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Catalytic activity, genotype of detoxifying enzymes and DNA-adducts in human placenta as risk factors for newborns

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Policyclic aromatic hydrocarbones (PAH) readely transforms to the strong electrophyles in placental tissue. If not neutralized, they could form DNA adducts, mutagenic and cancerogenic. The level of genomic PAH-DNA adducts in placenta could serve as the incides of genotoxic damage in fetus. The objective of this study was to elucidate the connection between activity, genotype of detoxifying enzymes, radioactive and chemical exposure and the level of PAH-DNA adducts in placenta. Term human placentas (166 specimen) were obtained in the regions of Ukraine, Belorussia and Poland with different level of radiational and chemical pollution. We measured: ethoxycoumarin O-deethylase (ECOD) and glutathione S-transferase (GST) activities as main placental I and II stages detoxifying enzymes (CYP1A1 and GST), relative amount of GSTP1-specific mRNA, CYP1A1 Ile462Val and GSTP1 Ile104Val polymorphisms and indices of tissue redox state. Competitive chemiluminescent immunoassay was improved for study PAH-DNA adduct level. The strong correlation was revealed between placental GST activity and PAH-DNA adduct level (r = - 0,86). Multifactorial regression analysis has shown that the higher is benzo(a)pyrene pollution in ambient air and radioactive exposure the lower is GST activity and the higher is PAH-DNA adducts. GST activity and intensity of lipide peroxidation are higher in carriers of CYP1A1 Ile462Val genotype comparing Ile462Ile. Placental GST activity was also higher in carriers of 104Ile isoform of GSTP1 comparing 104Val one, but does not depend from GSTM1 gene deletion. Polimorphisms studied are known to be associated with the risk of lung and some other types of cancer. Placenta is the tissue of fetal origin, easily available after delivery. We proposed to use genotyping of detoxifying enzymes in placenta as prognostic factor in child's life. Weak but significant inverse correlation was found between GST activity and the frequency of obstetrical pathologies while positive correlation with Apgar's index. The results evidenced that the placental detoxication efficiency, namely GST activity, is the factor of cancerogenic damage, at the same time it reflects environmental pollution and may be used, together with PAH-DNA adducts content, for risk evaluation in new-borns.

Risk Groups/Markers/Early Diagnosis

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Methylated DNA on tampons to detect endometrial and cervical cancer

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This proof of principle study aimed to define a new and simple strategy for detection of endometrial or cervical cancer using epigenetic markers. We investigated DNA isolated from vaginal secretion collected by tampon for aberrant methylation. Sodium bisulfite-treated genomic DNA was analyzed by means of MethyLight, a fluorescence-based, real-time PCR assay. Aberrant methylation of 38 genes in DNA obtained from vaginal secretion from the first five patients with endometrial cancer and the first four patients with benign disease was analyzed to determine appropriate genes for further study. The most appropriate genes for our further analyses were determined to be those that revealed the greatest difference in PMR (Percentage of fully Methylated Reference) values between patients with benign disease of the uterus and endometrial cancer. Five genes, namely RASSF1A, hMLH1, CDH13, HSPA2 and SOCS2, were selected for further analysis in 15 patients with and 109 patients without endometrial cancer. All endometrial cancer patients revealed three or more methylated genes, whereas 91% (99 of 109) of the patients without endometrial cancer had no or fewer than three genes methylated in their vaginal secretion. In addition we analyzed methylation of DNA obtained from cervicovaginal specimens of 13, 31 and five patients with no dysplasia/low-grade squamous intraepithelial lesion (SIL), high-grade SIL and invasive cervical cancer, respectively, collected on a tampon. Unsupervised hierarchical cluster analysis using solely information on DNA methylation of the 11 genes (SOCS1, CDH1, TIMP3, GSTP1, DAPK, hTERT, CDH13, HSPA2, MLH1, RASSF1A and SOCS2)was able to correctly predict the presence of all invasive cervical cancers: one of the two clusters formed, contained all five invasive cervical cancers as well as two high-grade SILs. The methods developed in this study provide the basis for a prospective clinical trial to screen asymptomatic women who are at high risk for endometrial and/or cervical cancer. An additional set of genes has to be defined to also correctly predict high grade SIL. (This study was supported by grants from "Fonds zur F rderung der wissenschaftlichen Forschung", P15995-B05 and P16159-B05 to W.M.)