Acta Oncologica, 2005; 44: 181–184

Taylor & Francis
Taylor & Francis Group

Abstracts of Theses from the Nordic Countries

Short abstracts of theses on oncologic subjects are published under this heading. The abstract should contain background, problems, results and conclusions and be an independent informative unit that can be read without access to the thesis. It should not contain references to literature, figures or tables in the thesis. A suitable size is about 500 words. The abstract can be sent to Acta Oncologica together with information about department, faculty and university and date of dissertation.

Modelling survival of patients with multiple cancers

SIRPA HEINÄVAARA

Finnish Cancer Registry, and Department of Statistics, University of Helsinki, Helsinki, Finland

With increasing number of subsequent primary cancers there is a growing concern to know how cancer patients survive with their subsequent cancer compared to those with their respective first cancer. Results of earlier studies have been conflicting and have not led to firm conclusions. One reason for conflicting results might be a lack appropriate methodology as survival from subsequent cancer has usually not been adjusted for an extra hazard due to an underlying first cancer.

This study presents four alternative models for estimating survival of patients with multiple cancers. Models are extensions and modifications to those proposed earlier for estimating relative and cause-specific survival of patients with a single cancer. The assessment of survival from subsequent cancer raised a need for introducing new concepts, especially when survival of patients with their multiple cancers of the same site is concerned. Survival estimates from cancer are compared between the models, and between a first and subsequent tumour of the same site. The importance of adjusting survival from subsequent cancer to that from a underlying first cancer is also highlighted.

The results show that survival from cancer as a first and subsequent tumour can be reliably assessed with the newly introduced models based either on the relative and cause-specific survival. The results also show that survival from cancer as a first and subsequent tumour may be dependent on the site of cancer and whether patients' cancers are of the same site or not. Nevertheless, survival from a subsequent cancer is not usually different from that from a respective first cancer. However, even with large population-based data, a lack of power often prevents the detection of modest differences in survival.

June 2003

The epidemiology of cervical cancer in Khon Kaen, Northeast Thailand

SUPANNEE SRIAMPORN

University of Tampere School of Public Health, University of Tampere, Tampere, Finland, IARC, Lyon, France, and Khon Kaen University, Khon Kaen, Thailand

The incidence of cervical cancer in Khon Kaen province, Thailand, is moderately high, with not much change over the last 15 years. Stage at presentation is considerably later than in the United States and Europe. There is about a two-fold variation in incidence between districts within the province. Eighty percent of cases are squamous cell carcinomas. Control through early detection and treatment remains the best approach for the time being. This can be through encouragement of women to present at an earlier stage of disease, which results in a much better prognosis. Stage at presentation can be improved along with better knowledge and awareness. This can be achieved in a short period of time, by health education programmes, as was shown among rural populations in India.

Otherwise, early detection through screening is the best-established method of reducing incidence and death. Current screening programmes in Thailand are not very effective. The quality of the smear taking, preparation, and reading in many programmes, particularly in developing countries, is not good. In Northeast Thailand the follow-up of women found to have a positive smear at screening is defective. The national cancer control programme aims to increase the coverage of screening, by limiting examinations to women at ages of 35, 40, 45, 50, 55 and 60. The population-based cancer registry in Khon Kaen provides an effective and economical method of evaluating the impact of early diagnosis and screening at community level.

Effects of risk factors of cervical cancer in Khon Kaen, Thailand are similar to studies elsewhere. Consistently, number of pregnancies and age at having first child were associated with the risk of cervical cancer. However, the usual risk factors of age at first sexual intercourse, number of sexual partners and a history of sexually transmitted disease among the subjects were not associated with risk of cervical cancer in Khon Kaen. The negative findings may be due to the small size of the studies, or to differences in the epidemiology – particularly with respect to infection with human papillomavirus (HPV) – in the Khon Kaen population.

The overall five-year survival of cervical cancer in Khon Kaen, Thailand is rather low (relative loss adjusted rate 57%) compared to results in developed countries. Extent of disease at diagnosis was the most important determinant of survival, implying that early detection is more important in improving outcome than improvement in the modality of treatment. Adjusting the estimate for cases lost to follow-up provided results that were similar to those obtained with the actuarial method, suggesting that use of the conventional actuarial estimate in the calculation of the relative survival was satisfactory for this population, and may be valid for the analysis of other population based cancer registry materials in developing countries.

September 2003

Physical activity and the risk of breast cancer

PIRJO RINTALA

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

Breast cancer is the most common cause of cancer death among women in the world and the incidence numbers are rising everywhere. There is great need to develop primary prevention strategies. Non-pharmacologically it might be possible to reduce the incidence of breast cancer by avoiding adult weight gain with healthy nutrition or by physical activity. The purpose of this study was to epidemiologically estimate the effect of physical activity on

ISSN 0284-186X print/ISSN 1651-226X online © 2005 Taylor & Francis
DOI: 10.1080/02841860510029680

the risk of breast cancer in Finnish female population. Cohort and case-control study designs were used. The subjects were a cohort of 30,548 women, economically active Finnish female population in the year 1970 classified according to the physical workload in their occupations, a cohort of 1,489 physical education and 8,572 language teachers, and 844 breast cancer cases with matched controls. The results showed that leisure time or occupational physical activity and physical activity while commuting decreased the risk of breast cancer. The effect of physical activity on the risk of breast cancer was small, but even 10–20% risk reduction means a decrease in the incidence of hundreds of breast cancer cases per year at the population level in Finland. According to results, effective aerobic physical activity should be regular, occurring several times per week, lasting at least 30 minutes per bout, and to be at least moderate in intensity. The study highlights the importance of promoting physical activity in diminishing the risk of breast cancer among the female population in large. Therefore, a physically active lifestyle should no longer be left to the individuals alone. Society, employers and the media should comprehensively take part in removing physical and psychological barriers, which may prevent an individual from having a physically active life.

November 2003

Psychological stress, personality and risk of breast cancer—Follow-up studies in the Finnish Twin Cohort

KIRSI LILLBERG

University of Helsinki, Helsinki, Finland

While the potential role of psychological factors in the aetiology of breast cancer has long been a topic of considerable scientific and public interest, little reliable epidemiological evidence has thus far accumulated on this issue. This study prospectively investigated the relationship between psychological stress, personality and risk of breast cancer.

The source population comprised 13 176 women, aged 18 years or more, from the population-based Finnish Twin Cohort. In health questionnaires mailed in 1975 and 1981, participants completed at least one of the following previously validated stress and personality measures: self-perceived stress of daily activities according to Reeder (n = 10 519), a 21-item life event inventory (n = 10 808, included only in the 1981 questionnaire), life satisfaction according to Allardt (n = 12 032), Eysenck neuroticism (n = 11 941), Eysenck extroversion (n = 12 009), Bortner type A behaviour (n = 11 272) and a brief measure of hostility (n = 10 682, included only in the 1981 questionnaire). The questionnaires also provided data on known breast cancer risk factors. From 1976 to 1996, all incident cases of breast cancer (n = 270, among the source population) were identified by record linkage with the Finnish Cancer Registry. Standard cohort analyses were based on Cox proportional hazards models which provided hazard ratios (HR) and their 95% confidence intervals (CI) of breast cancer by stress/personality factors. As a complementary approach, we conducted a nested case-control study of twin pairs discordant for breast cancer.

As expected, breast cancer risk was affected by known breast cancer risk factors such as age, nulliparity and late age at first birth.

After adjustment for potential confounding factors, breast cancer risk was not affected by any of the following stress and personality factors: stress of daily activities (multivariable HR for continuous score = 1.04, 95% CI 0.91–1.20), life satisfaction (0.99, 0.86–1.14), neuroticism (0.91, 0.79–1.02), extroversion (1.01, 0.88–1.16), type A behaviour (1.10, 0.96–1.26) and hostility (1.01, 0.87–1.17). These results appeared robust in multiple confirmatory analyses, e.g., when assessment of stress/personality and potential confounding factors was based on repeated measurements.

In contrast, both the accumulation of life events and single major life events increased breast cancer risk, and these relationships did not attenuate after adjustment for potential confounding factors, which also included body mass index, alcohol use, smoking and physical activity. Thus, the multivariable HR per one event increase in the total number of life events (possible range 0–21) recorded for the five years prior to the 1981 questionnaire compilation was 1.07 (95% CI 1.00–1.15); this risk estimate rose to 1.35 (95% CI 1.09–1.67) when only major life events were taken into account. Independently of total life events, divorce/separation (HR = 2.26, 95% CI 1.25–4.07), death of husband (HR = 2.00, 95% CI 1.03–3.88) and death of close relative/friend (HR = 1.36, 95% CI 1.00–1.86) were associated with increased risk of breast cancer.

No substantial joint effects of the stress/personality factors on breast cancer risk were observed. The discordant pair analyses provided results similar to those of the cohort analyses thus giving further credence to the overall findings and suggesting that familial factors are not important in the relationship between stress/personality and breast cancer risk.

These data do not support the existence of an important role for self-perceived stress and personality in the aetiology of breast cancer but do suggest one for life events. The null findings have a direct bearing on women's quality of life by decreasing breast cancer-related worry. The life event findings are intriguing, particularly in light of the possibility that life events may be a marker of some as yet unknown but potentially modifiable lifestyle characteristic that increases breast cancer risk; nevertheless, these findings should be interpreted with caution until repeated in other methodologically sophisticated studies.

December 2003

Role of socioeconomic status and reproductive factors in breast cancer—A case-control study

K. RAMACHANDRA REDDY

University of Tampere School of Public Health, University of Tampere, Tampere, Finland and Kidwai Memorial Institute of Oncology, Bangalore, India

In India the incidence rates of breast cancer among females are showing a rising trend. Breast cancer is the first leading site of cancer in 4 out of the 5 population based urban registries – Bangalore, Mumbai (Bombay), Delhi and Bhopal. In Chennai (Madras) it is the second but a tendency of breast cancer to rise over time has been observed. In the hospital based cancer registry at Kidwai Memorial Institute of Oncology (A Regional Center for Cancer Research and Treatment), Bangalore, about 500 cases of breast cancer are registered annually. In order to study the role of socioeconomic status vis-à-vis standard of living, reproductive factors and risk of breast cancer a hospital-based case–control study was undertaken. 360 cases of breast cancer confirmed microscopically and an equal number of controls without a history of any disease in the breast, gynecological organs or endocrine glands matched for age formed the subjects of the study. The major findings of the study were:

- The risk of breast cancer increased as the socio economic status increased. Compared to illiterate women (no schooling) women with secondary education (up to 10 years of schooling) had a significant and more than three-fold risk (adj. OR 3.14) and women with an educational level of college and above (11–15 or more years of schooling) had a two and a half-fold (adj. OR 2.49) significant risk of developing breast cancer. Women with higher income were at an elevated risk (adj. OR 1.46) compared with women with lower income.
- Women living in urban areas appeared to be at increased risk, (adj. OR 1.47) compared to women living in rural areas. Muslims were at an elevated risk (adj. OR 1.92) of developing breast cancer (significant) followed by Christians (adj. OR 1.63) compared with Hindus.
- Never-married women were at increased risk (adj. OR 8.74) of developing breast cancer compared with ever-married women. Nulliparous women had a two-fold risk (adj. OR 2.14) of developing breast cancer compared with parous women. Compared with parous women with more than six children, the risk among nulliparous women was found to be about three-fold (adj. OR 2.96).
- Women who delayed their first childbirth were at elevated risk of developing breast cancer. Compared with women whose age at first child-birth was below 20 years, women whose age at first child-birth was above 30 years were at more than two-fold risk (adj. OR 2.32) and women whose age at first childbirth was between 20–24 years were at almost two-fold risk (adj. OR 1.67) of developing breast cancer.
- Breastfeeding for a longer duration emerged as an apparent protective factor for the risk of breast cancer independent of age at first birth, parity and other potential confounding factors. Compared with women who breastfed for more than 18 months women who breastfed for less than 6 months were at significant and more than eight-fold risk (adj. OR 8.59). Ultimately it may be that breastfeeding accounted for much of the effect due to parity in this study. This is relatively consistent in other studies as well.
- Family history was rare in this material and most of the effects could be accounted for by socioeconomic status. Hence genetic inheritance in the aetiology of breast cancer appears to be not of importance in India, at least given the current distribution of risk factors. This may change if the environment changes and gene expression changes.

May 2004

Genetic epidemiology of prostate cancer

Fredrik Wiklund

Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

Prostate cancer is a major health burden throughout the world being the most common cancer among men in most developed countries, yet the etiology of prostate cancer is poorly understood. Evidence has accumulated supporting the existence of a hereditary form of prostate cancer. In linkage analysis several chromosomal regions have been suggested and fine mapping of promising loci have identified three candidate genes. However, conflicting reports of the effects of these genes, and failure to replicate suggested regions indicates a much more complex genetic basis of prostate cancer than first anticipated. Improved understanding of the genetic mechanisms underlying the development and progression of prostate cancer would be a major advance for improved prevention, detection and treatment strategies. This thesis evaluates different aspects of the genetic epidemiology of prostate cancer.

A genomic scan in Swedish hereditary prostate cancer (HPC) families localized two chromosomal regions with suggestive evidence for linkage. The strongest support was found on chromosome 19p with an allele sharing LOD score of 2.91 (genome-wide P value = 0.032). The second region showing suggestive evidence of linkage was observed in the centromeric region of chromosome 5. Linkage analysis of densely spaced markers on chromosome 8p22-23 confirmed (P = 0.03) previously reported linkage to this region. A systematic evaluation of the possible impact that the RNASEL gene have on prostate cancer was performed. No support for a role of the rare truncating mutation E265X was found, and analyses of common sequence variants provided limited evidence for association with prostate cancer risk. Considering the large and well characterized study population and high quality in genotyping (0.3% error rate) these results provide strong evidence against a role of RNASEL in prostate cancer etiology in Sweden. In a comprehensive evaluation of occurrence of other malignancies in HPC families, previously reported association between gastric and prostate carcinoma was confirmed. The increased risk was of the same magnitude in earily late onset HPC families and confirmed to only male relatives. A genome-wide linkage analysis, startified by occurrence of gastric carcinoma, identified a novel susceptibility locus on chromosome Xp21.

In summary, chromosome 5q and 19p represents the regions most likely to harbor susceptibility genes predisposing to prostate cancer in the Swedish population. A common genetic basis for both gastric and prostate cancer has been confirmed and a novel susceptibility locus on chromosome Xp21 has been identified. Our results provide further support for the assumption that genetics play a critical role in prostate cancer susceptibility. A growing body of evidence advocates the existence of multiple genes with small to moderate effect in the development of this disease. Future genetic epidemiological efforts utilizing efficient strategies to decrease the complexity of prostate caner genetics will likely succeed in the unraveling of the genetic influences on this common disease.

June 2004

Synovial sarcoma—Molecular, biological and clinical implications

Maria Törnkvist

Department of Oncology-Pathology, Cellular and Molecular Tumour Pathology, Cancer Centrum Karolinska, Karolinska Institutet, Stockholm, Sweden

Synovial sarcoma is a rare but mostly aggressive soft tissue tumor that mainly affects children and young adults. The tumor usually occurs in the vicinity of large joints, and may be subdivided into a classical biphasic type, a monophasic type or a poorly differentiated type, depending on histomorphological appearance. Synovial sarcoma is cytogenetically characterized by the recurrent and specific translocation t(X,18)(p11.2;q11.2), which results in fusion of the 5′ part of the *SS18* gene, and the 3′ part of either the *SSX1, SSX2* or *SSX4* gene. Since the resulting fusion gene *SS18-SSX* is specific for synovial sarcoma, it constitutes a valuable molecular tool at diagnosis.

In this thesis, a previously *SS18-SSX* negative case is described, where an unusual breakpoint variant was detected after method optimization, thereby confirming diagnosis. The case provided molecular information of the oncogenic properties of *SS18-SSX,* since the unusual breakpoint resulted in alteration of the predicted amino acid sequence, potentially encoding an altered fusion protein. A renal tumor was reinvestigated after a highly aggressive behavior, usually not compatible with the originally diagnosis of hemangiopericytoma. After molecular confirmation of the presence of *SS18-SSX,* the new diagnosis was synovial sarcoma. These cases underline the usefulness and necessity of molecular investigations of suspected, but due to unexpected fusion breakpoints or unusual locations not confirmed synovial sarcomas. In order to investigate downstream events of *SS18-SSX,* an antisense strategy was used in combination with a cDNA microarray. It was possible to compare the gene expression profile of *SS18-SSX* inhibited cells with non-inhibited, showing altered expression levels of genes involved in cancer-relevant functions like cell proliferation, apoptosis and DNA-repair. It has recently been shown that *SS18-SSX* is able to stabilize expression of cyclin D1, and that IGF-IR expression is associated with poor prognosis in synovial sarcoma. These aspects were further investigated here, suggesting a proliferative role of *SS18-SSX* since its expression allowed cells to remain in cycle even in the absence of mitogenic signals. On the other hand, inhibition of the IGF-IR caused massive cell death. A potential therapeutic strategy could use the continued cell cycle and kill the cells by inhibition of IGF1-IR.

Results presented in this thesis provide clues to the molecular, biological and clinical consequences of *SS18-SSX.* This information may be relevant for the development of specific therapeutic strategies against the highly malignant disease.

September 2004

Apoptosis in myelodysplastic syndromes—Effects of hemopoietic growth factors

Ramin Tehranchi

Department of Medicine, Division of Hematology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden

Increased apoptosis of hematopoietic progenitors is a hallmark of myelodysplastic syndromes (MDS) and results in ineffective hematopoiesis. Erythroid apoptosis is thought to be the main mechanism underlying the severe anemia observed in the low-risk subgroups, refractory anemia (RA) and RA with ringed sideroblasts (RARS). Clinically, treatment with Epo alone or in combination with G-CSF may significantly improve anemia and reduce bone marrow apoptosis. The synergistic effect between Epo and G-CSF is more prominent in RARS. The present study was designed to assess and characterize mechanisms underlying augmented apoptosis and ineffective erythropoiesis in MDS and to investigate the effects of hematopoietic growth factors. Bone marrow cells from 55 patients were used in the experiments. RA and RARS cells showed significantly higher spontaneous initiator (caspase-8 and -9) and effector (caspase-3-like) activities than normal bone marrow (NBM). G-CSF inhibited Fas-induced caspase activity, restored proliferation, and improved erythroid colony growth in RARS. There was no significant effect of G-CSF on Fas-induced changes in RA mononuclear cells. Caspase-9 activation was shown to be an essential mediator of apoptosis in MDS, but not in NBM. Selective inhibition of caspase-9 reduced both spontaneous and Fas-induced caspase-3-like activity, indicating a role for mitochondria-dependent apoptosis in MDS. We then developed an assay in which $CD34^+$ cells were cultured to mature erythroblasts for studies of mitochondrial function and signaling, as well as iron distribution during erythroid maturation. While absent in NBM, significant release of cytochrome *c* was seen at all stages of erythroid differentiation in RA and RARS, however, more prominent in RARS. This release was blocked by G-CSF during the whole culture period, with a peak effect between day 4 and 7, and by Epo during the latter phase of culture. We demonstrated that both freshly isolated glycophorin A^+ BM cells and erythroblasts during the second week of cultivation retained the G-CSF receptor. The synergistic effect of Epo and G-CSF was assessed, and the in vitro and in vivo effects of these growth factors were compared. Cytochrome *c* release and caspase activation were significantly less pronounced in MDS progenitors obtained from successfully treated non-anemic patients, and showed no further response to G-CSF in vitro, indicating that data obtained in the erythroblast model reflect relevant biological events in vivo. Epo significantly promoted growth of cytogenetically normal cells from patients with 5q-syndrome, but had no effect on bone marrow from patients with other aberrations. RARS progenitors showed an aberrant accumulation of mitochondrial ferritin (MtF) already at day 4, and a continuous increase during the culture period. RA erythroblasts showed only few positive cells, and NBM was negative for MtF. Hypothesizing a defect mitochondrial respiratory chain function in terms of ATP production in MDS, we developed a method for assessment of BM cells. However, no significant difference (all complexes or cytochrome *c*-dependent complex IV) was found between MDS and NBM. We demonstrated a significant over-expression (mRNA) of the pro-apoptotic genes for cytochrome *c,* Bid and Bax, as well as up-regulation of genes involved in erythroid differentiation (β-globin, GATA-1 and DLK-1) in MDS $CD34^+$ cells. β-globin was adequately expressed during erythroid maturation, while GATA-1 expression was significantly decreased, indicating a block of erythroid maturation at the transcriptional level. G-CSF showed no effect on mitochondrial ATP production, cytochrome *c* mRNA, or MtF. In fact, MtF expression increased in some RARS cultures. This indicates that G-CSF allows survival of MDS erythroblasts by up-regulating compensatory mechanisms for cell survival, rather than by a direct effect on mitochondrial function or iron distribution. In conclusion, we have shown strong evidence for mitochondria-dependent apoptosis in MDS and propose a model in which the increased sensitivity to external apoptotic stimuli is dependent on constitutive mitochondrial signaling mediated via cytochrome *c* release. Moreover, erythroid apoptosis, as well as defective erythroid maturation is initiated at the MDS stem cell level. Our data also provide a mechanistic explanation for the beneficial clinical effects of growth factor administration in MDS patients. We conclude that pro-erythroid growth factors can act both via inhibition of apoptosis, and via selection of cytogenetically normal progenitors.

September 2004