was observed among women born between 1870 and 1899. a total of 2,343 borderline turnouts were diagnosed between 1970 and 1993. The age-adjusted incidence rate has increased since 1970, reading 4.8 per 1000 000 person-years in 1989–93. The prognosis of ovarian cancer is still poor, and the crude 5-year relative survival was 36% in the Nordic countries in the late 1980s. in the present study, histology-specific long-term trench in prognosis of patients with ovarian cancer and borderline turnouts in Norway were examined The age-adjusted 5-year relative survival rate of patients with ovarian cancer increased steadily from 1954 to 1993. The increase in survival was most pronounced in women below the age of 65 years. No improvement was seen for women older than 75 years. The 5-year relative survival of the serous turnouts improved continuously from 1970 to 1993. For the mucinous tumours, an increase in relative survival was seen until 1984–88, thereafter the rate declined. In multivariate survival analysis, the RR of dying decreased with period diagnosis. For all patients with ovarian cancer, a RR of 0.5 (95% CI = 0.4–0.5) was seen in 1989–93 compared with 1954–58. Restricting the analysis to patients with epithelial cancer (197093), a RR of 0.6 (95% CI = 0.6–0.7) was seen in 1989–93 compared with 1970–73. In an analysis restricted to patients with epithelial cane., the patients with mutinous, endometrioid and clear cell turnouts had the lowest odds for having distant metastases. The age-adjusted 5-year relative survival rate of patients with borderline tumours was almost constant between 1970 and 1993, at a level of about 95% For these patients, age turned out to be the strongest prognostic factor. RRs of 11 and 34 were found for the age groups 65–74 and 75–89 years, respectively, compared with women younger than 45 years.

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## Ovarian cancer: Progress in chemotherapy

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In the last decade it has been shown that long-term survival is achievable for women with advanced ovarian cancer. With cisplatin-based combinations 10 year survival rates are about 20 percent and even 15 years after treatment patients survive free of disease. The present standard of care is paclitaxel 135 mg/m$^2$ in 24 hours with cisplatin. It can be expected that with paclitaxel in initial treatment programs the long-term survival rate will increase. A shorter time of administration and an increase of the dose of paclitaxel will enhance the incidence of neurotoxicity. For this reason carboplatin (a less toxic cisplatin analogue) appears to be an attractive agent to combine with paclitaxel. The combination causes less nausea and vomiting, less neurotoxicity and can be administered to outpatients. Current studies define the role of carboplatin, doxorubicin, gemcitabine and new drugs such as topotecan in combination with paclitaxel. There is a renewed interest for the intraperitoneal use of drugs but this route of administration remains investigational.

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## The management of recurrent epithelial ovarian cancer

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Recurrent epithelial ovarian carcinoma, i.e. relapse after a disease-free interval of at least 6 months following primary therapy, carries a poor prognosis, and the shorter the disease-free interval the worse the outcome. There has been considerable differences regarding the management, particularly, the role of surgery. In principle, recurrent disease has rarely, if ever, been considered as localized disease. Thus, it requires systemic therapy. Whether or not surgery has a place in combination with chemotherapy is still controversial. Clearly, if the recurrent tumor does not respond to chemotherapy surgery has little to offer, and is of palliative treatment. Should patients with recurrent ovarian carcinoma undergo cytoreductive surgery followed by chemotherapy as with primary disease? Alternatively, should they have induction chemotherapy, and only the responders be treated with interval surgery followed by further chemotherapy? These are some of the question that yet to be determined. Patients who initially responded to cisplatin based chemotherapy may well be treated again with such regimen. A response rate of 60% can be expected.

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## Genetic predisposition to multiple cancers

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Genes predisposing to cancer in childhood may be responsible of multiple tumours. P53 germline mutations account for a substantial part of second malignant neoplasms (SMN) after a first cancer in childhood. Among 33 patients treated in the Department of Paediatrics affected by a SMN and tested for p53, 8 (including 2 sibs) were found to be carriers of a germline mutation of this gene. Most of these cases displayed a family history suggestive of LFS. One case was due to a *de novo* mutation.

All the genes predisposing to cancer in childhood and possibly to SMN have not yet been identified and the observation of familial aggregation may be a good indicator of such genes. Some of them might interact with radiotherapy and chemotherapy which have been implicated in SMN occurrence. We instigated a case-control study (25 cases of SMN after a childhood cancer and 96 controls with no SMN) to evaluate the possible effect of unknown genetic factors, evaluated from familial aggregation, on the risk of SMN, and their potential interaction with the effects of treatment. We found an independent effect of both radiotherapy and family history on the risk of SMN, even after exclusion of cases with p53 mutations and Recklinghausen's disease. These results strongly suggest that other genes than the ones identified to date have to be looked for and that the follow-up of children treated for a cancer should take account of genetic predisposition.

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## The role of therapy in the incidence of second cancers

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**Purpose:** Recent UK data suggest at least 60% of children with cancer are cured. Therefore 1 in a 1000 of the general population will soon be survivors of childhood cancer. What are the risks of carcinomas among these adult survivors? Are there particular elements of therapy for childhood cancer which increase the risk of carcinoma development?

**Methods:** A cohort of 13279 patients who survived at least three years after diagnosis of childhood cancer between 1940 and 1983 was established using the population-based National Registry of Childhood Tumours. A case-control study was also established: cases were patients developing carcinoma and up to 4 controls were matched to each case. Cumulative doses of radiation and chemotherapy were compared between cases and controls.

**Results:** 69 carcinomas were observed in the cohort, 25 skin and 44 of other sites. By 30 years from three-year survival 2.5% of patients had developed a carcinoma, 1% of skin and 1.5% of another site. There were 12, 9, 9 and 8 cancers diagnosed in digestive, breast, thyroid and genitourinary tissue, respectively. The risk of carcinoma increased with increased exposure to radiation. Patients whose tissue had received 20–30 Gy and at least 30 Gy experienced 18 and 12 times the risk associated with unirradiated tissue, both of these relative risks being associated with $p < 0.001$.

**Conclusions:** These data have implications for monitoring patients treated in the past, and for planning future treatment protocols to achieve an optimum balance between the risks and benefits of different elements of treatment in the long-term.

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## Growth from child to adult – Interference by radiotherapy

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The advances in treatment of childhood malignancies is reflected in improvement of survival. But the results are marred by delayed sequelae caused by the inability of radio- and antineoplastic therapy to discriminate between normal and target tissue. Irradiation to a growing child interferes with tissue growth. Radiation damage of the skin and the subcutaneous tissue and muscle can be serious. Radiotherapy to the thorax in a pre-pubertal female causes atrophy of the breast. Radiation to the small and large intestines

gives as late sequelae malabsorption. Renal irradiation results in radiation nephritis and a picture of chronic nephritis appears later. Irradiation to the renal vessels can result in a development of malignant hypertension. Most striking is the growth retardation caused by radiation to bone and cartilage. Depending on the dose levels, different types of deformity may be induced in bones. If minimal injury is produced, a series of transverse growth arrest lines is noted in the metaphysis that progresses into the diaphysis and may eventually disappear. Irradiation of the epiphysial plate may result in stunting of the long bones. Femoral capital epiphyseal slippage may occur with a dose above 25 Gr. A significant degree of vertebral column deformity, which includes kyphosis, scoliosis, or lordosis is found after Wilms tumour treatment. After a variable time of growth retardation, normal bone growth may resume following exposure to doses in the range of 6 to 15 Gr. Permanent damage is produced with doses over 20 Gr. Mature bone and cartilage, when heavily irradiated with doses over 65 Gr, may undergo necrosis. The tolerance dose of fractionated radiation varies for the different tissues. Bone marrow, ovary, glands, testis, pubertal breasts and growing cartilage being most sensitive followed by kidney, lung. But all tissues will develop serious development disturbances with radiation dosis with over 60 Gr.

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## Cardiac late effects after anthracyclines

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Anthracycline (AX) cardiotoxicity (CTX) is one of the most serious late effects of otherwise successful cancer treatment. Clinically, it presents as chronic, progressive, dilatative cardiomyopathy, ultimately leading to congestive heart failure and death. Angiotensine converting enzyme inhibitors have been used in order to treat patients with relevant cardiac dysfunction and heart transplants have been successfully performed in cases of terminal heart failure. Oxidative stress, probably mediated by AX-iron complexes, is made responsible for the initial damage. While there is no universal consensus on how to monitor for early signs of AX-CTX, echocardiography is often described as the method of choice. The incidence of significant AX-CTX was once thought to be rather low, provided cumulative doses remain <500 mg/m$^2$. It has, however, now become clear that subclinical damage, often measurable by noninvasive means, occurs in a considerable number of patients, if not in all. Risk factors for severe CTX include high cumulative AX dose, high peak levels due to rapid application, additional stress to the heart such as mediastinal irradiation, as well as probably young age and female sex. Unfortunately, the heart does not recover with time, on the contrary, cardiac function often deteriorates even years after treatment. Successful approaches to reduce AX-CTX include scheduling (application by prolonged infusion) and coadministration of the iron-chelator ICRF-187. While randomized studies evaluating the influence of those cardioprotective measures on AX-antitumor-efficacy are scarce, it seems that any negative impact, if present at all, is not as large as the positive effect on CTX.

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## Analysis of a preventive-oriented strategy addressed to adults cured from a childhood cancer

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**Introduction:** Nowadays an increasing number of children recover from cancer and may become adults and productive members of our society. This may be a new field for preventive medicine: there is in fact a need to develop specific strategies and to define in this context the role of family physicians, pediatric oncologists, and other specialists.

**Objective:** To present a preventive-oriented strategy addressed to subjects cured from a childhood cancer and tailored to individual needs.

**Methodology:** In 1990 an "outpatient clinic for cured subjects" has been realized thanks to the contribution of our parents association. 397 subjects, who have withdrawn chemotherapy for over 2 years, are followed by a team which includes 3 pediatric oncologists, 1 social worker and 1 psychologist. The team also included several other specialists as consultants, working in the same hospital (dermatologist, surgeon, endocrinologist, gynecologist and orthopedic surgeon). We applied a program of personal intervention based on the clinical history of the patient and thus tailored to his specific needs. The outpatient clinic provides regular check-up (every 2 years) and is available for patients' requests and needs at any time. A computerized program has been prepared to manage and store all the information on the subjects.

**Conclusions:** The strategy allows to realize a preventive-oriented intervention and to gather information, lasting for several years. At the present time we are running a study on the "Satisfaction" of the subjects with the aim of revaluating and possibly modifying the organization of the program.

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## Late deaths of long term survivors after childhood cancer

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**Purpose:** When does life expectancy become similar to that of the general population after treatment solid tumours?

**Methods:** We reviewed charts of 1753 patients (pts.) aged below 16 when treated at IGR between 1942 and 1979 and who survived at least five years. We analyzed survival data.

**Result:** In 1992, we had 1562 survivals FU of 19 years (5 to 47) and a age of 25 yrs (5 to 54). 171 pts had died. Among these, the am of death was identified in 153 cases: a recurrence of the primary in 67 cases; a second malignant neoplasm (SMN) in 42; a late complication of treatment in 33; accidents in 34. Ninety per cent of the pts survived 5 to 50 years. During the first 20 yrs, recurrences and complications were the main causes of death, SMN after 20 yrs. Factors associated with prolonged survival are: diagnosis of Wilms and neuroblastoma surgical treatment, treatment before 1960.

The excess of mortality compared to the general population varied with time and tumor type.

A part from CNS and soit tissue tumors, the excess of mortality falls to zero 22 to 30 years after diagnosis.

**Conclusion:** in this population, heavily ted, with little or no chemotherapy, 70% of all 5 yrs survivors recover a normal life span after a maximum of 30 yrs.

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## Lymphatic mapping and sentinel node biopsy

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Lymphatic mapping can identify the (sentinel) lymph node that receives drainage directly from a primary cutaneous melanoma. The most reliable technique involves dynamic lymphoscintigraphy, followed by surgical exploration with the aid of a vital dye and a gamma detection probe. Patients with non-palpable metastatic disease can now be selected for regional node dissection in an early phase. The meaning of this approach in terms of regional tumour control and survival is currently being investigated.

Just last year, breast cancer was also shown to disseminate sequentially through the lymphatic system. Currently, a variety of scintigraphic and surgical techniques is being explored for lymphatic mapping in this disease. When the preliminary results are confirmed in a prospective randomized study, there will be a substantial reduction of the number of axillary node dissections without compromising survival and regional control, while the same prognostic and staging information will remain available.

Lymphatic mapping with sentinel node biopsy is one of the most interesting among the recent developments in surgical oncology and may have far reaching ramifications.

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## Immediate breast reconstruction in breast cancer

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The first important decision is whether the patient actually needs a mastectomy. Partial reconstruction of the breast after removal of large volumes of tissue involves use of the latissimus dorsi muscle. The newest technique involves removal of latissimus dorsi muscle and overlying fat without removing any skin from the back. Once the decision has been taken to perform a mastectomy the next option for reconstruction is whether this should be performed immediately or as a delayed procedure. The cosmetic results are significantly better with immediate than delayed reconstruction. The reasons why women wish breast reconstruction include to wear normal clothes, to feel balanced, to feel whole, so that they are less preoccupied with their physical state, to feel more feminine and so that they are less preoccupied with cancer. In general, patients who have reconstruction have reduced levels of psychological morbidity and higher levels of social and sexual function. Satisfaction with reconstruction is greater in patients af-