

Meeting Report

Workshop on Linkage Studies of Hereditary Breast Cancer

A significant proportion of breast cancer cases appear in women from high-risk families; depending on the relatives affected, age of onset, and laterality of the index tumor, the lifetime risk for women may approach 50% (1). The extent to which nongenetic factors play a role in the etiology of these apparently hereditary cases is unknown, but if one or more susceptibility genes responsible for a significant proportion of family clusters can be found, a better understanding of the relative contributions of heritable and nonheritable components in breast cancer etiology will follow.

The feasibility of applying the linkage approach to localizing a breast cancer gene was discussed at a recent workshop in Lyon, France, at the International Agency for Research on Cancer.¹ Members of several research groups from Europe and North America met to compare families with multiple women affected with breast cancer. A major limitation to linkage studies was felt to be phenotypic heterogeneity between these families. The extent to which variability is observed in clinical practice was illustrated by Dr. H. Lynch (Creighton University, Omaha, NE) who referred to several large American pedigrees that he has collected. Other possible sources of difficulty that were discussed include the effect of sporadic breast cancer cases obscuring an underlying genetic association (2), the need to confirm cancer diagnoses at all sites, and the lack of reliable preclinical markers. Families of interest could be roughly divided into four groups: those with breast cancer only; those with breast and ovarian cancers (which may appear in the same individual); those with the Li-Fraumeni syndrome (breast cancer, soft tissue and bone sarcomas, leukemia, brain tumors); and those with adenocarcinomas of various organs. Extending these syndromes to include other cancers or benign (or preclinical) lesions would increase linkage study power, but it was felt that current epidemiological knowledge is inadequate to support this practice. It was proposed by J. Garber (National Cancer Institute, Dana Farber Cancer Institute, Boston, MA) that the 24 kindreds of the Li-Fraumeni type in the Cancer Family Registry of the National Cancer Institute be compared with other families identified worldwide in order to better characterize the syndrome and to generate a base for a collaborative linkage study.²

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¹ This meeting took place November 28 and 29, 1989, and was jointly sponsored by the International Agency for Research on Cancer (IARC) and the Ligue Nationale Française contre le Cancer du Département de l'Ain. The participants were D. E. Anderson (M. D. Anderson Hospital, Houston, TX); N. Andrieu (Institut Gustave Roussy, Villejuif, France); C. F. Arlett (University of Sussex, Brighton, United Kingdom); D. T. Bishop (ICRF, Leeds, United Kingdom); J. Clayton (CHU Purpan, Toulouse, France); P. Devilee (University of Leiden, The Netherlands); B. Dutrillaux (Institut Curie, Paris, France); D. Easton (Institute of Cancer Research, Sutton, United Kingdom); J. Feunteun (IARC); J. Garber (National Cancer Institute, Dana Farber Cancer Institute, Boston, MA); C. Junien (INSERM, Unit 73, Paris, France); C. Larsson (Karolinska Hospital, Stockholm, Sweden); G. M. Lenoir (IARC); H. T. Lynch (Creighton University, Omaha, NE); J. McKay (MRC Human Genetics Unit, Edinburgh, United Kingdom); P. Moller (Norwegian Radium Hospital, Oslo, Norway); R. Montesano (IARC); S. A. Narod (IARC); B. A. J. Ponder (University of Cambridge, United Kingdom); M. Santibanez-Koref (Paterson Institute for Cancer Research, Manchester, United Kingdom); H. Sobol (Genetic Oncology Clinic, Centre Léon Bérard, Lyon, France); B. Sylla (IARC); L. Tomatis (Director, IARC); and J. Williamson (IARC). M-C. King (University of California, Los Angeles, Berkeley, CA) was unable to attend but generously provided data for discussion.

² A working group was established to study these families at a meeting on rhabdomyosarcoma held in Columbus, OH, December 1989 (contact: F. P. Li, Clinical Epidemiology Branch, National Cancer Institute, 44 Binney Street, Boston, MA). Li-Fraumeni families are being collected in the United Kingdom by J. Birch (Christie Hospital and Holt Radium Institute, Manchester) and in France by H. Sobol (Genetic Oncology Clinic, Centre Léon Bérard, Lyon).

When a linkage study is initiated the choice of chromosome to test may be guided by reports of both cytogenetic abnormalities in tumors and loss (or rearrangement) of marker alleles (3). The most specific chromosomal anomalies found in a series of 30 breast cancers analyzed by B. Dutrillaux (Institut Curie, Paris, France) were either gains of chromosome 1p or losses of 16q. The loss of heterozygosity of marker alleles (possibly relating to deletions of tumor suppressor genes) has led to the mapping of several cancer susceptibility loci, including that for multiple endocrine neoplasia type 1 and neurofibromatosis type 2. However, a high degree of specificity of chromosome involvement, as is seen in meningiomas and which led to the linkage of neurofibromatosis type 2 to chromosome 22, does not appear to be present in tumors of the breast. Markers on chromosomes 3p and 17p were absent in greater than 50% of 88 sporadic tumors reported by P. Devilee (University of Leiden, Leiden, The Netherlands). C. Larsson (Karolinska Hospital, Stockholm, Sweden) found chromosome 22 losses in 6 of 8 lobular carcinomas and chromosome 17 losses in 17 of 28 ductal tumors. In a study of 50 Norwegian breast cancer cases described by P. Moller (Norwegian Radium Hospital, Oslo, Norway) the most common losses involved chromosome 17p and the retinoblastoma locus (13q) (35% each). Despite common involvement of chromosome 17p in these studies, linkage data submitted by M. C. King (University of California, Los Angeles, Berkeley, CA) on 8 extended families exclude a region 20 centimorgans on either side of the 17p13.3 locus as defined by the probe YNZ22 (lod = -14.10; θ = 0.001). This finding contrasts with the result of J. McKay (MRC Human Genetics Unit, Edinburgh, Scotland), who reports a lod of 1.8 at the YNZ22 locus for a large Scottish family.

Several groups presented early results of linkage analyses. A positive association was reported by D. E. Anderson (M. D. Anderson Cancer Center, Houston, TX) for the Rh locus on chromosome 1 and the breast-ovary syndrome (lod = 2.61) (4); these findings differ from those of M. C. King, who effectively ruled out the locus for her panel of families, who are largely of the breast cancer only type.

Candidate gene loci that have been studied to date include several oncogenes and the retinoblastoma locus. Dr. King reports negative lod scores for chromosome regions containing *H-ras*, *K-ras*, *N-ras*, *myc*, *myb*, *erb-2A*, *int-2*, *raf-1*, and 13q (including RB1) (5, 6).

At a recent workshop on A-T³ it was suggested that as many as 20% of all breast cancers may be associated with A-T heterozygosity (7). P. Moller (Norwegian Radium Hospital, Oslo, Norway) and coworkers found 2 of 8 mothers of A-T patients with breast cancer, but meeting participants could not recall a case of A-T among their breast cancer pedigrees. C. Arlett (MRC, Brighton, United Kingdom) suggested the possibility that different genetic loci may be associated with different A-T complementation groups.

Several participants offered insights into the theoretical aspects of performing linkage studies on breast cancer. It was emphasized that many informative families may be required in

³ The abbreviation used is: A-T, ataxia-telangiectasia.

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order to generate sufficient study power and that the data will need to be analyzed under a range of models. Because of the number of comparisons anticipated, the conventional criterion for positive linkage (a lod score of 3.0) may not be sufficiently stringent. The results of exclusion mapping will require interpretation in the light of possible genetic heterogeneity.

At the close of the workshop it was proposed to reconvene annually to compare progress and to develop a linkage exclusion map. A subgroup was formed to establish uniform criteria for data analysis in order to ensure comparability. This group, consisting of T. Bishop (ICRF, Leeds, United Kingdom), J. Clayton (CHU Purpan, Toulouse, France), D. Easton (ICR, Sutton, Surrey, United Kingdom), and S. Narod (IARC, Lyon, France) propose that a network be developed whereby linkage data submitted by all interested groups be tabulated, summarized, and then redistributed to the contributors. It was recommended by the committee that data sets be analyzed under 4 models, including dominant with and without sporadics, recessive, and dominant concentrating on affected persons only. Interested persons who wish to either collaborate or furnish breast cancer families for study are urged to contact any of the participants. It is anticipated that group results will be presented at the next meeting scheduled for December 5 and 6, 1990 at the Imperial Cancer Research Fund, Lincoln's Inn Field, London (Contact: D. T. Bishop, ICRF, Leeds, United Kingdom; telephone: (0532)423 617; FAX: (0532)340 183.

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