Meeting Report

Molecular and Biochemical Methods in Cancer Epidemiology and Prevention: The Path between the Laboratory and the Population

AACR Special Conference in Cancer Research

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The proceedings of this meeting are dedicated to the memory of Dr. David T. Purtilo.

This conference, which was sponsored by the American Association for Cancer Research, was organized and chaired by David Schottenfeld (University of Michigan, Ann Arbor, MI) with the assistance of the program committee, composed of Myron E. Essex (Harvard University, Boston, MA), Curtis C. Harris (NCI, Bethesda, MD), Stephen S. Hecht (American Health Foundation, Valhalla, NY), Barbara Hulka (University of North Carolina, Chapel Hill, NC), Lewis H. Kuller (University of Pittsburgh, Pittsburgh, PA), Mortimer L. Mendelsohn (Radiation Effects Research Foundation, Hiroshima, Japan), Thomas E. Moon (University of Arizona, Tucson, AZ), and Paul A. Schulte (National Institute for Occupational Safety and Health, Cincinnati, OH). It took place in Naples, Florida, from September 23 to 26, 1992.

In his introductory remarks David Schottenfeld explained the process of planning for the conference and referred to a previous advisory workshop convened by the National Cancer Institute a year ago in Hawaii. A meeting report of that workshop appeared in Cancer Epidemiology, Biomarkers & Prevention (1: 519-522, 1992). The need and the potential for collaboration between epidemiologists and laboratory scientists were emphasized. The application of biomarkers to epidemiological research was discussed, stressing the need for documentation of the sensitivity, specificity, and predictive value of various biomarkers of internal dose exposure, biological response, or individual susceptibility. Paul Schulte followed with the first keynote address. He views the fusion of epidemiological and laboratory disciplines as the continuation of a historical trend that can provide epidemiologists and laboratory scientists with increasingly powerful tools and illustrated with examples of biomarkers which have reached a level of exquisite sensitivity such as the glycophorin A test, which identifies specific genotoxic damage to red blood cells. Some biomarkers persist for years after exposure, as in the case of the atomic bomb survivors, while others (e.g., micronuclei) indicate recent exposure. Curt Harris described the multiple interactions between epidemiology and laboratory sciences, emphasized the interindividual variability in the metabolism of carcinogens and provided examples of the use of biomarkers to identify individuals at the highest risk of cancer. For example, among individuals who smoke similar amounts of tobacco, the number of benz[a]pyrene covalent binding sites to DNA may vary 100-fold. He referred to the multiple mutations (around 1500) which may be seen in the p53 gene and explained the connections between specific exposures such as that of aflatoxin B and HBV and specific mutations such as the hot spot in codon 249 in liver cancer. After the above keynote addresses, the program was divided into seven sessions, each focusing on a specific issue.

Session 1 dealt with the assessment of exposure to genotoxic agents. Stephen Hecht chaired the session and covered the first subject: biomarkers of tobacco-specific nitrosamines, an important group of the many carcinogens in tobacco products, whose deadly impact on human health should not be underestimated, with population attributable risks in the range of 50-90% for aerodigestive tract cancers. The nitrosated derivatives of nicotine nitrosornornicotine and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone have organ specificity for the lung, oral cavity, esophagus, and pancreas and are likely to play an important role in the carcinogenesis of these cancers. Epidemiology and described a potentially useful way of combining the model of a continuum of events between an exogenous exposure and resultant diseases with studies developing or utilizing markers for those events. This can be visualized as a matrix with the continuum of biological events on one axis and laboratory, transitional, etiological, and applied studies on the other axis. This model was referred to, with slight variations, by other speakers. Schulte emphasized the need for studies in which different laboratory tools are evaluated before they are applied to large populations. Mortimer Mendelsohn described several techniques of biological dosimetry and illustrated with examples of biomarkers which have reached a level of exquisite sensitivity such as the glycophorin A test, which identifies specific genotoxic damage to red blood cells. Some biomarkers persist for years after exposure, as in the case of the atomic bomb survivors, while others (e.g., micronuclei) indicate recent exposure. Curt Harris described the multiple interactions between epidemiology and laboratory sciences, emphasized the interindividual variability in the metabolism of carcinogens and provided examples of the use of biomarkers to identify individuals at the highest risk of cancer. For example, among individuals who smoke similar amounts of tobacco, the number of benz[a]pyrene covalent binding sites to DNA may vary 100-fold. He referred to the multiple mutations (around 1500) which may be seen in the p53 gene and explained the connections between specific exposures such as that of aflatoxin B and HBV and specific mutations such as the hot spot in codon 249 in liver cancer. After the above keynote addresses, the program was divided into seven sessions, each focusing on a specific issue.

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2 The abbreviations used are: HBV, hepatitis B virus; HPV, human papilloma virus.
Meeting Report: AACR Special Conference

organ. DNA adducts of the above carcinogens are detectable in the lung tissue of smokers; hemoglobin adducts and urinary metabolites of these carcinogens have also been quantified in smokers. Steven Tannenbaum (MIT, Cambridge, MA) described the use of proteins such as albumin and hemoglobin as biomarkers of carcinogenic exposure. These proteins act as biological traps and allow for the identification of adducts. The example of 4-aminobiphenyl, a bladder carcinogen, demonstrated the utility of these biomarkers. 4-Aminobiphenyl adducts have been useful in studying exposure to environmental tobacco smoke and the susceptibility biomarker, acetyltransferase phenotype, which differs in frequency among various ethnic groups. Frederica Perera (Columbia University, New York, NY) expanded on the model of carcinogenesis proposed years ago that continues to be valid and useful. Dr. Perera described ongoing international studies that have used a variety of biomarkers to estimate relative risks in different occupational and environmental exposure settings. An important finding is the correlation between polycyclic aromatic hydrocarbon-DNA adducts and gene mutation at the HPRT locus in peripheral blood cells of factory workers. Some studies of biomarkers are at the transitional stage of evaluation for feasibility and validity before they can be used in intervention strategies for cancer prevention. John Groopman (Johns Hopkins, Baltimore, MD) described studies of aflatoxin exposure to demonstrate the importance of finding the most relevant biomarkers of the effects of the carcinogen and to extend the field of inquiry to chemoprevention. Aflatoxin β-N7-guanine, a major aflatoxin-DNA adduct excreted in urine, is the most meaningful indicator of aflatoxin exposure because it directly relates molecular effects that may be correlated with the risk of primary hepatocellular carcinoma. A recent study in China reported a remarkable synergistic effect between aflatoxin exposure, as measured by aflatoxin β-N7-guanine, and HBV carrier status for development of liver cancer. Oltipraz, an antischistosome drug to which more than 100,000 persons have been exposed, induces detoxification enzymes for several carcinogens, including aflatoxin. Chemoprevention trials are being developed using oltipraz.

Session 2, on biological markers of genetic susceptibility, was chaired by Louise Strong (M.D. Anderson, Houston, TX), who illustrated the application of genetic epidemiologic techniques in studies of families. Segregation analysis of cancer families of 159 childhood sarcomas pointed to a rare dominant gene as the best model to explain the clustering of tumors in such families, some of which were part of the original group of the Li-Fraumeni syndrome. Twelve kindreds contributed most of the evidence for a dominant gene. Fibroblasts from affected individuals became immortalized spontaneously in vitro and became tumorigenic after transfection with activated ras oncogene. Each of these transports is heterozygous for a distinct germline p53 mutation. She discussed the alternatives of defining syndromes on the basis of specific germline mutations as opposed to the characteristics of tumors and other pathologic conditions of the family members. Julian Peto (Institute of Cancer Research, Belmont, England) discussed the statistical methodology for genetic and how it can be useful in understanding the dynamics of the syndromes. He described an international consortium focusing on the BRCA-1 autosomal dominant gene of breast-ovary cancer susceptibility, localized in chromosome 17q. Mark Leppert (Howard Hughes Medical Institute, Salt Lake City, UT) stated that there are approximately 4000 genetic diseases which cover a wide range of disorders, from behavioral patterns to neoplastic diseases. He utilizes the extraordinary genetic resources of Utah and described the variants of familial colon cancer, frequently associated with abnormalities in the MCC and APC genes on chromosome 5. He explored the reasons for discrepancies between genotype and phenotype expression, which could be related to allelic variations, modifying genes, or the interaction of environmental factors such as diet. Kenneth Buetow (Fox Chase, Philadelphia, PA) described the use of family-based case-control genetic epidemiological studies of lung cancer and other neoplasms. In an ongoing study, an excess of cancer has been observed among siblings of probands. CYP2D6 and GST allele frequencies have been examined to explain the observed familial aggregation. The results suggest that a role for the GST locus may exist which differs by family history status.

Session 3 on viral agents was chaired by Myron Essex, who discussed different markers of oncogenic viruses which may indicate different stages in the transition from infection to neoplasia. He utilized the human T-lymophoma virus I-related lymphoma-leukemia syndrome to elaborate on the virus-neoplasia associations. The tax gene is likely always present in a carrier. The full genome is not always integrated in adult T-cell leukemia cells; however, in all cases the tax(pX) coding region is retained. This suggests that tax activity is essential for oncogenesis to occur. Tom London (Fox Chase) described recent advances in the epidemiology of primary hepatocellular carcinoma which now point to the need for large prospective studies. Vaccination against HBV has been available since 1983. Most primary liver cancers are preceded by HBV infection, chronic hepatitis, and cirrhosis. A large cohort study is planned in China utilizing different biomarkers. Nancy Mueller (Harvard University) utilized markers of viral infection in subjects infected with human T-lymphoma virus I in Japan. A model was presented of the natural history of disease progression encompassing infection of target stem cells, polyclonal expansion, monoclonal expansion, and finally leukemia. Antibodies to the tax protein and abnormal lymphocytes are utilized as markers. Wayne Lancaster (Wayne State University, Detroit, MI) discussed the role of different types of HPV (now more than 70) in cervical neoplasia. Different types are associated with low, intermediate, or high risk for cervical cancer. Methodological issues in the study of HPV-disease associations were discussed. Mark Schiffman (NCI) illustrated the problems of misclassification and showed how the weak association between HPV and cervical cancer turned into a much stronger association when better laboratory techniques were applied. He described a model of cervical carcinogenesis and the interaction of HPV with cells at different stages of the process.

Session 4 on dietary biomarkers in preventive intervention studies was chaired by Thomas Moon. He discussed the general strategy of chemoprevention studies based on the significant and consistent association between dietary factors and cancer risks. He illustrated these principles utilizing the Arizona study of the relationship between fatty acids and skin cancer. Gladys
Block (University of California, Berkeley, CA) emphasized the potential role of antioxidant vitamins (e.g., A, C, and E) in cancer prevention. She pointed out that 130 of 150 studies have detected significant inverse associations between antioxidant vitamins and cancer risk, especially for the lung, larynx, oral cavity, esophagus, stomach, pancreas, and breast. The antioxidants apparently act in synergy and prevent the oxidative damage to which cells are exposed from a variety of carcinogenic stimuli such as infectious agents, ionizing radiation, and chemical substances. Dr. Block pointed out that large populations in the United States have lower than recommended intakes of antioxidants. David Rose (American Health Foundation) discussed the changes in the levels of endogenous estrogen brought about by dietary interventions that alter the intake of fat and fiber. When premenopausal women reduce their dietary fat intake from the usual 38% of total calories to 20% there is a significant reduction in the luteal phase serum concentrations of estradiol and estrone. John Potter (University of Minnesota, Minneapolis, MN) explained the mechanisms of carcinogenesis, from diet-derived carcinogens to interactions of metabolizing enzymes and molecular alterations. He invoked gender differences in intestinal physiology to explain trends in the demographic patterns of the colon cancer epidemic.

Session 5 on steroid hormones in breast and prostate neoplasia was chaired by Lewis H. Kuller (University of Pittsburgh), who elaborated on the central role that the metabolism of steroid hormones, both estrogens and progestins, play in the pathogenesis of breast cancer. The levels of endogenous hormones and their metabolites are in part genetically regulated and influenced by dietary fat intake, obesity, body fat distribution, and menstrual (pre- or postmenopausal) status. Endogenous estrogen hormone levels are correlated with bone mineral density and risk mechanisms of coronary heart disease. Leon Bradlow (Strang-Cornell Laboratory, New York, NY) discussed the pathways of estrone metabolism, especially the implications of 2-hydroxylation, which appears to have limited potential for adversely affecting breast epithelial replication and differentiation, as contrasted with 16-hydroxylation, which results in the production of genotoxic or tumor-promoting metabolites. The search for chemopreventive agents is focusing on agents that increase E-2 hydroxylation. Indole-3 carbnil, derived from brassica vegetables, is such an agent and has shown promise in laboratory studies. James Gutai (Wayne State University), a pediatric endocrinologist, made reference to the biosynthetic pathways for testosterone, its active metabolite dihydrotestosterone, and the enzyme involved in this conversion, 5-a-reductase. David Schottenfeld gave an overview of the state of the art and future directions in the epidemiology of prostatic cancer. Approximately 30% of men over 60 years of age have “latent” carcinomas and only 10% of those become invasive. This proportion is higher for American blacks and lower for Asian-Americans. Hormonal and molecular biology models are being tested.

Session 6, on immune function in carcinogenesis, was chaired by Charles Rabkin (NCI), who discussed malignant tumors associated with retroviruses, especially human T-lymphotoxin virus 1 and human immunodeficiency virus 1. The model of pathogenesis being studied involves, sequentially, increased cell proliferation, polyclonal expansion, monoclonal expansion, and malignant transformation; the first steps may regress to normality. An increase in incidence of non-Hodgkin's lymphoma has been observed recently to be related to human immunodeficiency virus infection and immunodeficiency. A possible interaction with other carcinogens such as tobacco products and other viruses such as HPV is being studied. Ian Mcgrath (NCI) made reference to the multiple steps in the pathogenesis of lymphomas and multiple molecular lesions reported. Of special interest are frequent translocations in which the myc oncogene is located near immunoglobulin-regulating genes. David Purtilo (University of Nebraska, Omaha, NE) described the many manifestations of lymphoproliferation disorders and the renewed interest in the role of Epstein-Barr virus and immunodeficiency. Defects in immune surveillance mechanisms lead to immunosuppression and to new or reactivated infections with viruses such as Epstein-Barr virus, HPV, HBV, and possibly others. This was Dr. Purtilo's last scientific presentation. He died of a cerebrovascular accident shortly after the meeting. The organizers of the meeting and the Editors of Cancer Epidemiology, Biomarkers & Prevention were saddened by the premature departure of a perfect gentleman, a dear friend, and an outstanding scientist.

Session 7 was a panel discussion on the evaluation and application of biochemical and molecular markers, chaired by Barbara Hulka. She elaborated on the changes that the use of biomarkers is bringing to the practice of epidemiology. She advocated validation of biomarkers through the so-called transitional studies and made a plea to keep the analysis simple because "if you torture the data long enough, they will confess to almost anything." Arthur Schatzkin (NCI) discussed strategies to identify, with statistical methods, intermediate end points which represent steps in the chain of causation and therefore serve as adequate surrogate end points. The strategy was illustrated with analyses of the polyp prevention trial in which 2000 polyp bearers are prescribed a diet low in fat and high in fruits and vegetables. Markers of cell proliferation and genotypic abnormalities are utilized. Mark Schiffman further illustrated the statistical methods used in the study of HPV. Neil Caporaso (NCI) discussed the methodology used to analyze markers of genetic susceptibility such as debrisoquine metabolism. Nathaniel Rothman (NCI) continued the discussion of genetic susceptibility markers used and reviewed the state of the art for several of them, especially markers of the acetylator phenotype, which show marked inter racial variation.

In addition to the above sessions a very active poster presentation took place, with 33 posters covering the whole spectrum of cancer epidemiology, biomarkers, and prevention. Space limitations do not allow extensive discussion of the posters. Their titles follow below:

15. Le Marchand, L. Serum carotenoids and ascorbic acid as markers of compliance for an intervention trial with fruits and vegetables. Honolulu: Cancer Research Center of Hawaii, University of Hawaii.
18. Murphy, S. E. Hemoglobin mediated activation of 4-(methylamino)-1-(2-pyridyl)-1-butanone to metabolites which covalently bind to hemoglobin. Valhalla, NY: American Health Foundation.
24. Kang, D. H. Increase in concentration of benz(a)-pyrene tetrahydrodibenz(a,h)anthracene in urine during consumption of char-broiled beef. Baltimore: Johns Hopkins School of Hygiene and Public Health.
27. Vatten, L. J. Polyunsaturated fatty acids in serum phospholipids and risk of breast cancer. A case-control study from the Janus Serum Bank in Norway. Oslo: University Medical Center.
28. Wank, R. Reciprocal relationship of genes conferring susceptibility to squamous cell carcinoma of the cervix and insulin dependent diabetes. Munich: Institute of Immunology, University of Munich.
29. Wei, O. Reduced DNA repair capacity predisposes to skin cancer—a clinic-based case-control study. Baltimore: The Johns Hopkins University School of Hygiene and Public Health.
33. Yun, T-K. Preventive effect of ginseng intake against various human cancers: final report of case-control study on 1,987 pairs. Korea Cancer Center Hospital, Seoul, Korea.
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