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Clinical and genealogical analysis as first step in examination of patients with endometrial cancer

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Background: Nowadays endometrial cancer (EC) incidence does not tend to decrease in spite of improvement of medicamental and radiation therapy methods. That is why the evaluation of hereditary factors contributing to EC susceptibility would give a basis to cancer prevention through forming the high risk groups.
Aim: To establish the peculiarities and patterns of oncopathology distribution in families of EC patients and find out the role of genetic factorsin this disease development.
Material and Methods: Clinical and genealogical data of 134 stage I EC patients aged 39–80 (59.1±8.3) years. All women lived in Kyiv and Kyiv region and underwent inpatient treatment on oncogynaecological ward of Oncology institute of Medical Academy of Sciences of Ukraine. When conducting clinical and genealogical examination we considered the type of marriage of patients' parents: healthy parents, presence of cancer in one or both parents, as well as the data about the number of first- and second-degree relatives, their diseases and causes of death. Obtained information was elaborated using genetic and mathematical analysis.
Results: It was determined the association of different genesis tumors in 46.3% of EC patients' pedigrees. The association of reproductive system (endometrial and breast) malignancies, gastrointestinal and lung cancers was defined in EC patients' pedigrees, proving the role of hereditary factors in this pathology development. Moreover we have distinguished hereditary EC variants and EC forms comprising familial cancer syndrome (8.2 and 91.8% of patients with burdened familial history, respectively). Segregative frequency of endometrial, breast, gastrointestinal and lung cancer increased in families where one or both parents had cancer. According to estimated segregative frequencies we evaluated the probability charts of neoplasia occurrence in families where EC patient was a proband and it can be used for medical and genetic consultation.
Conclusion: Clinical and genealogical method is an essential part and one of the first steps in EC patients complex examination for determination of the hereditary factor in EC development that would help cancer prevention in members of families with burdened history.

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Differentiated markers of endometrical hyperplasias dependent on oncological burdened familial history

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Research suggests a new solution of an important task – establishing markers for differential diagnosis of endometrial hyperplasias, dependent on the patient's cancer burdened familial history, carrying out clinicogynecological studies and evaluating pro- and antiapoptotic indices in the endometrial tissues. Pathological conditions of the endometrium, declaring themselves in the form of menometorrhagias are registered in 68 % of the cases, whose morphologic substrate is endometrial hyperplasia in 77 % of observations. It has been proved that the presence of hyperestrogenia in 87 % of the cases in combination with a low level of progesterone in 78 % of the women hampers the development of full value transformations in the endometrium and results in the development of hyperplastic processes. It has been established that oncological diseases occur in the familial histories of patients with hyperplasias of the endometrium (5 times) more often than in healthy women, including endometrial carcinoma (5.5 times), hormonal-metabolic disorders (1.7 times), thyroid gland pathology (2 times) and that this is indicative of common factors of pathogenesis of hyperplasias and endometrial carcinoma. In case, of hereditary unburdened and hereditary burdened neoplastic transformation of the endometrium a sharp inhibition of the activity of caspase-1, caspase-3 and caspase-8, occurs in the latter however the caspase activity of the endometrium reaches the lowest values in inherited burdened uterine carcinoma. The autors have determined complex clinicogynecological and laboratory (apoptotic) criteria of differentiated treatment of patients, suffering from endometrial hyperplasias, depending on oncological burden of the herediatary history at the expense of isolating groups of genetic risk and a dynamic (once a year) control of state of apoptotic factors of the 1st and 2nd order and the activity of caspases-1, -3 and -8 in the endometrial tissue ablated during hysteroscopy (diagnostic curettage).

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p53, Bcl-2, Ki-67 expression and alterations in tumor-distant oral mucosa in patients with oral squamous cell carcinoma

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Aim: Investigation of the expression of p53, Bcl-2, Ki-67 in tumor tissue from patients with oral squamous cell carcinoma (OSCC) and in tumor-distant oral mucosa.
Material and Methods: Formalin-fixed biopsy specimens of tumors and tumor-distant mucosa were obtained from 17 patients with OSCC (male, age from 43 to 79 years). Most of the patients (14/17, 20 years, 20 cigarettes per day) have the smoking-drinking status and long-term professional contact with carcinogen and mutagen. The section of tumor-distant mucosa and tumors were classified according to the UICC criteria. Tissue sections were immunohistochemically stained using monoclonal antibodies: for p53 (clone DO-7), for Bcl-2 (clone 124), for Ki-67 (clone MIB-1) and En Vision "Daco Cytomation").
Results: The positive expression of p53 was found in all OSCC. High levels were detected in 12 tumors (70.58%). In tumor-distant mucosa revealed the progression of histopathological phenotype to hyperplasia, to dysplasia to carcinoma in situ. There were: hyperplasia (2), hyperplasia with area of mild dysplasia (4), mild dysplasia (1), high dysplasia (4), dysplasia with area malignum (5) and dysplasia with carcinoma in situ (1). The estimation of profile proteins of p53, Bcl-2, Ki-67 revealed the various level and combination of the expression in tumor-distant mucosa. p53 was detected in 88.2% cases of tumor-distant mucosa. Negative expression of p53 was found in tumor-distant mucosa in cases of hyperplasia. It was negative expression of Bcl-2 and Ki-67 in one case and the low expression in another case (1.6%, 3.6%, relatively). In specimen of hyperplasia with area of dysplasia mild and dysplasia mild in tumor-distant mucosa negative expression of Bcl-2 and Ki-67were in three cases and low in two cases (Bcl-2 only in one case, 1.5%; Ki-67 in

two cases, 0.5%, 1.2%). All specimens of dysplasia high, dysplasia high with area atypia and carcinoma in citu were positive for Bcl-2 and Ki-67 expression (individual variation Bcl-2, 2.6–16.4%; Ki-67, 5.8–13.4%). The high level of Bcl-2 (>10% cells staining) was observed in 50% cases and high proliferation in 30% cases.
Conclusion: Areas of cells with expression of p53, Bcl-2, Ki-67 are an indication of the transformation phenotype in tumor distant mucosa and represent high risk of development of second tumors after treatment. Diagnosis and prognosis for treatment of OSCC should not only be focused on the tumor but also on alterations in tumor-distant oral mucosa.

Prevention of miscellaneous cancers

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Changes in the system of proteolysis at the growth and metastasis of Lewis lung carcinoma upon development of cisplatin-resistance

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Drug resistance is critical in treating malignant tumors. At present, drug resistance, together with metastasis are considered as different manifestations of tumour progression. The interrelation of these processes with the system of proteolysis, which plays an important role in tumour progression, remains still weakly studied. The informative parameter revealing the abnormality in the proteolytic system is the proteinase-antiproteinase balance.

The aim of the work is to study the dynamics of the change of total proteolytic activity (TPA), the level of main proteinase inhibitor (α1-proteinase inhibitor, alpha1PI) in the blood plasma of C57B1/6 mice upon the growth and metastasis of Lewis lung carcinoma (LLC) with different resistance to the anticancer drug cisplatin.
Materials and Methods: The development of the cisplatin resistance was achieved by sequential intramuscular transplantations of carcinoma cells from cisplatin-treated animals. Three variants of drug resistant LLC (LLCR9, LLC19, and LLCR27 obtained in result of 9-, 19-, and 27-courses of cisplatin therapy, respectively) as well as the reference (sensitive) variant (LLC/S) have been used in our work. The studied indexes were determined on the day 10th, 15th, 20th, 25th, 28th after tumor transplantation. The intact animal blood plasma has been used as reference.
Results: A considerable change of the growth kinetics of LLC has been observed as a result of the decrease of carcinoma drug sensitivity. The growth rates of LLCR19 and LLCR27 tumours have increased considerably. Such modifications of the kinetic parameters of tumour have been preceded by the changes of TPA in the latent period of carcinoma growth (up to 10 days). The increase of TPA during this period correlates with the tumour growth rate. A considerable increase of alpha1PI (>60%) in the exponential phase of tumour growth (LLCR19 and LLCR27) leads to the subsequent growth deceleration. The value of TPA/alpha1PI ratio has shown that the development cisplatin-resistance of LLC is accompanied by the imbalance between proteolytic and antiproteolytic activities shifted to the activation of proteinases in blood plasma and deficiency of alpha1PI despite of the elevation of its level in blood plasma. A decrease of the cisplatin-sensitivity of LLC has been shown to proceed together with the considerable increase of the metastasis process.
Conclusion: The decrease of the cisplatin-sensitivity of LLC has been experimentally shown to be accompanied by the increase of tumour growth rate and metastatic activity and the imbalance between proteolytic and antiproteolytic activities. One may assume that the shift of the proteinase-antiproteinase balance in the blood plasma can be used for the prognosis of metastasis and for the search of the ways to prevent the metastasis through the influence on the proteolytic system.

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Multiple anticancer targets of chemopreventive curcumin in squamous cell lung carcinoma in vitro

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Introduction: Throughout the world, lung cancer is infamous for high mortality. Curcumin, a chemopreventive has chemotherapeutic potential but its mechanisms are still being elucidated. In this study, newer genes targeted by Curcumin were investigated to identify new targets for chemoprevention/therapy of squamous cell lung carcinoma (SCC) in vitro.
Methods: Lung squamous cell carcinoma cells (H520) were cultured in vitro. Apoptosis was detected in these cells after exposure to Curcumin (25μM) for 24 hours by morphological examination, MTT assay, flowcytometry and TUNEL assay. Microarray analysis of gene expression profiles on curcumin treatment was done. Real time quantitative RT-PCR and western blotting followed the microarray study.
Results: Curcumin (25μM for 24 hours) produced 29.8$\pm$2.1% cytotoxicity (MTT assay). Apoptosis was corroborated by flowcytometry (23.7$\pm$1.4%) and TUNEL (21.6$\pm$1.8%). Using microarray analysis, 34 genes were seen to be upregulated and 31 genes downregulated after curcumin treatment. Among several apoptosis related genes that were upregulated, Growth arrest and DNA damage gene, GADD45a and Peroxiredoxin-I were upregulated more than 2-fold. Real time quantitative RT-PCR and western blotting validated the results.
Conclusions: This study helps to identify novel putative intervention sites as chemopreventive and chemotherapeutic targets for curcumin in squamous cell lung carcinoma (SCC) in vitro and can contribute to better understanding of lung carcinogenesis and anticancer therapy.

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Prostate-specific antigen gene polymorphism and prostate cancer risk

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Prostate-specific antigen (PSA, kallikrein-related peptidase 3) is an androgen-regulated serine protease that is part of the kallikrein superfamily, produced predominantly by the prostate and primarily by secretory luminal epithelial cells. The action of androgens is regulated by androgen receptor (AR). After binding to androgen, the AR recognizes and binds androgen response elements (AREs) in the promoter regions of androgen regulated genes, such as the PSA gene. A single-nucleotide polymorphism in the ARE-I region at position –158 relative to the transcription