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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან თანამშრომლობითა და მისი პატრონაჟით

> ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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- 3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

- 4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.
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- 4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).
- 5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.
- 6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით tiff ფორმატში. მიკროფოტო-სურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სუ-რათის ზედა და ქვედა ნაწილები.
- 7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა უცხოური ტრანსკრიპციით.
- 8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.
- 9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.
- 10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.
- 11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.
- 12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CERVICAL TRANSFORMATION IN ALCOHOL ABUSE PATIENTS

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Alcohol has been the most common substance of use and abuse in human history and affects many organs [21]. Both acute and chronic alcohol abuse can induce significant defects in the body's defense against microorganisms (i.e., pathogens) by interfering with multiple aspects of the immune response [8] but especially chronic heavy drinking, affects all components of the adaptive immune system [15]. Alcohol use disorder is a risk factor for the development of several types of cancer mainly upper gastrointestinal cancers, liver and pancreatic cancers, larynx and lung cancers, and cervical cancer [22]. Cervical cancer is one of most common cancer in women worldwide and causal relationship between cervical cancer and infection, which harbors HPV in up to 99.7% of cases [7,10,19,26], so connection of cervical neoplasia development and immune status is reasonably logical.

Cervical cancer progresses slowly from pre-invasive cervical intraepithelial neoplasia (CIN) to invasive cancer. Screening asymptomatic women with regular Papanicolau (PAP) smears allows diagnosis of treatable pre-invasive lesions [20]. However, in developed countries, most cases of cervical cancer occur in women who have not had regular PAP smear screening as in alcohol abuse. As result development of cervical cancer could be more aggressive due to immune peculiarity and no controlled with detection on developed stage.

Prognostic signs of different localization carcinoma are investigated intensively with estimation of features for different condition and localization [9,17,24]. Comparison of different neoplasia such as breast, thyroid, colon, testis and other [9,16,17,24], the current clinical management of genitals malignancies is important for adequate managements of such patients or even those in need of a more aggressive treatment [12]. One effective means to decrease cervical cancer incidence and death is an early detection of cancer, its precancerous lesions or CIN [5] with detection of cellular dysregulation, that could be evidenced clinically by immunohistochemical study of some proteins, such as, p16 and Ki67 [13,25]. Named biomarkers are important for detection, prognosis, and targeted therapeutics of cervical neoplastic transformation and evaluation [1,2].

In connection with the above, the purpose of our work was detection of cervical neoplastic transformation in women with alcohol abuse.

Material and methods. We selected 13 cases of cervical neoplastic transformation (5 cases of invasive carcinoma and 8 case of CIN) which where detected occasionally during autopsy of alcohol abuse women died of chronic alcoholism (alcoholic hepar cirrhosis mainly). Age of women ranged from 24 to 46 years and

averaged 32.7 years. Comparison group was formed of 10 women of the same age with cervical cancer occasionally detected during autopsy (course of death was not connected with alcohol use). Tobacco smoking, contraceptives (oral contraceptive pills), age of first sexual intercourse, somatic pathology related (no related) to alcohol consumption, numbers of pregnancies were not taken into account.

The material was fixed in 10% neutral buffered formalin and Bouin's fluid for 10-12 hours and embedded in paraffin. From the prepared blocks made serial sections thick 5x10⁻⁶ m. Slides were stained with hematoxylin and eosin (H&E). Each block provided from 10 to 40 slides; only samples showing the original lesion were used. A total of two blocks were constructed, one with cervical transformation biopsies and the other with controls in which the absence of CIN was confirmed by review of the H&E stained slide. Immunohistochemical examination (IHC) was performed indirect immunoperoxidase reaction [3] with monoclonal antibodies (mAb) to Ki-67, p16; all used mAbs are manufactured by Thermo scientific, USA. The reaction was visualized using a set of UltraVision LP Detection System HRP Polymer & DAB Plus Chromogen (Thermo scientific, USA).

Microscopic study was performed with microscope «Olympus BX41» followed by morphometric study using "Olympus DP-soft 3.12" program. Staining was scored independently by two observers and a high level of concordance (90%) was achieved. All slides were independently reviewed twice and intra-observer disagreements (< 10%) were reviewed a third time followed by a conclusive judgment. Evaluation of expression was performed using a quantitative scale.

Positive Ki67 expression was diagnosed with nuclear stain in the intermediate and superficial cells. Ki67 staining in basal or parabasal cell was considered as negative. Positive p16 expression was interpreted according to presence (positive or negative), cellular location (nuclear and cytoplasmic), staining intensity (weak, moderate and strong) and dispersion pattern (diffuse or focal). Unstained, focal or sporadic epithelial staining was considered as negative. Negative control was performed in the same tissue without primary antibodies [1,5]. The distribution of p16 positive cells was evaluated according to the following scale: negative type of reaction (NT) - up to 5% positively stained cells, focal (FT) – from 5 till 80% of positive cells, diffuse (DT) - more than 80% (Fig.).

Counting of number of investigated structures was performed per $1 \times 10^{-6} \, \text{m}^2$ area of the tissue with coincident points $\times 100 \, \text{nn}$ mber total of points on the grid. All values are expressed as means, standard deviation (SD) and stan-

dard error of the mean (SEM) for statistical analysis [11]. The accepted level of significance was $p \le 0.05$.

The procedure was done strictly in compliance with the Helsinki Declaration after approval from the Regional Ethical Review Board at Odessa National Medical University, protocol 3, 17th October 2011.

Results and their discussion. The 13 cases of cervical transformation in alcohol consumption women were histopathologically diagnosed as follows: CIN I (3 cases), CIN II (2 cases), CIN III (3 cases), well-differentiated squamous cell carcinoma (3 cases), moderately differentiated squamous cell carcinoma (2 cases). As a result of IHC it has been detected that positive Ki-67 reaction is presented only in isolate nuclei of the basal and parabasal layer cells with low or moderate reaction intensity in the non injured squamous epithelium of cervix. On cases of CIN I, cells with a positive staining have been located predominantly in the parabasal layer. In some cases, there are single cells with more weakly colored nuclei in the middle and superficial layers of the epithelium. CIN II has been characterized by cells with a positive nuclear reaction to Ki-67 from 1/3 to 2/3 of the thickness of the epithelial cervix layer. For that degree of CIN, increased number of Ki-67 positive nuclei is observed in different epithelial layers with the majority of cells containing the IGH tag localized in the central parts of epithelium. High intensity of the Ki-67 reaction has been observed in majority cases despite of comparison group where intensity has been detected moderate mainly in that degree of CIN.

Dysplastic cells with nuclei that react positively to Ki-67 have been detected in all, mainly external, layers of the epithelium with high intensity of expression in CIN III. In some cases, the cells of the basal layer are Ki-67-negative in comparison group. There are no cases with low intensity of reaction in investigated group. Evaluation of expression for immunohistochemical staining to Ki-67 in CIN is presented in Table.

Squamous cell carcinoma has been characterized Ki-67 nuclear staining and present in 79.4% of cells (comparison group 69.3% of the cells, p<0.05) of well-differentiated squamous carcinoma (Table). Simultaneously, there is a significant difference in the distribution pattern of Ki-

67 in the cervical cancer versus normal cervical epithelium. So, the Ki-67 positive cells were confined to the basal epithelial layer in the normal cervical tissue whereas, in the cervical cancer specimens, Ki-67 expression was diffuse and present in the majority of cancer cells (Fig.) from the basal aspect to the surface of the malignant tumor that accord to literature data [1].

The p16-positive immunostain was diffuse and strong at nuclear and cytoplasmic localization, without differences regarding the intensity of reaction in different level of differentiated squamous cell carcinoma degree for first point of view. Simultaneously we observed weak intensity stain in the cytoplasm and nucleus of non-epithelial cells, such as fibroblasts, inflammatory cells, vascular endothelial cells. It has been found that in all cases with unchanged epithelium, there is no positive reaction with this antibody. Two variants of the reaction (NT and FT) have been identified in CIN I. Most often NT is occurred, in which negative staining has been observed along with observations with a weak reaction of less than 5% of basal cell cells. In cases with FT staining, a reaction has been observed more often of a weak intensity, mainly in the cells of the basal and parabasal layers of epithelium, along with a moderate intensity and positive reaction of the cells in the middle and superficial layers.

In the CIN II group, we found all three possible stains - NT, FT and DT. The reaction has been detected mainly in the lower ½ or ½ of epithelium in observations with DT and FT staining (Fig.), the staining intensity is mostly moderate, although a reaction of both weak and high intensity has been observed also. In cases with NT staining, the basal layer cells are poorly stained.

DT reaction has been predominated in cases of CIN III, FT has been observed also. In absolutely majority of cases, DT has been dominated by an intensive reaction in the cells of the whole epithelium sequence, and a moderate and high intensity reaction has been observed in the lower half of the epithelial layer. In some cases, we observe the absence of staining in the areas of the superficial layer along with the intensive reaction of most cells. The intensity of the reaction is predominantly moderate and pronounced in cases with FT staining.

^c expression for immuno			

	Ki-67		p16		
Histological types	Comparison	Alcohol	Comparison	Alcohol	
	group	group	group	group	
CIN I	13.7±2.1	29.1±4.6*	16.1±2.7	26.2±5.8*	
CIN II	29.5±3.6	49.3±3.9*	60.3±3.1	82.4±4.2*	
CIN III	54.2±4.1	68.5±5.2	82.3±4.0	89.3±5.0	
Well-differentiated squamous cell carcinoma	69.3±2.9	79.4%±3.1*	91.2±4.6	92.1±4.7	
Moderately differentiated squamous cell carcinoma	75.7±4.1	89.7±4.3*	93.7±5.1	94.8±5.9	

^{* -} p<0.05 significant between groups with and without alcohol abuse

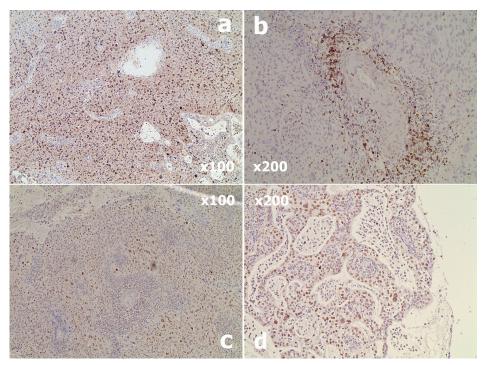


Fig. Immunohistochemical patterns in cervical transformation of alcohol abuse. Diffuse type of p16 spreading in well-differentiated squamous cell carcinoma, immunohistochemical study of p16, magnification x100 (a); moderate proliferative activity in CIN III, immunohistochemical study of Ki-67, magnification x200 (b); localization of p16 positive cells in CIN III, immunohistochemical study of p16, magnification x100, (c); high proliferation of well-differentiated squamous cell carcinoma, immunohistochemical study of Ki-67, magnification x200, (d)

DT staining has been encountered in all cases of cervical carcinoma with an intensive reaction in the cells of the entire epithelium. There is an increase in the intensity of the cytoplasmic reaction and an increase in the number of positively stained cells in zones with a tendency or suspected invasion. Different patterns of p16 signal were observed based on cellular location (nuclear and cytoplasmatic), staining intensity (weak, moderate and strong) and dispersion pattern (diffuse or focal). Percentage of cell with positive p16 staining was uneven in investigated groups as and Ki-67 expression (Table).

Significantly elevated incidence rate was found for cervical cancer due to compare the cancer morbidity in a large cohort of patients with alcohol use disorders [22]. However, such studies are difficult to interpret, because several factors affect antitumor immunity in human alcoholics, including malnutrition, vitamin deficiencies, and liver cirrhosis [15]. Women with alcohol abuse could be characterized increased risk of developing certain malignancies as result of their immune disorders development. Alcohol can modulate the activities of all of these cell populations by affecting the frequency, survival, and function of most of these cells, thereby interfering with pivotal immune responses. Emerging evidence also suggests that alcohol may affect immune functions by altering the balance and interactions between the host immune system and the entirety of microorganisms found in the host [21] that could be resulted in malignancies development.

These malignancies are commonly human papillomavirus (HPV)-related reflecting the high rate [10]. Due to immunosuppressive effects of alcohol use these women also have a high incidence of premalignant HPVrelated changes, such as high-grade squamous intraepithelial lesions as diagnosed on Pap smears and cervical intraepithelial neoplasia on cervical biopsy. Screening recommendations for alcohol abuse women reflect the need for vigilance in detecting and treating these lesions early. In addition, recent interest has focused on the use of cervical cancer screening, employing HPV-testing techniques, and on HPV vaccination in younger women to prevent initial infection and the subsequent development of cervical and other HPV-related cancers. Risk factors for cervical cancer include sexual intercourse at an early age, multiple sexual partners, tobacco smoking, long-term oral contraceptive use, low socioeconomic status, immunosuppressive therapy, and micronutrient deficiency [6]. Alcohol consumption, on the other hand, could not significantly appear to be related to risk of cervical abnormality. The notable exception was severe dysplasia, where a significant linear trend was observed with increasing frequency of consumption.

Proliferation of appeared malignant tumor is important characteristic for prognosis. Ki-67 is a nuclear

protein associated with cell proliferation and ribosomal RNA transcription. It is found in all active phases of the cell cycle and increasing the fraction Ki-67 positive tumoral cells is associated with a worsening of the prognosis for course of tumor [18]. Status of Ki-67 could be detected as an independent predictor disease free survival and presence of numerous Ki-67 positive stained cells is expected results for developed cervical carcinoma in our slides [7].

Level of Ki-67 is progressively increased in both investigated groups, but level of proliferation is significantly higher in group with alcohol abuse. So, percentage of cell with positive staining Ki67 was ranged from 29.1% to 89.7% in alcohol abuse group despite ranged from 27.41% to 75.3% in comparison group. It should be noted that dysplastic cells have been revealed with positively responding nuclei to Ki-67 in all cases, mostly outside, layers of the epithelium, the intensity of the reaction was moderate and high in peritumoral tissue. Simultaneously, positive staining p16 was ranged from 26.2% to 94.8% in alcohol abuse group despite ranged from 16.1% to 93.7% in comparison group with some peculiarities of staining localization and spreading. Mucosal organ "leakiness" resulting from chronic alcohol exposure also contributes, through a variety of mechanisms, to the cervical injury, a serious complication frequently associated with previous processes in cervix. Alcohol abuse also affects the tight junctions between the epithelial cells.

The rates of p16 and Ki67 expressions were directly associated with the severity of cervical lesions but should be interpreted result with caution [5]. Therefore, p16 overexpression, identified by immunostaining or enzyme-linked immunosorbent assay, can be considered as a marker of HPV infection and of activated expression of viral oncogenes and virus-induced cell cycle deregulation [14,23]. So, we observed significant difference between histological subgroups for Ki67 and p16. Such result must be evaluated carefully as there are data that meta-analysis of p16 overexpression could be associated with a favorable prognosis in patients with cervical cancer. Assessment of p16 expression could provide better prognostic information for patients with cervical cancer. Large scale, multicentre and well-matched cohort studies are warranted to clarify the prognostic effect of p16 expression on the outcome of cervical cancer [4]. Simultaneously such hesitation of p16 could be result of influence alcohol abuse. Our results revealed that p16 is overexpressed in the cervical cancer and precancerous lesions due to alcohol consumption.

Conclusion. There are some peculiarities in development of cervical cancer in women with alcohol consumption. Level of cellular proliferation is significantly higher with positive staining Ki67 ranged from 29.1% to 89.7% in alcohol abuse group despite ranged from 27.41% to 75.3% in comparison

group. Simultaneously, positive staining p16 was ranged from 26.2% to 94.8% in alcohol abuse group despite ranged from 16.1% to 93.7% in comparison group. Diffuse staining with p16, specific gravity of cells with positive IHC reaction with this protein and high reaction intensity can be used as a specific and sensitive method for detecting CIN III and invasive carcinoma in alcohol abuse.

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SUMMARY

CERVICAL TRANSFORMATION IN ALCOHOL ABUSE PATIENTS

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Patients with alcohol consumption have unclear risk of developing cervical cancer. The **purpose** of our work was detection of cervical neoplastic transformation in women with alcohol abuse.

We investigated 13 cases of cervical neoplastic transformation (5 cases of invasive carcinoma and 8 case of cervical intraepithelial neoplasia (CIN)) which where detected occasionally during autopsy of alcohol abuse women. Microscopic investigation with immunohistochemistry (IHC) was performed indirect to Ki-67, p16.

There are some peculiarities in development of cervical cancer in women with alcohol consumption. Level of cellular proliferation is significantly higher with positive staining Ki67 ranged from 29.1% to 89.7% in alcohol abuse group despite ranged from 27.41% to 75.3% in comparison group depend of transformation stage. Simultaneously, positive staining p16 was ranged from 26.2% to 94.8 % in alcohol abuse group despite ranged from 16.1% to 93.7% in comparison group. Diffuse staining with p16, specific gravity of cells with positive IHC reaction with this protein and high reaction intensity can be used as a specific and sensitive method for detecting CIN III and invasive carcinoma in alcohol abuse.

Keywords: Cervical neoplasia, Cancer, human immunodeficiency virus, proliferation, Ki67, p16.

РЕЗЮМЕ

ТРАНСФОРМАЦИЯ ШЕЙКИ МАТКИ У БОЛЬНЫХ АЛКОГОЛИЗМОМ

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Риск развития рака шейки матки у лиц, злоупотребляющих алкоголем, по сей день остается дискутабельным.

Целью исследования явилось изучение опухолевой трансформации шейки матки у женщин, злоупотребляющих алкоголем.

Исследовано 13 случаев цервикальной неопластической трансформации (5 случаев инвазивной карциномы и 8 - цервикальной интраэпителиальной неоплазии - CIN), которые случайно выявлены во время вскрытия женщин, злоупотреблявших алкоголем. Проведено микроскопическое исследование Ki-67, p16 с использованием иммуногистохимии (ИГХ).

У женщин, злоупотреблявших алкоголем, развитие рака шейки матки характеризуется особенностями. Уровень клеточной пролиферации у них значительно выше с положительным окрашиванием Ki-67 в диапазоне от 29,1% до 89,7%,

в группе сравнения этот показатель находится в пределах 27,41%-75,3% в зависимости от стадии трансформации. Положительное окрашивание p16 в основной группе варьирует от 26,2% до 94,8%, в группе сравнения - 16,1-93,7%. Диффузное окрашивание p16, удельный вес клеток с положительной ИГХ реакцией на этот рецептор и высокая интенсивность реакции могут быть использованы как специфический маркер выявления цервикальной интраэпителиальной неоплазии и инвазивной карциномы шейки матки при злоупотреблении алкоголем.

რეზიუმე

საშვილოსნოს ყელის ტრანსფორმაცია ალკოპოლიზმით ავადმყოფებში

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ალკოჰოლის ჭარბად მომხმარებელ პირთა საშვილოსნოს ყელის კიბოს განვითარების საშიშროება ღღესაც საკამათოა.

კვლევის მიზანს წარმოადგენდა საშვილოსნოს ყელის სიმსივნური ტრანსფორმაციის შესწავლა ალკოჰოლის ჭარბად მომხმარებელ ქალებში. სტატიაში განხილულია ცერვიკალური ნეოპლასტიკური ტრანსფორმაციის 13 შემთხვევა (5 ინვაზიური კარცინომა, 8 - ცერვიკალური ინტრაეპითელური ნეოპლაზიები), რომლებიც შემთხვევით აღმოჩნდა ალკოჰოლის ჭარბად მომხმარებელი ქალების გაკვეთის დროს. ჩატარებულია Ki-67, p16 მიკროსკოპული გამოკვლევა იმუნოჰისტოქიმიური მეთოდის გამოყენებით.

საშვილოსნოს ყელის კიბოს განვითარება ალკოპოლის ჭარბად მომხმარებელ ქალებში

ხასიათდება თავისებურებით. ამ ჯგუფის ქალებს უჯრედოვანი პროლიფერაციის დონე მნიშვნელოვნად მაღალი აქვთ Ki-67 დადებითი შეღებვის პირობებში (29,1%-დან 89,7%-მდე), შედარების ჯგუფში ეს მაჩვენებელი შეადგენს 27,41-75,3% გამომდინარე ტრანსფორმაციის სტადიისაგან. p16 დადებითი შეღებვა ძირითად ჯგუფში მერყეობდა 26,2-98,4% ფარგლებში, ხოლო შედარების ჯგუფში ამ მაჩვენებელმა შეადგინა 16,1-93,7%. უჯრედების ხვედრითი წონა იმუნოჰისტოქიმიის დადებითი რეაქციით ამ რეცეპტორზე და რეაქციის მაღალი ინტენსივობა შეიძლება გამოყენებული იყოს ცერვიკალური ინტრაეპითელური ნეოპლაზიის III სტადიის და საშვილოსნოს ყელის ინვაზიური კარცინომის გამოვლენის მარკერად ალკოჰოლის ჭარბად მომხმარებელ ქალებში.