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DNA methylation in serum of breast cancer patients: An independent prognostic marker

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Changes in the status of DNA methylation are one of the most common molecular alterations in human neoplasia. Because it is possible to detect these epigenetic alterations in the bloodstream of patients, we investigated whether aberrant DNA methylation in patient pretherapeutic sera is of prognostic significance in breast cancer. Using MethyLight, a high-throughput DNA methylation assay, we analyzed 39 genes in a gene evaluation set, consisting of 10 sera from metastasized patients, 26 patients with primary breast cancer, and 10 control patients. To determine the prognostic value of genes identified within the gene evaluation set, we finally analyzed pretreatment sera of 24 patients having had no adjuvant treatment (training set) to determine their prognostic value. An independent test set consisting of 62 patients was then used to test the validity of genes and combinations of genes, which in the training set were found to be good prognostic markers. In the gene evaluation set we identified five genes (ESR1, APC, HSD17B4, HIC1, and RASSF1A). In the training set, patients with methylated serum DNA for RASSF1A and/or APC had the worst prognosis ($P < 0.001$). This finding was confirmed by analyzing serum samples from the independent test set ($P = 0.007$). When analyzing all 86 of the investigated patients, multivariate analysis showed methylated RASSF1A and/or APC serum DNA to be independently associated with poor outcome, with a relative risk for death of 5.7. DNA methylation of particular genes in pretherapeutic sera of breast cancer patients, especially of RASSF1A/APC, is more powerful than standard prognostic parameters.

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Polyunsaturated fatty acids sensitise colon cancer cells to the apoptotic effects of sodium butyrate

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Dysregulation of the balance between cell growth and death in the colonic epithelium is associated with cancer promotion. Understanding how cell death in this self-renewing tissue is regulated and how it is influenced by interaction of specific dietary components, especially fat and fibre, could lead to improved treatment and prevention strategies for cancer. The important modulators of cytokinetics in the colonic epithelium are short-chain fatty acids, particularly butyrate, produced from dietary fibre. Supply of essential polyunsaturated fatty acids (PUFAs) of n-6 and n-3 types from dietary fat is proposed to be linked with the risk of colorectal cancer Therefore, in our experiments the effects of two types of PUFAs - arachidonic (AA, 20:4, n-6) or docosahexaenoic (DHA, 22:6, n-3) - on the response

of human colon adenocarcinoma HT-29 cells to sodium butyrate (NaBt) were investigated. The parameters reflecting cell proliferation and cell death were studied together with oxidative response, mitochondrial membrane potential (MMP) and changes of selected regulatory molecules associated with cell cycle (p27Kip1and p21Cip1/WAF1) and apoptosis (caspase-3, -9,PARP, Bcl-2, Bax, Bak, Mcl-1). After 48 h of treatment with either AA or DHA a significant increase of the corresponding PUFA in HT-29 cell lipids was observed. These cells were more sensitive to NaBt-induced apoptosis reflected by an increased % of floating cells, cells in subG0/G1 population, and cells with apoptotic morphology. This was associated with increased reactive oxygen species production, lipid peroxidation, decrease of MMP, activation of caspase-3 and -9, PARP cleavage, and changes in the expression of antiapoptotic Mcl-1 protein. Pre-treatment of cells with PUFAs attenuated cell cycle arrest caused by NaBt associated with increased p27Kip1 expression. The observed effects were modulated after inhibition of protein synthesis by cycloheximide, and only partially by the antioxidant Trolox. Taken together, PUFAs may have beneficial effects in the colon enhancing apoptosis induced by NaBt. Alteration of cell membrane lipid composition and potentiation of oxidative processes accompanied by changes in mitochondria followed by stimulation of apoptotic cascade components play a role in these effects. This work was supported by the Grant Agency (GA) of the Czech Rep (No. 524/04/0895) and GA of Academy of Sciences of the Czech Rep. (No. S5004009).

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The use of artificial neural network in identification of women with high risk for breast cancer

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Introduction: Breast cancer is the leading malignancy in females. So far, early detection is the best possible method for the control of this disease. Screening recommendations, presented by leading cancer organizations, agree on mammography being the screening method; however, there is no overall consensus over the screening interval and the age of women offered screening.

Objective: Individual risk for breast cancer in women within the same age group might differ significantly depending on family history and other factors. Identification of individual risk for breast cancer might enable early detection scheme adapted to women’s personal risk. METHODS In this paper the model based on Artificial neural network (ANN) is presented; the aim of this model is the identification of women at high risk for breast cancer based on risk factors. ANN models are particularly convenient for identification of systems with high number of variables. The work with ANN consists of 3 phases: (a) neural network architecture selection - number of units and layers of ANN; (b) model parameter estimation; and (c) model verification - testing the model by set of test patterns.

Results: As input data for ANN model we used data on risk factors (age, family history, age at menarche, age at menopause,