BIOMARKERS & ENVIRONMENTAL EXPOSURES:


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Biomarkers: What the heck are they??!!
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- "My Take" - "Just about anything"!!
- I really DO know something about biomarkers!
- More educated answers to follow, I promise!

Please don't leave!

Biomarkers: What are they?

- Preferential definition
- "Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention" - 1999 NCI/FDA Workshop

Biomarkers: What are they? (cont’d)

- Biological markers
- Indicators of variations in cellular or biochemical components or processes, structure, or function that are measurable in biologic systems or samples.
- Widely used in medicine, eg. measurement of creatinine in blood to assess renal function.
- Represent "signals" pertaining to health and disease and environment-organism interactions, eg. blood lead concentration serves as a marker of exposure and neurotoxicity.

Biomarkers: What are they? (cont’d)

- Three general categories:
- Exposure to chemical or physical agents
- Biomarkers of effects
- Biomarkers of susceptibility
Biomarkers: What are they? (cont’d)

- **Exposure biomarker**: Exogenous chemical or its metabolite(s) OR the product of an interaction between a xenobiotic and target molecule or cell that is measurable within an organism. Eg. cord blood measurements of PCBs and cotinine (a metabolite of nicotine used for maternal-fetal ETS exposure), blood COHgb levels for CO exposure, carcinogen-DNA adducts.

- **Effect biomarker**: Measurable alteration of an endogenous component within an organism that can be recognized as a potential or established health impairment or disease. Can be qualitative or quantitative and may be induced by lifestyle or environment. Eg. Alteration in pulmonary function in children due to ETS or bone marrow failure due to radiation or benzene toxicity.

- **Susceptibility biomarker**: Indicator of inherent or acquired property of an organism, ie. individual factors that can affect response to environmental agents due to genetic variability. Eg. glucose 6-phosphate dehydrogenase deficiency and methemoglobinemia from exposure to naphthalene mothballs (inability to reduce the oxidized iron in Hgb).

Biomarkers: Validation

- Understand the relationship of the biomarker to event or condition Eg. community-wide exposure assessment to environmental toxicants or measuring physiological effects of air pollutants.

- Sensitivity and specificity are critical to the validation process.

- Be able to assess the true exposure or disease (sensitivity).

- Ability to assess **lack** of exposure or disease (specificity).

Biomarkers: Validation (cont’d)

- A primary purpose of biomarkers in EH research and exposure/risk assessment is to identify exposed persons, and prevent pathological processes, ie. disease.

- Validation includes associating a biomarker with exposure, Eg. elevated blood lead levels AND linking it to an effect, Eg. neurotoxicity.

- Biomarker observed before disease onset may have a low predictive value as to effect, but be useful as an exposure biomarker, enabling long-term surveillance of an exposed population.

Biomarkers: Validation (cont’d)

- Estimates of the sensitivity of a biomarker must include its evaluation in an unexposed population or unexposed animals to determine a baseline value for the marker.

- The identification and validation of biomarkers is a complex process utilizing animal studies, refinements in analytical techniques and assays, and studies in special human populations.

Potential Pitfalls

- Experimental and analytical data that are established to demonstrate biomarker validity and performance must be carefully scrutinized.

- Molecular profiles may not be able to be duplicated by other laboratories.

- Experimental design must avoid chance and bias.

- Multiple site collection can confound the validity of biomarkers.

- Multiple site collection requires that specimens are collected and analyzed independently. This will minimize the introduction of bias.
Types of Biomarkers

- Virtually any body fluid, excretion or tissue can yield potential biomarkers.
- Proteins: The phenotype any cell expresses is a function of the proteins it produces. A disease state can be induced by altered protein expression or the protein can be a by-product of the disease itself.
- Proteins may represent host inflammatory or immune response, e.g., cytokines, antibodies, auto-antibodies (autoimmune disease).
- Sensitive analytical techniques are required to identify.

Techniques used include:
- Two-dimensional gel electrophoresis
- Differential in-gel electrophoresis
- Chromatography
- Immunoassays
- Enzyme-linked immunosorbent assays
- Mass spectrometry
- New technological platforms.

Types of Biomarkers (contd)

- Proteins (cont’d) Examples of protein biomarkers include:
  - Fetoprotein for hepatocellular carcinoma
  - CA-125 for ovarian cancer
  - Prostate-specific antigen (PSA) for prostate cancer.

- Transcriptional: DNA microarrays recently available as biomarker discovery tools.
- Can provide a broad view of which genes are up- or downregulated in a disease state provides high value and high volume of data relating to disease biology.

- Transcriptional-based biomarkers can be translated to other molecules, such as proteins.

Types of Biomarkers (cont’d)

- Genomic Markers:
  - Many diseases have a foundational genomic cause.
  - Most cancers, for example, demonstrate significant genetic mutations and/or chromosomal aberrations. The genomic disposition of altered cells can serve as a venue for identifying disease biomarkers.

- Mutations
- Chromosomal aberrations
- Microsatellite instability (stretches of DNA with a repeating sequence of nucleotides)

- Several physical and chemical agents may induce genomic alterations, e.g., ionizing radiation, sulfur mustard, benzene.

Types of Biomarkers (cont’d)

- Epigenomic Markers:
  - Epigenetics is the study of events that contribute to heritable changes in gene function that are not attributed to changes in DNA sequence.
  - May refer to changes in chromatin structure such as altered states of histones and other nuclear proteins.

- DNA methylation: Degrees of methylation may help to predict the stage and risk for developing certain cancers.

- Post-translational Modifications: PTMs of proteins are potential biomarkers for disease because regulate or “fine-tune” the activity of enzymes, receptors, and transcription factors that play leading roles in diseases. These biochemical processes are phosphorylation, glycosylation, acetylation, acylation, ubiquitination, sumoylation and prenylation.

Types of Biomarkers (cont’d)

- Other Biomarkers
  - Exfoliated and circulating cells
  - Metabolomics: The “metabolome” is the collection of all small-molecule metabolites resulting from all physiologic processes of a biological system.

- Metabolomic analysis of blood may yield molecular signatures.
- Enzyme Activity-based Profiling: Assess enzyme activity associated with a disease process-functional
- Imaging-based—e.g., PET scan.

Biomarkers in Environmental Health and Medicine

- Environmental health research
- Occupational and environmental exposure assessment
- Risk assessment
- Occupational pre-screening, biomonitoring and medical surveillance
- Provide foundation for scientific/medical evidence-based decision-making and environmental health public policy
- Forensic/medico-legal role
- Guide medical diagnosis and treatment
- Identify susceptible individuals/populations
Biomarkers in Environmental Health and Medicine

- Use of biomarkers in environmental and occupational health is increasing due to information demands related to health risks from environmental exposures.
- Health professionals, researchers, policy makers, and the general public have a “right to know” and make informed decisions regarding environmental health threats and human health effects.
- Can lead to preventive, proactive, protective and corrective actions.

Biomarkers and Population Studies

- Establish normal baseline values and in vivo distribution in animals and humans.
- Evaluate sensitivity and specificity of the marker in predicting a health outcome (e.g., asthma or genetic damage).
- Understand in detail the time course of response of the marker to a toxic chemical, with special attention to the recovery process.
- Develop a strategy for and a consensus on the use of multiple species in toxicologic studies.
- Develop human assays that use semen, saliva or urine, rather than tissue or blood, whenever possible.

Biomarkers and the Future

- "The Times They Are A-Changin" - Bob Dylan
- As newer biomarkers are discovered and developed, their presence in biomedicine, clinical prognosis and diagnosis and occupational and environmental health.
- Molecular epidemiology - capable of exposure assessment via molecular detection e.g., DNA-PAH adducts. May be applied to population studies.
- Emergence of other molecular classes and more advanced biotechnology and extended to entire biomarker panels for testing.

Biomarkers and Environmental Health Challenges

- Hundreds of untested existing and novel compounds.
- The potential for CBRNE attacks and toxic terrorism.
- Accidental community HAZMAT releases
- Illegal and uncontrolled hazardous waste sites
- The potential for mass exposures
Biomarkers: To Summarize….

- Can assess exposure, effects and susceptibility to diseases and exposures.
- Serve as valuable prognostic, diagnostic and monitoring tools in clinical medicine.
- Are important to environmental health and biomedical research.
- May be used for mass exposure assessments after a community HAZMAT release, CBRNE event and other toxicological emergencies.
- Given us a new perspective on epidemiological studies.
- The future holds much promise for the discovery, development and extensive use of biomarkers.

Questions & Answers

- ANY QUESTIONS OR COMMENTS ??
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