жев А.А., Лагода О.В. Некоторые аспекты профилактики нарушений мозгового кровообращения у пациентов с миелопролиферативными заболеваниями. Неврология. 2017;4(1):40-43. [Tanashyan MM, Kuznetsova PI, Raskurajev AA, Lagoda OV. Certain aspects of stroke prevention in patients with myeloproliferative diseases. Nevrologija. 2017;(4)1:40-43. (In Russ.)]

5. Жернякова А.А., Мартынкевич И.С., Шуваев В.А., Полушкина Л.Б., Фоминых М.С., Удальева В.Ю., Зотова И.И., Шихбабаева Д.И., Волошин С.В., Бессмельцев С.С., Чечеткин А.В., Абдулкадыров К.М. Факторы риска развития тромботических и геморрагических осложнений при эссенциальной тромбоцитемии. Онкогематология. 2017;12(2):30-38. [Zhernyakova AA, Martynkevich IS, Shuvaev VA, Polushkina LB, Fominykh MS, Udal'eva VU, Zotova II, Shichbabaeva DI, Voloshin SV, Bessmeltcev SS, Chechetkin AV, Abdulkadyrov KM. Thrombotic and bleeding risk factors in essential thrombocytemia. Klinicheskaja onkogematologija. 2017;(10)3:402-408. (In Russ.).] DOI: 10.17650/1818-8346-2017-12-2-30-38

6. Абдулкадыров К.М., Шуваев В.А., Мартынкевич И.С. Что нам известно об истинной полицитемии (обзор литературы и собственные данные). Онкогематология. 2015;10(3):28-42. [Abdulkadyrov KM, Shuvaev VA, Martynkevich IS. All we know about polycythemia vera: literature review and own experience. Onkogematologija. 2015;10(3):28-42. (In Russ.).] DOI: 10.17650/1818-8346-2015-10-3-28-42.

7. Duangnapasatit B, Rattarittamrong E, Rattanathammethee T, Hantrakool S, Chai-Adisaksopha C, Tantiworawit A, Norasetthada L. Clinical Manifestations and Risk Factors for Complications of Philadelphia Chromosome-Negative Myeloproliferative Neoplasms. Asian Pac J Cancer Prev. 2015;(16)12:5013-5018. DOI: 10.7314/APJCP.2015.16.12.5013.

8. Moulard O, Mehta J, Fryzek J, Olivares R, Iqbal U, Mesa RA. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. O Moulard, J Mehta, J Fryzek [et al.]. Eur J Haematol. 2014; 92(4):289-297. DOI: 10.1111/ejh.12256. DOI: 10.1111/ejh.12256.

9. Arellano-Rodrigo E, Alvarez-Larrán A, Reverter JC, Villamor N, Colomer D, Cervantes F. Increased platelet and leukocyte activation as contributing mechanisms for thrombosis in essential thrombocythemia and correlation with the JAK2 mutational status. Haematologica. 2006;91(2):169-175.

10. Sazawal S, Rathi S, Chikkara S, Chaubey R, Seth T, Saraya A, Das J, Mahapatra M, Saxena R. JAK2V617F mutation in patients with splanchnic vein thrombosis. Dig Dis Sci. 2010;55(6):1770-1777.

11. Vainchenker W, Delhommeau F, Constantinescu SN, Bernard OA. New mutations and pathogenesis of myeloproliferative neoplasms. Blood. 2011; 118(7):1723–1735.DOI:10.1182/blood-2011-02-292102.

12. Tefferi A, Rumi E, Finazzi G, Gisslinger H, Vannucchi AM, Rodeghiero F, Randi ML, Vaidya R, Cazzola M, Rambaldi A, Gisslinger B, Pieri L, Ruggeri M, Bertozzi I, Sulai NH, Casetti I, Carobbio A, Jeryczynski G, Larson DR, Müllauer L, Pardanani A, Thiele J, Passamonti F, Barbui T. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia. 2013;27:1874-1881. DOI: 10.1038/leu.2013.163

13. Tefferi A, Vannucchi AM. Genetic risk assessment in myeloproliferative neoplasms. Mayo Clinic proceedings. 2017;92(8):1283-1290. DOI: 10.1016/j.mayocp.2017.06.002

14. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, Orazi A, Tefferi A. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood cancer J. 2018; 8(2):15. DOI: 10.1038%2Fs41408-018-0054-y

15. Casini A, Fontana P, Lecompte TP. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. J ThrombHaemost. 2013; 11(7):1215-1227. DOI: 10.1111/jth.12265.

16. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study / A. Tefferi, E. Rumi, G. Finazzi [et al.] // Leukemia, 2013, V.27, P.1874-1881. DOI: 10.1038/leu.2013.163

17. Tefferi A. Genetic risk assessment in myeloproliferative neoplasms. Mayo Clinic proceedings. 2017, V.92, №8, p.1283-1290. DOI: 10.1016/j.mayocp.2017.06.002

18. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion / T.Barbui, J. Thiele, H. Gisslinger [et al.] // Blood cancer J, 2018, Vol.8, №2, P.15. DOI: 10.1038%2Fs41408-018-0054-y

19. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management / A Casini, P Fontana, TP Lecompte // J ThrombHaemost. 2013, V.11, №7, P.1215-1227. DOI: 10.1111/jth.12265.

M. P. Kirillina, V. I. Kononova, S. I. Sofronova, A. K. Ivanova, E. L. Lushnikova

# THE INCIDENCE OF DYSPLASTIC CHANGES IN CERVIX UTERI AMONG WOMEN OF DIFFERENT AGE GROUPS

DOI 10.25789/YMJ.2019.67.11

Yakutsk, Republic Sakha (Yakutia), Russia: **KIRILLINA Maria Petrovna –** Candidate of Biological Sciences, Senior Research Scientist, Head of Yakut Science Centre of Complex Medical Problems Laboratory, Head of NEFU Medical Institute Clinic Laboratory,kirillinamp@mail.ru,89142716881, **KONONOVA Irina Vasilievna** – Candidate of Medical Science, Research Worker of Yakut Science Centre of Complex Medical Problems Laboratory, irinakon.07@mail.ru 89243683673, **SOFRONOVA Sargylana Ivanovna** – Candidate of Medicine, Senior Research Associate, Head of Scientific and Organizational Department of Yakut Science Centre of Complex Medical Problems Laboratory, sara2208@mail.ru 89841094825, **IVANOVA Anna Konstantinovna -** Clinical Pathologist of NEFU Medical Institute Clinic, ivanova.ak11@gmail.com, 89248647588, **LUSHNIKOVA Elena Leonidovna**- Doctor of Biological Science, professor, the head of FSBIS Institute of Molecular Pathology and Pathomorphology "Federal Research Center of Fundamental and Translational Medicine" 630117,Novosibirsk,Timakova st.,2, pathol@inbox.ru8(383)334-80-03.

The article presents an analysis of the incidence of dysplasia degrees and cervical cancer (CC) in women of different age groups based on cytological studies from 2016 to 2018 inclusive. The frequency of incidence of CIN 1, CIN 2, CIN 3 and CC was determined, which is inversely dependent on the dysplasia degree in all age groups of women. While the incidence of CIN 2, CIN 3 and CC was decreasing, CIN 1 increased between 2016 and 2018. Women 26-35 years had the highest incidence of CIN 1, CIN 2 and CIN 3; also CIN 2 was detected in women 36-45 years, as in the first group; women of 46-55 years had a sharp rise in CC - it is 2.5 times higher than in previous two groups. The peak incidence of CC was in patients aged 56 years and older.

**Keywords:** screening, oncocytology, diagnosis, dysplasia, cervical cancer.

**Relevance.** According to various authors, cervical pathology makes up from 10 to 15% of all gynecological diseases [3]. Occurrence and development of the causes and mechanisms of cervix uteri pathological processes are rather complex and understudied process [2]. As is known, dysplastic changes in the cervix uteri epithelium are considered as precancerous states [6], there is evidence that one of the main conditions for the development of dysplasia and CC is the persistence of the human papillomavirus (HPV) [8,9].The state of local immunity, as a regeneration process control agent [1], has great importance in the development of dysplastic processes in the cervix uteri, as well as a hormonal state, since cell developing and differentiation in the stratified squamous epithelium of the cervix uteri is hormone-dependent. Because of the hormonal status in women depends on age, it determines the usefulness of studying the features of dysplastic changes in cervix uteri in different age groups, irrespective of the

HPV detection in patients. In addition, the frequency of epithelial dysplasia increases with age [6]. However, the greatest pathogenic effect of HPV manifests in young women, and it realizes in the development of cervical intraepithelial neoplasia (CIN) of severe degree [9], which requires careful study of age-related features of pathomorphological dysplasia presentation. Dysplasia is a morphological concept, so diagnosis is made only on the basis of cytological and histological data [6].Cells with dyskaryosis are cytologically detected in dysplasia of cervical smear. Depending on the severity of changes in the nucleo-cytoplasmic ratio and other structural features (shape, nuclei, content, and distribution of chromatin, inclusions in the cytoplasm) there are 3 degrees of CIN: CIN 1 (mild dysplasia), CIN 2 (moderate dysplasia) and CIN 3 (severe dysplasia) [7]. Cytological picture of CIN 1 is represented by relatively mature cells with relatively large nuclei. These cells are located separately or in the two-dimensional assembly of unchanged squamous epithelial cells. Cells retain signs of cytoplasmic differentiation characteristic of the surface and intermediate layers of the flat epithelium. Nuclei – slightly hyperchromic, with the same type of uniform granular structure of chromatin, nucleoli are absent. Signs of infection with the human papillomavirus (HPV) are often occurred . In CIN 2 the shape and size of cells resemble cells of immature squamous metaplasia, but with larger nuclei. The cytoplasm has a sharp contour (a distinction of squamous cell differentiation). Nuclear-cytoplasmic ratio is increased. There is hyperchromia of the nuclei, the granular structure of chromatin, and nucleoli are not visible. Sometimes signs of HPV infection are found. In cytological preparations with CIN 3 signs of atypia are more intensive. Sharp contours of the cytoplasm are visible in cells, making them relate to the squamous epithelium cells. Nuclear-cytoplasmic ratio strongly increased. Severe atypia is particularly visible in the nucleus: lumpy chromatin, nuclear membrane are irregular, nucleoli are absent. There are remote signs of HPV infection [5].

**Purpose of research.** To determine the features of the occurrence of dysplastic changes in cervix uteri in women of different age groups, we decided to analyze the frequency of incidence of CIN 1, CIN 2, CIN 3 and CC in cytological smears of women of different age groups who were examined from 2016 to 2018 inclusive; to identify the frequency and dynamics of CIN 1, CIN 2, CIN 3 and CC depending on the year of examination and age of women.

**Materials and methods of research:** The analysis of cytologic material of a cervix of 7600 women aged from 18 up to 88 years with the preventive and diagnostic purpose, during 2017 – 2018 is carried out to laboratory of a pathomorphology, histology and cytology of Clinic of Medical institute of NEFU.

The material of the study was smears from the mucosa of the cervix uteri and the cervical canal. Cytological diagnosis was carried out by staining, the method of Romanovskiy - Giemsa. Cytological diagnosis – degree CIN (cervical cancer) is made in accordance with the clinicopathologic classification of Y. V.Bokhman (1976). The incidence of CIN 1, CIN 2, CIN 3 (CC) in smears was expressed in percentage of the total number of women with dysplasia.

**Results and discussion.** The total number of patients with dysplastic changes in the cervix uteri of different degrees was 931 people. Of them, 128 women (13.7% of the total) went through cytological examination in 2016, 322 women (34.6 %) in 2017, and 481 women (51.6%) in 2018. Cytological material was studied in women according to the age groups, the distribution was as follows: women under 25 years - 144 people (15.5%), 26-35 years – 222 people (23.8%), 36-45 years – 212 women (22.7%), 46 – 55 years – 192 women (20.6%), 56 years and older – 161 women (17.3%).The CIN incidence of varying degrees is analyzed, as well as CC in the cytological smears of all women who underwent examination from 2016 to 2018 inclusive. It is clear that the highest rate is in CIN 1, which was registered in 578 women and amounted to 62.1% of all women studied, CIN 2 was found in 241 women (25.9%), and CIN3 was diagnosed in 97 women, which amounted to 10.4% of all cervical dysplasia in the examined group (pic.1,2).Cervical cancer was cytologically detected in 15 cases and amounted to 1.6% of the total number of examined women (pic.5).It should be noted that the high frequency of CIN 1 incidence is detected in the inflammation of the cervix when a cytological study reveals reparative atypical cells – equivalents of dysplasia. These phenomena often disappear after anti-inflammatory treatment, elimination of the viral agent [4].

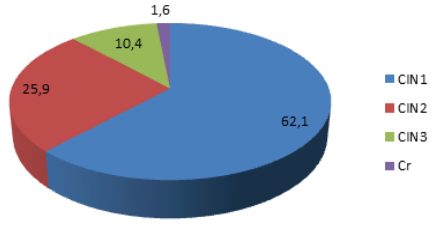


**Fig. 1.** The distribution of the incidence rate of the dysplasia of different degree for the period 2016-2018

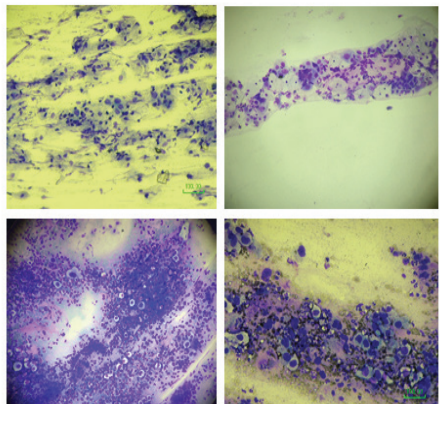

**Fig. 2** A – Cells with signs of mild dysplasia (CIN 1), B – cells with signs of moderate dysplasia (CIN 2), C, D– severe dysplasia (CIN 3), X200

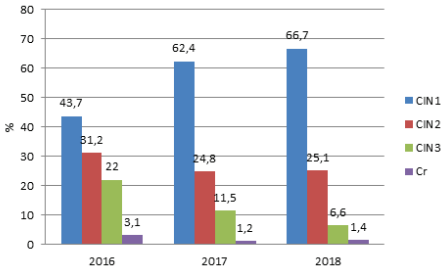


**Fig. 3.** Dynamics of incidence of dysplasia of different degrees for the period 2016-2018

As Fig.3 shows analysis of the frequency of CIN 1, CIN 2, CIN 3 incidence and CC over a three-year period (from 2016 to 2018 inclusive), depending on the year of the examination, CIN 1 is increasing from year to year while CIN 2 and CIN 3 are reducing. The frequency of CIN 1 incidence in 2018 increased by 52.6% compared to 2016, while the CIN 2 incidence decreased by 24.3%, and the CIN 3 incidence decreased 3.3 times. The incidence of CC decreased 2.2 times in the studied smears during a three-year period. It indicates a positive dynamics in the development of dysplasia. The growth of CIN1 can be

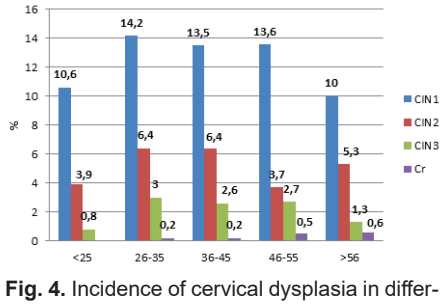


**Fig. 4.** Incidence of cervical dysplasia in different age groups

explained by reactive epithelial changes in various inflammatory diseases. Reduction of CIN2 and CIN3, CC can be associated with constant monitoring of patients and the development of dysplasia in the dynamics and effectiveness of the treatment.

In studying the incidence of cervical dysplasia depending on age, our analysis showed that the most frequently diagnosed cervical pathology in all age groups was CIN 1(pic.4).The maximum frequency of CIN 1(14.2%) incidence was observed in women of 26-35 age group, the minimum value of this indicator (10%) was in the group of 56 years and older. The maximum frequency of CIN 2 (6.4%) incidence was observed in the same population in two groups (26-35 years and 36-45 years). Both groups represent women of childbearing age. The minimum frequency of CIN 2 (3.7%) incidence was in the group of women 46-55 years. The highest incidence of CIN3 was observed in women aged 26-35 years and was 3%. The minimum incidence of CIN3 (0.8%) was in women under 25 years. The obtained data is indicating the maximum number of women who became ill at fertile age, and it is an alarming fact since this group of patients is not only a reproductive considerable part of the female population but also an active social group. Cervical cancer was detected cytologically in 15 cases and amounted to 1.6% of the total number of women examined. The maximum incidence of CC was observed in of 56 years and older age group-6 cases (0.6%). It should be noted that the incidence of CC increases depending on the age of patients. The rate is 2.5 and 3 times higher in women of 46-55 years and 56 and older age groups than in women 26-45 years age group (in women under 25 years, CC was not detected).The study confirms that the progression of the severity of dysplasia is going many decades [10]. Also, when the severity of dysplasia increases -the risk of its progression increases and the chance of regression decreases.

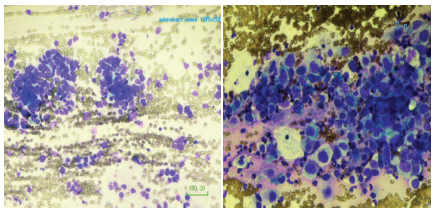

**Fig. 5.** A - adenocarcinoma of the cervix uteri, B - squamous cell carcinoma of the cervix uteri, X200

**Conclusion.** The frequency of CIN 1, CIN 2, CIN 3 and CC incidence in smears of cervix uteri and the cervical canal was inversely dependent on the degree of dysplasia in all age groups of women who were examined from 2016 to 2018.The incidence rate of CIN 1 increased from 2016 to 2018, while CIN 2 and CIN 3 and CC have been decreasing the rates. Analysis of the nature of CIN 1, CIN 2, CIN 3 and CC incidence, depending on age revealed that women of 26-35 years had the highest incidence of CIN 1, CIN 2 and CIN 3, women of 36-45 years had CIN 2 with the same frequency as in the previous group, and women of 46-55 years had a sharp increase in CC by 2.5 times, compared with the previous two groups, but patients of 56 years and older had the peak incidence of CC.

Regular cytological examination of cervix uteri leads not only to decrease in the number of newly diagnosed patients from year to year but also to absence or slowdown of negative dynamics and possible regression of existing pathological changes in cervix uteri. Prevention, early detection and effective treatment of malignant tumors is one of the most important part of modern medicine. The need of regular preventive examinations of women with the necessary cytological examination, clinical examination, and treatment of patients with background CC diseases is appears based on the data analysis of the incidence of dysplasia and CC. Such an arrangement should be optimized according to the age of women. Our results require special studies on developing the lines of approach on the main problems associated with the detection, prevention, and treatment of early forms of CC. However, at present, we recommend paying more attention to women born in 1980-1990 (age group 26-35 years), who most often had dysplasia of all degrees, including severe degree, women of 1960 (age group 46-55 years and older), who had a sharp increase of CC.

The paper was written as part of R&D "The epidemiological aspects of cancer on the Far North living environment, development of modern early detection methods, and prevention methods with high-informative fundamental research. (M06; 01; 01)" (№ 0556-2014-0006).

## References

1. Бабаева А.Г. Регенерация: факты и перспектива. М., 2009:336. [Babayeva AG. Regeneration: facts and perspective. M., 2009: 336. (In Russ.).]

2. Краснопольский О.Ф., Серова В.А., Туманова и др. Влияние инфекций на репродуктивную систему женщин. Российский вестник акушера- гинеколога. 2004;4(5):26-29. [Krasnopolsky OF, Serova VA, Tumanova et al. The effect of infections on the reproductive system of women. Russian vestnik akushera-ginekologa. 2004; 4(5): 26-29. (In Russ.).]

3. Новик В.И. Факторы эффективности цитологического скрининга рака шейки матки. Практическая онкология. 2010; 11 (2):66-71. [Novik VI. Factors of the effectiveness of cytological screening for cervical cancer. Prakticheskaya onkologiya. 2010; 11(2):66-71. (In Russ.).]

4. Полякова В.А. Онкогинекология. Медицинская книга.2001:192. [Polyakova VA. Medicinskaya kniga. 2001:192. (In Russ.).]

5. Полонская Н.Ю., Некрасов П.И., Роговская С.И. Повышение эффективности диагностики заболеваний шейки матки: в помощь цитологу и специалисту по кольпоскопии. Доктор.ру. 2015;2(12):6-9. [Polonskaya NYu, Nekrasov PI, Rogovskaya SI. Improving the efficiency of diagnosis of diseases of the cervix uterus: to help the cytologist and specialist in colposcopy. Doktor.ru. 2015; 2(12):6-9. (In Russ.).]

6. Прилепская В.Н. Заболевания шейки матки, влагалища и вульвы МЕД пре-информ, 2005:432. [Prilepskaya VN. Diseases of the cervix, vagina and vulva. MED pre-inform. 2005:432. (In Russ.).]

7. Сидельникова В.М. Первичная потеря беременности. Триада-Х. 2000:304. [Sidelnikova VM. Primary pregnancy. Triada-X. 2000:304. (In Russ.).]

8. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ. Epidemiological classification of human papillomavirus types associated with cervical cancer. N. Engl. J. Med. 2003; 348 (6):518-527.

9. Ed. Fattaneh A. Tavassoli, Peter Devilee. Pathology and Genetics of Tumours of the Breast and Female Genital Organs (WHO Classification of Tumours). Lyon.: IARC Press. 2003:266-268.

10. Richart R. M., Barron B. A. A follow-up study of patients with cervical dysplasia. Amer.J. Obstet. Gynecol.1969;105:386-393.