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Breast Cancer: Epidemiology, Methodology and Statistics; Workshop Report

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INTRODUCTION

ONLY 12 papers were submitted for the workshop. It is therefore possible to give each of them some attention in this report. The papers fell broadly into 6 major groups: general studies of risk factors (1 paper); exogenous hormones (4 papers); endogenous hormones (2 papers); genetic factors (2 papers); diet and obesity (2 papers); and clinical trial methodology (1 paper).

GENERAL STUDIES OF RISK FACTORS

Dr. A. Kalache opened the workshop by describing a case-control study of risk factors for breast cancer which he is conducting in the towns of Recife and Fortaleza in North East Brazil. Although North East Brazil is a poor, underdeveloped area, breast cancer is remarkably common there—indeed, in Recife and Fortaleza the incidence rate is close to that in England and Wales. Dr. Kalache's study, which includes a total of 650 cases of breast cancer, has now been completed. Preliminary results indicate that most of the generally accepted risk factors seem to be of importance in North East Brazil. In addition, the study suggests a modest protective effect of very high parity over and above that of early age at first-term birth and points to oral contraceptives as possibly increasing breast cancer risk. The latter effect may, however, be attributable to the fact that the 'Westernised' women seem to be at the greatest risk of breast cancer in North East Brazil and they also tend to be users of the pill. Kalache's preliminary data also suggest that diet may be relevant to breast cancer risk—cases ate more beef, pork and eggs than controls. Of special importance is the fact that women marry late in Recife and Fortaleza and are older at first-term birth—this may in part determine the high risk of breast cancer in North East Brazil. Dr. Kalache stressed that the analyses completed were preliminary ones, mostly dealing with variables considered singly. Important issues raised during the discussion included the difficulty of studying rapidly changing populations, and the relative advantages and disadvantages of hospital and community controls in case-control studies.

EXOGENOUS HORMONES AND BREAST CANCER

In the absence of Dr. P. Layde, Professor M. Vessey made a brief reference to the preliminary results of the large case-control study of oral contraceptives and breast cancer recently reported from the Centers for Disease Control in Atlanta, GA, U.S.A. [1] and also outlined the latest findings in a large-scale British study with which he was involved [2]. The American study included about 700 breast cancer cases and used community controls, while the British one included almost 1200 cases and used hospital controls. The findings in both studies were essentially completely negative, even though substantial numbers of subjects with more than 10 yr of oral contraceptive use were included. Despite the reassuring results of these and other investigations, the study of breast cancer and the pill will have to continue for many years yet before final conclusions can be drawn. There are many reasons for this including changes in types of pill, changes in types of recipient and lack of data in some subgroups of special interest. For example, the paper by Pike and his colleagues [3], concerning 163 very young women with breast cancer in Los Angeles, suggesting that prolonged oral contraceptive use before first-term pregnancy may increase breast cancer risk, continues to cause anxiety, although Pike's results were not supported by either of the large studies considered at the workshop.

Dr. D Schapira was less happy about the pill. He and his colleagues questioned nearly 1500 patients with breast cancer who attended the Saskatoon cancer clinic in Canada and found that women who had used the pill had a worse prognosis that those who had not, despite there being no significant differences between the groups in tumour size, axillary node involvement or oestrogen receptor status. However, there are some methodological issues which need to be considered in this study, which is still in the process of being analysed, and Dr. Schapira's preliminary findings should be treated with caution. It may be noted that other studies which have examined the prognosis of breast cancer in users and non-users of the pill have either found no effect of pill use or a modest beneficial effect.

Dr. L. Bergkvist concentrated on the possible relationship between menopausal oestrogen therapy and breast cancer. He reported the preliminary results of a most interesting record linkage study in an area of Sweden in which a population register, prescription data for oestrogens and cancer incidence data are being brought together. In total, the study cohort includes nearly 22,000 women over 35 yr of age. At present, after up to 5 yr of observation, the relative risk of developing breast cancer in women ever using oestrogen is 1.1. In due course this study should help to provide a definitive answer to the important question as to whether or not menopausal oestrogen therapy increases breast cancer risk—published studies on this topic are inconsistent and confusing.

Finally in this section of the workshop, Dr. Schapira presented further data from the study already described, but relating on this occasion to nearly 200 women with breast cancer who had taken thyroid supplements. He found these women to have a higher relapse rate than controls who did not take thyroid, even though the thyroid takers had smaller tumours. Dr. Schapira also presented evidence based on a small number of patients that thyroid taken *after* mastectomy may hasten relapse. Clearly, the long-continued discourse on the possible interrelationships between thyroid disease and its treatment and breast cancer still goes on.

ENDOGENOUS HORMONES AND BREAST CANCER

Dr. Y. Nomura presented his findings on the relationship between oestrogen receptor status and breast cancer risk factors in a study of about 450 Japanese breast cancer patients. Oestrogen receptors were assayed in primary tumours using the dextran-coated charcoal method and 55% of tumours were found to be positive. Dr. Nomura has described previously the absence of any relationship between oestrogen receptor status and menopausal status in Japanese women, and this was confirmed in the present analysis. In addition, in premenopausal patients there was little evidence of any association between oestrogen receptor status and recognised risk factors. This was not true for postmenopausal patients, among whom tumours occurring in those recognised to be at 'high risk' e.g. those who were nulliparous, those at an advanced age at first childbirth and those who were obese, were more likely to be oestrogen-receptor-positive. Dr. Nomura drew particular attention to the association with obesity in this group of women. In the discussion, Professor de Waard pointed out that oestrogen receptor positivity was also greater in obese women with breast cancer in a Dutch study with which he was involved.

Dr. P. Bruning reported on a complex study of diurnal variations in plasma prolactin and many other hormones in premenopausal women. Twenty of these had a family history of breast cancer, 20 were completely normal, 20 had been curatively treated for early breast cancer at least 6 months before the study and 20 had benign breast disease. These 4 groups of women were carefully matched for age, obesity index, parity and socioeconomic status. Blood samples were taken every 20 min from 3.00 p.m. to 11.00 p.m. for 1 day in the luteal phase of the cycle. The main conclusion of the study was that the 'early-evening prolactin peak' described in 1977 by Kwa and Wang [4] on the basis of observations made in Guernsey is too non-specific to be of use in identifying individuals at special risk of breast cancer. In addition, Dr. Bruning maintained that 'spot' samples are, in general, of little value in hormone research of this type because considerable fluctuations in individual hormone levels can take place within a few hours. This point of view was vigorously challenged by Dr. Bulbrook.

GENETIC FACTORS IN BREAST CANCER

A short overview of the various possible approaches to studying the influence of genetic factors in breast cancer was given by Professor F. Cleton. He then focused down on studies of genetic markers and indicated that these studies could be of two types—association studies and linkage studies. In association studies the frequency of the marker is measured in cases and controls—this approach, for example, showed up the strong association between HLA-27 and ankylosing spondylitis. Association studies are fairly easy to do but are very insensitive. In addition, if many markers are looked at, there is

the difficult problem of misleading chance associations to contend with.

In linkage studies families with several cases of the disease are investigated and segregation of cases and markers is sought. Such studies are obviously difficult to conduct and are complex to analyse and interpret.

Dr. J. Forbes reported some details of an association study from Melbourne in Australia seeking to establish whether breast cancer susceptibility is associated with any of 25 polymorphic blood and immunological markers. To this end, blood samples were drawn from about 250 unrelated breast cancer patients and the findings were compared with those in 748 blood donors of like ethnicity. In addition, Dr. Forbes is carrying out linkage analysis on a number of families where three or more individuals have breast cancer. The results obtained so far are consistent with certain HLA alleles being associated with some 'subdivisions' of breast cancer, e.g. HLA-A2 with sporadic premenopausal breast cancer, but the geneticists taking part in the workshop were, in general, sceptical about HLA/breast cancer associations.

Dr. M. King talked about the detailed linkage studies she had done in the U.S.A. involving 22 families and in Holland, in collaboration with Professor Cleton, involving 16 families. On the basis of the American data, Dr. King *et al.* in 1980 [5] had suggested that, in some families, a dominant gene increasing susceptibility to breast cancer might be located near the inocuous glutamate–pyruvate transaminase (GPT) marker gene. This result had stimulated a similar genetic analysis of 16 Dutch families, each including at least three cases of breast cancer in sisters or mothers and daughters. Chromosomal linkage of the hypothetical susceptibility gene to each of 21 polymorphic genetic markers assayed in blood samples (including blood groups, HLA groups, chromosome bands, red cell isoenzymes, etc.) was assessed with essentially negative results, although there were suggestive findings in regard to HLA alleles in four families and GPT in one family.

Professor Cleton stressed that genetic studies were handicapped by the lack of suitable polymorphic markers and said that DNA polymorphisms would be used in the future. He also referred briefly to the possible occurrence of specific oncogenes for breast cancer.

OBESITY AND BREAST CANCER

Dr. A. Papatestas presented data relating to two series of patients with breast cancer, one from New York and one from Athens, in which tumour characteristics, Quetelets index, serum cholesterol and serum triglycerides had been recorded. It was found that degree of obesity and serum triglycerides increased apparently independently with tumour stage, tumour size and degree of nodal involvement in women of both nationalities, but that serum cholesterol did not do so. In addition, obese women were found to have less-differentiated tumours than non-obese ones.

Dr. F. Boccardo and his colleagues have investigated the possible relationship between cholecystectomy and breast cancer in Italy by means of a case-control study. They estimate that women undergoing cholecystectomy or with cholelithiasis have about a two-fold increase in breast cancer risk, the effect being more marked in some subgroups than others and not explicable by adjusting for the influence of obesity. They are, however, not entirely happy about their choice of control groups and wish to collect information from a community-based control group before finalising their results.

In the discussion Dr. H.-O. Adami referred to a large-scale cohort study he had just completed in Sweden which did not show any association between cholecystectomy and breast cancer. Clearly this matter requires further assessment.

CLINICAL TRIAL METHODOLOGY

Finally, the workship participants had a brief discussion about randomisation in phase II clinical trials following a paper by N. Rotmensz from the EORTC Data Centre in Brussels. While this idea has much in its favour and complies with the general principle that randomisation should be started early, there are criticisms of the approach in view of the small numbers of patients involved and the need for very intensive study of individual patients in phase II trials.

CONCLUSIONS

The workshop participants were unable to draw any general conclusions from such a heterogeneous series of papers. It was felt, however, that the different contributions illustrated extremely well the need for a collaborative, interdisciplinary approach in epidemiology.

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