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Abstracts of Theses from the Scandinavian Countries

Abstracts of Scandinavian theses on oncologic subjects are published under this heading. The full theses are as a rule published by the universities or as supplements to different journals. They can usually be obtained after contact with the author.

Nuclear medicine and cytotoxic studies in renal cell cancer

MALIHA EDGREN

Department of Nuclear Medicine, Uppsala University, Uppsala, Sweden

Quantitative positron emission tomography (PET) examinations utilising the ^{11}C labelled amino acidL-methyl-^{11}C-methionine (MET) and the ^{11}C labelled serotonin precursor5-hydroxytryptophan (5-HTP) were performed in patients with advanced renal cell carcinoma (RCC). Thirteen patients were investigated with MET and 10 patients with 5-HTP. The results show that PET with MET and 5-HTP can visualise RCC and that MET PET can monitor treatment response. Plasma samples from patients with RCC showed elevated levels of the neuroendocrine markers chromogranin A, chromogranin B and serotonin. Immunohistochemical studies performed on RCC tissue specimens exhibit positive staining for neurone-specific enolase (NSE). Somatostatin receptor scintigraphy using ^{111}In-[DTPA-Phe^1]-octreotide was performed in 9 patients. Totally 68 tumour lesions were investigated. Forty of these (59%) showed a positive uptake of the hormone analogue. The results obtained indicate that there is a subpopulation of RCC that has neuroendocrine expression as shown in the 5-HTP PET, the somatostatin receptor scintigraphy and the elevated plasma markers. Immunocytochemical studies of RCC cell lines demonstrated the expression of the estramustine-binding protein (EMBP). This finding was also verified in tumour tissue specimens from patients with RCC. A positive immunostaining for EMBP was found in 12/16 (75%) of cases. In vitro experiments showed a cytotoxic effect of estramustine on in vitro cultured RCC cell lines. The cells were arrested at atypical metaphase. A nude mouse model was developed for the in vivo characterisation of RCC with respect to EMBP expression. The mice were heterotransplanted with RCC cells and a radiolabelled murine monoclonal anti-EMBP antibody showed a pronounced accumulation in the tumour cells. These findings form the basis for future studies whereby estramustine can be used as a cytotoxic agent in the treatment of RCC and anti-EMBP immunoscintigraphy for the selection of patients suitable for such therapy.

April 1995

Studies on therapeutic and prognostic factors in ovarian cancer

PEKKA VENESMAA

Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

Between January 1, 1977 and September 30, 1990, 771 operations (472 primary and 299 repeat operations) for ovarian cancer were performed on 536 patients. At least one complication followed primary surgery in 32% and secondary surgery in 14% of the patients. However, serious operative complications were rare even in patients who underwent extensive surgery with lymphadenectomy. The spread of the disease or patient age did not have any effect on the rate of complications. Mortality was low (1%) and associated with primary surgery only. On the whole, the surgical procedures, especially repeat operations, were safe.

Tumour DNA ploidy was analysed by flow cytometry from samples taken at primary (2–4 samples/patient) and at secondary surgery (2–5 samples/patient) in 26 patients. Tumour DNA ploidy changed in 68% of patients during chemotherapy. The most common change was loss of a DNA-aneuploid clone in tumors which were both DNA-aneuploid and DNA-diploid, i.e. heterogeneous, at primary surgery. Patients with such changes in DNA ploidy did also survive better than those with persistent aneuploid tumors or tumors changing into aneuploid, or stable DNA-diploid tumors. This suggests that heterogeneous tumors respond better to chemotherapy than uniformly DNA-aneuploid or DNA-diploid tumors.

Tumor-associated trypsin inhibitor (TATI) and CA 125 were determined in serum samples from 66 patients taken before primary surgery. TATI was elevated (>22 µg/l) in 27 patients (41%). These had a 5-year cumulative survival of 8%, whereas survival was 45% in 39 patients with normal preoperative values. By contrast, the preoperative CA 125 level did not predict survival. In multivariate analysis, patients with elevated preoperative TATI levels had a 2.3-fold relative risk of death (95% CI 1.2–4.2) compared to patients with normal levels. This result was comparable with the predictive value of primary residual tumor size, since patients with residual tumor larger than 2 cm in diameter had a 5.2-fold relative risk of death (95% CI 2.6–10.7) compared to patients with a smaller or no residual tumor. Thus, preoperative determination of serum TATI may have a place in the pretreatment evaluation of patients with advanced ovarian cancer.

Residual tumor was detected at second-look surgery in 23 of 28 patients with advanced ovarian cancer treated with chemotherapy. Preoperatively, pervaginal cul-de-sac cytology and abdominopelvic computed tomography (CT) detected 13 of the residual tumors. In 2 patients, both clinical examination and CT detected residual disease. Clinical examination revealed tumors not detected by CT in 2 patients. On the other hand in 3 patients residual disease was detected by CT. In 6 patients residual tumors were preoperatively detected only by cul-de-sac cytology. No false positive findings were encountered.

Forty-six patients with recurrent ovarian cancer were reoperated, and cancer samples for the subrenal capsule assay (SRCA) were collected from 23 of them. This test was not done in the remaining 23 control patients. SRCA was evaluable in 22 cases (96%), but it was used to guide the selection of chemotherapy only in 15 patients. The tumor was resistant to all cytostatics tested in 6 cases and toxic side-effects limited the clinical application of the test results in one case. Five of the 15 patients with the applicable SRCA result (33%) and 2 of the 7 patients with the inapplicable SRCA result (29%) survived at least three years. Taken together, no significant difference appeared in 3-year survival figures between the groups: 7 of 22 patients (32%) with the evaluable SRCA and 6 of 23 control patients (26%) were alive. Thus, it seems that the SRCA is of limited value in the selection of second-line chemotherapy in recurrent ovarian cancer.

Between January 1, 1977 and December 31, 1990, 523 women with epithelial ovarian cancer were treated in this institution. Cumulative survival and survival analysis with covariates (Cox model) were calculated. Multivariate analysis was used to assess the impact of surgery and chemotherapy on survival in 244 patients who had stage III epithelial ovarian cancer. The overall cumulative 5-year survival for patients with epithelial ovarian cancer treated in the period 1977–80 was significantly ($p = 0.001$) lower (33%) than that for patients treated in 1981–85 (49%) or 1986–90 (46%). The 5-year survival of women with stage III

ovarian cancer improved from 10% in 1977–80 to 27% in 1986–90. In these stage III patients, chemotherapy including cisplatin was associated with better survival than other chemotherapies both in patients with optimal surgery (1.0- vs. 2.9-fold risk of death) and those with suboptimal surgery (1.4- vs. 1.7-fold risk of death). These results suggest that cisplatin may be more important than surgery in improving survival in stage III epithelial ovarian cancer.

Radical surgery with lymphadenectomy, at least in patients with local disease, is currently the basis of accurate staging making possible to compare treatment results of separate institutions, but the therapeutic value of lymphadenectomy is still unproven. Still most women with ovarian cancer have an advanced disease at diagnosis and surgical removal of all cancer tissue is not possible. Therefore, these patients need to be treated for generalized disease, and an improved survival is possible only by more effective systemic therapy. Opinions on the benefit of secondary surgery are controversial. Therefore, less invasive methods such as laparoscopy, tumor imaging, cul-de-sac cytology and determination of tumor markers should be preferred in revealing the nature of the malignant process during and after chemotherapy.

May 1995

Mineral fibers—Occupational exposure assessment and epidemiological studies

NILS PLATO

Department of Occupational Health, Karolinska Hospital, Stockholm, Sweden

Occupational exposure to airborne mineral fibers may have effects on the lungs but information on exposure levels correlated to different outcomes is sparse, due to lack of past fiber measurements. The overall objective of this thesis was to contribute to the improvement of the exposure information in order to decrease misclassification of exposure in epidemiological studies. The aims were to develop methods to assess past mineral fiber exposure and to study exposure–response relationships in three different settings: lung cancer in Swedish man-made vitreous fiber production industries and prefabricated wooden house industry, respectively, and lung function among vehicle repair workers exposed to fibrous friction materials.

Past fiber exposure 1938–1990 was assessed in the rock/slag wool industry in Sweden by a multiplicative model based on five independent variables. Cumulative respirable fiber exposure was calculated for 1 487 workers. The highest fiber concentrations occurred during the mid 1940s when the levels were 15 times higher than in 1990.

Current fiber exposure was measured for workers with different job titles in eleven Swedish prefabricated wooden house factories. The counting in phase contrast optical microscopy was improved by the application of criteria concerning straight or convergent edges to exclude fibers with other origins, which demonstrated that less than 1/3 of the total respirable fibers had man-made vitreous fiber (MMVF) appearance. Calculations of past fiber exposure for 487 insulators in these industries were performed by a modified multiplicative model based on principles used in a model previously developed for the MMVF production industry. The highest fiber exposure occurred in the mid 1970s and was then similar (0.18 f/ml) to the average level in the MMVF production industry at the same time.

Past fiber exposure from repair of brake and clutch linings was assessed among 103 vehicle mechanics since the late 1930s. A combination of an additive and multiplicative exposure assessment model was developed for the cumulative calculations. A difference of two magnitudes was calculated between the highest and lowest exposed mechanics. The vehicle mechanics had a decrease in Tlco with 12.5% ($p < 0.01$), but the decrease for Tlco and other lung function variables were not significantly correlated to either cumulative fiber exposure or employment time.

The lung cancer mortality among 3 539 MMVF production workers was slightly elevated with 27 observed cases vs 23 expected, SMR = 117 (95% CI: 81–176). The highest lung cancer excess was found among workers with 2–9 years of employments and no exposure–response relationships were found. A decreased risk of lung cancer was found among 2 807 workers in the prefabricated wooden house industry where 14 lung cancer cases were observed vs 20.7 expected (SMR = 68; 95% CI: 37–113). These studies do not indicate that MMVF exposure at the assessed fiber levels increases the risk of lung cancer although the possibility of small risk increases cannot be excluded.

June 1995.

Magnetic fields and cancer—Epidemiological studies and a synthesis of evidence

MARIA FEYCHTING

Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, S-171 77 Stockholm, Sweden

In 1979, Wertheimer & Leeper reported an excess of cancer mortality in children living in homes with presumedly elevated magnetic fields. Since then, further epidemiologic research on people with residential as well as occupational exposure has followed. The aims of this thesis were to test the hypothesis that exposure to residential magnetic fields generated by high voltage power lines leads to an increased incidence of childhood cancer, and of leukemia and central nervous system tumors in adults; to investigate important aspects of magnetic field exposure assessment; to synthesize the available evidence on EMF and cancer through different meta-analytic techniques, and to assess some possibilities and limitations of these techniques.

A case-control study was conducted within a population of 430 000 subjects living close to power lines. Magnetic field exposure was estimated through spot measurements and theoretical calculations of the magnetic fields generated by the power lines at the time of the measurement and prior to diagnosis. The association with childhood cancer was further investigated in a pooled analysis of the data from the Swedish and Danish studies of residential magnetic field expsoure, and in a meta-analysis pooling the estimates from three Nordic studies, including also a cohort study from Finland.

The results provide support for the hypothesis of an association between exposure to residential magnetic fields from power lines and childhood leukemia. For other types of childhood cancer the evidence is inconclusive. For adults, there is some evidence of an association for acute and chronic myeloid leukemia. The study's most obvious weakness is the small numbers, and chance may be an explanation for the association between magnetic field exposure and childhood leukemia. Against this speak the consistent results in different subgroups of the population and in the Nordic countries, the magnitude of the association, the obtained confidence intervals, and the dose–response patterns. Control of potential confounding factors did not change the results. Analyses of various exposure estimates indicate that the time interval between diagnosis and measurement is of importance when estimating magnetic field exposure, and that distance to power line is related to childhood leukemia through the magnetic field.

The heterogeneity among existing EMF studies does not allow for a meta-analysis where all studies are combined into a common effect estimate. A synthesis of evidence were made through a narrative review, and meta-analyses were restricted to subsets of studies.

June 1995

Prognostic factors in prostatic adenocarcinoma assessed by cytometric and histological methods

SATU VESALAINEN

Department of Surgery, Faculty of Medicine,
University of Kuopio, Kuopio, Finland

A series of 325 patients with prostatic adenocarcinoma was diagnosed, treated and followed-up during 1971–1992 in the Department of Surgery, Kuopio University Hospital, Finland. The prognostic value of clinical, histological and cytometric variables was analysed. According to multivariate analysis M-category ($p < 0.0001$), T-category ($p = 0.0006$), Gleason score ($p = 0.0019$) and patient age ($p = 0.0002$) were independent prognostic factors for the entire cohort. Gleason grade was a superb prognosticator in comparison with the WHO and nuclear grades. Perineural infiltration ($p < 0.001$) and the density of tumour infiltrating lymphocytes ($p = 0.041$) were related to the survival in T1-2MO tumours. Apoptotic bodies were observed in poorly differentiated tumours. Morphometric nuclear features were of borderline significance as prognosticators in prostatic adenocarcinoma. Mitotic indices correlated significantly with T-category ($p < 0.001$), M-category ($p < 0.001$) and Gleason grade ($p < 0.001$). Flow cytometry provided adjunctional information to conventional histological assessments for determination of correct prognostic category, especially in Gleason grade 5–7. The expression of p53 protein in local tumours had no effect on prognosis while the expression of proliferating cell nuclear antigen was related to the increased progression rate of the T1-2MO tumours.

Tumour biology was an important factor in determining the final outcome irrespective of primary therapy in prostatic adenocarcinoma. Transurethral resection of the prostate may enhance the risk of tumour dissemination, especially in tumours with low intrinsic malignant potential. Deferred treatment can be preferable to patients with well-differentiated and low stage tumours having a life expectancy of less than 10 years.

June 1995

T-cell activation and cytotoxicity in malignant disease

BJØRN ØSTENSTAD

Institute of Immunology and Rheumatology, University of Oslo, Oslo, Norway

The thesis consists of 5 papers which are summarized as follows.

I. Serum samples were collected from 47 consecutive patients with metastatic malignant melanoma (MMM) or renal cell carcinoma (RCC) and analysed for soluble interleukin-2 receptors (sIL-2R) by means of an enzyme-linked immunosorbent assay (ELISA). The assay was a commercially available Cell Free IL-2R test kit utilising two monoclonal antibodies recognising two different epitopes on the soluble α-chain (CD25) of the receptor. Significantly elevated receptor levels were found in both groups compared to 30 healthy controls. However, no correlation was found between receptor-levels and clinical parameters like tumour burden and survival.

II. In this paper we describe the establishment of methods for the isolation of tumour-infiltrating lymphocytes (TIL) from colorectal tumours and from the lamina propria of unaffected mucosa in the resection margin of the same patients (LPL). The phenotype of freshly isolated lymphocytes from these two compartments as well as from the peripheral blood (PBL), were studied with flow cytometric analysis, with special focus on different lymphocyte subsets and the expression of activation markers. In all three compartments T cells dominated, but with significantly less natural killer (NK) cells among the infiltrating lymphocytes as compared to peripheral blood. It was found that TIL expressed significantly higher levels of the activation markers CD25 (IL-2R) and HLA-DR (MHC class II) than the PBL. Both TIL and LPL expressed significantly increased levels of the CD45R0 isoform, associated with memory cells, suggestive of a primed population. Spontaneous cytotoxicity tested against the NK-target K562 and the allogeneic colon cancer cell line CACO2 was undetectable in LPL and TIL preparations. However, lymphocytes from all three compartments responded well to IL-2 and developed potent LAK cell cytotoxicity. No increase in the numbers of NK cells were noted after culture, but 20–30% of the T cells now co-expressed the CD56 molecule ($CD3^+CD56^+$). LAK activity was noted in both the $CD4^+$ and the $CD8^+$ subsets.

III. To further characterise the immune response in the tumour area we used polymerase chain reaction (PCR) technology to investigate the T-cell receptor variable-region gene (V-gene) usage in freshly isolated lymphocytes to look for a possible oligoclonality of T cells in the tumour area. We found a limited heterogeneity in the V-gene usage of TILs from seven patients with colorectal tumours in contrast to what was found in LPL and PBL, suggesting a local antigen-driven immune response against the tumour.

IV. In order to test T-cell function measured by their capacity to induce apoptotic death in a target cell, we developed a new assay by combining two previously described methods. Because each T cell recognises only one very specific target, we had to circumvent the highly variable T-cell receptor. To accomplish this, we applied a redirected approach, where the target cell plays an active part in the recognition process. By expressing the monoclonal anti-CD3 antibody in the membrane, the target cell will "target" the invariant part of the TCR/CD3 complex of all T cells and induce signals as if the T-cell had recognised a specific target. We showed that these signals trigger the T-cell effector mechanisms so that the target cell is killed. By labelling the target cell nuclei with $[^3H]$thymidine, we found that the T cell rapidly induced DNA fragmentation in the target cell, and we demonstrated the characteristic "ladder" pattern of fragmented DNA consistent with apoptosis. This cytotoxicity assay using a universal T-cell target was shown to be a simple and rapid assay, which differentiated clearly between various T-cell populations.

With this test system, we showed that freshly isolated tumour-infiltrating T lymphocytes from human colorectal cancer effectively transduced signals through the CD3 complex and were able to respond by inducing apoptosis in the target cell.

V. Two alternative effector mechanisms for T-cell cytotoxicity has been described. Cyclic adenosine 3′, 5′,-monophosphate (cAMP) can inhibit cytotoxicity, as measured by the induction of target membrane lysis. In this paper we addressed the possible modulation of T-cell cytotoxicity tested in different assays, and found a dual effect of cAMP, depending on the test system and on the activation status of the T cell. Lymphokine activated killer T-cell (LAK-T) cytotoxicity was further enhanced by preincubating the effector cells with synthetic cAMP-analogs, when tested for the ability to induce apoptosis in the redirected system. This contrasts the inhibitory effect of cAMP found on spontaneous T-cell cytotoxicity and on NK-cell cytotoxicity.

Furthermore, we demonstrated that the enhancement effect most likely was mediated by the cAMP-dependent protein kinase type II (cAK II), which is the particular isoform of the enzyme associated with the centrosome and the microtubule organising centre.

June 1995

Evaluation of potential prognostic factors in breast cancer—A clinicopathological study with special reference to cell proliferation, DNA image cytometry, angiogenesis, and E-cadherin

SANNA SIITONEN

Pathology Unit and Department of Clinical Chemistry, Tampere University Hospital, Tampere, Finland

This thesis studied the potential prognostic value of PCNA immunohistochemistry in the evaluation of cell proliferation in axillary lymph node-negative breast cancer. The prognostic value of cancer cell with a DNA content of over 5c (> 5c-cells) and two factors contributing to metastatic potential, angiogenesis and E-cadherin expression, were also evaluated.

PCNA immunohistochemistry either from frozen sections or from archival, paraffin-embedded material after an appropriate antigen retrieval method can be used as a marker of cell proliferation in breast cancer. In archival material $PCNA_{19A2}$ immunohistochemistry, being an independent prognostic factor in axillary node-negative breast cancer, provides a useful alternative to DNA flow cytometric analysis of cell proliferation. The results of $PCNA_{PC10}$ immunohistochemistry were not associated with other markers of cell proliferation, although it may be considered a prognostic factor at the beginning of follow-up in breast cancer. The biological significance of the latter finding requies further evaluation.

Cancer cells with a DNA content exceeding the 5c level were detected in 45% of the axillary node-negative breast carcinomas studied. The > 5c-cell status provided clinically relevant prognostic information in axillary node-negative breast cancer, although it was not an independent prognostic factor in multivariate analysis because of its close relationship to other prognostic factors. > 5c-cell status had prognostic significance in subgroups of patients with diploid, low proliferative, and well differentiated tumors, suggesting that it adds prognostic information in cases that are otherwise thought to have a favorable course.

Microvessel quantitations from archival tissue sections can be reproducibly done as areal fractions or as the highest microvessel counts with either anti-VWF, anti-CD31 or anti-CD34 immunohistochemistry. Tumor neovascularization was not related to the other known prognostic factors in breast cancer, nor did it reveal prognostic information in a selected group of axillary node-negative breast cancer patients. Additional studies will be needed to establish the best way of assessing the angiogenic capacity of tumor cells and to find out whether this capacity has an effect on the metastatic potential of breast carcinoma.

Loss of normal E-cad expression was found in 52% of the invasive ductal carcinomas, 64% of the recurrent carcinomas, and in all the invasive lobular carcinomas studied. Reduced E-cad expression was an indicator of increased invasiveness and dedifferentiation in invasive ductal carcinomas. Loss of normal E-cad expression was also an independent predictor of shortened disease-free survival time in breast cancer. Adhesion-related processes may turn out to be valuable prognosticators, even though the value of reduced E-cad expression alone did not exceed that of nodal status in multivariate analysis.

June 1995

DNA methylation and point mutation detection in laboratory diagnostics of malignancy

JARKKO IHALAINEN

Department of Clinical Chemistry, University of Helsinki, Helsinki, Finland

The present work has as its aim the development of new techniques for the analysis of cancer by the diagnostic laboratory. This general aim has been approached in two ways: 1. by studying the applicability of hypermethylation alterations of DNA on the short arm of chromosome 11 to diagnostics in hematology and 2. by modifying a previously well established point mutation detection method, minisequencing, for simplified routine diagnostic use.

Alterations of the short arm band 15 of chromosome 11 are associated with many malignancies. The calcitonin A gene (CALCA) is located in this chromosomal area, and the 5'-end of the gene is known to show methylation differences in cancer and leukemia. In this work, methylation patterns of the calcitonin A gene 5'-area were studied in three types of chronic hematological disorders: 1. myelodysplastic syndromes, a group of diseases with poor hematological cell differentiation, 2. myeloproliferative diseases (polycythemia vera, essential thrombocythemia, myelofibrosis), which are characterized by excessive proliferation of hematopoietic cells and 3. elderly patients with idiopathic erythroid macrocytosis, indicative of an early hematological differentiation defect.

Myelodysplastic syndromes are characterized by frequent (88%) CALCA gene hypermethylation. Myeloproliferative disorders demonstrate strong hypermethylation only as the disease progress towards fibrosis of the bone marrow or acute leukemia. Elderly people with an unclassified hematological differentiation defect have hypermethylation at the CALCA area in 56% of cases.

To improve diagnostic laboratory analyses for oncogene point mutations, a simplified modification of the solid-phase minisequencing technique was developed. The new method utilizes a microtitration plate format, automatic pipetting and washing equipment and scintillating plastics and thus facilitates a large scale analysis of point mutations.

The applicability of solid-phase minisequencing was evaluated by studying KRAS mutations in cancer cells from thin needle biopsies of the pancreas. Pancreatic cancer is a suitable model for this kind of study, because about 90% of the adenocarcinomas of pancreas harbor KRAS mutations. When compared to a routine cytomorphological analysis, the point mutation detection method shows increased sensitivity.

June 1995

Association of silica dust exposure with lung cancer and other diseases

RIITTA-SISKO KOSKELA

Department of Epidemiology and Biometry, Finnish Institute of Occupational Health, Helsinki, Finland

The main purpose of the study was to investigate the possibility of a direct association between silica exposure and lung cancer. Mortality and morbidity from other diseases were also studied to clarify the silica-induced disease pattern.

The study included 1 026 granite workers hired between 1940 and 1971 by quarries and processing yards in three regions (Vehmaa, Kuru, and Viitasaari) in Finland; all of the workers were employed for at least three months. The type of granite was Balmoral red in Vehmaa, grey in Kuru and black in Viitasaari.

The morbidity and mortality of the cohort were followed from 1940 to 1989. The cytotoxicity of different granite fractions and the capacity of the fractions to induce reactive oxygen species (ROS) in human leukocytes were studied in vitro.

Excess mortality from lung cancer was observed in the cohort of granite workers exposed to pure silica. The regional analysis revealed that the risk for lung cancer mortality was 1.3-fold for workers in the Vehmaa region and 2.1-fold for those in the Kuru region when the groups were compared with the general male population. Only one lung cancer case was found in the small subcohort of the black granite area.

A regional case-referent analysis showed that the cases from Vehmaa were more exposed than their age- and smoking-matched referents, whereas the cases from Kuru were less exposed than their referents.

Similarly the cancer incidence study showed an excess of lung cancer, the rate ratio being 2.5 for a latency of 20 years or more. The excess came from the red and grey granite areas. In the grey granite area the cancer cases occurred within a shorter latency period than in the red granite area.

The granite workers had long periods of exposure and long periods of follow-up. They had no remarkable exposure history to potential concomitant carcinogens. Neither did smoking alone explain the excess of lung cancer. The amount of quartz was 36% in the Balmoral red granite of Vehmaa, 31% in the Kuru grey, and 0% in the Viitasaari black. The age-specific smoking habits were similar in the three cohorts. The physico-chemical composition of the dusts may explain the regional differences in the risk of lung cancer.

A simultaneous occurrence of lung cancer and pulmonary silicosis was rare. The age-standardized lung cancer mortality rate was similar for the cohort members with silicosis (being at most only 1.3-fold) and those without diagnosed silicosis. When the persons with silicosis were excluded from the cohort, the lung cancer mortality rates remained excessive. This finding suggests that silicosis is not needed as an intermediate pathological state before the appearance of lung cancer.

Inflammatory cells exposed in vitro to quartz produced potential DNA-damaging ROS. The strongest activity of grey and red granite was found in the quartz-containing fractions. Even in the cytotoxicity tests the quartz containing fractions of the grey and red granite caused the strongest lactic dehydrogenase release. However, plagioclase, the main constituent of black granite (60%), had approximately the same ROS-inducing activity as the quartz-containing fractions of red and grey granite.

Among other silica-induced diseases those originating in the respiratory tract were the most prominent. Mortality from respiratory diseases among granite workers was 2.1 times the expected value calculated from the general population. Of the deaths caused by respiratory diseases 30% were due to silicosis; the other causes were emphysema, chronic bronchitis, bronchial asthma, and pneumonia. In addition, lung tuberculosis caused five deaths. Excess morbidity from respiratory diseases was also observed. Excess disability was mainly due to silicosis and chronic bronchitis, whereas bronchial asthma was the most common disease receiving special compensation for medication.

Mortality from gastrointestinal cancers exceeded the national expected value; most of the deaths were due to stomach cancer. The excess occurred mainly in the grey granite area.

Increased morbidity (as determined by disability and specially compensated medication) was found for rheumatoid arthritis. Retrospective analysis of the records of all of the patients with rheumatoid arthritis in the cohort showed that a severe, serologically positive and erosive form of rheumatoid arthritis predominated among the heavily exposed persons.

Diseases of the urinary tract (chronic pyelonephritis and chronic nephritis) were slightly in excess. In addition, numerous probable or possible disease associations were identified (i.e., diabetes, glomerulonephritis, amyloidosis and mesenchymal cancers).

The cancer morbidity and mortality determined for the different granite areas, combined with the differences found in the biological activity of granite dusts and a hypothetical cancer-inducing mechanism by ROS, point to a direct role for quartz in cancer induction.

August 1995

Effect of screening for cancer on mortality, costs and quality of life in Finland

LORA HRISTOVA

University of Tampere, Tampere, Finland

The aim of this study was to evaluate the observed effect of mass-screening for cancer. Three screening programmes, which have been evaluated in public health practice or in randomised trials as efficient in mortality reduction, were estimated. The effect of the organised, nation-wide screening for cervical cancer, started in Finland in the mid 1960s, and the potential effect of screening for breast and colorectal cancer in Finnish population were assessed. Mass-screening for breast cancer was established in 1987, whereas colorectal cancer is only a potential candidate for mass-screening. The effect of these three screening programmes was measured in terms of mortality reduction, and changes in the quality of life and costs. Data on incidence, mortality, survival and size of the general population were employed in the estimation. Age-cohort log-linear models were applied in predicting future mortality rates with and without screening. The choice of the models depended on the age distribution of deaths from each particular site of cancer, on changes in public health policy, such as establishment of mass-screening, and on the goodness of fit of the model.

The number of deaths from cancer is expected to increase in future due to the increasing trend in cancer incidence rates and the ageing of the population. The predicted number of breast cancer deaths (without screening) in 2012–2017 is 35% higher than that observed in 1988–1992. For colorectal cancer these figures are 28% and 80% for females and males, respectively. The predicted numbers of deaths (without screening) from cervical cancer at the end of the predicted period were estimated to be approximately the same as before the establishment of the mass-screening programme in the 1960s. A total of 58 360 deaths from the cancers of considered sites were predicted to occur between years 1993 and 2017 if there were no screening programmes.

The effect of existing mass-screening for cervical cancer on the mortality was estimated on the basis of observed data, and the potential effect of breast and colorectal screenings was approximated according to the results of randomised trials. Approximately 18.7% (10 939) of deaths from those three sites of cancer were estimated to be avoidable by screening in 1993–2017 (3 221 from breast cancer; 4 045 from cervical cancer; 1 773 from colorectal cancer in females and 1 900 in males). This means that 71 904 life-years can be saved during the period. Deaths from breast, cervical and colorectal cancers avoidable in the period 2008–2012 present 6.9% of all the predicted cancer deaths in females. The predicted reduction in the number of colorectal cancer deaths was 1.6% of the total cancer deaths in men in the same period. For the entire population 4.1% of cancer deaths in 2008–2012 can be avoided.

Costs of the screening programmes were estimated considering direct costs of screening and savings from advanced disease treatment and terminal care. The total estimated costs of screening for cervical, breast and colorectal cancer in 2008–2012 is $131 mill. Cervical cancer screening was estimated to save $1.6–1.8 mill yearly in the predicted period. In 2008–2012 the costs per life year gained (LYG) was $18 744 for breast cancer and $7 036 and $7 861 for colorectal cancer in females and males, respectively.

Screening for cervical cancer has reached a phase when both the effect and costs are stable. Therefore, a stable cost-effectiveness ratio of about $1 500 saved per year of life gained was predicted for the future period. The effect of screening for breast and colorectal cancers is expected to appear gradually during the predicted period due to the increasing number (and percentage) of patients diagnosed by screening. When the screening programmes are assumed to achieve these optimal effect, the mortality reduction increases and treatment costs fall resulting in a substantial decrease in the cost-effectiveness ratio. In the last considered period (2008–2012) the costs per life year gained are approximately a half of those in the onset of screening.

An attempt was made to estimate the impact of mass-screening on the quality of life on population level including the psychological consequences of screening test, adverse effect for false positives and the advantages for those who would avoid radical treatment and advanced stage disease. The reduction in the number of life-years gained (LYG) after adjustment for quality of life was relatively small compared to the losses attributed to dementia for all the three primary sites in women. The difference between quality and dementia adjusted LYG is minor in men, due to the fact that men spend a smaller part of their remaining life in dementia, partly due to the shorter life expectancy. The effect of screening for cancer on the quality of life seems to be smaller compared to the effect of ageing in the age groups in which the prolongation of life due to screening appears. Finally cost-utility analyses were performed. The following costs per good quality LYG were estimated (in the period 2008–2012): $22 734 for breast cancer screening, $8 713 for colorectal cancer in females and $9 735 for colorectal cancer in males.

Cost assessment only cannot be considered as decisive when a public health policy is decided, and any cost to save human life is acceptable if the society is able or prepared to pay for it. Nevertheless there is a question whether it is justified to screen for breast and colorectal cancer if about 18–19% of the costs are spent on prolongation of life with poor quality. Further, more precise estimation of the quality of life related to screening for cancer is needed, based on individuals' self assessment and regarding age-specific quality of life.

August 1995

Support for women with breast cancer, and for the district and hospital nurses involved—An interventional study

MAJ-BRITT PÅLSSON

Department of Advanced Nursing, Umeå University, S-901 87 Umeå, Sweden

The purpose of this study was to investigate breast cancer patients' experiences of their illness and of traditional nursing care (TNC) or supportive nursing care (SNC) respectively, as well as nurses' experiences of support and of caring for cancer patients. An intervention including extended co-operation between the surgical ward and primary health care, shorter waiting times, and changed routines concerning the information about the diagnosis, as well as training and systematic clinical supervision for the nurses, was implemented. Newly diagnosed breast cancer patients (n = 47) from two county councils in the south-east of Sweden were interviewed (IV, V). Thirty-four of them completed scales about well-being, burnout, hopelessness, anxiety and depression (VII). The women who had TNC reported lack of professional support during the initial phase of the disease and suggested changes in the care similar to those implementd in the SNC. In the SNC group the women expressed feelings of safety and security after the professional support and the organizational changes in the care. There were significantly more single women and women who had had breast conserving surgery in the SNC group than in the TNC (VII). The hopelessness scores in the SNC group were significantly higher than in the TNC group.

Thirty-nine district nurses (DNs) were interviewed at baseline (I), and thirty-three of them completed scales about burnout, empathy, and sense of coherence (SOC) before and after systematic clinical supervision (VI). Twenty-three of the 39 DNs, as well as 9 hospital nurses (HNs) who participated in the clinical supervision were interviewed about their experiences of this intervention (III). Twenty-nine tape-recorded supervision sessions in three groups of DNs (n = 23) were analysed (II). Baseline interviews and analyses of the content of the supervisory sessions strongly emphasized that DNs experienced problems in the home care of seriously ill cancer patients. Deep human contacts were a source of both strain and enrichment. The clinical supervision was said to provide relief from undesirable thoughts and feelings, confirmation of themselves both as individuals and in their professional role, a broader and deeper knowledge and increased self-confidence. There were no significant differences in the burnout, empathy, and SOC scores between the supervisory group (n = 21) and a comparison group (n = 12) at the first and second measures, nor over time within the groups. There were some correlations between these phenomena and the Karolinska scales of personality, as well as correlations between burnout, empathy and SOC.

The groups of women were not entirely similar as regards demographic and medical characteristics, and the sample size of patients and nurses was small. It is obvious that patients in the TNC missed those factors that were implemented in the SNC, at the same time the latter women expressed hopelessness more often than those who had received TNC. This result may be due to the fact that support from nurses had made the women more prepared to express their feelings, that support had not been provided to an adequate extent or in the right way, or that the applied scales were not appropriate. The finding that the nurses experienced the clinical supervision as very positive but that, despite this, there were no significant differences in attitudes measured by scales within or between the groups, can be interpreted in a similar way. Consequently, further research is needed to judge the effects of intervention. The study has, above all, produced qualitative descriptions of patients' experiences of the nursing care after discharge from hospital, and of DNs' experiences of the care of cancer patients in their homes, and of systematic clinical supervision.

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Molecular genetic alternations in human thyroid tumors

JAN ZEDENIUS

Department of Surgery and Department of Molecular Medicine, Endocrine Tumor Unit, Karolinska Hospital and Institute, S-171 76 Stockholm, Sweden

Thyroid tumors are common among the general population, but only a minority are malignant. Thyroid carcinomas account

for 1% of all cancers reported. Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and medullary thyroid carcinoma (MTC) constitute the differentiated variants, while anaplastic thyroid carcinoma (ATC) is undifferentiated. Follicular thyroid adenomas (FTAs) are common. These sometimes show atypical features (AFTAs) or Hürthle cell type differentiation (HTA).

MTC may be part of the multiple endocrine neoplasia type 2 syndromes or occur sporadically. Since the RET proto-oncogene (RET) was confirmed to be the gene responsible for the MEN 2 syndromes, it has become possible to identify gene carriers with high accuracy. Gene carriers can now be offered prophylactic thyroidectomy, while non-carriers can be omitted from the screening programs.

In an attempt to identify chromosomal regions harboring putative tumor suppressor genes important for thyroid tumor development, 92 thyroid lesions of follicular origin were investigated for loss of heterozygosity (LOH) by the use of 50 polymorphic DNA markers representing all chromosome arms. The overall LOH frequency was rather low, the highest being for chromosomes 3q, 10q, 11p, 11q, 13q, and 22q (10–15%). However, detailed analysis with regard to the different histopathological diagnoses showed that LOH on the long arm of chromosome 10 was seen in 5 of the 8 tumors with atypical or malignant features, but in none of the 58 common FTAs investigated. In addition, the majority of HTAs showed LOH on either chromosome 3q or 18q. The finding of LOH on chromosome 10q in AFTAs and FTCs was confirmed in the next study, in which 15 FTCs, 19 AFTAs and 6 ATCs were investigated for LOH by deletion mapping chromosome 10 using 15 markers. One third of the tumors showed deletions involving the telomeric part of chromosome 10q, distal to D10S187. The results indicate that a region at the telomeric part of 10q may be involved in follicular thyroid tumor progression.

The TP53 tumor suppressor gene is mutated in several human malignancies. The occurrence of these mutations may have prognostic significance and can be detected by immunohistochemistry (IHC) as the mutated protein accumulates in the cell nuclei. The prognostic significance has also been claimed for thyroid tumors, as TP53 mutations were mainly detected in ATCs and poorly differentiated tumors. Therefore, 178 various thyroid tumors from 162 patients were investigated for p53 expression by IHC. Although 21 (12%) tumors were positive for p53 IHC, only five had mutations within exons 5–8 of TP53 (as detected by constant denaturing gel electrophoresis and direct DNA sequencing): one ATC, one FTC, one AFTA, and two PTC metastases, of which the primary tumors had no detectable mutation. Analysis of 35 tumors by IHC, showed that the expression of WAF1/p21 (one of the main down-stream targets of p53) is regulated by p53 in these cells. We also conclude that p53 IHC cannot be used for diagnostic or prognostic purposes in thyroid tumors.

The distinction between FTA and FTC relies mainly on the presence of capsular and/or vascular invasion. Matrix metalloproteinases (e.g. collagenases) play an important role in tumor cell invasion. Twenty-nine thyroid tumors of varying type and aggressiveness were analyzed for expression of the 72 kiloDalton type IV collagenase (Gelatinase A) by RNA in situ hybridization. Strong Gelatinase A mRNA expression was seen in 10 of 14 FTCs, in no FTAs, in all 4 ATCs, and in 4 of 5 PTCs. The expression was restricted to fibroblasts in the stroma adjacent or close to invading tumor cells. Twelve tumors analyzed for Stromelysin 3 showed no expression. The findings suggest that Gelatinase A contributes to the invasive process and to the spread of aggressive thyroid tumors.

In an initial study, 10 sporadic MTCs (and 10 pheochromocytomas) were investigated for mutations in RET exons 10, 11 and 16. The results indicate that all MTC should be investigated for RET mutations, as among these seemingly sporadic cases, one patient was shown to have a de novo germline MEN 2A mutation in RET. Furthermore, presence of a somatic mutation of codon 918 in exon 16 was associated with a significantly less favorable prognosis. To further investigate this significance, 46 sporadic MTCs were analyzed for the RET codon 918 mutation. The mutation was found in 29 tumors, and was significantly correlated to a poor outcome with regard to distant metastasis or tumor recurrence ($p < 0.001$).

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