Abstract of Theses from the Nordic Countries

Abstract of Nordic 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.

The role of hormone alterations in development of cancer cachexia. An experimental study with special reference to wasting of skeletal muscles

G. SVANINGER

Department of Surgery II, University of Göteborg, Sahlgrenska sjukhuset, S-413 45 Göteborg, Sweden

Cancer disease is associated with anorexia and increased energy expenditure, leading to tissue wasting. The mechanisms behind this process have not been fully elucidated.

The aim of this study was to evaluate to what extent hormone alterations are mediators behind the tissue wasting or rather reflect an adaptation to the state of malnutrition in association with cancer cachexia.

A well characterized and standardized sarcoma-model in mice was used. The control animal groups consisted of healthy freely-fed, pair-fed and pair-weighed mice. The food intake in pair-fed animals followed the spontaneous reduction of food intake in tumor-bearing animals, while pair-weighed animals had their food intake depressed to the level that loss of body tissues was comparable with that of tumor-bearing animals. Changes in body composition and composition of individual skeletal muscles were evaluated. Protein synthesis in skeletal muscles was estimated *in vitro* by incorporation of ^{14}C-phenylalanine and degradation by the release of tyrosine from incubated muscles. Plasma levels of thyroid hormones, insulin and growth hormone were measured. Adrenocortical activity was assessed by the urinary excretion of glucocorticoids. Impact on whole body and muscle composition, tumor growth and survival time following tumor implantation were determined in combination with and without hormone manipulation, which was achieved by hormone supplementation and glandular ablation.

Net loss of skeletal muscle mass was explained by reduced protein synthesis, while the muscle breakdown rate was unchanged. The development of cachexia was associated with falling plasma levels of thyroid hormones, progressively increasing growth hormone concentrations including spiked diurnal variations and raised adrenocortical activity. Low plasma insulin concentrations and a decreased response with slowly increasing plasma levels following refeeding were found in tumor-bearing animals. Control animals suffering from the same degree of malnutrition as tumor-bearing animals (pair-weighed) displayed similar hormone alterations. Thyroid hormone supplementation with physiologic doses had no impact on body composition or tumor growth, but increased the loss of body mass in food restricted controls. Insulin supplementation did not reduce loss of muscle mass in tumor-bearing animals, but increased body lipids in freely-fed controls. Protein synthesis in skeletal muscles from tumor-bearing animals was depressed to the same level as in muscles from pair-weighed controls. Muscles from tumor-bearing animals and pair-weighed controls displayed similar sensitivity and responsiveness as muscles from freely-fed controls following insulin stimulation of protein synthesis. Exogenous growth hormone had no impact on body composition or muscle mass, neither was tumor growth affected. The cachexia process was initiated even in animals subjected to adrenalectomy. However, such animals had significantly reduced survival time and died with a lower tumor mass. Pharmacologic doses of hydrocortisone normalized survival in adrenalectomized tumor-bearing animals but had no impact on tumor growth. Tumor-bearing animals died with severe hypoglycemia under all experimental conditions.

It is concluded that hormone alterations in association with cancer cachexia represent a manifestation of adaptive mechanisms to the wasting process, especially aimed at maintaining glucose homeostasis. Cancer cachexia can progress despite a normalization of plasma insulin and in the absence of glucocorticoids.

October, 1987

Exposure to sulphur compounds, cancer incidence and mortality in the Finnish pulp and paper industry

P. JÄPPINEN

Department of Public Health, University of Helsinki, Helsinki, Finland

The aims of this study were: 1) to evaluate workplace exposures in the pulp and paper industry, especially exposure to sulphur compounds, with the use of haem-synthesising enzymes as indicators and 2) to determine whether exposure to sulphur compounds affects selected parameters of health and, especially, to determine the cancer incidence and mortality of pulp and paper workers, with special emphasis on lung cancer and cardiovascular mortality.

The concentrations of sulphur dioxide, hydrogen sulphide, methylmercaptan, dimethyl sulphide and dimethyl disulphide were determined by the gas chromatographic method in 4 sulphite and 6 sulphate pulp mills, including the 2 sulphate mills from which the study population in the cancer incidence and mortality study originated. In the sulphite pulp mills, the highest concentrations of sulphur dioxide were detected at the chip conveyors (mean 7.4 ppm, range 0.7–18.0 ppm), control room levels (mean 6.4 ppm, range 0.4–18.0 ppm), and during washing in the bins (mean 4.1 ppm, range 0.3–10.5 ppm). In the sulphate pulp mills, the highest hydrogen sulphide concentrations were measured at the vacuum pumps of the evaporation plants (mean 2.00 ppm, range 0.17–20.0 ppm). The methylmercaptan and dimethyl sulphide concentrations followed the hydrogen sulphide emission pattern. The highest methylmercaptan concentrations were measured at the chip meters in the flowtype digesting process (mean 3.70 ppm, range 1.00–9.0 ppm). The highest dimethyl sulphide concentrations were measured at the same site (mean 4.74 ppm, range 0.40–12.0 ppm).

On the basis of the results of this study it was obvious that, in the sulphite mills there were notable seasonal variations in sulphur dioxide concentrations. For all the sulphur compounds monitored in the pulp mills, it should be noted that occasional peak concentrations occurred which were much higher than the low-level workplace concentrations of longer duration.

The analysis of reticulocytes for haem-synthesising enzymes was performed for 17 workers in pulp production with low-level hydrogen sulphide and methylmercaptan exposure. A clinical survey of 81 workers with occupational exposure to organic and inorganic sulphides was carried out with a 75-item questionnaire on subjective symptoms. Eighty-one controls matched with the exposed subjects for age and smoking habits but without exposure to sulphur compounds also filled out the questionnaire. A decreased activity of delta-aminolaevulinic acid synthase was observed in 8 persons of the 17 studied, as well as a decreased activity of haem-synthase in 6 persons. It could not be verified whether these changes were caused by the low prevailing levels of sulphur compounds or by cumulative effects of occasional peak concentrations.

The cancer incidence and mortality of a cohort of 3545 pulp and paper workers were assessed. The workers were divided into 6 subcohorts according to the following working areas: sulphite mill, sulphate mill, paper mill, board mill, maintenance department, and power plant. Each worker could be included in more than one subcohort. A cohort of 1223 sawmill workers served as a reference group. All the subjects in the study had worked continuously for at least one year in some of the work areas between 1 January 1945 and 31 December 1961. When the study period began (1 January 1945), 1450 of the total of 4768 workers studied were employed and working for the company. Cancer incidence was followed until 31 December 1980 and mortality until 31 December 1981.

The smoking habits of the study population were assessed by the questionnaire method. The prevalence of smoking was determined for the years 1956 and 1981. Smoking-adjusted standardised incidence ratios were calculated for each occupational group.

The risk of primary cancer in general in the pulp and paper industry did not differ significantly from that expected, being somewhat lower than expected among the men (196 obs., 203.8 exp., SIR 96) and somewhat more decreased among the women (47 obs., 57.9 exp., SIR 81). An excess of lung cancer was observed among the men (78 obs., 62.6 exp., SIR 125), especially among male board mill workers (40 obs., 18.1 exp., SIR 222). Among the male board mill workers, the risk of lung cancer was higher with an occupational exposure of 5 years or more, and it was most prominent after 20 years of latency. There were analogous excesses of lung cancer among those male pulp and paper, and especially board mill, workers who were employed for the first time after 1 January 1945. These excesses may have been work-related since differing smoking habits could not explain them.

The overall mortality for the entire pulp and paper cohort differed very little from that expected although the male workers showed a somewhat increased mortality (881 obs., 858.6 exp., SMR 103). There was an excess of deaths from diseases of the circulatory system among the men (489 obs., 404.9 exp., SMR 121) because of the excess of deaths from ischaemic heart disease found among the men in the sulphite mill, sulphate mill, paper mill, maintenance department and power plant, but not those in the sawmill. This finding was not explained by smoking or by other known risk factors of coronary heart disease and therefore may have been associated with occupational exposures.

The reply percentage in the questionnaire study was 86.2 for the alive subjects and 76.1 for the next-of-kin of the deceased subjects. From 1956 to 1981, the prevalence of smoking in the age group of 15–69 years had diminished 17.8% (from 55.1 to 37.3%) among the men, and had increased 8.1% (from 6.9 to 15.0%) among the women. On the basis of this study it can be said that postal questionnaires may be a feasible tool for assessing smoking habits in retrospective cohort studies.

November, 1987

Cancer risks in relation to serum levels of cholesterol and betalipoprotein. An epidemiologic study

S. TÖRNBERG

Department of General Oncology, Radiumhemmet, Karolinska sjukhuset, S-10401 Stockholm, Sweden

The aim of this dissertation was to study cancer risks in relation to serum levels of cholesterol and beta-lipoprotein (BLP), height, weight and blood pressure. The studied cohort consisted of 92839 individuals aged 18–74 years who were examined in a large scale health screening 1963–1965. The cohort was matched with the Swedish Cancer register until 1983 and with the Swedish Cause of Death Register until 1984. During the period of follow-up, 9035 cases of cancer in the cohort were reported to the Swedish Cancer Register and 27092 individuals were deceased. Cancer was the cause of death in 5618 and coronary heart disease in 10233 subjects.

Rectal cancer among men was positively correlated to serum levels of cholesterol and BLP. Colon cancer and rectal cancer risk among men increased with increasing levels of cholesterol and BLP, when analyzed combined. Stomach cancer was negatively correlated to serum levels of cholesterol and BLP whereas breast cancer risk among women <50 years of age was negatively associated with serum cholesterol and positively associated with BLP. Breast cancer risk was also positively associated with height, weight and blood pressure. Quetelet's overweight index was positively associated with cancer risk in women ≥50 years and negatively associated in those <50 years of age. Total cancer incidence and total cancer mortality were negatively correlated to serum cholesterol but the negative associations approached the normal risk level during the follow-up period. The validity of using a single cholesterol measurement in a prospective study, was tested by correlating serum cholesterol with mortality from myocardial infarction, a well established correlation. The risk increased with increasing level of cholesterol. The stability of serum cholesterol was studied in another cohort of 16281 individuals in whom measurements of serum cholesterol were available from repeated examinations in 1969 and 1971. The ratio between the correlation coefficients reflecting the long term variation of cholesterol was 0.89. Thus, both the validity and the stability of cholesterol were judged to be high.

The positive correlations found between serum cholesterol, BLP and some cancer sites, may reflect risk factors related to dietary habits. The negative correlations may reflect other mechanisms e.g. cholesterol lowering effect of an undiagnosed cancer, or factors affecting both serum levels of cholesterol and cancer risks. Attempts to lower increased serum cholesterol level is not likely to increase the cancer risks.

November 1987

DNA cytometry of osteosarcoma

H. C. F. BAUER

Department of Orthopedics, Karolinska Hospital, S-10401 Stockholm, Sweden

The relationship between cytochemical features and histomorphology in osteosarcoma, and the clinical significance of DNA content were investigated by microspectrophotometry (MSP) of tissue sections and flow cytophotometry (FCM) of cell suspensions.

MSP of tissue sections entails the methodological error of determining the DNA content of sectioned cell nuclei. By analyzing 184 normal mesenchymal cell populations, an upper limit of diploidy (normal DNA content) was deduced. Applying this upper limit for 42 sarcomas, 6 were diploid and 36 hyperploid. Comparative analysis of the same lesions by MSP of imprint preparations and by FCM disclosed complete agreement in ploidy classification (diploid versus hyperploid).

Retrospective MSP analysis of bone tumors is often impeded by previous demineralization in acid, which destroys DNA. EDTA as an alternative was found to slightly reduce Feulgen DNA ,stainability of osteosarcomas, but did not affect tumor ploidy determination. Hence, EDTA offers a means of retaining DNA stainability of bone tumors requiring demineralization.

MSP analysis of different histologic areas, and comparative FCM analysis of biopsy and surgical specimens, disclosed that individual osteosarcomas are cytochemically uniform despite

morphologic heterogeneity. Hence, a single tumor sample for DNA analysis can be relied upon as representative for the tumor as a whole.

In a consecutive series of 83 osteosarcoma patients treated by surgery and adjuvant Interferon, the 7-year survival rate was 0.44. MSP DNA analysis gave no significant prognostic information. Multivariate analysis identified 3 risk factors for tumor related death, i.e., male sex, proximal tumor location, and histologic grade IV. In a prognostication model, the 7-year survival rates, for patients with 0, 1, 2, or 3 risk factors, were 0.80, 0.59, 0.42, and 0.13 respectively. Hence, it is possible to identify subgroups of high grade osteosarcoma patients with different prognosis.

In a study of 166 primary bone tumors, the applicability of DNA analysis for differential diagnostic purposes was investigated. The series included high grade osteosarcomas, parosteal osteosarcomas and benign bone tumors, which may be mixed up histologically with osteosarcoma. Out of 166 tumors, 149 (90%) were histologically noncontroversial, whereas 17 (10%) posed diagnostic difficulties. In the diagnostically noncontroversial group, all benign and parosteal osteosarcomas were diploid, whereas 97 of 102 osteosarcomas were hyperploid. Hence, hyperploidy seems to be a characteristic feature of high grade osteosarcoma. In the diagnostically controversial group of 17 cases, uncertainty had prevailed as to benignity or malignancy. All 8 patients, who developed local recurrence or died, had hyperploid lesions. In contrast, none of the diploid lesions recurred.

The clinical significance of DNA analysis in osteosarcoma is mainly diagnostic. In general, it confirms the histopathologic assessment. Occasionally, it questions diagnosis, and provides information of decisive therapeutic implication. Applied routinely, ploidy determination can contribute to increased diagnostic accuracy of primary bone tumors.

December, 1987

Prognosis in soft tissue sarcoma

B. RÖÖSER

Department of Orthopedical Surgery, University Hospital, S-221 85 Lund, Sweden

In 81 patients with soft tissue sarcoma the local recurrence rate after surgery with a wide margin, as defined by Enneking et al. (1980), was analyzed. Subcutaneous sarcoma, even if high grade, without involvement of the deep fascia could be managed by local surgery with a wide margin alone. This procedure resulted in a risk of local recurrence of less than 0.1 even if definitive surgery was preceded by an incisional biopsy or a marginal excision. Thus, adjunctive radiotherapy is not indicated in these cases. The same applies to patients with intramuscular tumors who are operated with primary myectomy, i.e. removal of one or several muscles but not the whole compartment, without prior open biopsy. Thus even a muscular fascia is sufficient as tumor barrier in these cases. One half of all patients with soft tissue sarcoma of the extremities have subcutaneous tumors or tumors suited for myectomy. By contrast, in patients operated with a wide margin where the dissection had transgressed the tumor-containing muscle or loose areolar tissue the recurrence rate was 0.27.

Prognostic factors for local recurrence and tumor-related death were multivariately analyzed in 2 series of 144 and 88 patients with grades III and IV (high-grade) soft tissue sarcomas of the locomotor system. Marginal surgery, extracompartmental location and tumor necrosis increased the risk of local recurrence. In both series malignancy grade IV, tumor size >10 cm and tumor necrosis were risk factors for tumor-related death. In the first series also male sex was a risk factor and in the second series intratumoral vascular invasion by tumor decreased survival. In both series prognostication models were constructed; survival was lower with an increasing number of risk factors. By these prognostication models one half of the patients with grades III and IV soft tissue sarcoma could be predicted to have a prognosis as good as that in patients with grades I and II tumors, i.e. a survival rate of 90 percent after surgery with a wide or radical margin. Thus, these patients should not be included in trials with chemotherapy. For patients with many risk factors the prognosis was dismal even after surgery with a low risk of local recurrence. Many of these cases probably had occult spread already at presentation. These patients are candidates for trials with chemotherapy.

November, 1987

Occupation, smoking and lung cancer. Cohort studies based on Swedish register data

J. CARSTENSEN

Department of Cancer Epidemiology, Karolinska Institutet, Radiumhemmet, S-104 01 Stockholm, Sweden

The primary aim of this study was to analyse the lung cancer risks in various male occupational cohorts. The cohorts were defined from the population census of 1960 and followed in the Swedish cancer register during 1961–79. In the analysis, allowance for smoking was made using information from a random sample of one percent of the population in 1963.

In a 16-year follow-up of the men in the 1963 sample, there were clear correlations ($p<0.001$) between the amount of tobacco smoked and the risk of death due to cancer of the oral cavity and larynx, oesophagus, liver, pancreas, lung, and bladder as well as due to bronchitis and emphysema, ischaemic heart disease, aortic aneurysm, and peptic ulcer. Contrary to the results from some other countries, pipe smokers showed similar risk levels to cigarette smokers. The similarity in risks may partly be explained by a similar fraction of inhalers in the two groups in Sweden.

In the analysis of the census cohort, adjustment for smoking considerably reduced the differences in lung cancer risk between the occupations. A substantial variation remained, however. Compared with all men and after adjustment for age, residence, and smoking, significant ($p<0.01$) excess risks were found in assemblers and machine erectors, drivers, miners, packers and longshoremen, as well as in sheetmetal workers. Decreased risks were seen in artists and writers, chemical and cellulose workers, farmers, farm workers, forestry workers, public administrators, and teachers.

Few occupations showed significant ($p<0.05$) trends in the relative risks of lung cancer during the period 1961–79. Among foundry workers as well as for construction machine operators increasing time trends were seen, while members of the armed forces and blacksmiths displayed decreasing trends.

In bakers and pastrycooks, a decreasing time trend in the relative risk of lung cancer was seen in younger birth cohorts. The relative risk was significantly ($p<0.01$) higher in counties with a small fraction employed in large bakeries.

November 1987

Aspects of early diagnosis and treatment of breast cancer

L. HOLMBERG

Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden

The aim of this work was to investigate some aspects of the outcome of a randomized mammographic screening trial and to analyse the early results of trials of breast-conserving surgery from cosmetic and psycho-social viewpoints. In the screening study, women in the study group were offered screening every 2 to 3 years. Women in the control group were not offered screening. Among the 134 867 women aged 40–74 years at entry, the study group showed a 31% reduction in mortality from breast cancer. The overall actuarial and the disease-free survival rates during the first 7 years of observation were both similar in 94 patients with interval cancers and 178 patients with cancer diagnosed in the control group. Thus, a faster growth rate of a tumour does not seem to always entail a worse prognosis.

The increase in surgical in-patient care created by population-based screening offered to women over 40 and repeated every 2 to 3 years was estimated to amount to about 150% during the initial screening round. During the second round the number of operations tended to fall again.

Among women 50 years of age at entry into the screening study, the incidence of interval cancer rose to 50% of that expected without screening after three years. By contrast, among women 40–49 years at entry, the corresponding figure was 70% in the second year after screening, indicating a faster regrowth of the cancers in this age group.

The women's view of the cosmetic result after a segmental mastectomy for malignant or benign breast disease was analysed by a study in 263 patients. 96.5% found the new appearance of the breast very good (30.7%), good (44.0%) or acceptable (21.8%). The rate of cosmetic dissatisfaction was low. The segmental resections were thus cosmetically highly acceptable to the women. The psycho-social adjustment after breast-conserving therapy compared with that after mastectomy was assessed in an interview study in 99 women. The interviews were semistructured and conducted 4 and 13 months postoperatively. No statistically significant differences in psycho-social adjustment were found between the 2 treatment groups.

January, 1988