There was no association between mammographic density and intake of calcium, vitamins A, retinol, B_{12}, C and D and no association between mammographic density and combined intake of vitamin D and calcium. However, when examining mammographic density by month of screening, we observed that mean percent density was higher in women screened in April, May and June (21.5%, 20.5%, and 20.2%, respectively) compared to those screened in September, October and November (19.9%, 17.7%, and 17.1%, respectively), suggesting that vitamin D status may be important.
Conclusions: Overall, we found no association between the selected nutrients and mammographic density, although we observed a positive association with saturated fat in women with a normal BMI (23–25.9). We also observed a seasonal variation in mammographic density.

56 Pre-diagnostic serum 25-hydroxyvitamin D concentrations and the risk of ovarian cancer

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Background: The possible role of vitamin D in the prevention of ovarian cancer has been investigated in ecological and experimental studies and there are suggestions that vitamin D may be protective against ovarian cancer. There is however paucity of epidemiological studies exploiting the use of serum 25-hydroxyvitamin D and ovarian cancer risk even though this may represent the best way to determine if there is any relationship.
Materials and Methods: We investigated the relationship between serum 25-hydroxyvitamin D and ovarian cancer risk in a prospective population-based study nested within the Finnish Maternity Cohort (FMC), Finland. The FMC is a biorepository of serum samples of almost all pregnant women in Finland since 1983. It contains about 1.6 million serum samples. Within the cohort, 201 ovarian cancer cases were selected and for each case, 2 controls were matched for age ($\pm$1 year), parity and sampling season ($\pm$4 weeks). Odds Ratio and 95% CI were calculated using conditional logistic regression appropriate for matched data.
Results: We observed an increased risk, OR 1.8 (95% CI 0.9−3.5) of ovarian cancer comparing women within the lowest quintile of serum 25-hydroxyvitamin D concentrations to those within the highest quintile, but this was not statistically significant. There was also a tendency to a higher risk of ovarian cancer among women with insufficient serum 25-hydroxyvitamin D (<75 nmol/L) compared to those with sufficient concentrations (>75 nmol/L); OR 2.7, 95% CI 1.0−7.9.
Conclusions: Though we did not observe a statistically significant association between serum 25-hydroxyvitamin D and risk of ovarian cancer, there is evidence to suggest that some women (women with insufficient serum concentrations) may be at increased risk. Further studies are needed to investigate this relationship because presently, very few modifiable factors are known to have any impact on ovarian cancer risk.

57 Interaction between RFC1 and MTHFR genes polymorphisms and risk of paediatric acute lymphoblastic leukemia with common somatic alterations

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Background: Folate is an important substance for cell division and for maintaining homeostasis. Its metabolism is crucial for the prevention of chromosomal abnormalities. Depending on the folate intake and on the polymorphisms in folate-related genes, the risk of acute lymphoblastic leukemia (ALL) may be affected. We previously observed different risk patterns of Brazilian acute leukemias associated to *MTHFR 677 C>T* and *MTHFR 1298 A>C* polymorphisms. We now aim to address whether there is an interaction pattern between folate-related genes polymorphisms (*RFC1 80G>A, MTHFR 677 C>T* and *MTHFR 1298 A>C*) and the occurrence of somatic alterations commonly observed in ALL.
Material and Methods: From 2000 to 2009, children (0−14 years-old) newly diagnosed with ALL were included. Control group consisted of unselected children with no previous history of malignancy living in the same regions of cases. At the time of diagnosis, samples were routinely screened and subclassified according to the molecular-cytogenetic biomarkers. DNA from cases and controls were obtained from biological sample, which included fresh mononuclear cells or smears or peripheral blood or buccal cells. Genotyping was performed by standard polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) technique for determining *MTHFR 677C>T* and *MTHFR 1298A>C* and *RFC1 80G A* genetic variants. Maximum likelihood method was used to estimate the allelic frequencies and the goodness-of-fit of genotype distribution to Hardy–Weinberg equilibrium was ascertained by the chi-square test. Unconditional logistic regression methods were used in univariated and multivariated models. To increase the statistical power, heterozygous and mutant homozygous groups were combined and compared to wild-type groups.
Results: A total of 687 ALL cases [pro-B ALL (n, 122), c-ALL (n, 290), pre-B ALL (n, 140) and T-ALL (n, 42); 93 ALL samples could not be subclassified] and 605 controls were analyzed. 274 cases were diagnosed with somatic alterations, being *MLL* rearrangements (n = 90), *ETV6/RUNX1* (*TEL/AML1*) (n = 53), hyperdiploidy (n = 53) the most commonly observed. Univariate analyses of childhood ALL patients and controls demonstrated that *MTHFR 677C>T* results in a protector factor [OR = 0.60; 95% CI, 0.42−1.0], while the *RFC1 80G>A* genotype showed an increased risk but without statistical significance [OR = 1.90; 95% CI, 0.82–4.42]. A significant association for carriers of 677C>T was demonstrated for leukemias with *ETV6/RUNX1* [OR = 2.41; 95% CI, 1.03–5.62]. No significant associations were evident for either polymorphism with other molecular defined subgroups.
Conclusions: The results indicate that molecularly defined subgroups of leukemias have different etiologies and also confirm the importance of folate pathways in the development of childhood leukemia.

58 Human DNArepair genes and genetic susceptibility to melanoma: a candidate gene approach using sequenom platform

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Background: Cutaneous malignant melanomas (MM) represent aggressive neoplasms and its frequency is increasing rapidly. The key environmental risk factor is exposure to the ultraviolet (UV) component in sunlight, which causes various kinds of DNA damage, including bulky lesions and oxidative damage, which may lead to mutations, if not repaired efficiently. Thus, DNA repair is critical for maintaining the integrity of the genome. The nucleotide excision repair (NER) pathway deals with the main forms of UV induced DNA damage. Polymorphisms on these pathway genes might modulate cancer predisposition.
Materials and Methods: We present a case-control study including 640 Spanish MM patients and 340 control subjects. Phenotypic information was collected using a standardised questionnaire. All studied subjects gave informed consent. Functional (from coding and regulatory regions) SNPs with MAF < 0.5 were selected using HapMap database.
Results: Thirty SNPs in 17 genes belonging to the NER pathway were finally selected. Twenty five have been successfully genotyped using Sequenom platform (16 and 9 multiplexes respectively). The 5 remaining assays failed were designed by Taqman.
Conclusions: Associations with melanoma and pigmentary characteristics such as hair, skin and eye colour will be discussed. These results will confirm the contribution of excision repair genes to genetic predisposition to MM in Spain.

59 Colorectal cancer: candidate gene approach using obesity associated genes that show ancestral susceptibility

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Background: Colorectal cancer (CRC) and obesity are nutrition related, complex diseases which share both environmental and genetic risk factors. A number of studies have shown that complex diseases can be associated with ancestral risk alleles. In the evolutionary context, the mechanism of ancestral-susceptibility can be explained by continuous adaptation to varying environmental conditions. Due to a change in these conditions a former beneficial variant can become disadvantageous. In such a case, positive selection will drive the derived, protective or more beneficial allele to higher frequency. In this study we want to apply this framework to single nucleotide polymorphisms (SNPs) and genes that are associated with an increased risk of obesity to find new candidate genes for CRC.
Methods: To identify candidate SNPs we used a two step selection process. 1. We selected genes, for which ancestral alleles have been associated with increased risk of obesity. 2. We chose SNPs with a minimal allele frequency difference of 60% among the worldwide populations YRI, CEU, CHB and JPT, indicating a selective process. So far, we selected 9 SNPs in 3 genes (ENPP1, GAD2 and MTMR9) to test for an association with CRC. A hospital

based case-control study population containing 1228 CRC case samples and 782 control samples, recruited in nine oncological departments and five gastroenterological departments in the Czech Republic, was genotyped using KASPar Assays®.
Results: The preliminary results indicated one SNP in ENPP1 (rs1033398) to be associated with the risk of CRC (p_{trend} 0.016).
Conclusion: The application of the ancestral-susceptibility model to intertwined complex common diseases may be a promising method to detect candidate genes for CRC.

60 Predisposing genes in hereditary breast and ovarian cancer in the Czech Republic

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Background: We screened patients at high risk of developing breast or ovarian cancer for mutations in two major predisposition genes, *BRCA1* and *BRCA2* and further we focused on the role of additional genes that also influence the risk of breast/ovarian cancer. In this study we analyzed the role of *CHEK2*, *ATM* and *p53* genes in tumourigenesis.
Materials and Methods: A series of 705 unrelated patients selected for genetic testing was first analyzed for the presence of mutations in *BRCA1/2* genes and those tested negative were subsequently screened for alterations in other susceptibility genes. Complete coding regions were analyzed in *BRCA1*/2, *ATM* and *p53* genes; the *CHEK2* gene was tested for the most common point mutation 1100delC and for the genomic deletion of 5395 bp that leads to the loss of exons 8 and 9 and occurs frequently in the Slavic population. All identified gene alterations were confirmed and characterized by direct DNA sequencing.
Results: Within 705 analyzed individuals, 125 (17.7%) carried a *BRCA1* mutation and 34 (4.8%) a *BRCA2* mutation. Large deletions or complex genomic rearrangements detected at the *BRCA1* locus accounted for 12% (15/125) out of all identified *BRCA1* mutations. No large deletions were detected in the *BRCA2* gene. Pathogenic mutations in other tested genes were less frequent. Of the 545 tested patients, 9 (1.7%) carried pathogenic mutations in *CHEK2*, 5 (0.9%) in *ATM* and 3 (0.6%) in *p53*.
Conclusions: Mutations in *BRCA1/2* genes included 90% (159/176) of all identified gene alterations. However, our results also indicated that analysis of locally prevalent recurrent mutations in other susceptibility genes may be of an important clinical relevance. The most relevant of the other tested genes was *CHEK2* and the two recurrent mutations in this gene, 1100delC and deletion of exons 8−9, identified in four and five patients respectively, belong to frequent gene alterations identified in breast/ovarian cancer families. On the other hand, families with mutations in *ATM* and *p53* gene were rare and the role of these genes in breast tumourigenesis is limited. Two mutations in the *p53* gene were detected in cases of breast cancer prior to age 28 years that were not from families with Li-Fraumeni features.
Acknowledgments: Supported by grants from IGA MZCR No. NS10304-3/2009 and No. NS10566-3/2009, and from the Ministry of Education No. MSM002160808.

61 Influence of polymorphism-modified gene expression on breast cancer survival

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There is substantial evidence of an inherited component in breast cancer susceptibility. Along with the previously characterized high-penetrance genes BRCA1 and BRCA2, also moderate-penetrance (e.g. ATM, BRIP, CHEK2, PALP) and low-penetrance genes (e.g. TGFB1, CASP8, loci identified in genome wide association studies (GWA)) have been discovered. However, also prognosis and survival in breast cancer are at least partly heritable. In this study, we applied the candidate gene approach. Candidate genes were chosen following a systematic analysis of literature about different gene expression profiles in different breast cancer survival groups. Therefore, we were not looking for non-synonymous single nucleotide polymorphisms (SNPs) but rather for SNPs in promoter, 5′ and 3′ untranslated region (UTR). We focused on genes directly involved in the regulation of the cell cycle, such as cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors and genes involved in the assembly of the pre-replicative complex for DNA replication. Genotyping was done in a Swedish population using KASPar assays. The genotyping data were correlated with risk, traditional prognostic markers, e.g. estrogen/progesterone receptor status, and survival in a population-based case-control cohort.
We found 6 SNPs in 4 genes to have an influence on the overall survival of breast cancer. Some of these mutations were also associated with traditional prognostic markers. In addition, we found 2 SNPs being associated with susceptibility to breast cancer.
Our findings support the finding of the gene-expression publications, which have always ranked cell cycle control genes as the ones most distinctly expressed in different survival groups.

62 Pre-diagnostic circulating parathyroid hormone concentration and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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Background: Parathyroid hormone (PTH) has been proposed to play a promoting role in carcinogenesis. However, few epidemiologic studies have directly investigated its role in colorectal cancer (CRC).
Methods: A case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort was conducted with 1,248 incident, sporadic CRC cases matched to 1,248 controls. Circulating pre-diagnostic PTH and 25-hydroxy vitamin D (25-(OH)-vitamin D) concentrations were measured by enzyme-linked immunosorbent assays. Detailed dietary and lifestyle data were collected from questionnaires. Multivariate conditional logistic regression was used to estimate the incidence rate ratio (RR) with 95% confidence intervals (95%CI) for the association between circulating PTH and CRC risk. Effect modification by various risk factors was examined.
Results: High levels of serum PTH ($\geqslant$65 ng/L) were associated with increased CRC risk (RR = 1.41, 95% CI: 1.03–1.93) compared with the serum PTH between 30 and 65 ng/L. In sub-group analyses by anatomical sub-site the risk for colon cancer was RR = 1.56, 95% CI: 1.03–2.34, and for rectal cancer RR = 1.20, 95% CI: 0.72–2.01 ($P_{heterogeneity}$ = 0.21). In interaction analyses, among participants who had a low intake of dietary calcium, the association between high PTH and CRC was the strongest (RR = 2.49, 95% CI: 1.38–4.50; $P_{interaction}$ = 0.64). Further stratified and joint analyses suggested potential differences in PTH-CRC effect estimates according to 25-(OH)-vitamin D and body mass index (BMI) categories, however, none of them was statistically significant.
Conclusions: The results of this study suggest that high serum PTH levels may be associated with incident, sporadic CRC in Western European populations, independently of dietary calcium and 25-(OH)-vitamin D.

63 What is the risk of venous thromboembolism in patients with cancer? – a systematic review and meta-analysis

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Background: The association between cancer and thrombosis was first observed 145 years ago, and remains a very clinically relevant research area. Several review articles exist on the topic, but most are narrative reviews, with no systematic review in the present literature detailing the absolute risk of venous thromboembolism in cancer patients. A systematic review and meta-analyses were therefore performed to determine the incidence rates of VTE in different cancer types in high risk and average (population-based) risk cancer patients.
Methods: The Medline database from 1950–October 2009 was searched, along with the reference lists of identified papers and reviews. Included studies assessed the risk of venous thromboembolism (VTE), manifesting as deep venous thrombosis (DVT) and pulmonary embolism (PE), in patients with a range of primary malignancy types over a specified follow-up period (measured in person-years). Cohort risk groups were assessed based on previous cancer treatment regimens and stage of disease, with patients receiving