## UNIVERSITY OF CALIFORNIA

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Observer Variability in the Histologic Diagnosis of Breast Disease

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Public Health

by

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## TABLE OF CONTENTS

Introduction 1
CHAPTER I: Anatomy and Physiology of the Human Breast, and the Pathology of Benign Breast Disease and Breast Cancer. Review of Histologic Classification Systems for Breast Tissue
CHAPTER II: Statistics for the Assessment of Reliability 17
CHAPTER III: Previous Investigations of Observer Reliability in Medicine
CHAPTER IV: The UCLA Benign Breast Disease Study
CHAPTER V: File Cleaning and Preliminary Analysis
CHAPTER VI: Intra-Observer Reliability 90
CHAPTER VII: Inter-Observer Reliability127
CHAPTER VIII: Summary, Discussion, and Conclusions166
Appendices
Bibliography

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xi

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PUBLICATIONS

Stewart, M.E. Elements of study design: Surveys based on case 1981 records and tissue slides. Surgical Pathology Quarterly Index, April issue.

Stewart, M.E.First-aid for poisonous snakebite: Are currentlyGreenland, S.recommended procedures justified? Annals ofHoffman, J.R.Emergency Medicine 10:331-335.1981

Ratech, H.Uterine leiomyomas, serum cholesterol, and oralStewart, M.E.contraceptives: Epidemiologic differences in Los1981Angeles, California, and Albany, New York.Diagnostic Gynecology and Obstetrics 4(1).

Greenland, S. Australian work in treatment of poisonous snakebite (letter). Annals of Emergency Medicine Stewart, M.E. Hoffman, J.R. 11:228. 1982 Millet, V.E. Intestinal protozoan infection in a semicommunal Spencer, M.J. group. American Journal of Tropical Medicine and Chapin, M.R. Garcia, L.S. Hygiene 32:54-60. Yatabe, J.H. Stewart, M.E. 1983 Bateman, T.M. Coronary artery stenoses: Relationship between Gray, R.J. angiographic severity and impact on mean dias-Raymond, M.J. tolic pressure gradient. Journal of Thoracic and Miyamoto, A.T. Cardiovascular Surgery 85:499-507. Chaux, A. Kass, R.M. Lee, M.E. Stewart, M.E. Matloff, J.M. 1983 Bateman, T.M. Regional distribution of pulmonary blood volume: Gray, R.J. An index of pulmonary capillary wedge pressure Czer, L.S.C. determined from blood pool scintigraphy. Levy, R.L. American Journal of Cardiology 52:1404-1408. Stewart, M.E. DeRobertis, M.A. Brown, D.E. Matloff, J.M. Swan, H.J.C. Berman, D.S. 1983 Ellrodt, A.G. Severe neutropenia associated with sustained-Murata, G.H. release Procainamide. Annals of Internal Medicine 100:197-201. Riedinger, M.S. Stewart, M.E. Mochizuki, C. Gray, R.J. 1984

Gray, R.G. Chaux, A. Matloff, J.M. DeRobertis, M.A. Raymond, M.J. Stewart, M.E. Yoganathan, A. 1984 Bateman, T.M. Maddahi, J. Gray, R.J. Murphy, F.L. Raymond, M.J. Stewart, M.E. Swan, H.J.C. Berman, D.S. 1984 Czer, L.S.C. Gray, R.J. DeRobertis, M.A. Bateman, T.M. Stewart, M.E. Chaux, A. Matloff, J.M. 1984 Chaux, A. Czer, L.S.C. Matloff, J.M. DeRobertis, M.A. Stewart, M.E. Bateman, T.M. Kass, R.J. Lee, M.E. Gray, R.J. 1984 Bateman, T.M. Weiss, M.H. Czer, L.S.C. Conklin, C.M. Kass, R.M. Stewart, M.E. Matloff, J. Gray R.J. 1985

Bileaflet, tilting disc, and porcine aortic valve substitutes: In vivo hymodynamic characteristics. Journal of the American College of Cardiology 3:321-327.

Diffuse slow washout of myocardial thallium-201: A new scintigraphic indicator of extensive coronary artery disease. Journal of the American College of Cardiology 4:55-64.

Mitral valve replacement: Impact of coronary artery disease and determinants of prognosis after revascularization. Cardiovascular Surgery I 198 - I 207 (supplement to Circulation, Volume 20).

The St. Jude Medical bileaflet valve prosthesis. A five-year experience. Journal of Thoracic and Cardiovascular Surgery 88:706-717.

Fascicular conduction disturbances and ischemic heart disease: Adverse prognosis despite coronary revascularization. Journal of the American College of Cardiology 5:632-639.

## ABSTRACT OF THE DISSERTATION

Observer Variability in the Histologic

Diagnosis of Breast Disease

by

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Diagnostic reliability or reproducibility is important in medicine because treatment and prognosis depend to a large extent on diagnosis; it is also important in epidemiologic research, since a disease must be reliably diagnosed before exposures associated with its development may be investigated. Numerous studies of diagnostic reproducibility, both within between and observers, have demonstrated that the level of reliability attained in clinical diagnosis is frequently poor. To examine the reliability of histologic diagnosis of benign breast lesions and breast cancer, tissue slides from 1039 breast biopsies were independently classified by two expert surgical pathologists, using two major classification schemes. A subset of cases was examined twice by each pathologist. Intra-observer and intra-observer reliability were assessed using two techniques: ordinally-scaled agreement scores and kappa statistics. While excellent reliability was observed for classification of cases as cancer or benign disease, the degree of inter-observer reliability attained using either of

xvi

the two classification systems was for many of the benign lesions disappointing. While intra-observer reliability is generally found to be better than inter-observer reliability, this was not the case in this study; the intra-observer and inter-observer reliabilities This was probably due to the large proportion of were comparable. "difficult" slides which were reread by one or both pathologists and hence were available for the intra-observer reliability analysis. Over the past several years, many investigators have postulated that the more severe types of breast atypia (hyperplasias and intraduct papillary lesion) are precursors of breast cancer, while less-hyperplastic types of BBD such as fibroadenoma and cystic disease have no association with subsequent cancer. The finding of only slight-to-moderate reliability in the diagnosis of duct hyperplasia and lobular hyperplasia has implications for this hypothesis: specifically, rate ratios and risk ratios comparing cancer rates in patients with and without a history of the more hyperplastic-type benign lesions may be subject to a large degree of misclassification bias.