V, Zaharieva I, Heublein S, Thangarajah F, Friese K, Mayr D, et al. ESR1 promoter methylation in squamous cell cervical cancer. Anticancer research. 2014;34(2):723-7.

