with st PNET is unsatisfactory, and intensification of therapy is needed. In ependymomas the predominant site of failure is the primary tumour site. The irradiation of neuraxis did not improve survival. For ependymomas intensified local therapy is warrantable.

721 ORAL

Risk of second primary cancer in hereditary and non-hereditary retinoblastoma: results from a population based study with more than 40 years follow-up

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Purpose: To determine the risk of second primary cancer in retinoblastoma survivors, we have identified and followed the 240 patients diagnosed with the disease in Denmark between 1943 and 1995.

Methods: Data on treatment, heredity, mortality and observed/expected numbers of second primary cancers have been extracted from the Danish Cancer Registry, primary records from the clinical departments, the Danish Population Registry, and church records. Data on heredity are based on family history and genetic analysis. Median follow-up of the 210 retinoblastoma survivors is 25.2 years of age.

Results: At 40 years of age, the cumulative incidence (3%) and mortality (3%) of second primary cancer in the non-hereditary group (144 patients) is similar to the population at large. In contrast, the corresponding values for the hereditary group (96 patients) is significantly higher at 19% and 11%, respectively. Among the hereditary patients, the increased risk is the same for patients treated with or without radiation therapy for their primary disease. None of the patients have received chemotherapy. Except for a higher incidence (particularly of malignant melanomas), the second primary cancers are of the same type as the time- and age-specific cancers observed in the population.

Conclusions: Associated with hereditary retinoblastoma is an increased risk for second primary cancer. This is not linked to the use of radiation therapy but strictly to the genetic status of the patient

722 ORAL

Detection of relapse in childhood solid tumours

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Aims: Frequent follow-up, often with regular investigation, is a routine part of Paediatric Oncology. Many treatment protocols specify both the type and frequency of the investigations to be performed. There is however, little evidence as to the value of such surveillance in the detection of relapse. We thus conducted a retrospective study of relapse detection in a patient cohort.

Methods: A cohort of 316 children diagnosed with solid tumours between 1992 and 1996 was identified. This patient group had a minimum follow up period of 5 years from the end of treatment. Case notes were reviewed and numbers of clinic visits and surveillance investigations recorded. For any relapse that occurred the method of relapse detection was noted.

Results: The average age of the cohort was 5.4 years, and the mean period of follow-up was 5.9 years. 76 patients were excluded because they never achieved remission, or were lost to follow-up. 3417 routine clinic visits were made by this cohort. The frequency of clinic attendance varied from 11 visits/ patient/yr for those with bone tumours, to 6/yr per brain tumour patient in the first year after finishing treatment, although there was less variation in subsequent years. 1860 radiological investigations were performed on this patient group over this period. 60% of these were chest radiographs, 14% were ultrasounds, and 12% were MRI scans. Wilm's tumour patients had on average 11 radiological investigations/yr during this period of follow up, whilst brain tumour patients had only 3/yr. 37 relapses were detected in this cohort. 53% were detected symptomatically, 13% at routine clinic visits, and 27.5% on routine investigation. 81% of relapses occurred >1 year from the end of treatment. We calculated that routine MRI scan detected 1 unsuspected relapse for each 42 scans performed. Routine CT scan detected 1 relapse for every 129 scans performed, whilst routine chest radiography detected only 1 relapse for every 257 films. The low incidence of relapse detection by routine surveillance in this cohort raises questions as to the usefulness of such follow-up in children with solid tumours.

723 ORAL

CPMP guidance in paediatric oncology

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Background: Since 1990, the Committee for Proprietary Medicinal Products (CPMP) anticancer guideline has provided advice on the clinical investigation of anticancer agents, in particular of cytotoxic/cytostatic agents (Note for Guidance on Evaluation of Anticancer Medicinal Products in Man, CPMP/EWP/205/95). Recently, the CPMP has been working together with European paediatric oncology research groups, including the EORTC Children's Leukaemia Group, the Société Française d'Oncologie Pédiatrique (SFOP), the United Kingdom Children's Cancer Study Group (UKCCSG), the German Society of Paediatric Oncology and Haematology (GPOH), and experts from other European institutions, to produce specific guidance on paediatric oncology, with recommendations for regulatory submission, and phase I trial methodology.

Results: Promising new agents should be studied or made available to researchers, so as to avoid unnecessary delays in paediatric development. Prioritisation of agents for evaluation in children is critical. Factors to be considered include evidence of activity in pre-clinical models, mechanism of action, drug-resistance profile and activity observed in adults. It is recommended that a marketing authorisation application for anticancer agents for adult use should contain information on any past, ongoing or planned paediatric oncology development. A comprehensive overview of any pre-clinical testing in model systems of paediatric tumours should be provided. Data requirements and the timing of paediatric development should be discussed with the regulatory authorities. Sponsors should seek the advice of established international paediatric oncology co-operative groups, and regulatory authorities, early enough during the development so that agreed priorities can be followed, avoiding unnecessary delays. The existing consensus on the design of phase I trials (Smith, M., M. Bernstein, et al., (1998) "Conduct of Phase I trials in Children With Cancer." J Clin Oncol 16(3): 966-78) has also been reflected in the guideline.

Conclusions: Co-operation between the pharmaceutical industry, research groups, and health authorities worldwide can ensure a coherent approach to paediatric drug development in oncology. The paediatric addendum to the CPMP anticancer guideline can be consulted on the EMEA website (htpp://www.emea.eu.int). Finalisation is expected before the end of 2003.

724 ORAL

Caring for survivors of childhood cancers: the size of the problem

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Background: Survival for children with cancer has improved greatly, although many survivors have significant health problems from their illness or treatment, requiring long-term medical care. This study utilises survival and clinical data to estimate current and future numbers of long-term survivors and their disabilities, and considers how their care might be provided.

Materials & Methods: The West Midlands Regional Children's Tumour Registry provided data on 5,016 children aged 0-14 years diagnosed with cancer (or benign brain/CNS tumours) between 1960 and 1999. Future numbers of long-term survivors were estimated from actuarial survival rates. Treatment and late effects data were collected from their medical casenotes

on a cohort of patients surviving over 5 years. Their continuing care needs were then considered.

Results: Actuarial 5-year survival for all cancers combined increased from 23% for patients diagnosed in the 1960s to 70% for those diagnosed in the 1990s.The number of patients surviving their disease for 5 years or more grew from 98 in 1970 to 1,747 in 2000 and by 2005 could exceed 2,100. Among 948 survivors (52% of those in the Region), 5% had received surgery alone, 55% radiotherapy and 85% chemotherapy. Exposure to anthracyclines had occurred in 53% of survivors, to alkylating agents in 40%, to epipodophyllotoxins in 33% and to platinums in 14%. Cranial irradiation had been given to 34%, at 24 Gy or more in 14%. No chronic medical problems were recorded in 18% of patients; only 3% of brain/CNS tumour survivors had no problems recorded, compared with 11% of other solid tumour and 34% of leukaemia survivors. Organ or system damage/toxicity affected 36% and 30% had growth, endocrine or fertility disorders. Obesity/overweight was present in 18% and in some may have been due to as yet undiagnosed endocrine problems. Neuro-cognitive, mobility, visual, hearing, dental and cosmetic effects were also seen. Many patients had several problems recorded. Consequently few were suitable for postal follow-up and most require multi-disciplinary care.

Conclusions: The remarkable improvements in survival rates have resulted in a steady increase in the number of patients requiring follow-up per annum, mostly in specialist late effects clinics. Protocol-driven care permitting audit to determine the most cost-effective management is required.

Public health and costs

725 ORAL

Socio-economic status and breast cancer in Denmark

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Background: Breast cancer is the most frequent cancer in women, the incidence is increasing and the risk is highest in well-educated women. We studied:

The socio-economic differences in breast cancer incidence and mortality in Denmark measured by the women's own and the spouses occupation, and

The contribution of different socio-economic groups to the increasing incidence.

Material and Methods: 1 402 225 women aged 20-64 at the census in 1970 in Denmark were followed up for death, emigration, and incident breast cancer. During the period 1970-1995, 51 721 women developed breast cancer, and 21 576 died of breast cancer. Of the 1 402 225 women included in the study, 730 549 were economically active in 1970, and 480 379 women were both married and economically active. Socio-economic status was assessed based on the 1970 occupation.

Results: For women classified by their own socio-economic group, the standardised incidence (SIR) and the standardised mortality ratios (SMR) were highest in academics (SIR 1.39, SMR 1.29), and lowest in women in agriculture (SIR 0.77, SMR 0.75).

For married, economically active women classified by their own socio-economic group the SIR and SMR were highest in academics (SIR 1.40, SMR 1.44) and lowest in women in agriculture (SIR 0.76, SMR 0.76). Classified by their husbands' socio-economic group, the SIR and SMR were highest in women married to academics (SIR 1.21, SMR 1.16) and lowest in women married to men in agriculture (SIR 0.79, SMR 0.79). The gradient was thus steeper for women when they were classified by their own socio-economic group than when they were classified by their husbands' socio-economic group, and steeper for incidence than for mortality. From 1970 to 1995, the risk of developing breast cancer increased by 38% in women aged 50-64. All social groups contributed to this increase, but the increase was 45% in unskilled workers, and only 26% in academics.

Conclusion: In 1970-1995 academics had the highest risk of breast cancer in Denmark. The size of the social gradient in breast cancer occurrence was steepest when women were classified by their own occupation. The time trend in the social distribution tends to equalise the occurrence of breast cancer across social groups. As a consequence of this breast cancer is also expected to become more frequent.

We are currently studying how much of the socio-economic distribution, that can be ascribed to differences in fertility patterns. Fertility information was combining from the household information of the 1970 census and the Danish Fertility Database. This procedure created a file covering the entire reproductive history of women aged 20-39 in 1970.

726 ORAL

Influence of obesity on prognosis after breast cancer in Denmark.

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Background: There is evidence to suggest that obesity is associated with a poor prognosis after breast cancer. This may be due to several factors. Compared to lean women, obese women may be diagnosed with more advanced disease and respond poorer to adjuvant treatment.

Material and methods: With the aim of elucidating these points, we performed an analysis of 10.270 breast cancer patients diagnosed and treated in Denmark between 1977 and 2001 for whom information on height and weight at diagnosis was available in the database of the Danish Breast Cancer Co-operative Group.

Results: Univariate analyses showed that patients with a body mass index (BMI = weight/height squared) exceeding 30 had significantly larger tumours and more positive lymph nodes than patients with a BMI of 25 or less, while BMI was not related to histological type, grade or oestrogen receptor status. Survival was analysed by Cox proportional hazards models where the effect of obesity can examined in relation to other known prognostic factors. Since the intensities were not proportional for age at diagnosis and grade, the analyses were stratified for these variables. Adjusting for the effects of tumour size, tumour invasion into the fascia, number of removed and number of positive lymph nodes and treatment, there was an independent prognostic significance of BMI on overall survival, the adjusted hazard ratio of dying being 1.19 (95% confidence interval 1.09-1.30) for a BMI of 30 or more compared with a BMI of 25 or less. The effect of BMI on recurrence free survival was borderline significant (p=0.07). We examined the effect of adjuvant systemic treatment (chemotherapy or endocrine treatment) in patients grouped according to BMI and found both treatment modalities to be less effective in women with BMI exceeding 30.

727 ORAL

Prognostic characteristics and mortality from breast cancer in women using hormone replacement therapy (HRT).

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Background: Women currently using HRT regimen common in Europe might develop breast cancers with more favourable prognostic characteristics and experience a different overall mortality from breast cancer compared to never users.

Material and Methods: A nationwide cohort of Danish nurses was established in 1993. In total 23,178 nurses received a mailed questionnaire (response rate 86%), which was used as baseline information. Follow-up ended December 31st 1999. Follow-up for mortality ended October 22 nd 2001. Cases were ascertained using Danish registries. The Danish Breast Cancer Group Cooperation (DBCG) registry provided information on histology, tumour size, receptor-status, lymph node status, malignancy grade and stage of disease. Women with missing information on HRT, premenopausal women, women with a surgical menopause and hysterectomized women were excluded, leaving 10,874 women for analyses. Statistical analyses were performed using Cox Proportional Hazards model and Kaplan Maier survival analysis.

Results: A total of 244 women developed breast cancer during follow-up. Of these 172 women were diagnosed with invasive ductal carcinoma to which analysis on prognostic factors was limited. For current users of HRT compared to never users, the risk of developing breast cancer with a low malignancy grade and a high malignancy grade was RR= 3.88 (2.23-6.75) and RR= 2.09 (1.35-3.23), respectively. These two estimates were not statistically significantly different. Other factors such as receptor status, lymph node status and stage were similarly associated with highest risks for