

Meeting Report

AACR Special Conference: The Molecular and Genetic Epidemiology of Cancer

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Introduction

The AACR Special Conference on The Molecular and Genetic Epidemiology of Cancer was held January 18–23, 2003 at Waikoloa, Hawaii. Approximately 400 attendees from around the world heard state-of-the-art talks, many with new data on methods and applications. A range of sessions covered epidemiological, statistical, and laboratory methods; genetic susceptibility and human biomonitoring; intermediate endpoints; cancer interventions; biorepositories; ethics; and the impact of molecular epidemiology on other fields. In addition, 129 posters were presented, and participants benefited from both scientific sessions and the widespread, often animated informal discussions.

Carl Barrett opened the conference with the keynote address, reminding us that molecular epidemiology is not just about germ-line and somatic genetic changes and that other key concepts and processes, such as epigenetics and apoptosis, play critical roles in pathways of carcinogenesis.

Epidemiological and Statistical Issues

The first scientific session focused on epidemiologic and statistical issues and included sessions on sample size issues, multigene and gene-environment interactions, and the interface of molecular and genetic epidemiology.

The speakers introduced some little-used methods in an epidemiological setting. For instance, Stephanie London presented methods used in case-parent triad studies of childhood diseases. Timothy Rebbeck talked about applying computational approaches to detect functionally relevant alleles and grouping these alleles in the search for multigene interactions and about applying stopping rules, a method used in clinical trials to examine whether additional study subjects should be genotyped in association studies. Paul Pharoah wondered whether intermediate phenotypes (*e.g.*, hormonal levels and mammographic density) improve our understanding of why the common disease/common variant hypothesis has been slow to bear fruit. Qingyi Wei, David Phillips, and others picked up this theme later in the conference in relation to integrated measures of DNA damage and repair and DNA adducts.

Christine Ambrosone postulated that inconsistency of results in molecular epidemiology may stem from a lack of focus on mechanisms of action and biological plausibility in picking

candidate genes for specific cancers. Daehee Kang's presentation on a large breast cancer study (~1400 cases and ~1400 controls) and candidate genes in estrogen metabolism and DNA repair suggested that the use of larger sample sizes would also benefit the field, particularly when gene-environment and gene-gene interactions are examined.

Duncan Thomas discussed sample size estimates for studies involving gene-environment interaction (work with Jim Gauderman) and the impact of, variously, the way in which penetrance, dominance, and allele frequency are modeled, the nature of the exposure distribution, the magnitude of relative risks, and the complexity of the interaction demonstrated programs available on-line.² In the same session, Nathaniel Rothman presented work he has been undertaking with Sholom Wacholder trying to quantify the problem of a large excess of false positives and the issue of multiple comparisons in molecular epidemiology; he recommended the use of a new Bayesian statistic, "False Positive Result Probability."

Laboratory Challenges

The second theme of the conference covered laboratory challenges and included sessions on genotype *versus* phenotype; genetic polymorphisms in metabolism, DNA repair, and cell growth control; and high-throughput genotyping and bioinformatics.

Several approaches to understanding the relationship between genotype and phenotype were presented by David Hein, Peter Shields, and Daniel Nebert who closed with a plea for standardizing nomenclature for haplotypes.

John Wiencke presented a timely reminder that not all metabolic variation is deleterious, showing that there is a reduced risk of lung cancer among carriers of the *XRCC1* Q allele among African Americans and Hispanics. Ainsley Weston showed how cross-talk between molecular epidemiology and basic biology can be used to elucidate the impact of polymorphisms in cell cycle control genes. Roland Wolf presented data that brought into question the neatness of the canonical Vogelstein paradigm for molecular progression in colon cancer after loss of APC.

New methods were the focus in the session on high-throughput genotyping and informatics. Gareth Morgan demonstrated the utility of certain approaches to pooling DNA for genotyping and also spent time on potential drawbacks, particularly the inability to establish haplotypes or explore gene-environment interactions.

New Approaches in Human Biomonitoring

Novel approaches in human biomonitoring was the third theme of the conference, which included sessions on biochemical and immunological methods, chemical and spectroscopic methods,

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² <http://dceg.cancer.gov/POWER/and> <http://hydra.usc.edu/gxe>.

dietary measurements, assessment of complex exposures, and exogenous and endogenous DNA adducts. The sessions included presentations by Bernadette Schoket, Regina Santella, Mimi Piorier, and Peter Farmer on methods of measurement by ^{32}P -postlabeling, chemiluminescence and other immunoassays, immunohistochemistry, and mass spectrometry. Steve Hecht discussed the use of signature biomarkers of exposure, specifically urinary markers of tobacco-related exposure to nitrosamines and PAHs.³ Steve Tannenbaum's presentation focused on ways of increasing specificity using high-performance liquid chromatography and mass spectrometry methods to the point of being able to identify exact mass and structure of the relevant marker molecule.

Christopher Wild showed the value of undertaking parallel studies in humans and cells, in this instance exploring molecular progression in Barrett esophagus patients and studying the effects of acid and bile salts on esophageal cells *in vitro*.

Measuring diet remains a major problem for epidemiologic studies as a result of a wide variety of influences including real within-person variation; changes over time, both in behavior and food supply; measurement error; difficulties with memory and recall; and mismatches between foods analyzed for dietary tables and foods actually consumed. An approach to eliminating some of the flaws inherent in food frequency questionnaires involves the use of diaries, long thought impractical in the setting of large epidemiologic studies. Sheila Bingham, in the setting of the EPIC study of half a million individuals across Europe, demonstrated the value, even superiority, of this approach, comparing the data with biomarkers and with data generated using food frequency questionnaires.

Yasuhito Yuasa reported on increased methylation (more marked in males) of specific *HOX* genes (genes central to basic body design in animals) in gastric cancer and in its precursor condition, gastric intestinal neoplasia.

A session on assessment of complex exposures opened with a presentation from Blanka Binkova on monitoring PAHs in the Czech part of the "Black Triangle" (a very polluted industrial part of Europe also including Saxony, Germany and Silesia, Poland). She noted evidence of greater embryotoxicity due to PAHs in winter as compared with summer. Herman Autrup explored DNA adducts as biomarkers of exposure to air pollution. He noted more adducts in men than women and in winter than summer but, disappointingly, no correlation with other measures of PAH exposure. Mary Wolff has investigated the frequency and intensity of multiple environmental exposures (particularly pesticides) in cancer etiology. She showed that there is a complex relationship between body mass index (adipose acts as a reservoir for fat-soluble compounds) as a result of interindividual metabolic differences and differences in exposure, as well as changes in environmental concentration over time.

In the session on endogenous *versus* exogenous DNA adducts, Helmut Bartsch provided extensive data on lipid peroxidation and resulting etheno-DNA adducts and the ways in which these can be increased (*e.g.*, by exposure to an ω -6 δ fatty acid-rich diet (but why females and not males in both rats and humans?) and decreased (*e.g.*, by higher vegetables and fruit and vitamin E).

James Swenberg discussed both methods and problems in measuring DNA adducts. He drew particular attention to the flawed literature on the measurements of 8-OH-dG and to the

problems of artifact in measurement from underestimation using enzyme methods (such as the comet assay) to overestimation using high-performance liquid chromatography.

Intermediate End Points

The fourth theme of the conference focused on intermediate end points and included sessions on mutagenesis, DNA damage, and changes in gene expression.

In the session on mutagenesis, James Felton discussed methods of identifying and quantifying environmental exposures, using heterocyclic amines and the Ames test as the primary hooks on which to hang his narrative. He noted that we currently explain only 25% of the mutagenicity in meat with known compounds.

Richard Albertini discussed his work on somatic mutations in humans as mechanistic probes for exposure. He noted the value of using markers such as hypoxanthine phosphoribosyltransferase in "forward mode" as integrated indicators of both exposure and biological impact. He further described the capacity to use such markers in "reverse mode" to probe for cell kinetics and mutability in target cells. He demonstrated the increase of *in vivo* mutation frequency of hypoxanthine phosphoribosyltransferase with age, smoking, radiation, and so forth. He also noted the mutagenic effect of depleted uranium exposure in Gulf War veterans. In discussing DNA damage in the setting of the EPIC cohort study, Paolo Vineis noted the complex relations among exposure, adducts, genetic variability in repair capacity, and cancer, looking, eventually, to methods that allow us to integrate exposure, intermediate biology, early outcomes, and late outcomes in more sophisticated and informed models than current epidemiologic approaches allow. Stefano Bonassi presented data on micronuclei, but whether micronuclei predict cancer risk remains unresolved.

Martyn Smith discussed early somatic changes, particularly translocations, in hematological malignancies, the use of real-time PCR to detect these in Guthrie spots, and their possible *in utero* and early childhood causes and consequences. The critical events appear to be 2 orders of magnitude more common than the related leukemia. Sirrku Saarikoski described polymorphisms in *CYP2S1* and their possible relevance to lung cancer. Keiji Wakabayashi discussed gene mutations and changes in expression in colon carcinogenesis in rats, noting marked differences, for instance, in *APC* and β -catenin mutations between azoxymethane (8% and 75%, respectively) and the heterocyclic amine PhIP (50% and 50%).

Chronic inflammation and oxyradical overload diseases were central to the talk by Curtis Harris, who presented some of his continuing mechanistic and translational studies on the role of p53 in these disease processes. He painted a portrait of the increasingly complex roles of p53 as an integrator of DNA damage, hypoxia, and oncogene signals and their subsequent transmission to pathways influencing cell cycle, DNA repair, apoptosis, and senescence. The role of posttranslational modification of p53, as it functions as a sensor of stress and subsequent signal transducer, is becoming clearer and may eventually provide directions for prevention and therapy of ulcerative colitis, viral hepatitis, chronic gastritis, chronic pancreatitis, and their related cancers.

Cancer Interventions and Monitoring

The fifth theme of the meeting was built around cancer interventions and monitoring, and included sessions on prognostic markers, intervention strategies, biomonitoring, and the use of genomics and proteomics in population studies.

³ The abbreviation used is: PAH, polycyclic aromatic hydrocarbon.

Dongxin Lin described the association between a single nucleotide polymorphism in the *MMP-2* promoter region that disrupts an *SP-1* binding site and an elevated risk of gastroesophageal cancer. The possible role of genetic variability in determining response to cancer therapy and survival provided the focus for Jia Chen. She particularly noted that polymorphisms in thymidylate synthase appear to influence survival in colorectal cancer. Because many effective chemotherapeutic agents influence folate metabolism, these data are a timely reminder of the increasing likelihood of tailoring chemotherapy, not only for stage of disease, but also to take into account genetic metabolic variability.

In the session on intervention strategies, Young-Joon Surh presented data on the capacity of plant-derived agents, such as gingerol and genestein, to influence COX-2 expression. Hirota Fujiki described the role of green tea and derived catechins as effective agents in animal models and, possibly, in both prevention and treatment in humans.

Thomas Kensler used liver cancer as the centerpiece of his discussion on how to prevent environmentally induced cancers. He emphasized hepatitis B virus vaccination as primary prevention along with reducing aflatoxins in the food supply. He described a variety of agents with possible roles in secondary prevention (oltipraz, chlorophyllin, and broccoli sprouts), noting that this combined approach may ultimately halve the incidence of liver cancer in rural China.

In the session on biomonitoring, Kei Nakachi described his prospective study of the role (and the genetics) of natural killer cell activity in cancer: as assessed in 1986, those with low natural killer cell activity had a higher risk of subsequent cancer than those with medium or high activity.

Frederica Perera described her studies of mechanisms, genetic susceptibility, and markers of intervention efficacy particularly in studies of environmental influences on birth outcomes.

In the session on genomics and proteomics in population studies, Margaret Wrensch provided an overview of the challenges facing the incorporation of new tools into population studies, and Samir Hanash provided useful insights into the issues surrounding the use of such techniques in studies in the developing world, noting particularly the need for training, technology transfer, and equitability and the avoidance of exploitation.

Biorepositories

The sixth theme of the conference was the development and use of biorepositories and included a session on storage, processing, quality control, and distribution. Highlights included insights on quality control (including a disaster plan), appropriate methods research, access control, freeze-dried ferrets, technology, and maintaining inventory control, provided by Jim Vaught and Elaine Gunter.⁴

Ethics

The seventh theme was ethics and included a session on the ethical challenges in conducting research on the molecular epidemiology of complex traits. Paul Schulte spoke pointedly, particularly on the issue of distributive justice. Gail Geller discussed both the influence of media on public understanding of the risks and benefits associated with research on genetic susceptibility, and the involvement of children and adolescents in research.

Impact of Molecular Epidemiology

The final theme of the conference covered the impact of molecular epidemiology on other fields, and sessions included diagnostics, prevention research, and public health impact. Nicholas Lang spoke on the influence of molecular epidemiology on diagnostics and the capacity to improve staging, predict host response, and understand tumor biology.

Peter Greenwald considered how molecular epidemiology is influencing prevention research, particularly the development of biomarkers for early detection and the expanding possibilities for chemoprevention.

Finally, Ken Olden considered the impact on public health, asking "What are we missing?" and noting the rationale for the development of the Center for Toxicogenomics but reminding us all of the centrality of the environment in the causation of cancer. Quoting Judith Stearns, he said, "Genetics loads the gun, but environment pulls the trigger."

⁴ See this useful web site: www.isper.org.

BLOOD CANCER DISCOVERY

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