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FOREWORD

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Date

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INTRODUCTION

The purpose of this training program in biostatistics for breast cancer research is to provide biostatisticians with the requisite scientific knowledge to understand current issues in breast cancer research, and training in statistical and epidemiological techniques and research methodology related to breast cancer. The training leads to the doctorate of philosophy in biostatistics. The methods of training include formal course work in biostatistics, epidemiology and biology related to breast cancer, interdisciplinary seminars on current research and biostatistical topics in breast cancer research, and mentored research in collaboration with biostatistics faculty and breast cancer investigators.

TRAINING IN BIOSTATISTICS

To achieve the stated objectives of this training program in biostatistics for breast cancer research, the following steps have been and are being taken:

To obtain requisite scientific knowledge to understand current issues in breast cancer research, the trainees are required to regularly attend a special seminar series, "Statistical Methods in Cancer Research", and give presentations in this series. The list of topics and speakers for this seminar series for the academic year 1996--1997 is attached as Appendix 1. In addition, trainees are also required to attend the relevant talks from "Cancer Center Grand Rounds" and "Cancer Biology Seminars", listed as Appendix 2.

For training in statistical and epidemiological techniques and research methodology relevant to and necessary for breast cancer research, the trainees are advised and required to take:

- (1) theoretical courses in statistics and probability from the Departments of Statistics and Biostatistics,
- (2) relevant methods and applied courses in biostatistics from the Department of Biostatistics, and
- (3) courses in cognate areas proposed in the original grant applications from the Departments of Epidemiology, Environmental and Industrial Health, and other Departments in the Schools of Public Health and Medicine.

The trainees have been and are involved in mentored collaborative research in breast cancer with the breast cancer researchers from the University of Michigan Comprehensive Cancer Center (UMCCC) and with the faculty from the Department of Biostatistics.

DESCRIPTION AND EVALUATION OF CURRENT TRAINEES (TASK 9)

During the 1996--1997 academic year, four doctoral students, Ms. Monika Kester Mr. Lang Li, Mr. Rajat Mukherjee and Mr. Gong Tang were supported on this training program in biostatistics for breast cancer research. Ms. Kester was a continuing trainee

appointed in 1995. With the guidance and approval of the Steering Committee, two new trainees, Mr. Rajat Mukherjee and Mr. Gong Tang, were appointed to the training program in September of 1996, and one trainee, Mr. Lang Li, was appointed to the training program as of January of 1997. Mr. Li was one of the top applicants for the Ph.D. program in Biostatistics for the 1995--1996 academic year. He entered the program with BA in Mathematics, from Hunan University in China and MS in Statistics from New Mexico State University.

All four trainees have regularly attended Cancer Center's Grand Rounds (see Appendix 2), and are becoming involved in breast cancer research. As specified in the proposal, a seminar series on "Statistical Methods for Cancer Research" was run under the auspices of the training grant. This seminar included research presentations by faculty and journal club presentations by the trainees. The list of presentations is attached as Appendix 1.

Gong Tang.

Mr. Tang had a 6.6 GPA in coursework in 1996-97, and passed both theory and application parts of the Department's part 1 qualifying examination in the summer. Besides course work in statistics, Mr. Tang took Human Genetics I to learn the underlying genetic mechanism of breast cancer and related biological issues. He also studied the causes, prevention, pathology and current therapies for breast cancer. He worked with Dr. Penny Pierce from the Nursing School, one of the new Steering Committee members, on her project, "Knowledge, Beliefs, and Preferences of African American Women Concerning Breast Cancer Treatment". In this project, he had to develop an interface using EPI INFO for entry of the project's survey data on psychosocial domain of patients which affects their breast cancer treatment choice. He designed the interface for data entry and monitored the process. With help from Myla Strawderman, he worked on statistical aspects of two cancer protocols from Dr. Susan Urba, Division of Oncology, UMCCC.

Monika Kester.

Ms. Kester had an exceptional GPA of 8.225 in her coursework in 1996-97. She worked on Dr. Chenevert's project on "Rapid 4D MRI of Gad-DTPA Enhancement for Breast Lesion Characterization," funded by the Department of Defense Breast Cancer Research Program. The main objective of this project is to determine the diagnostic power of quantitative gadolinium-DTPA contrast enhancement rate constants in a prospective clinical imaging trial using a recently developed rapid 4-dimensional magnetic resonance imaging technique. To help the investigator better distinguish malignant lesions from benign lesions, she applied a discriminant analysis based on the estimated parameters from the contrast uptake model.

Rajat Mukherjee.

Mr. Mukherjee had a 7.25 GPA in coursework in 1996-97. He progressed in his first year of studies despite a very disruptive year. Immediately after his wedding in India in December his father died suddenly of cardiac arrest, necessitating his return to India for the funeral. He completed regular Ph.D. coursework in Mathematical Statistics, Statistical Computing, Linear Models, Categorical data Analysis and Advanced Survival Analysis. Mr. Mukherjee improved his knowledge and skills in statistical computing by learning SAS and Splus on a Unix platform. He worked on statistical analysis of tumor registry data collected at the University of Michigan Cancer Center. As part of the weekly journal club sessions he presented a discussion of a paper by Robert Gray on flexible methods for analyzing survival data using Splines, with application to breast cancer prognosis.

Lang Li:

Mr. Li joined the training program in January of 1997. He had a 6.2 GPA in coursework in 96-97, and he passed the theory part of the Department's Part 1 Qualifying examination in the summer. He has worked on a number of small UMCCC projects under the supervision of Dr. Kim. He also presented a paper at the journal club on the application of the generalized linear mixed model to longitudinal data, and carried out readings on books and periodicals related to breast cancer.

UPDATE ON PREVIOUS TRAINEES

Daowen Zhang (1994-95) received his Ph.D. in Biostatistics in 1996 and is currently doing post-doctoral training with Maryfran Sowers in the Department of Epidemiology at the University of Michigan. He is seeking a faculty position in Biostatistics.

Hua-Yun Chen (1994-96) passed his Part II examination and is currently carrying out his dissertation research with Dr. Little. His paper on missing covariates in survival analysis (Chen and Little 1997), motivated by a breast cancer application, won a prize as one of the three top student papers submitted to the ENAR Biometrics Society Spring Meeting. It was favorably reviewed by the Journal of the American Statistical Association and was revised and resubmitted to the journal. Mr. Chen is expected to complete his dissertation this year.

TRAINING PERSONNEL

The University of Michigan Comprehensive Cancer Center Biostatistics Core consisted of the following statistician staff: KyungMann Kim, Ph.D., Director of Biostatistics; Daniel Normolle, Ph.D., Senior Research Associate; Myla Strawderman, M.S., Research Associate II; and Songbai Wang, M.S.P.H., Research Associate I. In addition to the mentors from the UMCCC Breast Oncology Program and from the Biostatistics Department, all four statisticians from the UMCCC Biostatistics Core play an active role in supervising the trainees and in providing guidance and supervision for interaction with the UMCCC breast cancer investigators.

Two members of the Steering Committee, Drs. Chang and Merajver, rotated off the Steering Committee and were replaced by two new members, Dr. Penny Pierce of the School of Nursing and Dr. Thomas Chenevert of the Department of Radiation Oncology of the Medical School.

We have identified a new area of breast cancer cognate, Psychosocial Aspects of Breast Cancer. Dr. Pierce is a PI of a project, "Knowledge, Beliefs, and Preferences of African American Women Concerning Breast Cancer Treatment". In this project she is interested in identifying psychosocial domain of patients which affects their breast cancer treatment choice.

Dr. Chenevert is a PI of a project, "Rapid 4D MRI of Gad-DTPA Enhancement for Breast Lesion Characterization," funded by the Department of Defense Breast Cancer Research Program. The main objective of this project is to determine the diagnostic power of quantitative gadolinium-DTPA contrast enhancement rate constants in a prospective clinical imaging trial using a recently developed rapid 4-dimensional magnetic resonance imaging technique. With Dr. Chenevert, we can now provide strong training in one of the four original cognate areas, i.e., "Statistical Problems in Imaging Studies and the Screening and Detection of Breast Cancer".

CHANGE IN LEADERSHIP

The current principal investigator, KyungMann Kim, Ph.D., left the University of Michigan as of August 31, 1997 to become Director of Biostatistics at the University of Wisconsin Comprehensive Cancer Center and Professor of Statistics. With the approval of the project monitor, Professor Roderick Little assumed the directorship of the program for its fourth and final year. Dr. Little is Professor and Chair of the Department of Biostatistics, the University of Michigan School of Public Health, and Interim Associate Director of Biostatistics for the University of Michigan Comprehensive Cancer Center.

CONCLUSIONS AND FUTURE PLANS

The training program now has its full complement of trainees and is developing strong links with the Cancer Center and the Department of Biostatistics. The current training program terminates in the summer of 1998 and we had originally planned to develop a training program in biostatistics for cancer research for submission to the National Cancer Institute (Task 9). However this plan was delayed by the loss of the grant Principal investigator and Biostatistics Core Director Dr. Kim, who was recruited by the University of Wisconsin. This was a setback, but the program is continuing to provide high quality training and research in biostatistics applied to breast cancer problems under the leadership of Dr. Little. A national search is being conducted for Dr. Kim's permanent replacement, and we plan to develop an NIH training grant when that is completed and personnel are in place to develop a competitive proposal. The experience gained from the current training grant will be invaluable when that proposal is developed.

REFERENCE

Chen, H. Y. and Little, R.J.A. (1996). Proportional Hazards Regression with Missing Covariates. Under revision for *Journal of the American Statistical Association*.

Appendix 1.

Seminar: Statistical Methods in Cancer Research

Department of Biostatistics
University of Michigan School of Public Health
1996-1997

| Date | Speakers | Topic |
|-------------|----------------------------|--|
| Sept30, 96 | KyungMann Kim | Basic Principles of ROC Analysis |
| Oct 16, 96 | Monica Kester | My summer internship at BMS |
| Oct 30, 96 | Myla Strawderman | Issues in Disease Screening |
| Nov 25,96 | Dean Brenner | Problems In Image Analysis |
| Jan 13, 97 | Daniel Normolle | Tumor Growth in Animal Model: Part I |
| Feb 3, 97 | Gong Tang, Songbai Wang | EpiInfor for Data Entry |
| Feb 17, 97 | Daniel Normolle | Tumor Growth in Animal Model: Part II |
| Mar 3, 97 | Alfred Chang | Design Challenges in Immune Therapy |
| Mar 17, 97* | Lang Li | An Introduction to Random Effect Model and General Estimation Equation Model in Logistic Regression and Its Application |
| Apr 7, 97* | Monica Kester | Projecting individualized probabilities of Developing breast cancer for white females who are Being examined annually. JNCI 81: 1879-1886, 1989 |
| Apr 14, 97 | Songbai Wang | Continual Reassessment for Phase I Trials |
| Apr 21, 97* | Rajat Mukherjee | Flexible Methods for Analyzing Survival Data Using Splines, With Applications to Breast Cancer Prognosis. JASA 87:942-951, 1992. |
| Apr 28, 97 | KyungMann Kim | Group Sequential Methods for Clinical Trials |

* = Journal Club

**THE UNIVERSITY OF MICHIGAN
COMPREHENSIVE CANCER CENTER GRAND ROUNDS
1996 - 1997**

- 15 Martin Brown
Director of the Division Radiation Biology
Department of Radiation Oncology
Stanford Medical Center
"The Micro Environment of Solid Tumors
in Problem opportunity for Cancer
Therapy"
- 22 Filippo G. Giancotti, M.D., Ph.D.
Associate Professor of Pathology
Kaplan Comprehensive Cancer Center
"The Adapter Proding SHC Couples: A
class of Integrins to the Control of Cell
Cycle"

DECEMBER

- 13 Dr. Riccardo Dalla-Favera
Department of Pathology
Columbia University
College of Physicians and Surgeons
"Molecular Genetics of B Cell
Lymphoma"
- 20 Branimir I. Sikic, M.D.
Professor of Medicine
Division of Oncology
Stanford University Medical Center
"Moduation and Prevention of Multidrug
Resistance in Cancer Therapy"

1997

JANUARY

- 17 Thomas Carey, Ph.D.
Research Scientist of Otorhinolaryngology
University of Michigan
"Genetic Markers for Prognosis and
Distinguishing Metastases from Second
Primary Cancers"
- 31 Elizabeth Petty, M.D.
Assistant Professor of Internal Medicine
University of Michigan
"DNA Diagnostics for Familial Cancer
Syndromes: Discoveries, Dilemmas,
and Future Directions"
- Wendy Uhlmann, M.S.
Genetic Counselor of Molecular Medicine
And Genetics Clinic
University of Michigan

FEBRUARY

- 7 Amato Giaccia, M.D., Ph.D.
Department of Radiation Oncology
Stanford University
"P53, Hypoxia, and Apoptosis: Implications
for the Malignant progression of
Transformed Cells"
- 14 Stephen P. Ethier, Ph.D.
Associate Professor of Radiation Oncology
University of Michigan
"Growth Regulation in Human Breast
Cancer Cells: Common Themes and
Novel Observations in New Human
Breast Cancer Cell Lines"

**THE UNIVERSITY OF MICHIGAN
COMPREHENSIVE CANCER CENTER GRAND ROUNDS
1996 - 1997**

- | | | |
|----|--|--|
| 21 | Richard A. Gams, M.D. Director of Developmental Therapeutics Ohio State University | "Anti-Estrogen in the Management of Advanced Breast Cancer" |
| 28 | Vernon Sondak, M.D. Associate Professor of Surgery University of Michigan | |

MARCH

- | | | |
|----|--|---|
| 7 | Andrew F. Olshan, Ph.D. Department of Epidemiology School of Public Health University of North Carolina | "Molecular Epidemiology of Head and Neck Cancer" |
| 14 | Stephen Hecht, Ph.D. University of Minnesota Cancer Center | "Smoking and Lung Cancer: Approaches Using Carcinogen Biomarkers and Chemoprevention" |
| 21 | Doug Brash, Ph.D. Department of Therapeutic Radiology Yale School of Medicine | Skin Cancer and Sunlight: I cell and n-cell problems" |

APRIL

- | | | |
|----|--|---|
| 4 | Dr. Stephen George Professor of Biostatistics Duke University | "Eligibility, Criteria, Complexity and Generalizability in Multicenter Clinical Trials" |
| 11 | Mark Roth Memorial Lectures (8am-12pm) (More information will follow on this lecture. It will be held at Dow Auditorium in the Towsley Center.) | |
| 18 | Douglas Yee, M.D. Associate Professor of Medicine Department of Medicine Division of Medical Oncology University of Texas Health Center | "Insulin Like Growth Factors in Breast Cancer" |
| 25 | Robert B. Diasio, M.D. Chairman of Department of Pharmacology Division Director of Clinical Pharmacology University of Alabama at Birmingham | "Role of Dihydropyrimidine Dehydrogenase in FU Toxicity and Efficacy" |

THE UNIVERSITY OF MICHIGAN
COMPREHENSIVE CANCER CENTER GRAND ROUNDS
1996 - 1997

MAY

- | | | |
|----|---|---|
| 2 | M. Stephen Meyn, M.D., Ph.D. Department of Genetics Yale School of Medicine | "From Cradle to Grave: ATM and the Molecular Pathology of Ataxia- Telangiectasia" |
| 9 | Dr. David Livingstone Dana Farber Cancer Institute | "Functional Analysis of the BRCA1 Gene Product" |
| 30 | Jeffrey Green, M.D. Senior Investigator National Cancer Center | "Prostate and Mammary Tumor Progression in Transgenic Mice: Can We Interfere?" |