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POSSIBLE ROLE OF THE MICRONUCLEUS ASSAY IN DIAGNOSTICS AND SECONDARY PREVENTION OF CERVIX CANCER: A MINIREVIEW

Recent literature data are presented concerning micronuclei (MN) frequency in exfoliated cells of cervix cancer patients. These data strongly support a positive correlation between the MN level and malignization (changes from premalignant stage to cancer). It is suggested that the evaluation of frequency of MN in exfoliated cervical cells may be an additional criterion for establishing cervical cancer risk and the study of MN in cervix smears will increase the sensitivity and specificity of cytology which could impact in diagnostics and secondary prevention of cervical cancer.

Cervical cancer is the second most common cancer in women worldwide and the leading cause of cancer mortality in women in developing countries [1]. In the United States, over $6 billion is spent annually in the evaluation and treatment of low-grade cervical lesions, many of which do not develope into full-blown cancer. In developing countries cervical cancer goes undetected because of the cost of testing and the lack of resources and trained personnel to screen and diagnose the disease [1]. The goal of one of the programs of the National Cancer Institute is to assess the emerging technologies of fluorescence and reflectance spectroscopy and quantitative cytology and histopathology for the diagnosis of cervical cancer. All of these technologies should decrease mortality, morbidity, and the cost of treating cervical cancer.

Recently Leyden et al. [2] examined factors associated with the diagnosis of cervical cancer among women enrolled in health plans and concluded that to reduce the incidence of invasive cervical cancer, the Papanicolaou (Pap) cervical cytology screening (which helps to reduce cervical cancer rates through the detection of premalignant lesions) should be improved. This test is of extremely importance in cancer prevention. Recent publication has shown that during first 18 months after the last negative screening Pap test in women with > or = 3 prior negative tests, cancer incidence increases to an estimated 4–5 per 100,000 woman-years in each of the subsequent 2 years [3].

It is well known that some specific human papilloma viruses (HPV) are associated with cancer and dysplasia of cervix, penis, anus, vagina, and vulva [4, 5]. These viruses selectively infect the epithelium of skin and mucous membranes and it results in numerical and structural chromosome aberrations, chromosomal instability, increased aneuploidy, and these events initiate cervical carcinogenesis. The micronucleus [fragment of chromosomes and/or whole chromosome lagged in the mytosis] assay (MN) can register both numerical and structural chromosomal aberrations, and MN can be easily detected in exfoliated human cells [6, 7]. Since HPV infection induces cytogenetic instability in cervix cells, it can be evaluated by means of MN assay. Indeed, it has been shown that in exfoliated cervical cells of patients with moderate and severe dysplasia a significantly higher frequency of MN level was observed compared with healthy women [8]. The same effect was shown by a group

of Mexican investigators – significantly increased MN frequency in cervix cells of women with invasive cancer and low- and high-grade squamous intraepithelial lesions [9]. A correlation between MN frequency and grade of cervical lesion, and a positive linear trend between the MN frequency and increased cervical cancer risk was also shown [9]. Moreover, a retrospective study was performed to investigate the frequency of cells with MN in Pap smears from patients, and a strong correlation was observed between these two parameters – MN frequency and grade of cervical lesions [10]. Application of molecular cytogenetic technique (FISH) supports this observation in 143 women [11].

The results obtained in Armenia (71 studied patients in total) and India (55 studied patients) are in agreement with the mentioned data – substantial increase in MN level in exfoliated cervix cells of cervix cancer patients [12–16]. Gandhi and Kaur found a correlation between the stage of cancer and MN number in exfoliated cervical cells. It is noteworthy, that they also found that along with increase of MN level in cervix cells urothelial cells MN increased [14–16]. Strong correlation was registered between the mentioned two parameters.

HPV DNA can be detected in 95 to 100 % of cervical cancer specimens, and it has been called a «necessary cause» of cervical cancer [4, 5]. Based on the data obtained by numerous investigations, one can propose that increased level of MN in exfoliated cervical cells is a consequence of HPV infection leading to cancer. And, hence, both HPV infection (HPV DNA) and increased MN level in cervix cells are «necessary causes» of displasia and cervical cancer. It is of extremely importance that in urothelial cells of women suffering from cancer of cervix significantly increased number of MN was also observed [16]. Based on the mentioned data, some investigators [9,10, 14–16] proposed that MN test in exfoliated cervix and urothelial cells should be applied in mass-screening programs in developing countries based on high correlation between the results in MN assay in exfoliated cervix cells and Pap test on one the hand, and a correlation between cancer and increased MN level in urothelial and cervix cells on the other.

It is of extremely importance that MN frequency depends on the stage of disease. In the study in India the increment of cells with MN in the first stage of cancer was 7-fold and at higher stages 11–14-fold higher compared with the level observed in healthy females [16]. It has been shown that MN level increased from the control level with the progression of premalignant changes in the cervix (2.4–3.2-fold [9] and 2.7–4.2-fold increase [10]) to cancer (4.7-fold [9] and 5.6–7.7-fold [10] increase compared with appropriate control levels). These data strongly support a positive correlation between the MN incidence and cancer progress (changes from premalignant stage to cancer).

According to aforementioned it may be suggested that evaluation of the frequency of MN in exfoliated cervical cells may be an additional criterion for establishing cervical cancer risk and the study of MN in Pap smears will increase the sensitivity and specificity of cervical cytology which could impact in diagnostics and secondary prevention of cervical cancer.

РЕЗЮМЕ. Представлены литературные данные последних лет об уровне микроядер (МЯ) в эксфолиативных клетках шейки матки. Эти данные свидетельствуют о положительной корелляции между уровнем МЯ и озлокачествлением (изменениями от предопухолевого состояния к опухоли). На основании представленных данных предположено, что повышенный уровень МЯ в эксфолиативных клетках шейки матки является дополнительным прогностическим фактором в диагностике рака шейки матки. Изучение МЯ в мазках, полученных с шейки матки, может повысить чувствительность и специфичность цитологических исследований, а также повлиять на диагностику и вторичную профилактику рака этой локализации.

РЕЗЮМЕ. Наведено літературні дані останніх років щодо рівня мікроядер (МЯ) в ексфоліативних клітинах шийки матки. Ці дані свідчать про позитивну кореляцію між рівнем МЯ та виникненням злоякісності (зміни від передпухлинного стану до пухлини). На підставі наведених даних можна припустити, що підвищений рівень МЯ в ексфоліативних клітинах шийки матки є додатковим прогностичним фактором у діагностиці рака шийки матки. Вивчення МЯ у мазках, що отримані з шийки матки, може підвищити чутливість та специфічність цитологічних досліджень, а також вплинути на діагностику і вторинну профілактику рака цієї локалізації.

REFERENCES

1. *Follen M., Crain S., Macaulay C., Basen-Engquist K., Cantor S.B., Cox D., Atkinson E.N., Mackinnon N., Guillaud M., Richards-Kortum R.* Optical technologies

for cervical neoplasia : Update of an NCI Program project grant // Clin. Adv. Hematol. Oncol. – 2005. – **3**. – P. 41–53.
2. *Leyden W.A., Manos M.M., Geiger A.M., Weinmann S., Mouchawar J., Bischoff K., Yood M.U., Gilbert J., Taplin S.H.* Cervical cancer in women with comprehensive health care access: attributable factors in the screening process // J. Natl. Cancer Inst. – 2005. – **97**. – P. 675–683.
3. *Sawaya G.E., Sung H.Y., Kinney W., Kearney K.A., Miller M.G., Hiatt R.A.* Cervical cancer after multiple negative cytologic tests in long-term members of a prepaid health plan // Acta Cytol. – 2005. – **49. –** P. 391–397.
4. *Bosch F.X., Sanjose S. de* Human papillomavirus and cervical cancer—burden and assessment of causality // J. Natl. Cancer Inst. Monogr. – 2003. – **31.** – P. 3–13.
5. *Chen Y.C., Hunter D.J.* Molecular epidemiology of cancer // Cancer J. Clin. – 2005. – **55. –** P. 45–54.
6. *Nersesian A.K.* The micronucleus test in human exfoliative cells as a method for studying the action of mutagens/carcinogens // Tsitol. Genet. – 1996. – **30. –** P. 91–96.
7. *Majer B.J., Laky B., Knasmuller S., Kassie F.* Use of the micronucleus assay with exfoliated epithelial cells as a biomarker for monitoring individuals at elevated risk of genetic damage and in chemoprevention trials // Mutat. Res. – 2001. – **489. –** P. 147–172.
8. *Chakrabarti R.N., Dutta K.* Micronuclei test in routine smears from uterine cervix // Eur. J. Gynaecol. Oncol. – 1988. – **9. –** P. 370–372.
9. *Leal-Garza C.H., Cerda-Flores R.M., Leal-Elizondo E., Cortes-Gutierrez E.I.* Micronuclei in cervical smears and peripheral blood lymphocytes from women with and without cervical uterine cancer // Mutat. Res. – 2002. –**515. –**P. 57–62.
10. *Guzman P., Sotelo-Regil R.C., Mohar A., Gonsebatt M.E.* Positive correlation between the frequency of micronucleated cells and dysplasia in Papanicolaou smears // Environ. Mol. Mutagen. – 2003. – **41. –** P. 339–343.
11. *Olaharski A.J., Sotelo R., Solorza-Luna G., Gonsebatt M., Guzman P., Mohar A., Eastmond D.A.* Tetraploidy and chromosomal instability are early events during cervical carcinogenesis // Carcinogenesis. – 2005. – **27**. – P. 337–343.
12. *Nersesyan A.K.* Micronuclei and other nuclear anomalies in exfoliated cells of gynaecological cancer patients // Polish J. Environ. Studies. – 2002. – **11.** – P. 58–61.
13. *Vardazaryan N.S.* Investigation of cytogenetic disturbances in exfoliated human cells by means of micronucleus assay. PhD thesis. – Yerevan, 2004.
14. *Gandhi G., Kaur B.* Elevated frequency of micronuclei in uterine smears of cervix cancer patients // Caryologia. – 2003. – **56**. – P. 217–222.
15. *Gandhi G., Kaur B.* The micronucleus test in uterine epithelial cells of cervix cancer patients // J. Hum. Ecol. – 2003. – **14. –** P. 445–449.
16. *Gandhi G., Kaur B.* The micronucleus test in urothelial cells and uterine smears of cervix cancer patients: a comparison // Int. J. Hum. Gen. – 2003. – **3**. – P. 121–126.

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