SCIENTIFIC REVIEWS AND LECTURES

I.V.Kononova, F.A.Zakharova, M.P.Kirillina, P.V. Nikiforov, S.N.Mamaeva, S.R.Antonov, A.N.Pavlov, N.A.Nikolaeva

# DIAGNOSTIC SIGNIFICANCE OF THE HUMAN PAPILLOMA VIRUS DETECTION IN BLOOD

DOI 10.25789/YMJ.2018.64.30

**ABSTRACT**

There is still no clear understanding of the human papillomavirus infecting, as well as its eliminating process from the body. It is known that cervical cancer is caused by human papillomavirus in 99 percent of cases, but only in a small number of human papillomavirus infected women leads to develop cervical cancer. At the same time, based on cytological and histological analysis of the women cervical samples, it is currently impossible to establish criteria that would indicate the malignant progression possibility. Blood, as a unique tissue with specific and nonspecific protective adaptive mechanisms, can be a source of crucial information about the human body papillomavirus infecting. The article provides an overview of the research devoted to the human papillomavirus detection in blood and identifies unresolved issues arising from these studies.

**Keywords:** papillomavirus, HPV, blood, viremia.

Human papillomaviruses (HPV) are small double-stranded DNA viruses that infect epithelial cells. Approximately one third of them have tropism to the genital epithelium. These viruses can be divided into high-risk types (including HPV-16, -18, -31 and -33), which are associated with the development of anogenital malignant neoplasms and low-risk viruses (including HPV-6 and -11) that induce hyperproliferative lesions, but they are associated with malignant neoplasms rarely [24]. Types 16 and 18 are responsible for most cases of cancer caused by human papillomaviruses [26].

In the case of cervical cancer, HPV is the causative agent in about 99 % of incidents [20]. It is widely known that only in a small number of women infecting HPV leads to the development of invasive cancer. It is not yet possible to establish reliably the based on cytological and histological tests criteria that indicate the progression of pathological changes to cervical cancer [31].

Until nowadays, we have not clear understanding the cellular immune response mechanisms that contribute to the HPV elimination [23]. The innate immunity, including macrophages, natural killer T-cells is thought to play a crucial role in the first line of defense against HPV infection [27].

Insufficient knowledge of the HPV-infecting and HPV-eliminating expands the field of investigations. The research clarifying blood significance in these processes is of particular interest.

It is supported for a long time that HPV does not cause viremia. Previously, HPV DNA found in blood was interpreted as DNA from metastatic tumor cells [4].

Over time, due to molecular biology improvement, evidence has emerged of the HPV presence in the blood of patients with malignant tumors, pre-carcinogenic changes, and in healthy people. Instead, previously, blood in healthy people was considered to be sterile [12].

To date, the HPV genes presence in the blood has been shown in a significant number of studies.

Peripheral blood mononuclear cells (PBMCs) from women with cervical cancer detected HPV types 16 and 18 genes [10], women with asymptomatic urogenital HPV infection - genes 6, 11, 16, 18 [22], HIV-infected pediatric patients (median of age 13.2 years) - HPV-16 genes [4]; men with infected HPV-16 sperm - HPV genes of the same type [21]. PBMCs of healthy blood donors, it was also possible to detect the HPV-16 genes [4]. In Australia, from healthy blood men donors from PBMC, many various genes of HPV types belonging to the skin beta and gamma papillomaviruses, alpha papillomavirus mucous were identified. Herewith high-risk HPV genes were found in 1.7% of cases. It is shown that HPV is attached to the cell surface, not inside [15]. Evidence of HPV reproduction in the PBMCs is currently absent.

In the serum, HPV-16 and 18 genes were found from patients with cervical cancer [25, 3], rectal cancer, oropharyngeal cancer [3], and squamous cell head and neck cancer [6]. HPV-16 DNA was found in the serum of patients with breast cancer [11, 5], as well as with benign breast neoplasms [5].

In plasma from patients with cervical cancer, DNA of HPV 16 and 18 types [7,1,16], 45, 51, 52 types [16] was determined. From patients with asymptomatic cervix infection in the plasma, DNA of HPV 45, 51, 16 types was detected, and HPV-16 showed the highest viral load [17].

In cord blood HPV types 6, 11, 18, 52 DNA was detected [30].

In whole heparinized blood HPV 16 and 18 type genes were found from patients with cervical cancer [9] and lung cancer [29].

Data on the HPV type matches in the blood and in the cervix is different. Some researchers found that the HPV type in the cervix and in the blood is the same [14,9], in other studies it was shown that the HPV type may not coincide [17,8].

The results of studies on the correlation between the HPV DNA presence in the blood and the cancer starting prognosis are contradictory as well. Some studies suggest that HPV DNA detection in blood samples may be a useful severity marker of the diseases associated with HPV, metastasis, or recurrence [7, 6, 17, 18, 19]. However, Peedicayil et al. showed that detection of HPV DNA in plasma is not a prognostic marker for cervical cancer recurrence [2].

Many notions remain without a clear explanation, including how HPV enters the blood, whether viremia is a natural stage of HPV infecting, and how blood participates in the HPV eliminating.

Being the oldest human companions, HPV is considered by researchers as a source for exploring evolutionary several million year history [13]. To achieve such evolutionarily successful lifestyle, HPV must avoid host protection systems through immune evasion [28].

In other turn, the human body connected with HPV in over million years, ought to develop efficient physiological mechanisms that contribute to the virus removal.

**Conclusion.** The high potential of blood as a unique tissue that unites the whole body and possessing specific and nonspecific protective and adaptive mechanisms, determines the continuing considerable interest in scientific research.

**References**

1. Arias Y. Human papillomavirus (HPV) detected in restored plasma DNA from women diagnosed with pre-invasive lesions and invasive cervical cancer / Y.Arias, E.Carrillo, F. Aristizabal // Colom-

bia Médica. - 2010. – Vol. 41. – Issue 2. – P. 148-154. – URL: http://colombiamedica.univalle.edu.co/index.php/comedica/article/view/696/794 Дата обращения: 18 сентября 2018.

2. Can recurrence of cervical cancer be predicted by human papillomavirus DNA in nodes or plasma? / A. Peedicayil [et al.] // Journal of Low Genital Tract Disease. – 2009. – Vol. 13. – Issue 2. P. 102-106. - doi: 10.1097/LGT.0b013e31818c66e6.

3. Circulating human papillomavirus DNA detected using droplet digital PCR in the serum of patients diagnosed with early stage human papillomavirus-associated invasive carcinoma / E. Jeannot [et al.] // The Journal of Pathology: Clinical Research. - 2016. – Vol. 2. - Issue 4. – P. 201-209. – doi: https://doi.org/10.1002/cjp2.47

4. Could human papillomaviruses be spread through blood? / S. Bodaghi [et al.] // Journal of Clinical Microbiology. - 2005. – Vol.43. – Issue 11. – P. 5428–5434. http://doi.org/10.1128/JCM.43.11.5428-5434.2005

5. Detection and Analysis of Human Papillomavirus (HPV) DNA in Breast Cancer Patients by an Effective Method of HPV Capture / T. Wang [et al.] // PLoS ONE: 2014. – Vol. 9. – Issue 3. - e90343. – doi: https://doi.org/10.1371/journal.pone.0090343

6. Detection and quantitation of human papillomavirus (HPV) DNA in the sera of patients with HPV-associated head and neck squamous cell carcinoma / R.B. Capone [et al.] // Clinical Cancer Research. - 2000. – Vol. 6. – Issue 11. – P. 4171-4175.

7. Detection and quantitation of human papillomavirus DNA in the plasma of patients with cervical carcinoma / S.M. Dong [et al.] // Cancer Epidemiology, Biomarkers & Prevention. - 2002. – Vol. 11. – Issue 1. – P. 3-6.

8. Detection and Quantitation of Human Papillomavirus DNA in the Plasma of Patients with Cervical Carcinoma / S.M. Dong [et al.] // Cancer Epidemiology, Biomarkers & Prevention. - 2002. – Vol. 11. – Issue 1. – P. 3-6.

9. Detection of HPV 16 and HPV 18 DNA in the blood of patients with cervical cancer / P. Kay [et al.] // Journal of Medical Virology. - 2005. – Vol. 75. – Issue 3. – P. 435-439 – doi: https://doi.org/10.1002/jmv.20294

10. Detection of human papillomavirus types 16 and 18 mRNA in peripheral blood of advanced cervical cancer patients and its association with prognosis / C.J. Tseng [et al.] // Journal of Clinical Oncology. - 1999. – Vol. 17. – Issue 5. – P. 1391- 1396.

11. Detection of human papillomavirus DNA in breast cancer of patients with cervical cancer history / A. Widschwendter [et al.] // Journal of Clinical Virology. - 2004. – Vol. 31. – Issue 4. – P. 292-297. – doi: https://doi.org/10.1016/j.jcv.2004.06.009

12. Drennan M. What is 'Sterile Blood'? / M. Drennan // British Medical Journal. – 1942. - Vol.2. – P. 526. - doi: https://doi.org/10.1136/bmj.2.4269.526

13. Evolution of human papillomavirus type 18: an ancient phylogenetic root in Africa and intratype diversity reflect coevolution with human ethnic groups / C.K. Ong [et al.] // Journal of Virology. - 1993. – Vol. 67. – Issue 11. – P. 6424-6431.

14. HPV DNA in plasma of patients with cervical carcinoma / N. Sathish [et al.] // Journal of Clinical Virology. – 2004. – Vol. 31. – Issue 3. – P. 204-209. – doi: https://doi.org/10.1016/j.jcv.2004.03.013

15. Human papillomavirus DNA detected in peripheral blood samples from healthy Australian male blood donors / A.C. Chen [et al.] // Journal of Medical Virology. - 2009. – Vol. 81. – Issue 10. – P. 1792-1796. – doi: https://doi.org/10.1002/jmv.21592

16. Human papillomavirus DNA detection in plasma and cervical samples of women with a recent history of low grade or precancerous cervical dysplasia / C.E. Cocuzza [et al.] // PLoS ONE. - 2017. – Vol. 12. – Issue 11. - e0188592. – doi: https://doi.org/ 10.1371/journal.pone.0188592

17. Human papillomavirus DNA detection in plasma and cervical samples of women with a recent history of low grade or precancerous cervical dysplasia / C.E.Cocuzza [et al.] // PLoS ONE. – 2017. – Vol. 12. – Issue 11. - e0188592. - doi:10.1371/journal.pone.0188592

18. Human papillomavirus DNA in plasma of patients with cervical cancer / W. Pornthanakasem [et al.] // BMC Cancer. – 2001. – Vol. 1:2. – doi: http://doi.org/10.1186/1471-2407-1-2

19. Human papillomavirus DNA in sera of cervical cancer patients as tumor marker / A. Widschwendter [et al.] // Cancer Letter. – 2003. – Vol.202. – Issue 2. – P. 231–239. – doi: https://doi.org/10.1016/j.canlet.2003.09.006

20. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide / J. M. Walboomers [et al.] // The Journal of Pathology. – 1999. - Vol. 189. – Issue 1. – P. 12-19. – doi: https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

21. Human papillomavirus proteins are found in peripheral blood and semen Cd20+ and Cd56+ cells during Hpv-16 semen infection / C. Foresta [et al.] // BMC Infectious Diseases. - 2013. – Vol. 13:593. - https://doi.org/10.1186/1471-2334-13-593

22. Identification of human papillomavirus DNA sequences in peripheral blood mononuclear cells / C.C. Pao [et al.] // American Journal of Clinical Pathology. - 1991. – Vol. 95. – Issue 4. – P. 540-546.

23. Longworth M. S. Pathogenesis of Human Papillomaviruses in Differentiating Epithelia // M.S. Longworth, L.A. Laimins // Microbiology and Molecular Biology Reviews. – 2004. – Vol. 68. – Issue 2. – P. 362–372. – doi: http://doi.org/10.1128/MMBR.68.2.362-372.2004

24. Longworth M.S. The Binding of Histone Deacetylases and the Integrity of Zinc Finger-Like Motifs of the E7 Protein Are Essential for the Life Cycle of Human Papillomavirus Type 31 // M.S. Longworth, L.A. Laimins // Journal of Virology. – 2004. – Vol. 78. – Issue 7. – P. 3533-3541. - doi: 10.1128/JVI.78.7.3533-3541.2004

25. Low incidence of HPV DNA in sera of pretreatment cervical cancer patients / V.W. Liu [et al.] // Gynecologic Oncology. - 2001. – Vol. 82. – Issue 2. – P. 269-272.

26. Lowy D.R. Reducing HPV-Associated Cancer Globally /D.R. Lowy, J. T. Schiller // Cancer Prevention Research. – 2012. – Vol. 5. - Issue 1. – P. 18-23. - doi: 10.1158/1940-6207.CAPR-11-0542

27. Sasagawa T. Immune responses against human papillomavirus (HPV) infection and evasion of host defense in cervical cancer // T. Sasagawa, H. Takagi, S. Makinoda // Journal of Infection and Chemotherapy. - 2012. – Vol.18. – Issue 6. – P. 807-815. – doi: https://doi.org/10.1007/s10156-012-0485-5

28. Stanley M.A. Epithelial Cell Responses to Infection with Human Papillomavirus / M.A. Stanley // Clinical Microbiology Reviews. – 2012.- Vol. 25. – Issue 2. – P. 215–222. – doi: http://doi.org/10.1128/CMR.05028-11

29. The presence of human papillomavirus type 16/18 DNA in blood circulation may act as a risk marker of lung cancer in Taiwan / H.-L. Chiou [et al.] // Cancer. - 2003. – Vol. 97. – Issue 6. – P. 1558–1563. – doi: https:// doi.org/10.1002/cncr.11191

30. Transplacental transmission of Human Papillomavirus / R.L. Rombaldi [et al.] // Virology Journal. - 2008. – Vol. 5:106. – doi: https://doi.org/10.1186/1743-422X-5-106

31. Woodman C.B.J. The natural history of cervical HPV infection: unre-

solved issues / C.B.J. Woodman, S. I. Collins, L.S. Young // Nature Reviews Cancer. – 2007. – Vol. 7. – P. 11–22.

**The authors**

1. Kononova Irina Vasilyevna – Candidate of Medical Sciences, the Research Worker of YSC CMP Department of epidemiology of chronic non-communicable diseases Laboratory of Precancerogenesis and Malignant Tumors, e-mail: irinakon.07@mail.ru, 677000, Yakutsk, Sergelyakhskoye shosse, 4, FGBNU "The Yakut Scientifc Center of Complex Medical Problems";
2. Zakharova Fedora Apollonovna – Doctor of Medical Sciences, Professor of North-Eastern Federal University named after M. K. Ammosov Medical Institute Department of Normal and Pathological Physiology, 677000, Yakutsk, ulitsa Belinskogo, 58.
3. Kirillina Marya Petrovna – Candidate of Biological Sciences, the Leading Research Worker – the Head of YSC CMP Department of epidemiology of chronic non-communicable diseases Laboratory of Precancerogenesis and Malignant Tumors, 677000, Yakutsk, Sergelyakhskoye shosse, 4, FGBNU "The Yakut Scientific Center of Complex Medical Problems"; the Head of North-Eastern Federal University named after M. K. Ammosov Medical Institute Pathomorphology, Histology and Cytology Educational and Scientific Laboratory, Yakutsk, ulitsa Belinskogo, 58.
4. Nikiforov Petr Vladimirovich – Doctor of Medicine, Oncologist, Surgeon of GBU Yakut Republican Oncology Center General Surgery Department, 677000, Yakutsk, ulitsa Sverdlova, 3, k.2.
5. Mamaeva Sargylana Nikolaevna - Candidate of Physical and Mathematical Sciences, the Associate Professor of North-Eastern Federal University named after M. K. Ammosov Physics and Technology Institute Department of General and Experimental Physics, 677000, Yakutsk, ulitsa Belinskogo, 58.
6. Antonov Stepan Romanovich – Candidate of Physical and Mathematical sciences, the Associate Professor of North-Eastern Federal University named after M. K. Ammosov Physics and Technology Institute Department of Radio Physics and Electronics, 677000, Yakutsk, ulitsa Belinskogo, 58.
7. Pavlov Aleksandr Nikolaevich – the Head of North-Eastern Federal University named after M. K. Ammosov Physics and Technology Institute Department of Radio Physics and Electronics Laboratory, 677000, Yakutsk, ulitsa Belinskogo, 58.
8. Nikolaeva Nadezhda Anatolyevna – the Assistant of North-Eastern Federal University named after M. K. Ammosov Physics and Technology Institute Department of General and Experimental Physics, 677000, Yakutsk, ulitsa Belinskogo, 58.

I.T. Terentiev, M.A. Varlamova, N.I. Pavlova, A.T. Dyakonova, N.A. Solov'eva, S.K. Kononova, Kh.A. Kurtanov

# NECESSITY OF SCREENING PATIENTS WITH STENTING FOR ACUTE CORONARY SYNDROME BY *CYP2C19* POLYMORPHISM

DOI 10.25789/YMJ.2018.64.31

**ABSTRACT**

The *relevance* of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

One of the main drugs for antiplatelet therapy in cardiology is clopidogrel, the use of which can reduce the incidence of thrombotic complications. Clopidogrel is the most famous member of the thienopyridine group. Clopidogrel remains the main drug for antiplatelet therapy in patients who received stenting of the coronary vessels for acute coronary syndrome. The rationale and design of the observational study aimed at testing the hypothesis that the high frequency of the genetic polymorphism of cytochrome CYP2C19*2 is associated with coronary stent thrombosis is presented.

**Keywords:** Clopidogrel, coronary stenting, the acute coronary syndrome, personalized therapy, clopidogrel resistance, paradoxical response, genetic polymorphisms.

The relevance of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

According to the World Health Organization (WHO), mortality from cardiovascular disease is 31% and is the most common cause of death worldwide. In the territory of the Russian Federation, this figure is 57.1%, of which the share of CHD falls more than half of all cases (28.9%), which in absolute terms is 385.6 people per 100 thousand people per year. For comparison, mortality from the same cause in the European Union is 95.9 people per 100 thousand people a year, which is 4 times less than in our country. The incidence of IHD increases dramatically with age: in women from 0.1-1% at the age of 45-54 to 10-15% at the age of 65-74 years, and in men with 2-5% at the age of 45-54 years to 10 -20% at the age of 65-74 years. Despite the multiply increased possibilities of modern conservative therapy of the above pathology, in the absence of effect, surgical methods of treatment are performed:

1. Percutaneous coronary intervention - balloon angioplasty with the installation of a stent (a metal frame that preserves the restored lumen of the vessel);
2. Coronary bypass - the imposition of shunts around the affected areas of the coronary arteries. As a shunt, one uses his own veins (usually the subcutaneous vein of the thigh) or the internal thoracic artery of the patient.

Percutaneous coronary intervention (PCI) is one of the widely used methods for treating patients with acute coronary syndrome. In the Russian Federation, in 2012 the number of PCI increased by 13,049 procedures or 20.9%, compared to 2011, and amounted to 75,378 procedures. The average for Russia, indicator of the frequency of PCI performance per 1 million population in 2012 was 531 [3]. It is important to note that, despite the obvious success of the use of PCI, this method has certain complications. Thus, among patients who underwent coronary stenting, the frequency of such a