

MOLECULAR EPIDEMIOLOGY
(Pub Hlth 525)
Spring Quarter 2005

Time: Tuesday, 6:00-9:00PM

Location: Large Conference Room, Dept. of Preventive Medicine
Suite 1102, 680 N. Lake Shore Drive

Instructor: Peter Gann, MD, ScD
Professor
Department of Preventive Medicine
(312) 908-8432
pgann@northwestern.edu

I. Course Description

This course covers both the major theoretical concepts and practical issues involved in conducting research involving molecular biomarkers in human populations. Recent advances in basic science and technology are revolutionizing the field of epidemiology, creating vast opportunities for studying the relationship between variations at the molecular or cellular level and the early detection, etiology or prognosis of important diseases. Class topics include: the theoretical advantages of biomarkers, criteria for evaluating potential markers, sample collection and storage, laboratory quality control considerations, issues in epidemiologic study design and analysis, ethical/legal concerns, and discussion of specific examples of research involving molecular markers of internal dose, susceptibility, early pathological alteration, and prognosis. Important barriers in current methods and newly emerging technologies (e.g., proteionomics) also be discussed. The course will emphasize examples from the cancer research literature.

II. Prerequisites

Introduction to Biostatistics (PH302)
Introduction to Epidemiology (PH304)
- or equivalent, per approval of the Instructor

III. Course Objectives

Students completing this course will develop an understanding of the major theoretical and practical issues involved in conducting research that integrates laboratory and epidemiological techniques. After completion of the course, students should be able to:

- a. Identify the criteria used to evaluate a potential biological marker in epidemiological research and apply these criteria to selected examples.
- b. Describe the role of biomarkers in population research, including their advantages and limitations.

- c. Describe the major problems in collecting, storing and processing various biological samples for human population studies, including principles of quality control for laboratory assays.
- d. Critically evaluate the major study designs used in molecular epidemiology, and describe the important issues to be addressed re: study validity and precision.
- e. Identify and describe the important ethical and legal issues involved in using human fluid or tissue specimens for research in an epidemiological context.
- f. Critically evaluate the use of biomarkers as indicators of the internal dose of exogenous substances such as environmental toxins and micronutrients.
- g. Describe the major challenges involved in studies using biomarkers as indicators of early pathological change, in the context of individual risk assessment or chemoprevention.
- h. Describe the major challenges involved in studies using biomarkers for early detection/screening or for evaluation of prognosis.
- i. Critically evaluate efforts to study the role of genetic variation in disease causation.

IV. Teaching Format

This course will be taught as a participatory seminar. The instructor will present brief lectures to introduce conceptual material. Students will be expected to read the assigned materials (which will include original research papers) and come to class prepared to discuss them. Students will also make oral presentations on assigned topics.

V. Student Evaluation

60% of the student evaluation will be based on the quality of participation in the seminar discussion, including assigned oral presentations. 40% will be based on the assigned paper. By the mid-point of the course, each student will submit a one-page prospectus for a paper on a specific topic related to use of biomarkers in the context of internal dose, early pathogenesis, screening, prognosis, or genetic variation. Papers should be no more than 5 pages in length, should be double-spaced, and must critically discuss at least two original articles on the topic. Further instructions on the paper will be provided in class.

VI. Textbook

Application of Biomarkers in Cancer Epidemiology, ed. Toniolo P, et al. IARC Press, Lyon, France, 1997

Additional textbook reference (optional): Biological Markers in Epidemiology, eds. Hulka BS, Wilcosky TC, and Griffith JD. Oxford University Press, 1990.

Note: relevant sections from these texts will be posted on Blackboard

VII. Course Evaluation

The MPH Program administers web-based course evaluations to students for each course near the end of the quarter. ***Your completion of both the unit (course) and faculty evaluation components is required; failure to complete either of the evaluations will result in an incomplete grade until the evaluations are submitted.*** You will be sent the web link and instructions via email later in the quarter. You will have about two weeks time to complete the evaluations before grades are submitted.

VIII. Course Outline

March 29 *Overview of the Course*

Historical and Theoretical Foundations

- Framework Notes: a conceptual foundation
- Definition of a biomarker, traditional vs. molecular epidemiology
- Advantages and disadvantages of molecular-based population studies
- Criteria for evaluating a potential biomarker (incl. statistical issues)

Readings:

1. "Framework Notes" from Instructor or see Blackboard
2. Hulka BS. "Overview of Biological Markers", Chapter 1 in Biological Markers in Epidemiology, Oxford U Press, 1990
3. Wilcosky TC, Griffith JD, "Applications of Biological Markers", Chapter 2, *ibid*

April 5 *Transitional Studies: evaluating a biomarker*

- Discuss example in class: salivary hormone levels

Collecting and Storing Samples/ Quality Control for Laboratory Assays

- Collecting and processing blood components, DNA and more unusual biological media
- Design and maintenance of biosample repositories
- Principles of effective quality control for lab assays in clinical/epidemiological studies

Readings:

1. Schulte PA, Perera FP. "Transitional Studies", p.19-29 in Applications of Biomarkers in Cancer Epidemiology, IARC Press, 1997
2. Vineis P. "Sources of Variation in Biomarkers", p. 59-71, *ibid*
3. Gann PH, et al. Saliva as a medium for investigating ...Cancer Epid Biomarker Prev 10:59-64, 2001
4. Michaud DS, et al Reproducibility of plasma and urinary sex hormone levels.. Cancer Epid Biomarker Prev 8:1059-64, 1999

April 12 *Issues in Epidemiological Study Design and Analysis*

- Cohort, nested case-control and conventional case-control designs
- Matching and other methods for controlling confounding; effect modification
- Repeated measures per individual
- Regression dilution

Readings:

1. Hunter DJ. "Methodological issues in the use of biological markers in cancer epidemiology: cohort studies", p. 39-44, in IARC text.
2. Rothman N, et al. Incorporating biomarkers into cancer epidemiology: a matrix of biomarker and study design categories. *Cancer Epid Biomarker Prev* 4:301-11, 1995.
3. Buist D, et al. Bone mineral density and endogenous hormones and risk of breast cancer in postmenopausal women. *Cancer Causes Control* 12:213-22, 2001.
4. Gann PH, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels. *Cancer Res.*59:1225-30, 1999.

April 19 *Ethical and Legal Issues in Molecular Epidemiology*

- Informed consent, including consent for use of archived samples
- Ownership of biological samples
- Confidentiality, reporting results to participants

Biomarkers of internal dose and biologically effective dose

- Occupational/environmental toxins
- DNA and protein adducts
- Nutritional biomarkers: ex: fatty acids, micronutrients, phytochemicals

Readings:

1. Schulte PA, et al. "Ethical and social issues in the use of biomarkers in epidemiological research", p. 313-318, IARC text
2. Kulynych J, Korn D. The effect of the new federal medical privacy rule on research. *NEJM* 346:201-204, 2002.
3. Groopman JD, Kensler TW. The light at the end of the tunnel for chemical-specific biomarkers: daylight or headlight? *Carcinogenesis* 20:1-11, 1999.
4. Lampe JW, et al. Signatures of environmental exposures using peripheral leukocyte gene expression: tobacco smoke. *Cancer Epid Biomarkers Prev* 13:445-453, 2004.

April 26 *Discussion of student paper prospectuses*

Markers of early pathological change

- Challenges in validating markers of early pathogenetic events
- Surrogate intermediate endpoint biomarkers in prevention trials
- Identifying high-risk individuals

No readings this week (finish discussion of previous readings)

- May 3 *Molecular markers for screening/early detection*
- Molecular methods for early cancer detection: proteins (prostate specific antigen, CA-125)
 - Early cancer detection: genetic alterations
 - Early detection of other major diseases

Readings:

1. Pepe MS, Etzioni R, Feng Z, et al. Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst.* 93:1054-1061, 2001.
2. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostate cancer. *JAMA* 273:289-294, 1995.
3. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 359:572-577, 2002.

- May 10 *Molecular markers of prognosis and treatment response*
- Molecular pathology: FISH, immunohistochemistry, tissue microarrays and automated image analysis
 - Circulating markers of prognosis
 - Design and analysis of prognosis studies
 - Markers for predicting response to a specific treatment

Readings:

1. van Boxel-Dezaire AHH, et al. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. *Ann Neurol* 45:695-703, 1999.
2. van Boxel-Dezaire AHH, et al. Contrasting responses to interferon β -1b treatment in relapsing-remitting multiple sclerosis: does baseline interleukin-12p35 mRNA predict the efficacy of treatment? *Ann Neurol* 48:312-322, 2000.
3. (optional) Camp RL, et al. Automated subcellular localization and quantification of protein expression in tissue microarrays. *Nat Med* 8:1323-1327, 2002.

- May 17 *Susceptibility: genetic polymorphisms and complex diseases*
- Defining and identifying polymorphisms
 - Linkage disequilibrium, functional significance
 - Design and analysis issues: family-based and non-family based designs, effect modification, multiple comparisons, “whole genome” analysis

Readings:

1. Willett WC. Balancing life-style and genomics research for disease prevention. *Science* 296:695-698, 2002.
2. Holtzman NA, Marteau TM. Will genetics revolutionize medicine? *NEJM* 343:141-144, 2000.

- May 24 *Special topics and emerging technologies*
- DNA arrays, gene expression arrays, proteomics
 - Student selected topics
- May 31 Discussion of student papers. Concluding issues.
- June 7 Finals Week – NO CLASS???