Opening Address

S1 The changing concepts in treating breast cancer

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The new concepts of treatment result from new knowledge about the natural history of breast cancer and from the fact that patients population is changing.

Genetic studies have shown that breast cancer progresses from a well differentiated form to a more aggressive one. On the other hand, imaging techniques are able to detect very minimal cases and today 25% of patients have non-palpable tumours and more than 50% are classified as T1. These changes have revitalised methods for effective non-mutilating local treatments.

Axillary dissection is likely to be performed only in sentinel node positive patients and preoperative chemotherapy is likely to be expanded. Timing of surgery, according to menstrual phases, is under investigation.

Systemic treatments are becoming more and more used and research into low-toxicity combination of drugs, high dose treatments and predictors of chemosensitivity are in progress.

Wednesday, February 25, 1998 **17.00–18.45**

Session 1 Epidemiology and Its Lessons

S3 Diet and breast cancer: Lessons from experimental studies

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Epidemiological studies have identified several risk factors in human breast cancer including familial history, susceptibility genes, and reproductive factors. However, the majority of breast cancer cases present without specific risk factors indicating that the etiology of this disease is generally not well understood. The incidence of human breast cancer is high in industrialized nations and has been linked to lifestyle, especially diet. Diet is a complex mixture of nutritive and nonnutritive components and contains carcinogens, anticarcinogens, and promotional factors. The rat model is invaluable for investigating the role of specific dietary components on the multistep process of mammary gland carcinogenesis including initiation, promotion, and progression. The suitability of the rat model lies with the ease in which hormone-dependent mammary gland tumors are generated and in the similarities between the species in mammary gland development and tumor pathogenesis. The heterocyclic amines (HCAs) derived from cooked meats are one class of mutagens/carcinogens found in the human diet. These compounds undergo metabolic activation forming DNA adducts that can cause mutations and initiate the process of carcinogenesis. Studies have shown that the mammary gland from both humans and rats metabolically activate several HCAs. One HCA, 2-amino-l-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), first identified in fried hamburger, is a mammary gland carcinogen in rats. In the preneoplastic stage of rat mammary gland carcinogenesis, PhIP forms high levels of DNA adducts in mammary gland epithelial cells and enhances the proliferation in terminal end bud (TEB) epithelial structures that could potentially facilitate the fixation of genetic mutations at the site of mammary gland cancer development. Dietary fat is a strong promoter of PhIP-induced rat mammary gland carcinogenesis increasing both tumor incidence and aggressiveness. Although the mechanisms of promotion by a high fat diet are not clearly known, in the current model, a high fat diet further enhances the proliferation in the TEBs after PhIP exposure. Thus, experimental studies in rats support the notion that specific dietary components could play an important etiological role in a percentage of human breast cancers.

S5 Prevention of breast cancer

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Present prospects of breast cancer prevention are being developed in three main areas: a) genetics, to understand the real importance of familial breast cancer and of genetic testing; b) lifestyle, to study various risk factors, including delayed first pregnancies and decreased number of pregnancies and months of breast feeding; c) chemoprevention, to identify chemical agents potentially capable to inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells. Different target populations for breast cancer chemoprevention may be recognised. Primary chemoprevention may involve a wide population of healthy women who have a moderate risk for non-penetrant genetic factors (e.g., one first-degree relative with breast cancer) or because of exposure to known promoting agents (e.g., hormone replacement therapy). A second level of primary chemoprevention may involve a limited population at very high risk because of highly penetrating genetic predisposition to cancer (e.g., BRCA-1 mutation carriers). Secondary chemoprevention may involve subjects with premalignant or early malignant lesions, e.g., breast atypical hyperplasia and carcinoma in situ or microinvasive disease. High costs are inherent to prevention trials using clinical endpoints. Also, the risk of unexpected detrimental effects has recently been highlighted and much emphasis has been put on the search for intermediate, surrogate endpoints. Surrogate endpoints are biological markers or events that may be assessed or observed prior to the clinical appearance of the disease, and that bear some relationship to the development of that disease. They are intermediate in the sense that they occur sometime between a given intervention that affected the disease process and the time of the clinical diagnosis of the disease. The use of surrogate endpoint biomarkers in pivotal cancer chemoprevention trials may lead to a rational choice of agents which are likely to affect cancer incidence in subsequent phase III trials.

Thursday, February 26, 1998 **8.30–10.00**

Session 2 Genetics of Breast Cancer

S7 Experimental pathology and breast cancer genetics: Looking at malignant and premalignant tissues using new technologies

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The goal is to understand the critical events in carcinogenesis and to apply this to new approaches to diagnosis, prevention and treatment. It is clear that breast cancer is an heterogeneous disease at the molecular level, thus raising the possibility of a future functional classification based on mechanisms rather than morphology. These molecular phenotypes will also confer predictive value on the potential of the tumour to invade, metastasise, and respond or be resistant to new therapeutic strategies which are targeted to the molecular abnormalities. The difficulty is how to identify which of the 30,000 genes expressed by a typical cancer cell are the ones involved in these processes. Many tumours have such a multitude of molecular changes in an individual tumour that it is difficult to identify those changes that are critical to tumour progression from epiphenomena of an unstable genome. The identification of the earliest events in carcinogenesis must be the best hope as we will then able to target the events that predispose to the other secondary changes before they can occur.

One way forward is in the application of molecular (genomics) and protein profiling (proteomics) to obtain a profile of individual tumours. The applications of technology to facilitate, these analyses, including, comparative genomic hybridisation, laser guided microdissection of *in situ* breast cancer, microarray technology to study expressed cDNAs and 2 D gels with mass spectroscopy of complex protein samples will be discussed. The analysis of these data will require a large investment in bioinformatics. Thus computing and modelling of cancer will become increasingly important in the next decade to identify relevant molecules as therapeutic targets and as diagnostics.