OCCUPATIONAL CANCER AND CARCINOGENESIS

EXPOSURE TO SOLVENTS AND RISK OF HEMATOLYMPHOPOIETIC MALIGNANCIES: EVIDENCE FROM THE "ITALIAN CASE-CONTROL STUDY ON HEMATOLYMPHOPOIETIC MALIGNANCIES."

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We have conducted a population-based case-control study in Italy. The study covered 11 Italian areas (Varese, Forlì, Siena, Latina, Ragusa, Imperia, Florence, Novara, Vercelli, and Verona provinces plus the city of Turin). All newly diagnosed cases of Non-Hodgkin’s Lymphomas (NHL), Hodgkin’s disease, all leukaemias types and Multiple Myeloma (MM) which occurred in males and females aged 20 to 74 years in the 1991-1993 period, were identified. The control group was formed by a random sample of the general population resident in each of the areas under study, stratified by sex and five-year age groups. Cases and controls were participating in a person-to-person interview. 2,737 cases and 1,779 controls agreed and gave a complete interview on education, lifestyle factors, occupational history, medical history, specific medications, and family history. The cases and controls, subject to specific questionnaires (about 50 for specific industrial and agricultural activities. Questionnaires of all interviewed people in 8 areas (2,428 cases and 1,530 controls) were evaluated by expert industrial hygienists who, blind to disease status, recorded their judgment on probability of exposure and intensity of exposure for a list of groups of chemicals and individual chemicals. For categorical models reported here, exposure was categorized as never, low, medium or high. For those in the medium/high level of exposure there was an increased risk of NHL (combined with Chronic Lymphocytic Leukemia [CLL]) because of substantial biological similarities between the two diseases) for exposure to toluene (OR 1.8, 95% CI 1.1-2.6), xylene (OR 1.7, 95% CI 1.0-2.6) and benzene (OR 1.6, 95% CI 1.0-2.4). There was a high degree of correlation among benzene, xylene and toluene exposure, so that disentangling the role played by each exposure separately was not possible. Subjects exposed to all three aromatic hydrocarbons (benzene, toluene and xylene, medium/high intensity level) had an OR of 2.2 (95% CI 1.1-4.5). Concerning all leukaemia types (ICD IX 204-208), we found a slight increased risk for exposure to benzene in medium/high category (OR=1.4, 95% CI 0.8-2.4). When we look at the specific subtypes of leukaemia we found no association between exposure to any chemical classes or specific solvent and myeloid leukemia (ICD XI 205) in the medium/high intensity levels and an increased risk for Lymphatic Leukemia (ICD IX 204) in particular for CLL, for exposure to benzene at medium/high level (OR 2.1, 95% CI 1.0-4.2). Our results support the hypothesis that solvent exposure may be a risk factor for hematolymphopoietic malignancies.

CANCER RISKS IN A HISTORICAL UK COHORT OF BENZENE-EXPOSED WORKERS

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A cohort of 5514 workers who had been occupationally exposed to benzene in 1966/67 or earlier had been assembled by the former Factory Inspectorate and the Medical Research Council from details provided by 233 employers in England and Wales. The cohort was followed up for mortality (1968-2002) and cancer registrations (1971-2001). National mortality rates and cancer registration rates were used to calculate standardised mortality ratios (SMRs) and standardised registration ratios (SRRs). Mortality was close to expectation for all causes (Obs 2430, 95%CI 97 to 105, SMR 101) and significantly elevated for cancer of the lip (Obs 2, SMR 974, 95% CI 118 to 5519), lung cancer (Obs 294, SMR 121, 95% CI 107 to 135), secondary and unspecified cancers (Obs 68, SMR 140, 95% CI 109 to 178), acute non-lymphocytic leukaemia (ANLL) (Obs 14, SMR 183, 5% CI 100 to 307), and all neoplasms (Obs 761, SMR 109, 95% CI 101 to 117). Significant deficits were shown for three non-malignant categories (mental disorders: Obs 8, SMR 50, 95% CI 21 to 98; diseases of the digestive system: Obs 51, SMR 76, 95% CI 56 to 100; accidents: Obs 23, SMR 55, 95% CI 35 to 82); SMRs for other leukaemia, lymphomas and multiple myeloma were close to or below expectation. There was some evidence of under-ascertainment of cancer registrations, although significantly elevated SRRs were shown for lung cancer (Obs 293, SRR 119, 95% CI 106 to 134) and cancer of the pleura (mesothelioma) (Obs 15, SRR 237, 95% CI 133 to 391). Many study subjects would have been exposed to carcinogens other than benzene (eg asbestos, rubber industry fumes, founded fumes, polycyclic aromatic hydrocarbons) and the excesses of lung cancer and mesothelioma are likely to reflect exposures to these other carcinogens. The carcinogenic effects of benzene exposure on the lymphohaematopoietic system were limited to ANLL, and appear to be small in absolute terms.

CHANGES IN METHYLATION PATTERNS IN SUBJECTS EXPOSED TO LOW-DOSE BENZENE

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High-dose exposure to benzene, an ubiquitous environmental pollutant, is associated with an increased risk of acute myeloid leukemia (AML) in exposed subjects, but mechanisms of leukemogenesis and risks associated with lower exposures are largely unknown.

Since AML is accompanied by profound epigenetic alterations, to assess if benzene exposure lead to a genome-wide hypermethylation and to a hypomethylation or hypomethylation of specific genes, we tested the degree of methylation of five sequences (Alu, LINE, MAGE, p15, H19) in DNA obtained from whole blood sample of a subgroup of the Italian population (Milan area, Italy), composed by 77 gasoline station attendants (median exposure 61 µg/m³), 77 traffic police officers (median exposure 22 µg/m³) and 57 referents (median exposure 6 µg/m³). These subjects are well-characterised in terms of individual airborne exposure, urinary biomarkers (t,1-muconic acid, S-phenylmercaptic acid, urinary benzene), genetic polymorphisms, DNA-SSB, blood cell count and questionnaire data (demographic, education, tobacco smoke, alcohol, leisure time activity, personal medical history, residence, work history). DNA methylation was investigated by means of PCR amplification and pyrosequencing on bisulfite-treated DNA. Alu and LINE-1 repetitive elements were used to estimate global DNA methylation. Hypomethylation of MAGE and hypermethylation of p15 was detected. H19 allele-specific methylation was determined as a marker of Loss of Imprinting (LOI).

A significant reduction in global methylation measured in Alu (-9.95%, p=0.027) and LINE-1 (-23.28% p<0.01) was observed for a 10-log units increase in airborne benzene exposure. Airborne benzene was associated with hypermethylation in p15 (+3.54%, p=0.018) and hypomethylation in MAGE (-4.85%; p=0.049), while H19 methylation was not significantly different in the three groups.

Our findings suggest that low-dose benzene induces in healthy subjects epigenetic alterations that are qualitatively similar to those found in malignant cells and need to be further evaluated.

CAUSE-SPECIFIC MORTALITY OF A COHORT OF RUBBER MIXERS

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Introduction: amines (beta-naphthylamine, nitrosamines), solvents, dusts (e.g. talc, carbon black, asbestos) have been described as determinants of high incidence of tumors (mainly bladder, larynx, lung cancer and leukaemia) in rubber workers. Rubber mixing is among the jobs with the highest exposure risk. Few carcase studies have been conducted on rubber workers exposed in the past to high levels of benzene. We report the results of a case-control study that evaluated the risk of cancer and non-cancer deaths among a cohort of 1,777 male workers employed in “rubber mixing”, hired between 1929 and 1978. Vital status was ascertained by means of mailing follow-up. Standardized Mortality Ratios were computed using the manual workers population of Torino as a reference, in order to reduce the healthy worker effect and the confounding from social class, since no information was available on subjects’ lifestyle habits. Observation period went from 1/1/1971 to 31/12/1995. 1,277 rubber Mixing workers and 1,500 controls were evaluated by expert industrial hygienists who, blind to disease status, recorded their judgment on probability of exposure and intensity of exposure for a list of groups of chemicals and individual chemicals. For categorical models reported here, exposure was categorized as never, low, medium or high. For those in the medium/high level of exposure there was an increased risk of NHL (combined with Chronic Lymphocytic Leukemia [CLL]) because of substantial biological similarities between the two diseases) for exposure to toluene (OR 1.8, 95% CI 1.1-2.6), xylene (OR 1.7, 95% CI 1.0-2.6) and benzene (OR 1.6, 95% CI 1.0-2.4). There was a high degree of correlation among benzene, xylene and toluene exposure, so that disentangling the role played by each exposure separately was not possible. Subjects exposed to all three aromatic hydrocarbons (benzene, toluene and xylene, medium/high intensity level) had an OR of 2.2 (95% CI 1.1-4.5). Concerning all leukaemia types (ICD IX 204-208), we found a slight increased risk for exposure to benzene in medium/high category (OR=1.4, 95% CI 0.8-2.4). When we look at the specific subtypes of leukaemia we found no association between exposure to any chemical classes or specific solvent and myeloid leukemia (ICD XI 205) in the medium/high intensity levels and an increased risk for Lymphatic Leukemia (ICD IX 204), in particular for CLL, for exposure to benzene, toluene and xylene. Those exposed to benzene at medium/high level had an OR of 2.1 (95% CI 1.0-4.2). Our results support the hypothesis that solvent exposure may be a risk factor for hematolymphopoietic malignancies.
mixers still alive at 1971 were included in analysis. Cause of death was retrieved for 259 of 277 subjects (93.5%). Results: overall mortality was significantly increased (SMR=136; 90%CI. 123-151). Mortality from all neoplasms (103 obs.; SMR=133; 90%CI. 112-156) and leukemia (9 obs; SMR=142; 90%CI. 90-227) was significantly higher than expected. Whereas non-significant excess mortality was observed for lung (29 obs.; SMR=112), larynx (5 obs.; SMR=180), liver (8 obs.; SMR=175), prostate (6 obs; SMR=217), stomach (10 obs.; SMR=150) and bladder cancers (5 obs.; SMR=138). Cancer mortality was higher among workers employed more than 10 years. Among non malignant diseases, a statistically significant increased mortality from cerebrovascular diseases was found (28 obs.; SMR=178; 90%CI. 127-245); the number of deaths from ischemic heart diseases (36 obs.; SMR=113) and cirrhosis (18 obs.; SMR=134) was larger than the expected, although not significantly. Conclusions: excesses of cancer of lung, larynx, bladder, stomach and leukemias are in agreement with previous studies. The choice of a reference population composed of urban manual workers, who belong to the same socioeconomic class of the cohort, reduces the probability that the observed excesses are attributable to confounding by lifestyle habits.

EXPOSURE TO BENZENE AND RISK OF BREAST CANCER AMONG SHOE FACTORY WORKERS IN ITALY
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Background: Little is known about the role of environmental factors in the induction of breast cancer. Some studies suggested a possible role of organic solvents and specifically of benzene.

Objectives: To analyse the risk of breast cancer among women under the hypothesis that low exposures to benzene could be a risk factor for solid cancer with a latency period longer than for leukemia in a cohort of women exposed to benzene in a shoe-factory in Florence, Italy.

Methods: This retrospective cohort consisted of 797 women workers at January 1, 1950 followed up 1950 to 2002 for mortality and 1985-2000 for incidence. Standardised Mortality Ratios were calculated for a sub-cohort of 797 women - for whom cumulative exposure (CE) to benzene was estimated - based on mortality rates of Tuscany. Standardised Incidence Ratios were calculated for 735 women out of 797 - alive on 1985 (first year of availability of incidence data provided by the Tuscan Cancer Registry. Results: Sixteen deaths for breast cancer occurred in the whole cohort; 13 were the breast cancer deaths in the 797 women sub-cohort. The SMR was equal to 95 (95% CI: 19-181) for less than 30 years of latency equal to 151 (95% CI: 79-290) for 30 or more years of latency. No differences were observed among women with different classes of CE exposure. In the sub-cohort of 735 women, 24 cases of breast cancer occurred. The SMR was equal to 133 (95% CI: 72-247) for a latency period less than 30 years and 105 (95% CI: 62-177) for a latency period equal or greater than 30 years. The SMR was equal to 201 (95% CI: 28-1430) in the >40 pmm-years and less than 30 year latency period category.

Conclusion: There is some suggestion of elevated incident breast cancer risk in the highest exposure group, but small numbers limit confidence in this finding.

THE RISK OF CANCER AMONG OFFSHORE WORKERS IN NORWEGIAN CONTINENTAL SHELF
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Introduction: Benzene and polycyclic aromatic hydrocarbons are known carcinogenic substances. Offshore workers, who have participated in exploration and production of gas and oil on the Norwegian continental shelf for the last 35 years, have been exposed to these substances in varying degree. We wanted to estimate the differences in incidence of all cancer types and length of survival in these workers compared to the general working population in Norway.

Methods: A historical cohort will be established using the Registry of Employers and Employees, which includes information on all Norwegian employers and their employees. The cohort will include all workers with the Norwegian continental shelf as their workplace at any time in the period from 1980 and up to 2004, approximately 70,000 individuals. A reference population of 400,000 workers will be drawn from the general working population from the same register. Up to 6 reference workers will be linked to each offshore worker at time of this work (first exposure). Incidence rates, matched on sex, age and municipality. The total cohort will be linked to the Norwegian Cancer Registry for the same period for registration of all cancer types, and to the Registry of Causes of Mortality for the analysis of differences in length of survival or remission after the date of diagnosis.

Results: Incidence ratios, using Poisson regression, and survival ratios, using the Cox’s proportional hazard regression model, will be presented for main cancer types between groups of offshore workers and the general working population.

Conclusion: The results will enable us to evaluate whether workers in upstream petroleum industry in Norway have been exposed to carcinogenic substances to such a degree that they have had an increased frequency of cancers. The size of the study will permit an evaluation of a possible increased risk also for workers with relatively low exposure.

CANCER RISK ASSESSMENT IN WORKERS EXPOSED TO DICHLOROBENZIDINE
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Material and Methods: all the 61 workers exposed to DCB were included. Two series of urine samples were taken: firstly in usual professional working activity, secondly just after a one month period of holidays (non-exposure). The contamination of workers was evaluated with the Ames test (strains TA 98, 100) and with measurement of urinary levels of DCB.

Results: exposure assessment and research for bladder lesions were fully accomplished. DCB exposures in this facility appeared to be low, yet with the need of some improvement. Despite high exposure to DCB in the past, no bladder tumor was found, even with a combination of two new screening tests.