Abstracts

Opening session

001 BIRTH WEIGHT AND RISK OF CANCER

M. Ahlgren[1], J. Wohlfahrt[1], T. Sørensen[2], M. Melbye[1]. [1]*Danish Epidemiology Science Centre at Statens Serum Institut, Denmark;* [2]*Institute of Preventive Medicine, Copenhagen University Hospital, Denmark*

Introduction: It is well established that prenatal biological processes are important for the development of some childhood cancers, whereas less is known regarding their influence on adult cancer risk. Of interest, birth weight has been associated with risk of breast and testicular cancer, whereas studies of prostate cancer, for example, are less conclusive. Lack of appropriate materials has limited the possibilities to address whether prenatal exposures are important for the development of cancer in general.

Methods: We investigated the relationship between birth weight and risk of cancer in a Danish cohort of 106 504 women and 110 825 men born between 1930 and 1975. Birth weights were obtained from school health records and information on cancer was obtained by linking the cohort with the Danish Cancer Registry. Follow up was done from 1 April 1968 until 31 December 1997. A total of 7529 cases of primary invasive cancer were diagnosed in the cohort during 5 858 074 person–years of follow up.

Results: Analyses of site specific cancers revealed that most cancers have a positive linear association to birth weight. Departures from a linear association were statistically significant for testicular and prostate cancers that showed a V shaped association and Hodgkin's lymphoma that showed an inverse V shaped association to birth weight. Excluding the three exceptions, the trends for the individual cancer sites were not statistically different from an overall trend of RR = 1.10 (95% CI 1.05 to 1.15) per 1000 g increase in birth weight. This trend was the same in men and women and in all age groups. No confounding effect was found of age at first birth and parity in women.

Conclusion: Birth weight has a linear association with cancer risk in general, with 10% increase in risk per 1000 g increase in weight. Few cancers showed non-linear associations with birth weight, among which a V shaped association for cancers of the prostate and the testis was particularly striking. We hypothesise that the biological explanation behind the association between birth weight and cancer at different sites should be sought in a common pathway, with some superimposed opposing factor(s) influencing male hormonal cancer.

002 RESIDENTIAL PESTICIDES AND MELANOMA: A CASE CONTROL STUDY ON CUTANEOUS MELANOMA IN ROME

C. Fortes[1], S. Mastroeni[1], A. Blair[2], F. Melchi[3], M. Pilla[1], M. Alotto[1], G. Antonelli[1], P. Pasquini[1]. [1]*IDI/IRCCS, Clinical Epidemiology, Rome, Italy;* [2]*NIH/NCI, Occupational Epidemiology Branch, Bethesda, USA;* [3]*IDI/IRCCS, Dermatology Unit, Rome, Italy*

Introduction: Although exposure to sunlight can be considered the major aetiological factor for the development of melanoma, recent data suggest that many but not all cutaneous malignant melanoma have a strong association with sunlight. The present study was designed to evaluate the relationship between cutaneous melanoma and the residential use of pesticides.

Methods: A hospital based, case control study of melanoma was conducted on subjects aged >18 years living in the Latium Region and admitted to the reference hospital of skin disease for central south Italy, IDI-IRCCS in Rome, in the period from May 2001 to May 2003. Cases (n = 304) were patients with a new histologically confirmed diagnosis of primary malignant cutaneous melanoma. Controls (n = 305) were recruited among patients with non-dermatological diseases admitted to the same hospital during the study period. They were frequency matched to cases by sex (1:1) and age (in 5 year age strata). Exposure characteristics were obtained by interviewing study subjects.

Results: After careful control for sun exposure, residential pesticide use was associated with an increased risk for melanoma (OR 1.50; CI 95% 1.07 to 2.10). In a multivariate model, considering sun exposure, phenotypic traits, number of nevi and the use of pesticides, duration of pesticides use (⩾20 years) was associated with 4 times the risk (OR 4.12; CI 95% 1.69 to 10.48) for melanoma.

Conclusions: Our results indicate that pesticide exposure may be associated with an increased risk for melanoma.

003 TRANSMISSION OF RESISTANT HIV IN GERMANY: RESULTS FROM THE HIV SEROCONVERTER STUDY OF THE ROBERT KOCH INSTITUTE

G. Poggensee[1], C. Kücherer[2], J. Puscher[1], S. Somogyi[2], O. Hamouda[1]. [1]*Robert Koch Institute, Department Infectious Diseases Epidemiology, Berlin, Germany;* [2]*Robert Koch Institute, Retrovirology Group, Berlin, Germany*

Introduction: The German HIV seroconverter study, a prospective nationwide cohort study, was initiated in 1997 in order to analyse factors influencing the progression of disease in patients with known duration of infection and to assess the dynamics of the spread of resistant HIV.

Methods: Patients with a documented last negative HIV test and first positive HIV test within 3 years or an acute HIV seroconversion (defined by laboratory test criteria) are included in the study. Demographic and clinical data are collected anonymously by standardised questionnaires with yearly follow ups and blood samples are taken for HIV sub typing and genotypic/phenotypic drug resistance testing.

Results: End of 2003, for 330 drug naive study participants (12 females, 318 males) resistance testing was performed (41% of all recruited seroconverters). Transmission of drug resistant HIV (at least one drug) was detected in 50 study participants (15.2%). The transmission rate decreased from 20% in 1996 to 6% in 2000 and thereafter increased again; in 2003, the transmission rate was 13.8%. PI, NRTI, and NNRTI mutations were observed in 20 (40%), 13 (26%), and 28 (56%) patients, respectively. Multi-drug resistant HIV strains with resistance against two or three classes of antiretroviral drugs were detected in 8 (16%) study participants. Among the study patients, men having sex with men were significantly more at risk to harbour resistant HIV ($p = 0.03$). Antiretroviral therapy was initiated in 140 patients (42%; drug-sensitive HIV 120; resistant HIV 20). In 16 patients with resistant HIV a regimen including a drug with predicted reduced efficacy was initiated. The therapeutic regimen was changed in 30% of seroconverters infected with resistant HIV-1 on average after 11 months (range 5–16) and in 23% of study participants infected with a drug sensitive virus after 14 months (range 1–48; $p > 0.05$).

Conclusion: The HIV seroconverter study of the Robert Koch Institute provides important virological and epidemiological data on the transmission of resistant HIV in Germany. The results indicate a higher level of transmission of resistant HIV in patients acquiring the virus by homosexual contacts as compared to other modes of exposure. The investigation of the clinical impact of these findings is a major question of future research of the HIV seroconverter study. In particular, the duration of virological response to antiretroviral therapy with respect to the genotypic pattern of resistance associated mutations in the viral genome at baseline could be a valuable tool to identify prognostic markers of therapy failure.

004 EXPLORING THE EFFECTS OF THE MTHFR C677T POLYMORPHISM ON THE RISK OF CLUBFOOT: AN ANALYSIS OF CASE PARENT TRIADS IN THE UK

L. Sharp[1], Z. Miedzybrodzka[2], A. Cardy[1], J. Inglis[2], L. Madrigal[2]. [1]*University of Aberdeen, Epidemiology Group, Aberdeen, Scotland;* [2]*University of Aberdeen, Department of Medical Genetics, Aberdeen, Scotland*

Introduction: Clubfoot is a relatively common developmental disorder of the lower limb, affecting 1–4 per 1000 births worldwide. Little is known about clubfoot aetiology, but both genetic and environmental factors are believed to be involved. The B vitamin folate plays a crucial role in DNA synthesis and methylation. Low folate status in pregnant women has been implicated in several congenital malformations and there is some limited evidence that folate may have a role in clubfoot. The enzyme methylenetetrahydrofolate reductase (MTHFR) operates at a key branch point in folate metabolism. The *MTHFR* gene contains a C→T polymorphism at position 677, and the variant allele is associated with reduced enzyme activity. We used a case parent triad design to investigate whether the MTHFR C677T polymorphism affects risk of non-syndromic clubfoot.

Methods: Children with clubfoot and their biological parents were identified from records maintained by orthopaedic surgeons treating clubfoot in Scotland and northeast England and from the UK support group for children with lower limb deformities. Participating parents and children provided an oral DNA sample. Mothers completed questionnaires seeking information on use of folic acid supplements immediately before, or during, the pregnancy with the clubfoot affected child. Oral DNA was amplified by PCR and C677T genotype determined by digestion with HinfI. Log linear based models were used to calculate relative risks (RR) associated with maternal and child alleles and to investigate interactions between genotype and maternal folic acid supplement use.

Results: 375 case parent triads took part, 261 cases (70%) were male, 211 (60%) had bilateral clubfoot, 4% were born before 1980, 14% in 1980–89, 75% in 1990–99, and 7% in 2000–02. Maternal genotype did not influence clubfoot risk, but child genotype did. For children, compared to those with the CC genotype, heterozygotes (CT) had slightly reduced clubfoot risk (RR = 0.75, 95% CI 0.57 to 0.97) and homozygous variants (TT) substantially reduced risk (RR = 0.57, 0.37 to 0.91; p for trend = 0.006). 51% of mothers took folic acid supplements in the three months prior to, or the first trimester of, the index pregnancy. There was no evidence of an interaction between maternal or child alleles and maternal use of folic acid supplements. The RR of clubfoot was reduced for TT/CT *v* CC genotypes both in children whose mothers did not take folic acid (0.69, 0.48–0.99) and in children whose mothers did take folic acid (0.74, 0.52−1.05).

Conclusions: This is the first report of a specific genetic polymorphism associated with clubfoot. The direction of the association is intriguing and might suggest DNA synthesis could be relevant in the development of clubfoot. However, the mechanisms of clubfoot are poorly understood and the folate metabolism pathway is complex. Further research is needed to elucidate the role of the folate pathway in clubfoot.

005 CONSUMPTION OF FRUITS AND VEGETABLES, AND EXPRESSION OF THE MISMATCH REPAIR GENE HMLH1 IN HUMAN COLORECTAL CANCER: A PROSPECTIVE STUDY

P. Wark[1], M. Weijenberg[2], P. Veer[1], G. Wijhe[1], G. Muijen[3], A. Goeij[4], R. A. Goldbohm[5], Piet A. Van den Brandt[2]. *[1]Wageningen University, Division of Human Nutrition, Wageningen, The Netherlands; [2]University of Maastricht, Department of Epidemiology, Maastricht, The Netherlands; [3]University Medical Centre Nijmegen, Department of Pathology, Nijmegen, The Netherlands; [4]University of Maastricht, Department of Pathology, Maastricht, The Netherlands; [5]TNO Nutrition and Food Research, Zeist, The Netherlands*

Introduction: Striking clinical and pathological differences exist between colorectal carcinomas with and without defects in the mismatch repair system. Such defects are mainly due to loss of expression of the *hMLH1* gene. Animal and in vitro studies suggest that fruits, vegetables and folate are associated with expression of mismatch repair genes in the colon and rectum.

Methods: Associations between consumption of fruits and vegetables and expression of the hMLH1 mismatch repair gene were evaluated in The Netherlands Cohort Study using a case cohort approach. In 1986, 120 852 men and women aged 55–69 years completed a questionnaire on dietary and other postulated risk factors for cancer. After 7.3 years of follow up and with exclusion of the first 2.3 years, hMLH1 protein expression was assessed in colorectal cancer tissue obtained from 725 incident colorectal cancer patients using immunohistochemistry. hMLH1 protein expression was absent in 61 cases (8.4%). Risk ratios (RR) were computed to compare cases with and without hMLH1 expression to the sub cohort. In this abstract, preliminary results based on 38 cases without and 432 with expression of hMLH1 are reported. During the conference, results based on the entire study population will be presented.

Results: Consumption of fruits was associated with hMLH1 deficient colorectal carcinomas ($RR_{highest\ v\ lowest\ tertile}$ 0.28; 95% CI 0.12 to 0.66), but not with carcinomas expressing hMLH1 ($RR_{highest\ v\ lowest\ tertile}$ 0.96; 95% CI 0.74 to 1.24). Total consumption of vegetables was not associated with both types of tumours (without hMLH1 expression: RR 0.78; 95% CI 0.38 to 1.16; with hMLH1 expression: RR 0.91; 95% CI 0.71 to 1.16). Brassica vegetables, folate, and vitamin C tended to be inversely associated with hMLH1 deficient carcinomas, but not with carcinomas expressing hMLH1.

Conclusions: These analyses suggest that inverse associations between consumption of fruits, brassica vegetables, folate, and vitamin C might be confined to the subgroup of hMLH1 deficient colorectal carcinomas.