risk and clinical tumor characteristics. Survival probabilities were compared between different subgroups.

As a novel finding several SNPs seemed to associate with the hormone receptor status. The strongest association was observed between the variant allele of the SNP in the ITGB4 gene and estrogen receptor negative (ER-) tumors (OR 2.09, 95% CI 1.19-3.67). Moreover, the ITGB4 SNP was associated with survival. The variant allele carriers had a worse survival compared to the wild type genotype carriers (hazard ratio [HR] 2.11 95% CI 1.21-3.68). The poor survival was significantly associated with the aggressive tumor characteristics: high grade, lymph node metastasis and high stage. Since the variant allele of the investigated SNP in the ITGB4 gene may cause a loss of the binding site for the miRNA miR-34a, the SNP may increase the expression of the ITGB4 gene and enhance the ability of integrin β4 to promote tumor cell growth, survival and invasion, and thus partly explain the observed bad survival of the carriers of the variant allele.

As the ITGB4 SNP seems to influence tumor aggressiveness and survival, it may also have prognostic value in the clinic. Since integrin-associated proteins are involved in all major signal transduction pathways regarding proliferation and survival they are likely candidates for targeted therapies. The observed genetic variation may also cause inter-individual variation in the response to integrin targeted therapy.

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Loss of expression of Claspin in tumour cells may be involved in breast carcinogenesis

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Breast cancer is the most common cancer among women. Familial forms may be associated with germ-line mutations in BRCA1/2. However, these mutations have incomplete penetrance, suggesting involvement of other genetic/environmental factors. As BRCA1/2 interact with other cellular proteins in a common DNA damage repair pathway, it is likely that alterations in genes that encode these proteins may modify the risk of breast cancer development in BRCA1/2 mutation carriers or in familial cases in which BRCA1/2 mutations are not identifiable. Claspin is a recently described protein that participates in DNA replication and DNA damage response, being an important checkpoint mediator essential for ATR-dependent activation of Chk1. It may also interact with BRCA1. We have thus investigated whether alterations in Claspin could be associated with increased breast cancer risk. DNA from 32 familial (characterized for BRCA1/2 mutations) and 36 sporadic breast cancer cases (all patients being followed at IPO Coimbra FG, EPE), and 60 healthy controls was screened for germline mutations in Claspin coding sequence and splice junctions using PCR-SSCP and DNA sequencing. We have detected two single nucleotide polymorphisms (Asn525Ser and IVS10+16), which co-segregated in most cases, two novel mutations (on 5'UTR-68 and codon 744) and one novel polymorphism (codon 6). The 5'UTR-68 and codon 744 mutations were found in only two of the 153 individuals analysed, one with familial and the other with (apparently) sporadic breast cancer. The Gly6Asp variant was over-represented in sporadic breast cancer patients. These findings suggest the association of this variant with an increased risk for the development of breast cancer. Preliminary data have shown that co-segregating polymorphisms were associated with loss of expression of Claspin in breast tumour cells, while expression was retained in normal cells. These data suggest a role for Claspin as a tumour suppressor, which may be related to its function in the control of DNA replication and triggering of cell cycle checkpoint responses, namely through activation of Chk1.

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Combined effects of p53 and p73 polymorphisms on head and neck cancer risk and progression - an Italian case-control study

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Background. The purpose of this study is to analyze the effects of selected p53 and p73 polymorphisms, their combination and the interaction with lifestyle habits, in association with head and neck cancer (HNC) risk and progression in an Italian population.

Methods. Two hundred and eighty-three cases and 295 hospital controls were genotyped for p53 polymorphisms on exon4 (Arg72Pro), intron 3 and 6, and p73 G4C14-to-A4T14. Modification of the effect measures on HNC by age, gender, alcohol, smoking and familiarity for cancer was tested through homogeneity tests across strata estimates from logistic regression analysis.

Results. We showed a statistically significant association between p73 variant allele and cancer of the oral cavity [Odds Ratio (OR) = 2.51; 95% CI: 1.19 – 5.35]. An effect modification of p73 variant allele by age was observed [OR= 12.85 (95% CI: 2.10 – 78.74) among those aged less or equal to 45 years at diagnosis, versus an OR of 1.19 (95% CI: 0.72 – 1.96) among those >45; p-value for homogeneity among strata estimates = 0.013]. Also, an OR of 3.60 (95% CI: 1.30 – 9.92) among current smokers carrying p73 variant allele was observed, versus an OR of 1.32 (95% CI: 0.80 – 2.19) among ex- and never-smokers with the identical genotype (p value of heterogeneity among strata estimates= 0.10).

From the gene-gene interaction analysis, it was observed that in all of the combinations individuals carrying two risk genotypes had not an additional risk compared to those with only one risk genotype, except those carrying both p53 intron and p73 mutant alleles, showing an OR of 2.22 (95% CI: 1.08-4.56). A poorer survival resulted among carriers of p53 intron 6 variant allele (Hazard Ratio = 0.49, 95% CI: 0.21 – 1.09).

Conclusion: This study shows that p73 G4C14-to-A4T14 polymorphism might be a risk factor for HNC, especially among young subjects. For the first time our study shows that individuals carrying the unfavourable variant of both p53 intron 3 and p73 exon 2 have an additional risk to develop HNC. Larger studies are required to confirm our results.

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Solid cancer incidence in the Republic of Belarus (1970-2007) - 16 years before and 22 years after Chernobyl accident

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Background: Despite of many studies of the relation between huge radiation contamination by different radioactive elements and changes of cancer incidence rates in Belarus, the question on the consequences of this disaster has not still lost its actuality.

Methods: The data of obligatory cancer registration were studied for the past 38-years. Age Standardized Incidence Rates (ASRWorld per 100 000) in males and females (urban and rural) were calculated.

Results: From 1970th to 2007th 969 714 new cancer cases (485797 (50,1%) - in males and 483917 (49,9%) - in females) have been established in Belarus. In the analysis five main types of time-related ASR trends were distinguished. (1) Considerable decrease was shown in ASR of males and females stomach cancer as in lip cancer in males. (2) No considerable changes in ASR were detected for liver, pancreas, esophagus, larynx, lung and bladder female cancers. (3) Constant growth of ASR was noted for colon cancer and melanoma of skin in both males and females and for breast, corpus uteri and renal female cancers. (4) ASR for female and male recto-sigmoidal cancer and male cancers of oesophagus, larynx, lung and bladder had been increasing till the middle of the 90s to be fixed at a certain level then. Thyroid cancer incidence jumped immediately after disaster from 0,45 in 1970th and 0,77 in 1986th to 3,1 in 2003d (males) and from 0,81 in 1970th and 1,71 in 1986th to 14,7 in 2003d (females). Since 2003d morbidity has been flatten out in males and started decreasing in females (12,3 in 2007th). The highest level of thyroid cancer incidence is noted in Gomel, Mogilev and Brest regions (most radiation contaminated). (5) Incidence rates for skin cancers in the both sexes, prostatic and renal cancer in males slowly increasing from the 70s started growing rapidly in the middle of the 90s.

Conclusions: Despite of differences in structure and dynamics of cancer incidences in males and females the total number of new cancer cases was equal in both sexes. The above-mentioned ASR trends may be indicative of the impact of some environmental factors at certain periods of time which are modifying cancer incidence trends. Now we are working at cancer mapping through 118 administrative areas of Belarus to study mentioned above tendencies in details and propose some possible carcinogens to provide a basis for further analytical epidemiological studies.

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Capacity of Belorussian population cancer registry to identify occupational skin cancer in Polotsk-city

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Background: In the end of 80th 25 cases of carcinoma of skin of the arm (C44.6) in workers of Polotsk Glass Fiber Enterprise were occasionally

found. All affected workers were operators and had a long term direct professional contact with lubricating agent N80.

The aims: The purpose of this work was to estimate the possibility of determination of localization of carcinogenically dangerous production by data of Belorussian cancer registry.

Materials and methods: Skin cancer in two close settled cities Polotsk and Novopolotsk and whole Belorussian urban population was estimated by data of Belorussian Cancer Registry for 1990-2006. Standardized incidence ratios (SIRs) were calculated using the Belorussian urban population incidence rates to generate expected numbers. We have used in the study GIS methodology to make the Atlas of skin cancer SIR time (1978-2005) distribution by 117 regions of Belarus.

The results: We have designed some criteria for primary identification of occupational risk factors in small towns based on data of Population Cancer Registry. There are high numbers of cancer cases with specific localization and morphology, younger mean age of patients and plurality of tumors. Since 1990 to 2006 it was established 956 cases of skin cancer (C44) in Polotsk, 856 cases in Novopolotsk and 61586 in Belarus. According to Atlas of Skin cancer Standardized Incidence Ratios distribution Polotsk region seems to have high skin cancer risk in compare with other Belorussian areas. The proportions of C44.6 localization were 6,5% in Polotsk, 4,3% in Novopolotsk and 3,9% in Belarus. But in the same time among C44.6 cases the proportions of squamous cell carcinoma were 66% in Polotsk, 32% in Novopolotsk and 20% in Belarus. The next feature is the number of plural primary malignant tumors (10 double and 4 triple of metachronous tumors C44.6 in Polotsk against 1 of double tumors in Novopolotsk). The mean age of diseased of carcinoma C44.6 was 55,0 in Polotsk and 62,7 in Novopolotsk and 68,7 years in Belarus. SIR of C44.6 for Polotsk (SIR=2,18; 95%CI=1,67-2,82) and Novopolotsk (SIR=1,58; 95%CI=1,11-2,18) were significantly higher than in whole population. Thus we can conclude that presence of significant professional carcinogenic factor in small city could be discovered in population based descriptive epidemiological study.

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Mouse mammary tumor virus (MMTV)-related sequences in the juvenile acute myeloid leukemia patients

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Background: MMTV-homologous sequences were found earlier in DNA samples from tumor tissue and lymphoid cells of sporadic/familial breast cancer (BC) and Non-Hodgkin's lymphomas + BC patients. Two female BC patients in our cancer-register had child suffered with acute leukemia (AL). We have analyzed a primary patients with AL to verify this observation. Material and Methods: Peripheral blood and bone marrow DNA samples obtained from 11 primary patients with acute myeloid leukemia (AML) and 6 ones with acute lymphoblastic leukemia (ALL) were analyzed by PCR using specific primers for gp52-coding area of the env MMTV gene and Sag-coding area of 3'LTR MMTV. PCR products of 665 bp and 725 bp were cloned in pGEM-T vector and sequenced. RT PCR using primers for the env MMTV gene was performed to evaluate MMTV-homologous sequence expression. Results: 4 bone marrow DNA samples from 11 patients (3 boys of 9, 11,13 years old and 1 girl of 15 years old) were the env /LTR MMTV-positive, one boy has mother with BC and young healthy brother. While five ALL patients (3 - 11 years old) were MMTV-negative by PCR. Sequencing of the env MMTV and 3'LTR –related cloned PCR products has found 93-94% homology to the exogenous env MMTV gene (C3H starin and Mus musculus MMTV), and 92% homology to SAG protein gene of Mus musculus MMTV. The sequence transcripts were revealed by RT PCR. ORF finder has shown one Frame of 567 bp long in gp 52-coding area of the env MMTV sequence and one Frame of 563 bp long in Sag-coding sequence. BLAST analysis puts the sequences into tree clusters between endogenous MMTV RNA env gene / right LTR (Mtv 17) and Mus musculus mammary gland cDNA branches. Conclusions: MMTV-homologous sequences were firstly revealed in 4 from 11 juvenile patients with AML. It indicates that MMTV-related virus might involves both in lymphomas and in leukemia in human by infection of dendritic and/or pluripotent hemopoetic stem cells. A possible ways of MMTV infection in AML patients are under discussion.

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Glutathione-S-transferase T1, M1 and P1 polymorphisms as risk factors for early onset lung cancer

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Lung cancer (LC), the leading cause of cancer death worldwide, is considered the result of complex interactions between environmental - predominantly smoking - and genetic factors. It is supposed that a particularly strong genetic component exists in the group of individuals with early onset LC. Glutathione-S-transferases (GSTs) are among the central enzymes involved in cellular detoxification.

A case-control study was carried out to identify GST genetic polymorphisms that might modify the risk of developing early onset LC. 638 Caucasian patients under the age of 51 with confirmed primary LC and 1300 cancer free control individuals, matched by age and sex, were included in this analysis. Overall, 5 SNPs in the GSTP1 gene and deletion polymorphisms in GSTM1 and GSTT1 were analysed. Genotyping of the GSTP1 polymorphisms was carried out using MALDI-TOF (matrix assisted laser desorption/ionization time-of-flight) mass spectrometry. A new semi quantitative real-time multiplex PCR assay on the LightCycler 480 was established for genotyping GSTM1 and GSTT1 copy numbers.

Conditional logistic regression analysis adjusted by smoking was applied to assess polymorphism-associated ORs. The GSTP1 SNP rs1138272 homozygous variant genotype was associated with an increased risk of LC overall (OR 3.14; 95% CI 1.01-8.96, p=0.032). For GSTP1 SNP rs4891 an increased risk of LC associated with the homozygote variant genotype was observed in the group of heavy smokers (>21 packyears) (OR 1.76; 95% CI 1.05-2.84, p=0.032). Interestingly, for GSTT1 an effect was only observed in the group of heavy smoking women, where carriers of at least one null allele showed an increased risk of LC (OR 2.33; 95% CI 1.31-4.14, p=0.004). However, all these findings were not significant after Bonferroni correction for multiple testing. An effect of GSTP1 SNP rs1695 was detected only among individuals with GSTT1 null genotype (OR 3.36; 95% CI 1.36-8.32 p=0.009), however, gene-gene interaction was not significant (p=0.07).

Our results do not support a main effect of GSTP1, GSTM1 and GSTT1 genotypes with regard to LC. However, further studies, including gene-gene interaction analysis, will be necessary. To the authors' knowledge the current study is the first investigation of GSTT1 and GSTM1 deletion polymorphisms as risk factors for early-onset LC, employing a method that distinguishes between homozygous wild-type and heterozygous individuals.

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Melanocortin receptor 1 variants and melanoma risk - a study on two European populations

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The G-protein coupled Melanocortin receptor 1 (MC1R) is a pivotal component of melanin synthesis in melanocytes. The gene encoding MC1R is highly polymorphic and many variants are associated with an increased risk of melanoma. At least five variants are strongly associated with high risk phenotypes of red hair and fair skin (RHC alleles; D84E, R142H, R151C, R160W and D294H) in Caucasians.

We investigated two European populations, German and Spanish, for the effect of MC1R variants on risk of malignant melanoma and on disease outcome. 1298 melanoma cases (595 German and 703 Spanish cases) and 1582 healthy controls (1038 German and 544 Spanish controls) were genotyped by direct sequencing. The risk of any variant in the German population (odds ratio OR 1.59, 95% confidence interval CI 1.24-2.05) was comparable to the risk observed in the Spanish population (OR 1.84, 95% CI 1.42-2.40). Carriers of two variants were at twice the risk than carriers of only one polymorphism indicating a gene dosage effect of this risk factor.

Despite similarities in the risk associated with MC1R variants, we also observed subtle differences in the two populations. RHC variants were more frequent in German than in Spanish population. However, an association between RHC variants and increased risk of melanoma was found in both populations (German: OR 2.40, 95% CI 1.81-3.19, Spanish: