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CLASSIFICATION OF DCIS; CLINICAL CONSEQUENCES

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Treatment of the increasing number of screen detected non-invasive breast cancers is a major problem. The classical ablative, therapy results in nearly 100% cure rate, but may be an overtreatment. The alternative, breast conservation, is being studied in running randomized trials; answers to the most important end points, risk of dying of metastasized. recurrent disease, or of side effects of treatment, requires long follow up.

In patients, not eligible for the trials, several tumour characteristics play a role in treatment choice. The *extent* defines the possibility of breast conservation. The *adequacy of excision* (min. tumour free margin) may be used to define the need for radiotherapy. As the *well differentiated DCIS* seem lesions with a low risk of transition into invasive carcinoma, and the subsequent carcinomas are of low grade malignancy, a wait and see policy with close, mammographic and clinical follow up may be applied for these lesions.

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DUCTAL CARCINOMA *IN SITU*—PROGNOSTIC SIGNIFICANCE OF HISTOLOGICAL TYPES

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In a controlled clinical trial 114 patients with biopsy proven ductal carcinoma *in situ* were treated by breast conserving surgery without postoperative radiation. Intraductal comedocarcinoma was found in 41%, cribriform and papillary types were found in 22%. The proportion of high-grade lesions and low-grade lesions being 1:0.6.

Recurrences were found in 19%. High-grade DCIS was associated with a 15.3%, low-grade DCIS with a 12.2% recurrence rate. The recurrences did not show any correlation with the age of the patient nor the type and size of the lesion within the range of 2–46 mm. Optimal preconditions for mammographic follow-up seems to be of greater importance for the outcome of the patient than the size and type of the DCIS and the age of the patient.

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CONTROVERSIES IN DIAGNOSIS AND TREATMENT OF DUCTAL CARCINOMA *IN SITU* OF THE BREAST; THE SURGICAL ROLE

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Mastectomy cures nearly 100% of DCIS and still now, wide-spread lesions need a mastectomy but the surgical role will include the possibility of an immediate or delayed reconstruction.

For small often infraclinic lesions a conservative surgery is advocated. This approach is difficult and may be hazardous if there is not a close collaboration between the radiologist, the surgeon and the pathologist. When an infraclinic lesion mainly microcalcifications have to be checked, the surgeon will decide if in order to locate the lesion he needs only two orthogonal views or will ask the radiologist to put a hook. He has to choose the best site of incision with a carcinologic but also cosmetic approach. The specimen is orientated by markers and the quality of the incision is immediately checked by X-ray. A wider excision may be immediately performed. The surgeon will not ask for a frozen section but will demand to the pathologist a complete detailed report with the nature of the lesions but also: the size, the location in the specimen, and a careful study of the margins. In our state of knowledge about DCIS the surgeon must always keep in mind that in a conservative procedure for a DCIS there is always a risk to miss the opportunity to cure the patient by a mastectomy.

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DOES RADIOTHERAPY INFLUENCE DCIS?

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The influence of radiotherapy (RT) on DCIS can best be judged from randomized clinical trials. The situation is complicated by the heterogeneity of DCIS with regard to both pathology and extent so that subset analysis might be of importance. Also, since RT may only delay time to recurrence long FU is required.

Published results are only available from the NSABP trial. In the 1993 report, with a median FU of 43 months, breast recurrence was reduced from an annual rate of 5.1%/yr to 2.1%/yr with RT: RR = 0.40, $P < 0.001$. Of note in this trial is 1—the high rate of recurrence possibly due to the limited extent of surgery and degree of mammographic evaluation, 2—RR higher than the RR seen for invasive cancers (typically around 0.20), and 3—the apparent greater reduction in invasive compared with non-invasive recurrences. In the 1995 report, with a median FU of 48 months, the reduction with RT was similar for low-grade and high-grade lesions, but less for lesions without compared to with comedo-necrosis.

These short-term results indicate a positive influence by RT, but additional FU and the results of other trials will be necessary to make firm conclusions.

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PRIMARY PREVENTION OF LARGE BOWEL CANCER

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Epidemiological studies have emphasized the major role played by diet in the aetiology of large bowel cancer either as initiator, promoter or inhibitor of carcinogenesis. There is fairly consistent evidence concerning the protective effect of vegetables. There is some evidence relating fat intake, protein intake or caloric intake to colorectal cancer, while fiber intake or calcium intake seems to be inversely related to colorectal cancer. Available data are not sufficient to serve as a basis for firm, specific dietary advice. In the present situation, it is attractive to investigate available hypotheses within the framework of intervention studies. As there is considerable evidence that a high proportion of colorectal cancers arise in adenomas, adenoma recurrence and adenoma growth appear to be one of the most appropriate end points of intervention studies. Four intervention studies have been published so far. One of them suggests a protective effect of antioxidant vitamins on adenoma recurrence and three of them conclude in the absence of effect of these vitamins. A protective effect of lactulose on adenoma recurrence has also been suggested. Three studies are currently evaluating the effect of calcium supplementation, three studies the effect of fiber supplements, two studies the effect of antioxidant intervention. The results of these studies will be available within three years. If one of the evaluated interventions proves efficient, the benefits of a simple, safe and inexpensive prophylaxy for a very common cancer will be clear.

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IDENTIFYING RISK THROUGH FAMILY HISTORY ASSESSMENT

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Almost 40 years ago, Wolfe analyzed the family histories of a set of bowel cancer cases and showed that mortality through bowel cancer was over three times as common in the relatives of cases as in the relatives of controls. This basic observation has been repeated in a number of subsequent studies. More recent studies have attempted to delineate different family structures and the differences in risk between those structures. Two basic observations are apparent: (1) Relatives of early onset cases and (2) relatives of families with multiple cases are at particularly increased risk. For instance, relatives of cases diagnosed before the age of 45 years have a five-fold increased risk. Some of this increased risk must be due to the rare, dominant syndromes such as Hereditary Non-Polyposis Colorectal Cancer. While families which can be clearly diagnosed with this syndrome are rare, it may be that a considerable fraction goes undiagnosed. Alternatively, other genetic mechanisms or common exposures to environmental factors may be relevant. In summary, as a screening device, family history provides a valuable tool for recognizing a subset of those predisposed to bowel cancer.

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MOLECULAR DIAGNOSIS AND SURGICAL THERAPY OF HEREDITARY COLORECTAL CANCER

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Familial adenomatous polyposis (FAP) which is caused by APC gene mutations is a paradigm for presymptomatic molecular diagnostics and preventive surgical treatment. Sigmoidoscopy identifies symptomatic probands and presymptomatic relatives presenting with hundreds of colorectal adenomas. If sigmoidoscopy does not confirm FAP in relatives,

either due to late onset of adenoma development or noncarrier status, molecular testing may identify affected patients or exclude noncarriers. Since combined clinical/molecular diagnosis can identify affected relatives about twenty years earlier than symptomatic probands, sixty of our probands but none of the presymptomatic relatives presented with colorectal cancer. Restorative proctocolectomy followed by an ileoanal J-pouch procedure prevents colorectal cancer and preserves sphincter function in FAP patients. Although familial adenomatous polyposis accounts for less than 1% of all colorectal cancers, hereditary nonpolyposis colorectal cancer (HNPCC) may account for up to 15%. Presymptomatic molecular diagnosis of FAP and HNPCC and preventive surgical treatment might be effective tools to further decrease mortality due to colorectal cancer.

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COLORECTAL CANCER AND THE NEED FOR SCREENING
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Colorectal cancer is the second commonest killing cancer in Europe. However, there is some cause for hope. First, the adenoma-carcinoma sequence offers a convenient target for screening; intervention during the benign period of the sequence might allow cancer prevention. Second, surgical treatment of colorectal cancer at an early pathological stage is almost always curative. Over the past two decades a major research effort has gone into screening strategies, mainly into faecal occult blood testing. There is guarded optimism while we await the outcome of European RCTs. Another potentially important method of screening in colorectal neoplasia is flexible sigmoidoscopy which, applied once around age 60, might allow cancer prevention by adenoma removal. A very large trial of this modality, involving 200,000 people, is about to start in the U.K.

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THE PHENOMENON OF CANCER CLUSTERING
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There is a long history of disease 'clusters'; although in many reports the term cluster had only an impressionistic meaning without indication of the numbers of cases expected in the time and place in question. A large number of apparent clusters published throughout this century have involved leukaemia and initial reports were essentially non-quantitative and based on astute clinical observations and *ad hoc* investigations. From the 1930s onwards there were a few wide ranging searches for clusters with some elementary statistical analysis. Such was the **Ashington Cluster** involving three cases of AML, one of ALL and one CLL arising in a small mining village. From around 1970 the field was extended with analysis of large computerised databases becoming a reality and statistical methodology emerging. The phenomenon of space-time interaction was developed and demonstrated in childhood leukaemia in the U.K. The most recent phase of cluster research has generally involved sophisticated statistical analysis of aggregations of cases around point sources such as nuclear power installations. Perhaps the most interesting aspect of clustering at the present time is the consensus emerging that the residences at onset of cases of childhood leukaemia show weak evidence of a general tendency for spatial clustering. This is consistent with shared exposure to localised aetiological agents and is providing a clue as to where to look for aetiological factors for childhood leukaemia.

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CANCER AND NUCLEAR INSTALLATIONS
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We describe here the main results of studies of cancer mortality and morbidity in the populations residing in the vicinity of nuclear plants. Reports from the U.K. have described increases in leukaemia and lymphoma risks in children living near nuclear installations. Paternal preconceptional exposure to radiation had been suggested as an explanation, but this explanation has since been dismissed. An infectious aetiology has also been suggested, based on the observation of an excess risk of leukaemia and non-Hodgkin's lymphoma after population mixing both around the sites of some nuclear facilities in the U.K., and in other circumstances.

In all other countries where the problem has been studied (U.S.A., Canada, Germany, France, Sweden), no excess morbidity or mortality has been observed in the vicinity of nuclear installations. The power of these studies were reasonable. For instance in a French study, the expected number of deaths around installations was equal to 200, and therefore the probability of detecting an increase of 25% was 95%, with a type I error of 5%.

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CHILDHOOD CANCER INCIDENCE IN RELATION TO DISTANCE FROM THE FORMER NUCLEAR TESTING SITE IN SEMIPALATINSK, KAZAKHSTAN
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There are few data on cancer risk following atmospheric nuclear explosions. Rates of childhood cancer between 1981 and 1990 in the four administrative zones of Kazakhstan were studied to assess the relationship, if any, with distance from nuclear testing sites. Risk of various cancers among children aged 14 years and younger were estimated in relation to distance from (1) a site where testing in air was performed before 1963, (2) a site where underground testing took place thereafter, and (3) a reservoir, known as "Atom Lake", created by four nuclear explosions in 1965. Risk of acute leukaemia rose significantly with increasing proximity of residence to the testing areas, although the absolute value of the risk gradient was relatively small. The relative risk for those living less than 200 km from the air-testing site was 1.76 compared with those living 400 km or more away from the site. Similar relative risks were observed for the underground site and "Atom Lake". There was also some evidence of increased risk of brain tumours in association with proximity to the test sites. In two of the four zones studied, there was substantial regional variation in acute leukaemia rates which was not attributable to distance from the test site. The findings may be affected by potential confounders, notably urban/rural status and ethnic factors but tend to confirm an association with increased risk of childhood leukaemia and exposure to radioactivity from atmospheric nuclear explosions.

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RISKS OF EXPOSURE TO RADON GAS
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Radon is a radioactive gas that occurs naturally in the earth's crust as part of the decay chain of uranium-238. It has recently been appreciated that by far the greatest source of exposure to ionizing radiation arises from the inhalation of radon indoors. There is conclusive proof that inhaled radon and its decay products can cause lung cancer, both from animal experiments and from the study of men who have worked in mines of uranium and other igneous rocks where radon levels are exceptionally high. At the present time, estimates of the risk of lung cancer from inhaled radon indoors are based on the miners studies. If these estimates are correct, then radon would be the second most important cause of lung cancer after cigarette smoking. However, there are many uncertainties in extrapolating from the mining to the indoor environment. Direct assessment of the risk of indoor radon exposure is currently in progress.

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CANCER AND ELECTROMAGNETIC FIELDS
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There are several studies on the cancer risk of children exposed to electromagnetic fields. The results are controversial with a majority suggesting an increased risk of childhood cancer to be associated with exposure magnetic fields. The only population-based cohort study until now included all 135,000 Finnish children aged 0–19 years who during 1970–89 lived within 500 m of overhead power lines of 110–400 kV in magnetic fields calculated to be $\geq 0.01\ \mu$T. Cancer cases of these children were picked up from the countrywide Finnish Cancer Registry, and the observed numbers of various cancers were compared with the expected ones based on national incidence rates. In the whole cohort, 140 cancers were observed and 145 expected. The only statistically significant excess was found in nervous system cancer in boys (but not in girls) who were