

Linkage

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The Vitamin D Pooling Project: Examining Relationships to Cancer

Claims regarding the health benefits of vitamin D have increased recently and now include not only benefits for osteoporosis but also for cancer, cardiovascular disease, diabetes, multiple sclerosis, and rheumatoid arthritis. In the specific case of cancer, however, the evidence has been mixed:

- Laboratory-based research indicates tumor suppression by 1,25-dihydroxy-vitamin D3.
- Higher latitude, a surrogate measure for lower levels of ultraviolet B (UVB) solar radiation and lower vitamin D, correlates with higher rates for several cancers.
- Clinical and epidemiologic studies are inconclusive on the relationship between blood vitamin D levels and risks for common cancers, although protective effects on the risk of colorectal cancer and possibly of breast cancer have been suggested in several studies.

Despite the lack of definitive evidence, there have been widespread calls for high-dose vitamin D supplementation, intended to boost its circulating blood levels to various theoretical target thresholds.

NCI launched the Vitamin D Pooling Project (VDPP) in 2007 with the goal of providing reliable estimates of the relative risk of cancer that would fill the gaps in our knowledge of the associations between vitamin D levels and cancer. Through the use of the resources available in the NCI Cohort Consortium and under the leadership of **Patricia Hartge, Sc.D.**, Deputy Director of the Epidemiology



Stephanie Weinstein

DCEG Linkage

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Vitamin D Pooling Project Members: (left to right) Christian Abnet, Kai Yu, Michal Freedman, Stephanie Weinstein, Rachael Stolzenberg-Solomon, Patricia Hartge, and Demetrius Albanes. (Not shown: Wong-Ho Chow, Lee Moore, Mark Purdue, Nathaniel Rothman, and Jocelyn Weiss.)

and Biostatistics Program, and Virginia Hartmuller, Ph.D., of NCI's Division of Cancer Control and Population Sciences (DCCPS), funding was allocated for measuring circulating 25-hydroxyvitamin D (25[OH]D) in prospectively collected and stored samples of plasma and serum from eight extramural cohorts supported by DCCPS and from two DCEG cohorts.

The VDPP's steering committee, chaired by Dr. Kathy Helzlsouer of Mercy Medical Center in Baltimore, Maryland, included representatives of the 10 participating cohorts, with support from Nonye Harvey, M.P.H. (DCCPS). **Stephanie J. Weinstein, Ph.D.**, Nutritional Epidemiology Branch (NEB), with assistance from **Demetrius Albanes, M.D.** (NEB), directed the VDPP data coordinating center.

The VDPP made the strategic decision to examine associations between vitamin D and cancer at several less common sites, including cancers of the endometrium, kidney, ovary, pancreas, stomach, and esophagus, as well as non-Hodgkin lymphoma. Limited epidemiological data had suggested associations between these cancers and vitamin D levels, but associations at

these sites could not be studied by individual cohorts with sufficient statistical power. The cohorts participating in the VDPP represented a range of geographic latitudes (see Figure 1), vitamin D intake and blood levels, various correlates of exposure, and racial/ethnic populations, enabling robust testing of the vitamin D hypothesis.

As expected when a large pooling effort is carried out across multiple cohorts, the VDPP investigators faced several challenges in data management and analysis, such as how to harmonize the incoming data that were specific to each cohort. Because the concentration of 25(OH)D in the blood may vary substantially by season of the year, when analyzing the data investigators took into consideration when the blood was collected by using techniques that included tight case-control matching on the date of the blood draw, creation of season-specific and season-standardized cutpoints, and stratification by season. In addition, because several clinical definitions are used to assess states of vitamin D "deficiency," "sufficiency," or "adequacy" based on blood levels, the VDPP defined overall pooled data-specific cutpoints to standardize these definitions.

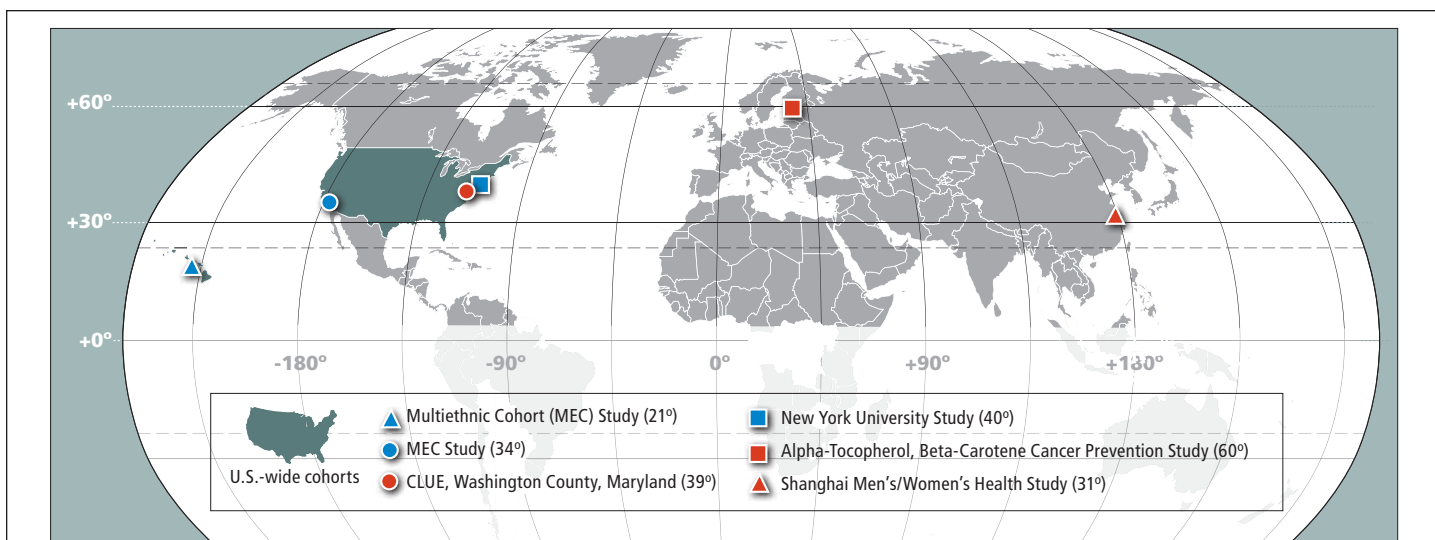


Figure 1. Map showing variations in latitude for cohorts participating in Vitamin D Pooling Project. U.S.-wide cohorts include the Cancer Prevention Study II, the Health Professionals Follow-Up Study, the Nurses' Health Study, and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (with 11 screening centers).

The results from the VDPP were published in nine articles in the July 1, 2010, issue of the *American Journal of Epidemiology* (*AJE*), including an overview, a description of the project design and methods, findings on the correlates of circulating vitamin D, and six cancer site-specific reports. Investigators found that women and men with higher concentrations of circulating vitamin D did not experience reduced risk for any of the cancers examined during the follow-up periods for the cohorts. The analysis of pancreatic cancer, however, which was led by **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB), found a significantly *elevated* risk in a relatively small number of subjects with circulating 25(OH)D greater than 100 nmol/L, which represents approximately the 95th percentile of the U.S. population. These data have prompted concern that in efforts to raise vitamin D levels in the blood, dosages are being prescribed that might expose the population to an increased risk of pancreatic and possibly other tumors. In the aggregate, the observational findings from the VDPP, based on nearly 5,500 cancer cases and 6,700 controls, have

provided no evidence of a protective role for higher vitamin D status in the relatively rare cancers that were studied, but they have pointed to a potential adverse effect for pancreatic cancer, which calls for further investigation.

In an accompanying *AJE* editorial, Mr. Tim Byers of the Colorado School of Public Health concluded that "...even though there was consistency in the overall null observations across most of the cohorts in this pooled analysis, there

was some variation. It is easy to imagine that, without this collaborative analysis, we might have been led down several blind alleys derived from analyses of various subgroups and interactions. We all should be grateful to the Vitamin D Pooling Project of Rarer Cancers investigators for having saved us from years of false leads as well as for their vision and skill in carrying out this outstanding collaborative project." ■

—Demetrius Albanes, M.D.,
and Stephanie J. Weinstein, Ph.D.

DCEG SCIENTIST APPEARS IN NCI CANCER BULLETIN VIDEO

The video interview of **Sholom Wacholder, Ph.D.**, Biostatistics Branch, for the *NCI Cancer Bulletin's* "In Their Own Words" series is available on the Bulletin web site and also on YouTube. In the video, Dr. Wacholder discusses his role in the clinical trial of a vaccine for human papillomavirus. To watch the video, go to <http://go.usa.gov/OwU> and click on the Play arrow.



Sholom Wacholder

DCEG GAINS TWO EARL STADTMAN INVESTIGATORS

Jill Koshiol, Ph.D., Infections and Immunoepidemiology Branch, and **Douglas Stewart, M.D.**, Clinical Genetics Branch, have been selected as two of the first four NIH Earl Stadtman Investigators. Named after a notable biochemist and mentor at the National Heart, Lung, and Blood Institute, the Stadtman program is a trans-NIH recruitment initiative designed to attract the most talented early-career scientists to NIH. Drs. Koshiol and Stewart were selected from among 800 initial applicants, of whom just 20 were interviewed.

Dr. Koshiol joined DCEG in 2005 as a cancer prevention fellow. Her work explores the role of various infectious agents, such as human papillomavirus (HPV) and Epstein-Barr virus, in human cancer. She has authored more than 20 publications and has received several competitive research funding awards, including the NCI Director's Innovation Award and DCEG Intramural Research Awards.

Dr. Koshiol developed an interest in epidemiology upon hearing her father, a pediatrician, call epidemiologists “the detectives of the scientific world.” She studied at the University of Cambridge in England for a year and saw the place where John Snow removed the handle from the well pump to stop a cholera outbreak in 19th century London. She then earned a Ph.D. in epidemiology at the University of North Carolina at Chapel Hill. Her interests in infection-related cancer originated in her work on human immunodeficiency virus (HIV) and HPV in relation to cancer while employed as a research assistant at GlaxoSmithKline in Research Triangle Park, North Carolina.

“The difficulty with cancer is that many of the causal factors we know about are

hard to modify,” she said. “Age is the number one risk factor for cancer, but you can't do anything about that. However, infectious agents are modifiable. We can target them through vaccines or pharmaceuticals and maybe prevent the cancer.”

As a tenure-track investigator, Dr. Koshiol will continue her studies of infection and cancer risk, focusing on the role of the immune response as a mediator between infection and cancer. Although HPV is a common infection, most women with the virus clear it; only women with persistent HPV infection are at increased risk of cervical cancer. Dr. Koshiol hopes that a better understanding of the role of the immune response in cancer risk will help doctors identify women who will not clear the virus, leading to targeted screening and better follow-up.

Dr. Stewart came to DCEG from the National Human Genome Research Institute (NHGRI), where he was in the Physician Scientist Development Program. His research focuses on neurofibromatosis type 1 (NF1), a genetic disorder that features the growth of multiple cutaneous or subcutaneous tumors of peripheral nerves. Dr. Stewart has investigated the role of biallelic inactivation and how variations in gene expression influence the NF1 phenotype. Dr. Stewart has served with Brigitte Widemann, M.D., of NCI's Center for Cancer Research, as a coprincipal investigator of a Bench-to-Bedside Award and co-Director of the Trans-NIH Neurofibromatosis Clinic. He and his colleague Dr. Eric Legius of Catholic University in Leuven, Belgium, have published the first genetic, functional, and clinical evidence of an association between



Jill Koshiol

NF1 and painful tumors in the fingertips known as glomus tumors.

“The glomus body is a little structure that no one thinks about,” Dr. Stewart explained. “I remember seeing it once in my histology textbook in medical school and never thinking of it again.” He approached Dr. Legius after hearing him speak on glomus tumors and recalling that he himself had seen neurofibromatosis patients with fingertip pain. Now he is especially gratified by spreading awareness about the occurrence of these tumors in NF1.

Dr. Stewart always has had an interest in biomedical research, particularly genetics. He earned an M.D. at the University of Pennsylvania, then worked as a clinical fellow at the Children's Hospital of Philadelphia. He went on to a research fellowship at Penn, where he mapped genes involved in polycystic ovary syndrome before joining NHGRI in 2004. He has received several awards and was nominated for

a Distinguished Mentor Award as an NIH postdoctoral fellow.

In DCEG, Dr. Stewart will continue his research on *NF1*, with a focus on tumorigenic mechanisms. He hopes that his work will help scientists and physicians understand why phenotypes vary among people with *NF1* gene mutations, even within the same family. He also speculates that in the long term, a panel of specific genes or alleles that predict phenotype will help the most severely affected patients receive treatment before tumors arise.

As Stadtman investigators, Drs. Koshiol and Stewart enjoy the independence and intellectual freedom of academic research and appreciate the value of working across scientific disciplines. Dr. Stewart likes the ability to switch between clinical and research roles, and Dr. Koshiol values the special opportunities to collaborate across



Douglas Stewart (Photograph credit: Bill Branson)

NIH and with outside partners. Both Drs. Stewart and Koshiol also noted the important role that mentoring plays early in one's scientific career. "Compressing and articulating all of your interests into one clear sentence

is important for getting jobs, receiving grants, and figuring out what you're doing in life," Dr. Stewart said. "I'd never thought about it until a senior person told me that I needed to." ■

—Frances McFarland Horne, Ph.D., M.A.

SHAHINAZ GADALLA RECEIVES MERIT AWARD

Shahinaz Gadalla, M.D., Ph.D., Clinical Genetics Branch (CGB), recently received a Merit Award for her outstanding performance as an NCI Cancer Prevention Fellow. The award places her in the top 10 percent of Cancer Prevention Fellows and recognizes the outstanding progress she has made during her fellowship.

Dr. Gadalla has worked in CGB since September 2008. After earning a medical degree from Ain Shams University in Cairo, Egypt, Dr. Gadalla joined the epidemiology program at the University of Maryland, Baltimore, where she earned a master's degree in 2005 and then a Ph.D. in epidemiology in 2008.

The Merit Award is based on Dr. Gadalla's overall performance as a Cancer Prevention Fellow, including her research publications as well as the periodic progress assessments made by her mentors. Dr. Gadalla said that she was thrilled to receive the award, and she gave credit to

Mark H. Greene, M.D., Chief of CGB, and **Sharon A. Savage, M.D.**, a CGB tenure-track investigator, for their mentorship.

"Epidemiologic research is critically important to understand the causes of cancer and the impact of cancer treatment in order to decrease cancer mortality and improve the lives of cancer survivors," Dr. Gadalla said of the work she does. In one of her projects, she is analyzing the outcomes of hematopoietic stem cell transplantation in patients with the hereditary disease dyskeratosis congenita. In addition, she has led a study to assess whether the length of telomeres in cells from donors and recipients after stem cell transplant can predict outcomes in patients with acquired severe aplastic anemia. In 2009, this work earned her a competitive DCEG Intramural Research Award.

"Working at NCI has been a tremendous experience," Dr. Gadalla stated. "The available



Shahinaz Gadalla

resources, open communication among researchers, strong mentorship, and high-quality science make working here extremely rewarding." Dr. Gadalla hopes that her research will contribute toward progress in cancer prevention.

—Amber K. Boehm, Ph.D.

DCEG WELCOMES VISITING SCHOLAR ROSS PRENTICE

DCEG hosted Dr. Ross L. Prentice as a Visiting Scholar in June. Dr. Prentice is Director of the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center in Seattle, Washington and a professor in the Department of Biostatistics at the University of Washington School of Public Health. DCEG recognized Dr. Prentice for his vision and pioneering research contributions in biostatistics, epidemiology, and methods development.

Dr. Prentice obtained his B.Sc. in mathematics from the University of Waterloo in Ontario, Canada, and received his M.Sc. and Ph.D. in statistics from the University of Toronto. Early in his career, he received the American Public Health Association's Mortimer Spiegelman Award for outstanding achievement by a young public health statistician. More recently, he has received the American Association of Cancer Research/American Cancer Society Award for research excellence in epidemiology and prevention as well as Harvard University's Marvin Zelen Leadership Award for exceptional leadership that has influenced the theory and practice of statistical science. In addition, Dr. Prentice has received the President's Award from the Committee of Presidents of Statistical Societies and the R. A. Fisher Lectureship in recognition of his seminal work on statistical methods. Dr. Prentice is a member of the Institute of Medicine at the U.S. National Academies.

Dr. Prentice currently serves as principal investigator of the NIH-sponsored Clinical Coordinating Center for the Women's Health Initiative (WHI), which oversees a clinical trial and



Ross Prentice (middle) with Joseph Fraumeni and Robert Hoover.

observational cohort study with more than 161,000 participants. These studies have examined the effects of hormone replacement therapy and dietary intake, including vitamin D and calcium supplementation, in the prevention of breast and colorectal cancer as well as other health outcomes. He also heads the WHI Statistical Methods for Medical Studies project, which focuses on developing statistical methods for disease prevention, epidemiological studies, and biomarker research.

Robert N. Hoover, M.D., Sc.D., Director of the Epidemiology and Biostatistics Program, welcomed Dr. Prentice and applauded him for the breadth and depth of his research. In his introduction, Dr. Hoover noted, "Statisticians know Dr. Prentice for his groundbreaking methods development and his refinement across multiple areas of statistics. Epidemiologists and clinical trialists know him as a paradigm-shifting methodologist leading to

high-impact research. There are few people who would be on the short list of leaders in all three of these fields."

During his Visiting Scholar seminar, Dr. Prentice addressed the benefits and challenges of conducting intervention trials. He presented his research from the WHI Postmenopausal Hormone Therapy Trials, which examined health outcomes among postmenopausal women receiving estrogen and progestin and revealed an increased risk among these women for coronary heart disease and invasive breast cancer. These findings led to a dramatic change in clinical practice, with millions of women stopping the use of hormone therapy, resulting in a decline in national breast cancer rates. Dr. Prentice also discussed dietary assessments and the development of biomarkers for nutrients and physical activity, and he outlined the need for enhanced preventive intervention studies as well as large-scale collaborative efforts to understand a broad spectrum of chronic diseases.



Ross Prentice

Following the seminar, DCEG tenure-track investigators met with Dr. Prentice during a brown-bag luncheon. The discussion, facilitated by **Hormuzd A. Katki, Ph.D.**, Biostatistics Branch (BB), touched on the challenges of balancing time between scientific and administrative duties and transitioning to senior-level positions.

Dr. Prentice participated in two seminars during the afternoon. The first, led by Nutritional Epidemiology Branch investigators **Amanda J. Cross, Ph.D.**, and **Charles Matthews, Ph.D.**, focused on the role of biomarkers for dietary assessments as well as on measurement tools for physical activity and ways to attenuate measurement error.

In a session hosted by BB senior investigator **Barry I. Graubard, Ph.D.**, Dr. Prentice spoke on “Statistical issues in epidemiologic studies and randomized trials.” He highlighted data analysis, outcome measures, and study design in the WHI Postmenopausal Hormone Therapy Trials. In particular, he discussed the challenges of determining clinical endpoints and the need for intermediate or surrogate measures. The discussion closed with comments on the analysis of high-dimensional

biologic data, such as that generated by genome-wide association studies (GWAS), and methods for correcting methodological bias.

The following morning, Dr. Prentice participated in a seminar on “high-density ‘omics” chaired by Dr. Hoover. During the seminar, Dr. Prentice presented his work in genomic and proteomic studies. He then ended the day by meeting individually with **Joseph F. Fraumeni, Jr., M.D.**, Division Director, **Nilanjan Chatterjee, Ph.D.**, Chief of BB, and BB investigator **Sholom Wacholder, Ph.D.**

Reflecting on his program as a Visiting Scholar, Dr. Prentice said, “I had a marvelous visit to DCEG. We spent much of the time discussing topics in genomics, proteomics, methods development, and nutritional and physical activity biomarkers as they relate to population aspects of cancer research. Many of the leading experts in these areas reside at NCI, especially in DCEG. It was most enjoyable to be immersed in this stimulating environment for these two days.” ■

—Saloni Nayar, M.P.H.

NEW FREEZER IMPROVES EFFICIENCY AND STORAGE CAPACITY OF DCEG BIOSPECIMEN REPOSITORY

In July, **Joseph F. Fraumeni, Jr., M.D.**, Division Director, **Shelia Hoar Zahm, Sc.D.**, Deputy Director, **Karen E. Pitt, Ph.D.**, special assistant for biological resources, Office of the Director, and **Marianne K. Henderson, M.S.**, Chief of the Office of Division Operations and Analysis, visited the Wedgewood complex of the Fisher BioServices Central Repository in Frederick, Maryland, to observe the installation of DCEG’s new



Inspecting the New Freezer: (from left) Kathleen Groover, of Fisher BioServices, with Marianne Henderson, Karen Pitt, Joseph Fraumeni, Shelia Zahm, and Mark Cosentino, repository contracting officer’s technical representative for SAIC-Frederick, Inc. (Photograph credit: Jonathan Summers)

–80° C walk-in cold room. This leading-edge storage system will improve efficiencies and reduce costs for the processing and storage of biospecimens by DCEG. The system features redundant power sources, which will make it safe for biospecimens and it offers “green” benefits by reducing energy costs and occupying less floor space than would an equivalent number of upright freezers. The new freezer will store approximately 2.2 million specimens. Fisher BioServices performs the majority of the biospecimen storage and handling operations for DCEG through a subcontract with SAIC-Frederick, Inc.

DCEG HOSTS DISTINGUISHED LECTURER DAVID CHRISTIANI

The Occupational and Environmental Epidemiology Branch (OEEB) hosted Dr. David Christiani as a Distinguished Lecturer in Occupational and Environmental Cancer in June. Dr. Christiani is the Elkan Blout Professor of Environmental Genetics in the Harvard School of Public Health's Department of Environmental Health and Department of Epidemiology. He also is the Director of the National Institute for Occupational Safety and Health-funded Harvard Education and Research Center for Occupational Safety and Health. The Center's objective is to conduct research and train occupational safety and health professionals in the field of public health.

Dr. Christiani is recognized internationally for his pioneering work in the fields of occupational health and molecular epidemiology. He has studied the health effects of occupational and environmental exposures in Bangladesh, China, and Taiwan, including exposures to endotoxins, polycyclic aromatic hydrocarbons, petrochemical emissions, and arsenic in drinking water. He was an early pioneer in the field of molecular epidemiology, using biological markers to study the relationship of environmental pollutants to cancers of the lung, bladder, and skin as well as to acute respiratory diseases. Dr. Christiani also was one of the first American epidemiologists to study chronic occupational disease in China. His landmark 30-year cohort study of cotton-textile workers in Shanghai, China has used molecular tools to evaluate the effects of endotoxin exposure on lung disease.

Dr. Christiani is conducting genome-wide association studies (GWAS) of lung cancer etiology and survival, as well as



David Christiani (second from right) with Joseph Fraumeni, Mary Ward, and Debra Silverman.

acute lung injury, and he is using tumor genetics to assess exposure-related disease, including gene-environment interactions.

At his DCEG seminar titled Somatic Tissue Analysis in the Molecular Epidemiology of Lung Cancer, Dr. Christiani discussed findings from two studies of non-small cell lung cancer. In the first study, he used genome-wide analysis of tumor tissue to investigate whether certain single nucleotide polymorphisms (SNPs) in tumor tissue are predictive factors in early-stage disease; he concluded that five SNPs may be important for tumor progression and prognosis. In the second study, he assessed the impact of disease, genomic loci, and biological function on copy number alterations. He concluded that copy number variations are clustered by position and by acquired function, which might suffice for malignant transformation of normal cells.

During his visit, Dr. Christiani also spoke on "Reflections on environmental

exposures and cancer in the 21st century: The future of environmental epidemiology" at a meeting of OEEB staff. In addition, Dr. Christiani met with a number of OEEB investigators about their research projects. In particular, he discussed benzene and trichloroethylene studies in Asia with **Qing Lan, M.D., Ph.D., M.P.H.**, and **Nathaniel Rothman, M.D., M.P.H., M.H.S.**, and the Shanghai Women's Health Study with **Wong-Ho Chow, Ph.D.**, **Melissa Friesen, Ph.D.**, **Bu-Tian Ji, M.D., Dr.P.H.**, and others. He also met with **Kenneth P. Cantor, Ph.D., M.P.H.**, **Nicole Deziel, Ph.D.**, **Mary H. Ward, Ph.D.**, and **David Wheeler, Ph.D., M.P.H.**, to discuss their work on environmental cancer and met with DCEG interest groups on lung and urologic cancers. In addition, Dr. Christiani held a luncheon meeting with predoctoral and postdoctoral fellows on epidemiologic research strategies and career development. ■

—Qing Lan, M.D., Ph.D., M.P.H.,
Nathaniel Rothman, M.D., M.P.H., M.H.S.,
and Mary H. Ward, Ph.D.

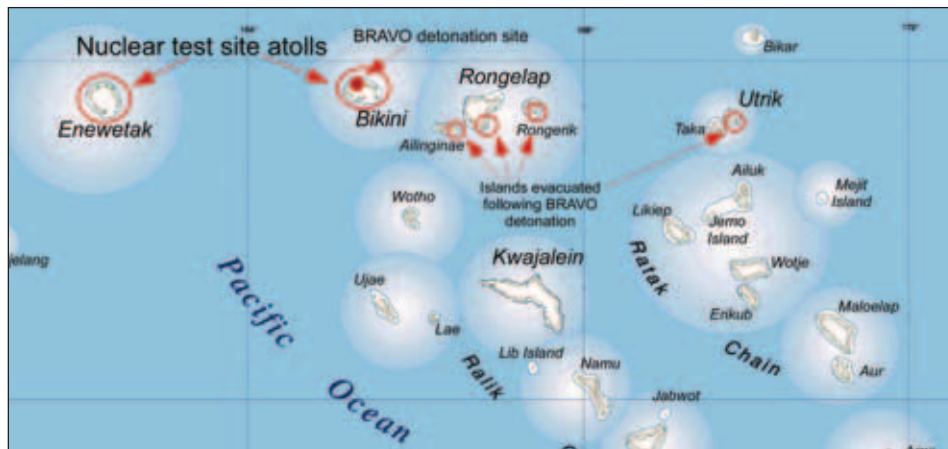
REPORT PUBLISHED ON DCEG'S RESEARCH ON THE MARSHALL ISLANDS

The journal *Health Physics* published a special issue in August titled “Radiation Doses and Cancer Risks in the Marshall Islands from U.S. Nuclear Weapons Tests.” This collection of eight scientific papers represents an extensive effort by DCEG scientists and collaborators to estimate the radiation doses and related cancer risks experienced by residents of the Marshall Islands who were exposed to radioactivity from the U.S. atomic testing program. The papers include analyses of external doses, internal doses, and projections of cancer risk as well as the methodologies used to reconstruct the doses and the associated risks.

Between 1946 and 1958, the United States tested 66 nuclear weapons on or near the Bikini and Enewetak atolls, which had been evacuated prior to the testing. Populations living elsewhere in the Marshall Islands archipelago, however, were exposed to measurable levels of radioactive fallout from 20 of these tests.

The U.S. Senate Committee on Energy and Natural Resources asked NCI in 2004 to provide its expert opinion on the baseline cancer risk and the number of cancers expected among the Marshall Islanders as a result of radioactive fallout from U.S. nuclear tests. A preliminary report by DCEG staff was prepared, based on a number of conservative assumptions designed to avoid underestimating the actual cancer risks, using data that could be collected quickly to provide a timely response.

During the next three years, investigators collected, analyzed, and systematically integrated all available historical information with more contemporary measurement data on environmental



Locations of U.S. nuclear weapons tests in the Marshall Islands.

radiation. This comprehensive approach allowed investigators to reconstruct estimates of exposure for every atoll and from all nuclear tests conducted in the Marshall Islands and to revise estimates of the number of excess (i.e., radiation-related) cancers for all exposed residents. In June 2010, three Radiation Epidemiology Branch researchers leading the effort—**André Bouville, Ph.D.**, **Charles E. Land, Ph.D.**, now retired, and **Steven L. Simon, Ph.D.**—presented the results to members of the U.S. Senate Committee on Energy and Natural Resources and to officials from the Department of Energy and the Department of the Interior. ■



August 2010 issue of *Health Physics*

AGRICULTURAL HEALTH STUDY TEAM MEMBERS RECEIVE AWARD

In September, the Agricultural Health Study (AHS) Pesticide Exposure Study team, which includes Occupational and Environmental Epidemiology Branch investigators **Michael C.R. Alavanja, Dr.P.H.**, and **Aaron E. Blair, Ph.D., M.P.H.**, scientist emeritus, along with members of the Environmental Protection Agency (EPA), the National Institute of Occupational Safety and Health, and the National Institute of Environmental Health Sciences, received the U.S. EPA Office of Research and Development's Bronze Medal. The award was given in recognition of the team's outstanding exposure research support to the interagency AHS, which has been recognized internationally as a model epidemiological study that integrates rigorous pesticide exposure assessment with molecular and population-based cancer incidence analyses.

WORKSHOP ON MALE BREAST CANCER KICKS OFF POOLING PROJECT

In May, DCEG's Hormonal and Reproductive Epidemiology Branch (HREB) and the NIH Office of Rare Diseases cosponsored an inaugural meeting and workshop to assemble investigators for a male breast cancer (MBC) pooling project. Organized by **Louise A. Brinton, Ph.D.**, Chief of HREB, the meeting brought together investigators representing 21 case-control or cohort studies with data that could contribute new insights into the etiology of MBC. Previous studies have been hindered by small numbers, given that MBCs account for less than 1 percent of all breast cancers. This international effort currently includes studies from the United States, Canada, and several European countries. The project's organizers are still seeking collaborators from other parts of the world, including Asia, Australia, and the Middle East.



Male Breast Cancer Workshop Participants: (front) Mark Sherman, Marjorie McCullough, Julie Buckland, Dominick Parisi, Eleni Petridou, Eva Negri, Ann Hsing, Marianne Ewertz, Louise Brinton, Domenico Palli, Karen Michels, and Sabah Quraishi; (back) Michael Cook, Anthony Swerdlow, Kirk Snyder, Valerie McCormack, Larry Kolonel, David Thomas, Stephen Van Den Eeden, Hakan Olsson, Ken Johnson, and Danny Carreon.

The workshop focused on how data from various investigations may be combined and harmonized to clarify the genetic and environmental

determinants of MBC. Because biologic samples have been collected for a number of the studies, it will be possible to evaluate the role of highly penetrant genes (*BRCA2* appears to be especially predictive of MBCs) as well as more common genetic polymorphisms, especially those involved in hormone metabolism and tumor suppression. Alterations of endogenous hormones (e.g., estrogen to androgen levels) also will be researched whenever possible along with nutritional factors (e.g., energy balance).

The pooling project will analyze questionnaire data from more than 2,000 MBC cases, making it the largest effort to date to clarify the origins of this rare tumor. Participants also will attempt to collect tissue samples to evaluate whether, as with female breast cancers, there are etiologically distinct sub-groups of tumors. ■

—Louise A. Brinton, Ph.D.

RADIATION EPIDEMIOLOGY BRANCH INVESTIGATORS PRESENT AT CONFERENCE

In June, several members of the Radiation Epidemiology Branch (REB) participated in the 55th Annual Conference of the Health Physics Society in Salt Lake City, Utah. **André Bouville, Ph.D.**, and **Steven L. Simon, Ph.D.**, organized a special session on NCI dosimetry studies. During the session, REB presentations included Dr. Bouville on "Overview of fallout dosimetry methods and history of studies"; **Vladimir Drozdovitch, Ph.D.**, on "Reconstruction of exposures from nuclear tests in Kazakhstan"; **Dunstana Melo, Ph.D.**, on "Organ dose reconstruction for hyperthyroid patients treated with ¹³¹I"; **Brian Moroz** on "Predictions of dispersion and deposition of fallout from nuclear testing using a meteorological computer model"; and Dr. Simon on "Radiation doses to Marshallese associated with exposure to local and regional radioactive fallout from Bikini and Enewetak nuclear weapons tests" and "Overview of reconstructing past medical exposures in support of epidemiologic and health risk studies at NCI."

REB investigators also were invited to give talks during the conference. Dr. Bouville spoke on "Dosimetry for NCI Chernobyl studies (thyroid diseases)" and "Scientific committee 6-3 report: Uncertainties in internal radiation dose assessment"; **Ethel S. Gilbert, Ph.D.**, presented on "The needs of a 'customer' of dose reconstruction" and "Second cancers and cardiac effects after radiotherapy"; and Dr. Simon spoke on "Radiation organ doses received by U.S. radiologic technologists: Estimation methods and findings" and "Summary of NCRP report No. 158: Uncertainties in the measurement and dosimetry of external radiation."

WORKSHOP TACKLES HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

DCEG held a workshop in April on the etiology of hepatocellular carcinoma (HCC) in the United States. Motivated by the recent increase in the incidence of HCC in this country, the workshop organizers assembled investigators involved in U.S.-based cohort studies to form an HCC pooling project. The event was funded by the NIH Office of Rare Diseases Research and organized by **Katherine A. McGlynn, Ph.D., M.P.H.**, a senior investigator in the Hormonal and Reproductive Epidemiology Branch (HREB).

Dr. McGlynn opened the workshop by presenting an overview of the epidemiology of HCC in the United States. She noted that HCC, with an incidence rate of roughly 6.0 per 100,000 persons, is not a common tumor among the general population, but its incidence has been increasing for several decades (see Figure 1). Of all the major cancers, liver cancer had the second greatest annual percentage increase in incidence (2.3 percent) and the single greatest percentage increase in mortality (2.0 percent) between 1999 and 2006. These increases are particularly worrisome because liver cancer has an extremely poor prognosis. At only 13 percent among whites and 9 percent among blacks, the five-year survival rate is the third worst among major cancers.

In geographic areas of the world with elevated rates of liver cancer, such as eastern Asia and sub-Saharan Africa, the majority (i.e., 80 percent) of cases are associated with chronic hepatitis B or hepatitis C virus infection and/or consumption of food contaminated with aflatoxin B1. Conversely, in low-rate areas, such as the United States, a smaller proportion of liver cancer is explained by known risk factors.

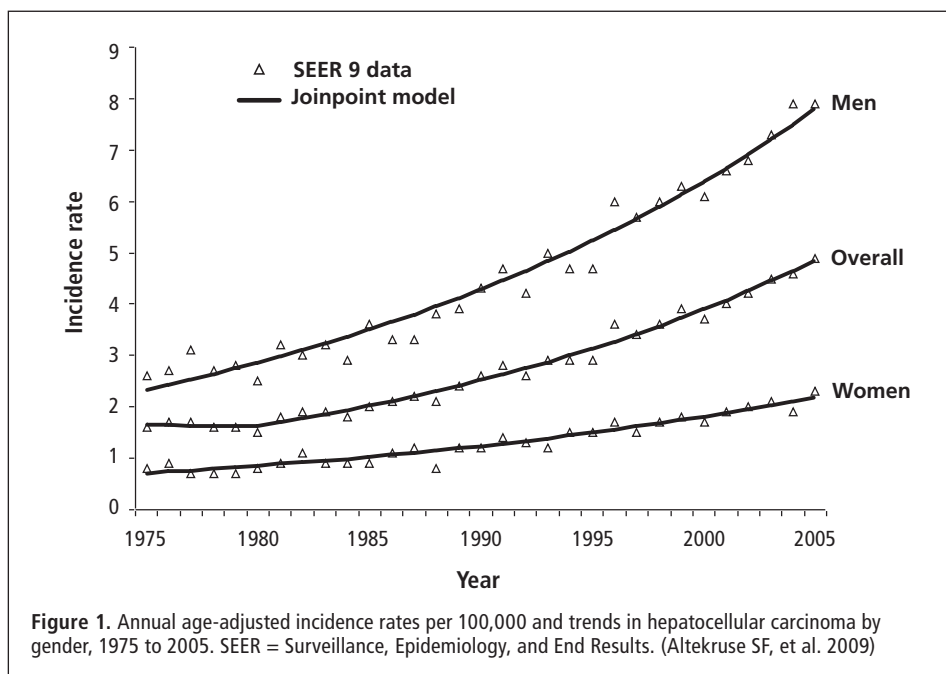


Figure 1. Annual age-adjusted incidence rates per 100,000 and trends in hepatocellular carcinoma by gender, 1975 to 2005. SEER = Surveillance, Epidemiology, and End Results. (Altekruse SF, et al. 2009)

Following Dr. McGlynn's remarks, presentations were given on a number of novel HCC hypotheses. Dr. Ellen Chang of the Cancer Prevention Institute of California described evidence that exposure to sunlight and vitamin D may be inversely related to the development of HCC. She also spoke on the possible relation of the disease to the use of nonsteroidal anti-inflammatory drugs. **Christina Persson, Ph.D.**, a postdoctoral fellow in HREB, discussed the possible roles of reproductive factors, hormones, and exposure to pesticides in the development of the disease. **Fatma Shebl, M.D., Ph.D.**, a postdoctoral fellow in the Infections and Immunoepidemiology Branch, spoke on the mechanism of chronic inflammation in HCC. Dr. McGlynn reviewed the evidence that type 2 diabetes and related morbidities, such as obesity and metabolic syndrome, are precursors to HCC. Nutritional Epidemiology Branch investigators **Neal D. Freedman, Ph.D., M.P.H.**, and **Rashmi Sinha, Ph.D.**, led a roundtable discussion on dietary risk factors.

Currently, the HCC pooling project consists of 16 cohort studies from the NCI Cohort Consortium: the NIH-AARP Diet and Health Study; the Agricultural Health Study; the Breast Cancer Detection Demonstration Project Follow-up Study; the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial; the U.S. Radiologic Technologists cohort; the American Cancer Society's Cancer Prevention Study; the Health Professionals Follow-up Study; the Physicians' Health Study; the Nurses' Health Study; the Women's Health Study; the California Teachers Study; the CLUE study; the Black Women's Health Study; the Iowa Women's Health Study; the New York University Women's Health Study; and the Women's Health Initiative. All of the studies are providing questionnaire data for analysis, and those that collected biosamples are providing serum. To date, approximately 1,500 HCCs have developed among participants in the pooling project studies. ■

—Katherine A. McGlynn, Ph.D., M.P.H.

REGISTRY DATABASE STUDIES WORKING GROUP

Some of the most important known cancer risk factors include certain medical conditions and their treatments. AIDS, autoimmune diseases, hepatitis B and C virus infection, and obesity, for example, can profoundly affect health and increase cancer risk. In addition, such medical interventions as immunotherapy, chemotherapy, and radiation therapy can promote the development of malignancies.

These medical conditions and treatments, as well as related laboratory tests, are frequently recorded in large databases that can be used to study cancer. DCEG's Registry Database Studies Working Group was created this year to foster strategic epidemiologic collaborations in this area. According to the Working Group's chair, **Eric A. Engels, M.D., M.P.H.**, Infections and Immunoparasitology Branch (IIB), "There are already substantial efforts and expertise in research within the Division and elsewhere at NCI using these valuable databases. The Working Group wants to bring interested investigators together to share their experience, foster collaboration, and develop new resources."

One important resource is the SEER-Medicare database, which links cancer registry data from NCI's Surveillance, Epidemiology, and End Results (SEER) program with claims data from Medicare, the U.S. federal health insurance program for people aged 65 or older, some disabled people younger than age 65, and people of all ages with end-stage renal disease (i.e., with permanent kidney failure treated with dialysis or a transplant). Working Group member Joan L. Warren, Ph.D., of NCI's Division of Cancer Control and Population Sciences (DCCPS), oversees this data resource, which has been used



Registry Database Studies Working Group: (front) Katherine McGlynn and Joan Warren; (back) Michael Cook, Eric Engels, Ruth Pfeiffer, and Jill Koshiol. (Not shown: Lindsay Morton and Meredith Shiels.)

extensively by health service researchers to study access to care and treatment outcomes.

Drs. Engels and Warren, along with other members of the Working Group, including **Katherine A. McGlynn, Ph.D., M.P.H.**, Hormonal and Reproductive Epidemiology Branch (HREB), and **Ruth M. Pfeiffer, Ph.D.**, Biostatistics Branch (BB), have recently developed epidemiologic approaches that use SEER-Medicare data to perform nested case-control studies on specific cancers within the Medicare population. For each disease case identified within the Medicare population, the investigators select a number of matched controls (i.e., those who have not developed the disease by the time it has occurred in the identified cases) from within the same population. Because this approach involves studying only the cases and the related controls, rather than the entire specified population, it can be significantly less expensive and less time consuming to collect and analyze the data. Recent DCEG studies incorporating SEER-Medicare data in this manner

have evaluated diabetes as a risk factor for hepatocellular carcinoma; AIDS, autoimmune conditions, and solid organ transplants as risk factors for skin cancer; and autoimmune conditions and blood transfusions as risk factors for hematologic malignancies.

Lindsay M. Morton, Ph.D., Radiation Epidemiology Branch, is using the data resource to identify the risk factors for second primary cancers, and **Michael B. Cook, Ph.D.** (HREB), is using the data to identify reasons for the upward trend in adenocarcinoma. The Working Group has established a monthly brown-bag seminar series to build on this work, encourage collaboration, and facilitate additional research.

In addition to SEER-Medicare projects, DCEG investigators are using other large registries and administrative data sources. For example, the HIV/AIDS Cancer Match Study, led by Dr. Engels, links data from population-based registries of people infected with the human immunodeficiency virus (HIV) with data from multiple U.S. cancer

registries. The results are helping to identify cancers that occur excessively in relation to immunosuppression and to monitor trends in the risk of cancer associated with changes in HIV therapy.

Of related interest is the Transplant Cancer Match Study, which links data from the U.S. solid organ transplant registry with data from cancer registries to examine the spectrum of cancer risk associated with transplantation. When complete, it will be the largest population-based study of cancer risk in transplant recipients, with data on more than 150,000 individuals from 13 states, and will encompass detailed information on underlying medical conditions, including infections, and immunosuppressive therapies.

Another valuable data resource is the U.S. Military Cancer Institute (USMCI). DCEG and the USMCI established a collaboration in 2006 to estimate cancer incidence and mortality rates in the military population and to study the effects of medical history, medication use, occupation, and other risk factors for cancer. DCEG affiliates who are involved in this collaboration include Dr. McGlynn, cochair of the effort, **William F. Anderson, M.D., M.P.H.** (BB), **Susan S. Devesa, Ph.D.** (BB), Dr. Engels, **Philip S. Rosenberg, Ph.D.** (BB), and **Shelia Hoar Zahm, Sc.D.**, DCEG Deputy Director. "We continue to be very excited about our ongoing collaboration with the military," Dr. McGlynn said. "The Department of Defense medical care system is the largest health maintenance organization in the country and one that includes diverse racial/ethnic populations. The USMCI link offers tremendous opportunities to study cancer and premalignant conditions that occur in younger persons."

Jill Koshiol, Ph.D. (IIB), another Working Group member, is teaming with DCCPS's Cancer Research Network (CRN), a network of U.S. health maintenance organizations, to study medical risk factors for cancer, starting with hematologic malignancies. The CRN offers broad coverage of the U.S. population, with access to data on cancer incidence and outcomes, precursor lesions, medical conditions, laboratory test results, and medication use.

The trend toward centralization of medical care, growth of electronic medical records, and public health surveillance will provide additional opportunities for epidemiological research. The Working Group also is exploring ways to link registry and administrative databases to biospecimen resources, including tumor tissue, which would greatly enhance the value of these data resources for further research. ■

DCEG STAFF CONTRIBUTE TO THE SOCIETY FOR EPIDEMIOLOGIC RESEARCH MEETING

The Society for Epidemiologic Research (SER) held its annual meeting in Seattle, Washington in June. The theme of this year's meeting was "Epidemiology in an Interconnected World." Several DCEG investigators participated in the event by giving talks or presenting posters of their work. **Jonathan Hofmann, Ph.D.**, Occupational and Environmental Epidemiology Branch (OEEB), presented "Long-term variation in serum 25-hydroxyvitamin D concentration among participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial" during the panel session "Recent findings in vitamin D and cancer."

Poster presentations included the following:

Louise A. Brinton, Ph.D., Chief of the Hormonal and Reproductive Epidemiology Branch (HREB): *Hormonal risk factors for lung cancer in women*

Michael B. Cook, Ph.D. (HREB): *Helicobacter pylori and gastric atrophy in relation to the risk of esophageal squamous cell carcinoma in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study*

Cher Dallal, Ph.D. (HREB): *Plasma leptin levels, LEPR Q223 polymorphism and mammographic breast density*

D. Michal Freedman, Ph.D., M.P.H., Radiation Epidemiology Branch (REB): *Multiple indicators of ambient and personal UV exposure and risk of non-Hodgkin lymphoma (NHL)*

Gretchen L. Gierach, Ph.D. (HREB): *Coffee consumption and breast cancer risk in the NIH-AARP Diet and Health Study*

Kathryn Hughes Barry, M.P.H. (OEEB): *Genetic variation in metabolic genes, occupational solvent exposure, and risk of NHL*

Cari Meinhold Kitahara, M.H.S. (REB): *Total cholesterol and cancer risk in a large prospective study in Korea*

Gwen Murphy, Ph.D., M.P.H., Nutritional Epidemiology Branch (NEB): *Prospective study of serum cysteine levels and esophageal and gastric cancers in China*

Gila Neta, Ph.D., M.P.P. (REB): *Distribution and determinants of in utero pesticide mixtures using a principal component analysis*

Elizabeth Ruder, Ph.D., M.P.H., R.D. (NEB): *Birth characteristics and age at menarche: Results from the Dietary Intervention Study in Children (DISC)*

Sara Schonfeld, Ph.D., M.P.H. (REB): *Hormonal factors and endometrial cancer risk by parity*

Britton Trabert, Ph.D. (HREB): *Are placental characteristics an indirect marker of in utero hormone exposure?*

UPPER GASTROINTESTINAL CANCER RESEARCH GROUP

Upper gastrointestinal (UGI) cancers, which include malignant neoplasms of the esophagus and stomach, cause more than 1.1 million deaths per year worldwide, a total second only to that for lung cancer. Incidence rates for esophageal and stomach cancers vary 100-fold by geographic region and, in some regions, 10-fold by gender, with intriguing differences by histologic type and subsite. In Western countries, for example, incidence rates of esophageal adenocarcinoma (EAC) have multiplied rapidly during the past several decades, increasing nearly fivefold between 1975 and 2004 among U.S. white men. In contrast, esophageal squamous cell carcinoma (ESCC) is the dominant cell type among high-risk populations from developing countries.

DCEG's UGI Cancer Research Group brings together investigators to increase the exchange of information and foster collaborative research on these tumors. Since the group's inception in 2006, its proposed projects have resulted in seven DCEG Intramural Research Awards and seven NCI Director's Innovation Awards.

Members of the Research Group are conducting investigations on UGI cancers in several countries, including those with extremely high incidence rates, such as Brazil, China, Iran, and Kenya. These projects aim to understand and prevent UGI cancers using etiologic approaches, early detection, and a variety of interventions. Investigators are studying such risk factors as diet and nutrition, environmental chemicals, microbes, and genetic susceptibility. Emphasis is placed on molecular epidemiology, with evaluation of biological samples that include



UGI Cancer Research Group Members: (front) Mary Ward, Tram Lam, Ying Gao, Jill Koshiol, and Shih-Wen Lin; (middle) Philip Taylor, Christina Persson, Alisa Goldstein, Wong-Ho Chow, Mahboobeh Safaeian, Paula Hyland, Gwen Murphy, and Maria-Constanza Camargo; (back) Christian Abnet, Farin Kamangar, Arash Etemadi, Sanford Dawsey, Charles Rabkin, Michael Cook, Mark O'Doherty, and Neal Freedman. (Not shown: Mark Roth.)

prospectively banked blood, esophageal balloon cells, and tumor and adjacent normal tissue from both high- and low-risk populations.

Group members have published a number of interesting findings from high-risk populations, including associations between polycyclic aromatic hydrocarbon adduct concentrations in tissue and SCC, consumption of hot tea as a risk factor for ESCC, and the relationships between genetic polymorphisms in *PLCE1* at 10q23 and elevated risk of both ESCC and gastric cardia adenocarcinoma. In addition, investigators have shown that daily treatment with 50 µg of selenium, 30 mg of vitamin E, and 15 mg of beta-carotene in a nutrient-deficient, high-risk population in China led to decreased mortality from all causes and all cancers (especially gastric cancer) and that these beneficial effects were evident up to 10 years after supplementation ended. The UGI group also has played a pivotal role in the Barrett's Esophagus

and Esophageal Adenocarcinoma Consortium and a genome-wide association study (GWAS) using the UGI cohort consortium.

Founders of the UGI Cancer Research Group include Nutritional Epidemiology Branch (NEB) investigators **Christian C. Abnet, Ph.D., M.P.H., Sanford M. Dawsey, M.D., Neal D. Freedman, Ph.D., M.P.H.,** and **Mark J. Roth, M.D.**; former NEB member Dr. Farin Kamangar, now at Morgan State University in Baltimore, Maryland; **Wong-Ho Chow, Ph.D.**, Occupational and Environmental Epidemiology Branch; **Jill Koshiol, Ph.D.**, Infections and Immunoepidemiology Branch; and **Philip R. Taylor, M.D., Sc.D.**, Genetic Epidemiology Branch. More information about the UGI Cancer Research Group is available at <http://dceg.cancer.gov/neb/research/ugcrg>. ■

—Christian C. Abnet, Ph.D., M.P.H.,
Neal D. Freedman, Ph.D., M.P.H.,
and members of the UGI Cancer
Research Group

NIH RECOGNIZES 2011 FARE WINNERS

Eight DCEG fellows have received the NIH Fellows Award for Research Excellence (FARE), which recognizes scientific research by intramural post-doctoral fellows and predoctoral fellows conducting their doctoral dissertation research at NIH. Fellows submit abstracts of their research, which are reviewed by a panel of NIH postdoctoral fellows and principal investigators. Winners receive a \$1,000 travel stipend to attend and present their work at a scientific meeting. This year's awardees, listed below along with the titles of their abstracts, represent five DCEG branches.

Carrie R. Daniel, Ph.D., M.P.H., Nutritional Epidemiology Branch (NEB): "Meat-cooking carcinogens and risk of renal cell carcinoma"

Yi-Ping Fu, Ph.D., Laboratory of Translational Genomics (LTG): "NOTCH2 in breast cancer: Association of SNP rs11249433 with gene expression in ER-positive breast tumors without TP53 mutations"

Ying Gao, M.D., Ph.D., M.P.H., Genetic Epidemiology Branch: "DNA repair gene polymorphisms and tobacco smoking and the risk of colorectal adenoma"

Stephanie M. George, Ph.D., M.P.H. (NEB): "Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer"

Sarah Nyante, Ph.D., Hormonal and Reproductive Epidemiology Branch (HREB): "TGF-beta pathway SNP association with TGF-beta receptor 2 expression and breast cancer risk"

Ju-Hyun Park, Ph.D., Biostatistics Branch: "Estimation of effect size distribution from genome-wide association studies and implications for future discoveries"

Wei Tang, Ph.D. (LTG): "Exploring molecular phenotypes of *JAZF1* genetic associations with several human diseases through siRNA studies and coexpression profiling"

Britton Trabert, Ph.D. (HREB): "Marijuana use and testicular germ cell tumors"

More information about the FARE competition is available at <http://felcom.od.nih.gov/subCommittee/fare.aspx>. ■

DCEG OUTSTANDING RESEARCH PAPERS OF 2009

Each year, DCEG recognizes fellows and staff scientists/clinicians for exceptional publications during the previous calendar year. The Division's Senior Advisory Group judges the competition based on the papers' impact, innovation, and clarity of thought and language.

Five postdoctoral fellows were selected for Outstanding Research Paper Awards in 2009:

Stella Koutros, Ph.D., Occupational and Environmental Epidemiology Branch (OEEB): "Heterocyclic aromatic amine pesticide use and human cancer risk: Results from the U.S. Agricultural Health Study," *International Journal of Cancer*

Tram Kim Lam, Ph.D., Genetic Epidemiology Branch (GEB): "Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk," *Carcinogenesis*

Idan Menashe, Ph.D., Biostatistics Branch: "Underlying causes of the black-white racial disparity in breast cancer mortality: A population-based analysis," *Journal of the National Cancer Institute*

Huei-Ting Tsai, Ph.D. (formerly of GEB): "Evidence of serum immunoglobulin abnormalities up to 9.8 years before diagnosis of chronic lymphocytic leukemia: A prospective study," *Blood*

Chu-Ling Yu, Sc.D., Radiation Epidemiology Branch: "Cause-specific mortality in long-term survivors of retinoblastoma," *Journal of the National Cancer Institute*

The winner in the staff scientist/clinician category was:

Dalsu A.N. Baris, M.D., Ph.D. (OEEB): "A case-control study of smoking and bladder cancer risk: Emergent patterns over time," *Journal of the National Cancer Institute*



Recipients of the 2009 Outstanding Research Paper Awards with Joseph Fraumeni: Tram Kim Lam, Idan Menashe, Stella Koutros, Dalsu Baris, Chu-Ling Yu, and Joseph Fraumeni. (Not shown: Huei-Ting Tsai.)

2010 DCEG SUMMER FELLOWS RECOGNITION AND POSTER EVENT

The 12th Annual DCEG Summer Fellows Recognition and Poster Event celebrated the accomplishments of 34 summer fellows, high school to doctoral students, who worked with 46 DCEG scientist-mentors on various research projects. The fellows were chosen from among 370 applicants. The event, organized by **Kristin Kiser, M.H.A., M.S.**, fellowship coordinator in DCEG's Office of Education (OE), and **Tess Lee**, OE program assistant, featured poster presentations by the summer fellows, giving them the opportunity to discuss their research projects with staff mentors across DCEG. Many of the students also presented their work at the NIH Summer Student Poster Session.



Summer fellows with event speakers and OE staff.

Joseph F. Fraumeni, Jr., M.D., DCEG Director, **Shelia Hoar Zahm, Sc.D.**, DCEG Deputy Director, and

Jackie Lavigne, Ph.D., M.P.H., Chief of OE, participated in the event as featured speakers, passing along their experience

2010 DCEG Summer Fellows Posters and Projects

Ida Ahmadizadeh, University of Michigan
Folate and bladder cancer risk in New England
Mentor: **Dalsu A.N. Baris, M.D., Ph.D.**, Occupational and Environmental Epidemiology Branch (OEEB)

Kristine Albanes, Bethesda-Chevy Chase High School
IGFs and melanoma risk
Mentors: **Barry I. Graubard, Ph.D.**, Biostatistics Branch (BB), and **Jacqueline Major, Ph.D.**, Nutritional Epidemiology Branch (NEB)

Matthew P. Banegas, University of Washington
Validation of the Gail model for U.S. Latinas
Mentors: **Mitchell H. Gail, M.D., Ph.D.**, and **Hormuzd A. Katki, Ph.D.** (both of BB)

Alexandra Berg, Williams College
Soft tissue cancers in the HIV/AIDS population
Mentor: **Eric A. Engels, M.D., M.P.H.**, Infections and Immunopidemiology Branch (IIB)

Peter Brauhöhler, Bowdoin College
Sequencing PRDM9 and RNF212 using SNP500 reference samples
Mentors: **Stephen J. Chanock, M.D.**, Chief of the Laboratory of Translational Genomics (LTG) and Director of the Core Genotyping Facility (CGF), and **Joseph Kovacs** (LTG)

Dianna Buckett, Claremont McKenna College
Relationship between single nucleotide polymorphisms of IL28B and natural clearance of hepatitis C virus
Mentors: **Thomas R. O'Brien, M.D., M.P.H.** (IIB), and **Ludmila Prokunina-Olsson, Ph.D.** (LTG)

Evan Caporaso, University of Maryland
Blunt end, hydroxylated amplicons: Optimizing NGS library preparation protocols
Mentors: **Joseph Boland** and **Amy Hutchinson, M.S.**, (both of CGF)

Tyrisha Clary, Georgetown University
Exploring the gene characterization of melanoma through co-expression analysis
Mentor: **Xiaohong Rose Yang, Ph.D., M.P.H.**, Genetic Epidemiology Branch (GEB)

Kim Dessoffy, Ohio University
Reasons for blocked genetic communications in hereditary breast and ovarian cancer families
Mentors: **Laura M. Koehly, Ph.D.**, National Human Genome Research Institute, NIH, and **June A. Peters, M.S., C.G.C.**, Clinical Genetics Branch (CGB)

Jason Douglas, Rush Medical College
Serum C-reactive protein and risk of pancreatic cancer in two nested, case-control studies
Mentor: **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB)

Robert Hagerty, Bethesda-Chevy Chase High School
Insulin-like growth factors and risk of stomach cancer
Mentors: **Demetrius Albanes, M.D.**, and **Jacqueline Major, Ph.D.** (both of NEB)

Nadia Hoekstra, Boston College
Exposure assessment for dietary and drinking water nitrate and nitrite in the New England Bladder Cancer Study
Mentors: **Briseis Kilfoy, Ph.D.**, and **Mary H. Ward, Ph.D.** (both of OEEB)

Lauren Hurwitz, Johns Hopkins University
VHL somatic inactivation and EPAS1 germline variation among clear cell renal cell carcinoma cases
Mentor: **Lee E. Moore, Ph.D.** (OEEB)

Rebecca Imran, University of Miami
A study on computed tomography image analysis of stomach variation
Mentor: **Choonsik Lee, Ph.D.**, Radiation Epidemiology Branch

Alpana Kaushiva, University of Maryland, Baltimore County
miRNA profiling in samples of normal and tumor bladder tissue and serum
Mentors: **Yi-Ping Fu, Ph.D.**, **Patricia Porter-Gill**, and **Ludmila Prokunina-Olsson, Ph.D.** (all of LTG)

Catherine Kennedy, Winston Churchill High School
Investigation of the regulatory potential of the chr5p15.33 pancreatic cancer GWAS locus
Mentor: **Laufey Amundadottir, Ph.D.** (LTG)

Christine Kiruthu, University of Maryland, Eastern Shore
25-hydroxyvitamin D and melanoma: A nested case-control study of middle-aged male smokers in Finland
Mentors: **Demetrius Albanes, M.D.**, and **Jacqueline Major, Ph.D.** (both of NEB)

Roslyn Lee, Thomas S. Wootton High School
Alterations of ROBO1 in esophageal squamous cell carcinoma (SCC) from a high-risk population in China
Mentors: **Nan Hu, M.D., Ph.D.**, and **Philip R. Taylor, M.D., Sc.D.** (both of GEB)

in cancer research and their vision for the future.

Students interested in applying for 2011 summer fellowships with DCEG are encouraged to learn more about the Division's research and to complete a short summary application at <http://dceg.cancer.gov/fellowships/summer-program>. Starting in mid-November, students may go to the NIH Summer Program web site (www.training.nih.gov/student/index.asp) to complete the full online application. ■

—Kristin Kiser, M.H.A., M.S.

Reflections from 2010 DCEG Summer Fellows

I have thoroughly enjoyed my summer experience at NCI. I had an excellent mentor who is very committed to training and possesses a contagious passion for his work. The training staff at DCEG have been welcoming, supportive, and very responsive to my needs. This summer has been an unforgettable and truly rewarding experience. —Anayansi Lombardero

I entered my fellowship with an expectation of gaining exposure to the intricate details of the research process, but I am leaving with much more than I anticipated. I received a solid, multifaceted foundation in scientific discovery that will be invaluable to my future career in medicine. —Andrew Para

NIH truly provides an outstanding opportunity for students to come and learn from the best scientists in the world. It has given me the chance to see what goes on inside NCI and to be involved in the common goal of cancer research. The DCEG staff provided a comfortable and productive learning environment where I felt right at home. —Crystal Speaks

Luyang Liu, Barnard College
Exploring the epigenetic regulation of JAZF1 expression in prostate cell lines through in vitro and in vivo DNA-protein interaction studies
Mentors: **Ludmila Prokunina-Olsson, Ph.D.**, and **Wei Tang, Ph.D.** (both of LTG)

Anayansi Lombardero, University of Montana
The tobacco industry's tactics to influence advertising regulations and target women and youth in Spain
Mentors: **Neil E. Caporaso, M.D.** (GEB), and **Mark Parascandola, Ph.D., M.P.H.**, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences

Paige Maas, Johns Hopkins University
Modeling racial heterogeneity in breast cancer incidence by multiple tumor characteristics
Mentors: **William F. Anderson, M.D., M.P.H.** (BB), **Nilanjan Chatterjee, Ph.D.** (Chief of BB), and **Samiran Sinha, Ph.D.**, Texas A&M University, Department of Statistics

Kishan Mistry, Richard Montgomery High School
TaqMan genotyping at CGF: Older technology still the gold standard in follow-up studies
Mentors: **Amy Hutchinson, M.S.**, and **Michelle Manning** (both of CGF)

Adam Mummy, Montgomery Community College
Association of bladder and gastric cancer risk variant Rs2294008 in PSCA with altered gene expression in human tissues
Mentors: **Indu Kohaar, Ph.D.**, and **Ludmila Prokunina-Olsson, Ph.D.** (both of LTG)

Natalia Orduz, University of Maryland, College Park
Genetic mapping of the UGT1A region associated with bladder cancer
Mentors: **Ludmila Prokunina-Olsson, Ph.D.**, and **Wei Tang, Ph.D.** (both of LTG)

Whitney Osborne, George Washington University, School of Public Health and Health Services
Body fat distribution and the risk of hypertension and diabetes in the India Health Study
Mentors: **Carrie R. Daniel, Ph.D., M.P.H.**, and **Rashmi Sinha, Ph.D.** (both of NEB)

Munkhzul Otgonsuren, Georgetown University
Accelerometer-measured physical activity in three regions of India
Mentors: **Charles E. Matthews, Ph.D.**, and **Steven C. Moore, Ph.D.** (both of NEB)

Andrew Para, Michigan State University
Effect of freezing conditions on bacterial enzyme activity in human fecal samples
Mentors: **Roberto Flores, Ph.D., M.P.H.**, and **James J. Goedert, M.D.** (both of IIB)

Kerry Pettigrew, Centre for Cancer Research and Cell Biology, Queens University Belfast, Northern Ireland
Fine-mapping of the KLK3 locus in prostate cancer
Mentor: **Laufey Amundadottir, Ph.D.** (LTG)

Helen Reed, University of California, Berkeley
Bone marrow findings in inherited bone marrow failure syndromes
Mentors: **Blanche P. Alter, M.D., M.P.H.**, and **Neelam Giri, M.D.** (both of CGB)

Aurielle Rowe, Hagerstown Community College
Enhancing sequence capture: Fluidigm® Access Array™ performance and optimizations
Mentor: **Joseph Boland** (CGF)

Jennifer Sloan, Denison University
Synthesis of epidemiologic results for selected pesticides
Mentor: **Laura Beane Freeman, Ph.D.** (OEEB)

Crystal Speaks, Tulane University School of Public Health
Age-period-cohort analysis of testicular cancer by histology and race
Mentors: **Michael B. Cook, Ph.D.**, and **Katherine A. McGlynn, Ph.D., M.P.H.**, both of the Hormonal and Reproductive Epidemiology Branch

Kathleen Tatem, St. Mary's College of Maryland
Attention deficit hyperactivity disorder and smoking in an adult Italian population
Mentor: **Neil E. Caporaso, M.D.** (GEB)

Daberechi Ukwuani, Colonel Zadok Magruder High School
Investigation of the regulatory potential of the chr1q32.1 pancreatic cancer GWAS locus
Mentor: **Laufey Amundadottir, Ph.D.** (LTG)

Xiaoru Wu, Columbia University
Goodness of fit test for the analysis of secondary phenotype in case-control association studies
Mentors: **Jing Qin, Ph.D.**, National Institute of Allergy and Infectious Diseases, Biostatistics Research Branch, Division of Clinical Research, and **Kai Yu, Ph.D.** (BB)

DCEG INVESTIGATORS PARTICIPATE IN PAPILLOMAVIRUS CONFERENCE

The 26th International Papillomavirus Conference was held in July in Montreal, Quebec, Canada. This five-day event, including the annual Clinical Workshop and Public Health Workshop, brought together research scientists, clinicians, epidemiologists, and public health workers to discuss and foster integrative research to improve understanding of the biology, natural history, diagnosis, and treatment of human papillomavirus (HPV)-related cervical cancer. Several DCEG investigators participated in the event by chairing workshops, leading panel discussions, and giving oral or poster presentations.

Philip E. Castle, Ph.D., M.P.H., Hormonal and Reproductive Epidemiology Branch (HREB), cochaired and provided a summary for the workshop on cervical intraepithelial neoplasia grade 2 (CIN 2). He also spoke on

“HPV testing for the triage of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL): Principles and results” and provided closing comments for the session “The comprehensive value of HPV tests in prevention and management.” In addition, he presented “A risk-based model for integrating new technologies, including HPV vaccination and new biomarkers, into cervical cancer prevention programs.” Finally, Dr. Castle gave a plenary talk titled “New molecular markers for cervical cancer screening: Distinguishing hype from hope.”

Nicolas Wentzensen, M.D., Ph.D., M.S. (HREB), cochaired and provided closing remarks for the workshop “Use of molecular markers potentially usable for cervical cancer screening or triage of screen-positive women: The template of

p16.” During the workshop, he presented “Evaluation of *p16* immunostaining approaches toward standardization” with **Diane Solomon, M.D.**, an adjunct investigator in HREB. Dr. Wentzensen also discussed “Biomarkers for triaging CIN 2” during the CIN 2 workshop “Impact of performing multiple biopsies on the detection of precancer in the NCI Oklahoma University Health Sciences Center (OUHSC) Biopsy Study” and gave a poster presentation titled “A competitive serology assay shows protection against HPV infection by natural titers in the Guanacaste Natural History Study.”

Drs. Castle and Wentzensen co-lead a workshop with **Mark Schiffman, M.D., M.P.H.**, Clinical Genetics Branch (CGB), titled “Young researchers’ community of practice: How to manage a research team.”

DCEG STAFF WIN PLAIN LANGUAGE AWARDS

Several DCEG staff members were recognized with “gold awards” at the annual NIH Plain Language Awards ceremony in May.

The Agricultural Health Study (AHS) Executive Committee, including Occupational and Environmental Epidemiology Branch investigators **Michael C.R. Alavanja, Dr.P.H.**, and **Laura Beane Freeman, Ph.D.**, the AHS field station staff in North Carolina and Iowa, and the AHS Coordinating Center were recognized along with Rhonda DeJoyce from the NCI Office of Communications and Education (OCE) and **Jennifer Loukissas, M.P.P.**, Office of Communications and Special Initiatives (OCSI), for the publication *The Agricultural Health Study Update 2009*.

In addition, **Joseph F. Fraumeni, Jr., M.D.**, DCEG Director, **Kristin Kiser, M.H.A., M.S.**,

Office of Education (OE), **Jackie Lavigne, Ph.D., M.P.H.**, Chief of OE, **Wendy Schneider-Levinson (OCSI, formerly of OCE)**, and the OE Advisory Group won for the bookmark brochure titled *Challenge Yourself: Be an NCI Fellow!*

Plain language avoids both jargon and highly technical language, includes only necessary details, and engages the reader through the use of active voice; short sentences and paragraphs; and easy-to-understand tables, lists, and other design features.

These awards are part of an NIH-wide initiative to promote the use of plain language in all materials created for the public or within government. Criteria for the award include how clearly the material answers users’ questions and whether the language is appropriate for the intended audience.

Plain language avoids both jargon and highly technical language, includes only necessary details, and engages the reader through the use of active voice; short sentences and paragraphs; and easy-to-understand tables, lists, and other design features.

For more information about the NIH Plain Language Initiative, visit: <http://execsec.od.nih.gov/plainlang>.

Additional presentations included **Rolando Herrero**, Infections and Immunoepidemiology Branch (IIB), “Efficacy of a bivalent HPV 16/18 vaccine for the prevention of 1-year HPV persistence by age group and sexual history: Randomized trial in Guanacaste, Costa Rica”; **Allan Hildesheim, Ph.D.**, Chief of IIB, on “Additional data needed for a systematic review on efficacy of prophylactic HPV vaccination”; **Hormuzd A. Katki, Ph.D.**, Biostatistics Branch, on “Risk of cervical precancer or cancer in 330,790 women undergoing co-testing with HPV testing and Pap smears” and a poster on “Clinical management guidelines based on risk of cervical precancer or cancer”; **Troy Kemp, Ph.D.** (IIB), on “HPV 16/18 L1 virus-like particle (VLP) vaccine induces cross-neutralizing antibodies that may mediate cross-protection”; **Aimee Kreimer, Ph.D.** (IIB), on “Oral HPV persistence at 6 and 12 months among healthy men: The HPV in Men (HIM) Study” and “Proof of principle: Efficacy of fewer than 3 doses of a bivalent HPV 16/18 vaccine against incident persistent HPV infection in Guanacaste, Costa Rica”; **Carolina Porras, M.Sc.** (IIB), on “Switch from cytology-based to HPV-based cervical screening: Implications for colposcopy” and a poster on “The percentage and severity of cytologic abnormalities vary by HPV genotype: A population-wide analysis”; **Mahboobeh Safaeian, Ph.D.** (IIB), on “Epidemiologic study of anti-HPV 16/18 seropositivity and subsequent risk of HPV 16 and 18 infections”; and Dr. Schiffman on “Absolute risks of CIN and cancer in a 16-year prospective study of type-specific HPV infection” and “HPV: Natural history of the infection from the epidemiological and clinical perspective.”

Other DCEG poster presentations included **Anil K. Chaturvedi, Ph.D.** (IIB), on “Oral and anal HPV infection among HIV-infected men and women,” “International trends in incidence for HPV-related head and neck cancer sites,” and “Estimated population-level burden of HPV-positive oropharynx cancers among smokers and never smokers in the United States”; **Sarah Coseo** (IIB) on “Longitudinal analysis of type-specific HPV infection, viral load, and cytologic abnormality in the Guanacaste Cohort” and “Seroprevalence and determinants of HPV 16/18 seropositivity among women in Costa Rica”; **Joseph Dauner, Ph.D.**, Laboratory of Translational Genomics, on “The relationship between memory B cells and systemic antibodies after HPV VLP vaccination”; **Julia C. Gage, Ph.D., M.P.H.** (CGB), on “High prevalence of

carcinogenic HPV among older women in Nigeria: Can we still screen with HPV testing?”; **Ligia A. Pinto, Ph.D.** (IIB), on “Development of a GuHCl-modified ELISA for measuring the avidity of anti-HPV VLP antibodies” and “The relationship between memory B cells and systemic antibodies after HPV VLP vaccination”; **Lauren Wilson, Sc.M.** (HREB), on “Analysis of HPV genotype patterns in the ASCUS/LSIL Triage Study (ALTS) for cervical cancer using unsupervised hierarchical clustering”; and **Hannah P. Yang, Ph.D., Sc.M.** (HREB), on “Determinants of multiple lesions and lesion size in a large series of loop electrosurgical excision procedures (LEEPs).” ■

—Cherie M. Vitartas, M.P.H.

DCEG FELLOWS PRESENT AT THE 2010 NIH SPRING RESEARCH FESTIVAL

Four DCEG postbaccalaureate fellows and one postdoctoral fellow presented posters as part of the 2010 Spring Research Festival, which took place in May. This two-day event was sponsored by the NIH Office of Intramural Training and Education. The NIH-wide festival included poster presentations by 260 postbaccalaureate fellows as well as fellows in the Clinical Research Training Program, the Howard Hughes Medical Institute-NIH Research Scholars Program, and the NIH Undergraduate Scholarship Program.

DCEG posters for the 2010 Spring Research Festival were as follows:

Functional analysis of risk variants in the NR5A2 gene associated with pancreatic cancer susceptibility

Leonard Addae, Laboratory of Translational Genomics (LTG)

Mentor: **Laufey Amundadottir, Ph.D.**

Personal and family history of depression and risk of lung cancer

David E. Capo-Ramos, M.D., M.P.H., Genetic Epidemiology Branch

Mentor: **Maria Teresa Landi, M.D., Ph.D.**

SNP analysis of NCF4 exons in patients with inflammatory bowel disease

Joseph Kovacs (LTG)

Mentor: **Stephen J. Chanock, M.D.**

The genomic and functional characterization of pancreatic cancer risk variants in the ABO gene

Stephanie Shao (LTG)

Mentor: **Laufey Amundadottir, Ph.D.**

Analysis of JAZF1 function through mRNA expression assays and siRNA studies

McAnthony D. Tarway (LTG)

Mentor: **Ludmila Prokunina-Olsson, Ph.D.**

SCIENTIFIC HIGHLIGHTS

GENETICS

Estimating Penetrance Using Family Data

The authors propose a formal statistical inference framework for the evaluation of the penetrance of a rare genetic mutation using family data generated under a kin-cohort design, where phenotype and genotype information from first-degree relatives (siblings and/or offspring) of case probands carrying the targeted mutation is collected. The approach is built upon a likelihood model with some minor assumptions, and it can be used for age-dependent penetrance estimation that permits adjustment for covariates. Furthermore, the derived likelihood allows unobserved risk factors that are correlated among family members. The validity of the approach is confirmed by simulation studies. The approach is applied to estimating the age-dependent cancer risk among carriers of the *MSH2* or *MLH1* mutation. (Zhang H, Olschwang S, Yu K. Statistical inference on the penetrances of rare genetic mutations based on a case-family design. *Biostatistics* 2010;11:519–532)

Estimating Susceptibility Loci Effects

The authors present a set of tools for estimating the number of susceptibility loci and the distribution of their effect sizes for a trait on the basis of discoveries from existing genome-wide association studies (GWAS). They propose statistical power calculations for future GWAS using estimated distributions of effect sizes. Using reported GWAS findings for height, Crohn disease, and breast, prostate, and colorectal cancers, they determine that each of these traits is likely to harbor additional loci within the spectrum of low-penetrance common variants. These loci, which can be identified from sufficiently powerful

GWAS, together could explain at least 15% to 20% of the known heritability of these traits. However, for breast, prostate, and colorectal cancers, which have modest familial aggregation, this analysis suggests that risk models based on common variants alone will have modest discriminatory power (63.5% area under the curve), even with new discoveries. (Park JH, Wacholder S, Gail MH, Peters U, Jacobs KB, Chanock SJ, Chatterjee N. Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nat Genet* 2010;42:570–575)

Evaluating Rare Polymorphisms

Most current genetic association studies look for single-nucleotide polymorphisms (SNPs) with a relatively large minor allele frequency (MAF) (e.g., > 5%) in the search for genetic loci that underlie a susceptibility for complex diseases. Growing evidence from recent empirical data and simulations suggests that the causal genetic polymorphisms, including SNPs and copy number variants (CNVs), for common diseases have a wide spectrum of MAFs, ranging from rare to common. Unlike the analysis for common genetic variants, statistical approaches for the analysis of rare variants receive very little attention. The authors propose two novel approaches for the analysis of rare genetic variants. Simulation studies and two real examples demonstrate the advantages of the proposed methods over existing methods. (Li Q, Zhang H, Yu K. Approaches for evaluating rare polymorphisms in genetic association studies. *Hum Hered* 2010;69:219–228)

Genetic Pathway Analysis

The authors applied a pathway-based approach to a GWAS of 1,145 breast cancer cases and 1,142 controls. Pathways were retrieved from three databases:

KEGG, BioCarta, and NCI Protein Interaction Database. Genes were represented by their most strongly associated SNP, and an enrichment score (ES) reflecting the overrepresentation of gene-based association signals in each pathway was calculated. Finally, hierarchical clustering was used to identify pathways with overlapping genes, and clusters with an excess of association signals were determined by the adaptive rank-truncated product (ARTP) method. A total of 421 pathways containing 3,962 genes were included in this study. Of these, three pathways (syndecan-1-mediated signaling, signaling of hepatocyte growth factor receptor, and growth hormone signaling) were highly enriched with association signals ($p_{ES} < 0.001$, false discovery rate [FDR] = 0.118). Clustering analysis revealed that pathways containing key components of the RAS/RAF/mitogen-activated protein kinase canonical signaling cascade were significantly more likely to have an excess of association signals than would be expected by chance ($p_{ARTP} = 0.0051$, FDR = 0.07). (Menashe I, Maeder D, Garcia-Closas M, Figueroa JD, Bhattacharjee S, Rotunno M, Kraft P, Hunter DJ, Chanock SJ, Rosenberg PS, Chatterjee N. Pathway analysis of breast cancer genome-wide association study highlights three pathways and one canonical signaling cascade. *Cancer Res* 2010;70:4453–4459)

LIVER CANCER

Meat and Fat Intake

The authors prospectively examined the relationship of consumption of meat and associated exposures with chronic liver disease (CLD) mortality ($n = 551$) and hepatocellular cancer (HCC) incidence ($n = 338$) among 495,006 men and women participating in the NIH-AARP Diet and Health Study. Inverse associations were found between white meat

and risk of CLD (hazard ratio [HR] for fifth vs. first quintile = 0.52) and HCC (HR = 0.52). Consumption of red meat was associated with higher risk of CLD (HR = 2.59) and HCC (HR = 1.74). Among types of fat, results were strongest for saturated fat (for CLD, HR = 3.50; for HCC, HR = 1.87). After mutual adjustment, risk estimates persisted for saturated fat, red meat, and white meat. Heme iron, processed meat, nitrate, and nitrite were positively associated with CLD but not with HCC. The results suggest that consumption of red meat and saturated fat may be associated with increased CLD and HCC risk, whereas eating white meat may be associated with reduced risk. (Freedman ND, Cross AJ, McGlynn KA, Abnet CC, Park Y, Hollenbeck AR, Schatzkin A, Everhart JE, Sinha R. Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP Cohort. *J Natl Cancer Inst* 2010; 102(17):1354–1365)

LUNG CANCER

Beta-carotene Supplementation and Markers of Risk

To elucidate the molecular mechanisms that might underlie the adverse effects of supplemental beta-carotene on lung cancer incidence among cigarette smokers, the authors studied the immunohistochemical expression of cytochrome P450 1A1, 1A2, and 2E1; retinoic acid receptor beta; activated protein-1 elements; cyclin D1; and Ki67 in lung tumors and, when available, adjacent normal tissues obtained from incident cases in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. Archival lung tissue was available from 52 men randomized to receive 20 mg of beta-carotene per day and 30 men randomized to the placebo arm, all of whom were diagnosed with incident non-small cell lung carcinoma during the course of the trial. In normal-appearing bronchial epithelium,

positive staining for cyclin D1 was observed in 23% of cases in the beta-carotene group and 0% of cases in the placebo group ($p = 0.04$), with no differences in expression noted in lung tumor tissue ($p = 0.48$). No significant differences were found in Ki67 expression

in normal or cancerous lung tissue between intervention groups, although a small increase in staining in tumors was noted among cases in the beta-carotene vs. placebo group (88% vs. 71% of cases stained positive, respectively; $p = 0.13$). Contrary to expectation, beta-carotene

MAJOR EDITORIALS, COMMENTARIES, AND REVIEWS BY DCEG SCIENTISTS

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Zhang L, Beane Freeman LE, et al. Formaldehyde and leukemia: Epidemiology, potential mechanisms, and implications for risk assessment. *Environ Mol Mutagen* 2010;51:181–191

Berrington de González A. Sample-size efficiencies via the multiple-primary cancer study: Why fewer cases may not mean less work. *Epidemiology* 2010;21:373–375

Castle PE. Screening: HPV testing for cervical cancer: The good, the bad, and the ugly. *Nat Rev Clin Oncol* 2010;7:364–365

Castle PE, Katki HA. Benefits and risks of HPV testing in cervical cancer screening. *Lancet Oncol* 2010;11:214–215

Kinney W, Stoler MH, Castle PE. Special commentary: Patient safety and the next generation of HPV DNA tests. *Am J Clin Pathol* 2010;134:193–199

Hunter DJ, Chanock SJ. Genome-wide association studies and “the art of the soluble.” *J Natl Cancer Inst* 2010;102:836–837

Chow WH, Dong LM, et al. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010;7:245–257

Gail MH, Mai PL. Comparing breast cancer risk assessment models. *J Natl Cancer Inst* 2010;102:665–668

Goldin LR, Slager SL, Caporaso NE. Familial chronic lymphocytic leukemia. *Curr Opin Hematol* 2010;17:350–355

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Brownson RC, Hartge P, et al. From epidemiology to policy: Toward more effective practice. *Ann Epidemiol* 2010;20:409–411

Lubin JH, et al. Body mass index, cigarette smoking, and alcohol consumption and cancers of the oral cavity, pharynx, and larynx: Modeling odds ratios in pooled case-control data. *Am J Epidemiol* 2010;171:1250–1261

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Prokunina-Olsson L, Chanock SJ. Cancer sequencing gets a little more personal. *Sci Transl Med* 2010;2:20ps8

Zhang L, McHale CM, Rothman N, Chanock SJ, et al. Systems biology of human benzene exposure. *Chem Biol Interact* 2010;184:86–93

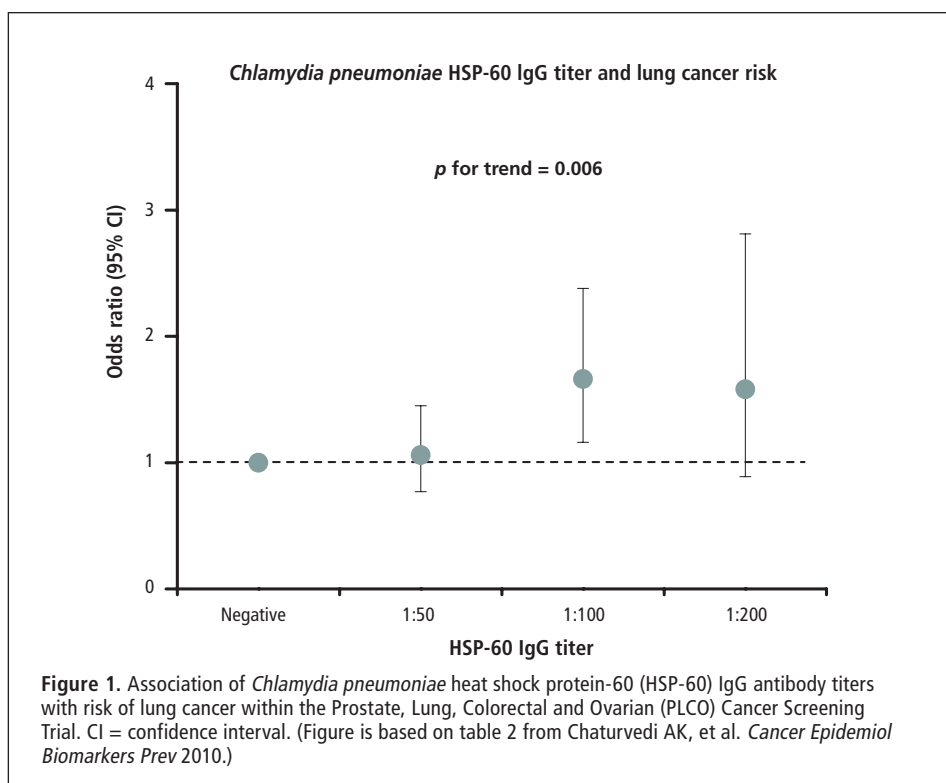
Schiffman M, Wentzensen N. From human papillomavirus to cervical cancer. *Obstet Gynecol* 2010;116:177–185

Colditz GA, Taylor PR. Prevention trials: Their place in how we understand the value of prevention strategies. *Annu Rev Public Health* 2010;31:105–120

supplementation had no apparent effect on retinoic acid receptor-beta expression. These findings suggest that male smokers supplemented with beta-carotene may have had an increased risk of lung cancer due to aberrant cell growth. (Wright ME, Groshong SD, Husgafvel-Pursiainen K, Genova E, Lucia MS, Wolff H, Virtamo J, Albanes D. Effects of beta-carotene supplementation on molecular markers of lung carcinogenesis in male smokers. *Cancer Prev Res [Phila]* 2010;3:745–752)

Chlamydia Pneumoniae

The authors evaluated the relationship of *Chlamydia pneumoniae* infection with prospective risk of lung cancer using traditional serologic markers and *Chlamydia* heat shock protein-60 (CHSP-60) antibodies, a marker for chronic chlamydial infection, in a case-control study of 593 lung cancers and 671 controls nested within the screening arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *C. pneumoniae* seropositivity by microimmunofluorescence IgG or IgA antibodies was not associated with lung cancer. In contrast, individuals seropositive for CHSP-60 IgG antibodies had increased risk of lung cancer (odds ratio [OR] = 1.30), and risk increased with increasing antibody titers (p for trend = 0.006) (see Figure 1). CHSP-60-related risk did not differ significantly by lung cancer histology, follow-up time, or smoking. CHSP-60 seropositivity was associated with increased risk two to five years before lung cancer diagnosis (OR = 1.77; p for trend = 0.006), arguing against reverse causality. Results suggest the potential for reducing lung cancer risk through treatments targeted toward *C. pneumoniae* infections and chronic pulmonary inflammation. (Chaturvedi AK, Gaydos CA, Agreda P, Holden JP, Chatterjee N, Goedert JJ, Caporaso NE, Engels EA. *Chlamydia pneumoniae* infection and risk for lung cancer. *Cancer Epidemiol Biomarkers Prev* 2010;19:1498–1505)



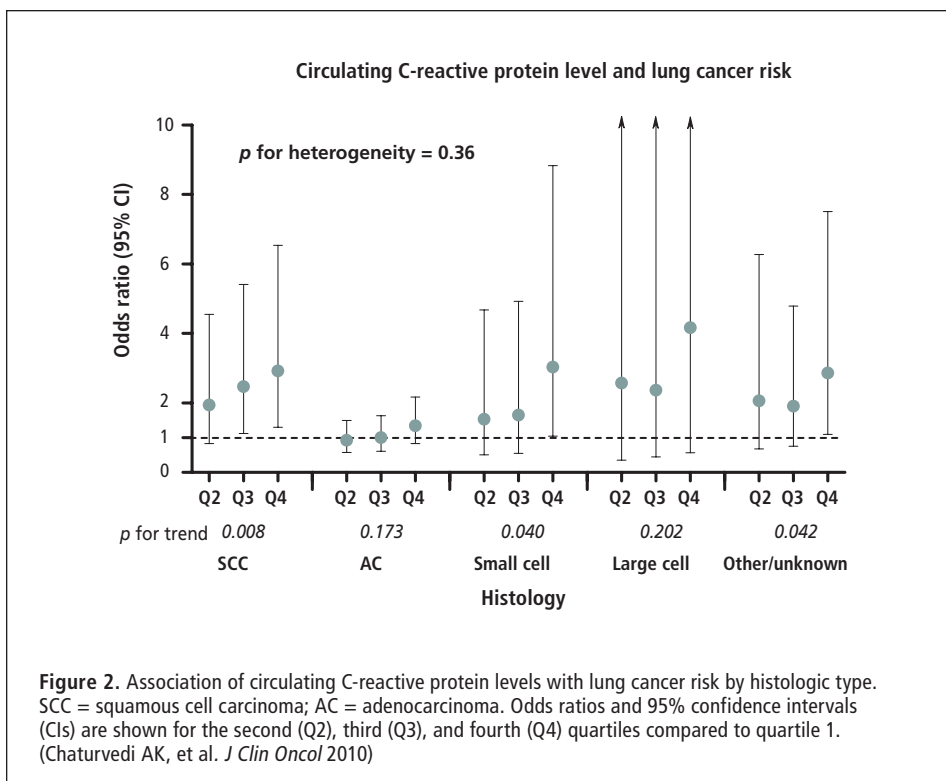
C-reactive Protein

Researchers investigated the role of circulating high-sensitivity C-reactive protein (CRP), an inflammation biomarker, and five common CRP SNPs in a study of 592 lung cancer patients and 670 controls with available prediagnostic serum and 378 patients and 447 controls with DNA within the PLCO Cancer Screening Trial. Elevated baseline CRP levels were associated with increased lung cancer risk (OR = 1.98 for fourth quartile [Q4, ≥ 5.6 mg/L] vs. Q1 [< 1.0 mg/L]). The association did not differ significantly by histology, follow-up time, or smoking status, but was most apparent for squamous cell carcinomas (SCC) (OR = 2.92) (see Figure 2), for the period two to five years before lung cancer diagnosis (OR = 2.33), and among former smokers (OR = 2.48) and current smokers (OR = 1.90). Although CRP SNPs and haplotypes were associated with CRP levels, they were not associated with lung cancer risk. Ten-year standardized absolute risks of lung cancer were higher

with elevated CRP levels among former smokers (Q4 [2.55%] vs. Q1 [1.39%]) and current smokers (Q4 [7.37%] vs. Q1 [4.03%]). Results suggest an etiologic role for chronic pulmonary inflammation in lung carcinogenesis. (Chaturvedi AK, Caporaso NE, Katki HA, Wong HL, Chatterjee N, Pine SR, Chanock SJ, Goedert JJ, Engels EA. C-reactive protein and risk of lung cancer. *J Clin Oncol* 2010;28:2719–2726)

5p15.33 Locus and Adenocarcinoma

GWAS of lung cancer reported in populations of European background have identified three regions on chromosomes 5p15.33, 6p21.33, and 15q25 that have achieved genome-wide significance. These studies have been performed primarily in cigarette smokers, raising the possibility that the observed associations could be related to tobacco use, lung carcinogenesis, or both. The authors conducted a GWAS of lung adenocarcinoma in never-smoking females (584 cases and 585 controls) among Han Chinese in Taiwan and found that the most significant association was for



rs2736100 on chromosome 5p15.33 ($p = 1.30 \times 10^{-11}$). This finding was replicated independently in seven studies from East Asia totaling 1,164 lung adenocarcinomas and 1,736 controls ($p = 5.38 \times 10^{-11}$). A pooled analysis achieved genome-wide significance for rs2736100. This SNP marker localizes to the *CLPTMIL-TERT* locus on chromosome 5p15.33 ($p = 2.60 \times 10^{-20}$, allelic risk = 1.54). Risks for heterozygote and homozygote carriers of the minor allele were 1.62 and 2.35, respectively. In summary, results show that genetic variation in the *CLPTMIL-TERT* locus of chromosome 5p15.33 is directly associated with the risk of lung cancer, most notably adenocarcinoma. (Hsiung CA, Lan Q, Hong YC, Chen CJ, Hosgood HD, Chang IS, Chatterjee N, Brennan P, Wu C, Zheng W, Chang GC, Wu T, Park JY, Hsiao CF, Kim YH, Shen H, Seow A, Yeager M, Tsai YH, Kim YT, Chow WH, Guo H, Wang WC, Sung SW, Hu Z, Chen KY, Kim JH, Chen Y, Huang L, Lee KM, Lo YL, Gao YT, Kim JH, Liu L, Huang MS, Jung TH, Jin G, Caporaso N, Yu D, Kim CH, Su WC, Shu XO, Xu P, Kim IS, Chen YM, Ma H, Shen M, Cha SI, Tan

W, Chang CH, Sung JS, Zhang M, Yang TY, Park KH, Yuenger J, Wang CL, Ryu JS, Xiang Y, Deng Q, Hutchinson A, Kim JS, Cai Q, Landi MT, Yu CJ, Park JY, Tucker M, Hung JY, Lin CC, Perng RP, Boffetta P, Chen CY, Chen KC, Yang SY, Hu CY, Chang CK, Fraumeni JF Jr, Chanock S, Yang PC, Rothman N, Lin D. The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. *PLoS Genet* 2010;6:e1001051)

LYMPHOHEMATOPOIETIC MALIGNANCIES

Hepatitis B Virus

The authors assessed the association between chronic hepatitis B virus (HBV) infection and subsequent development of non-Hodgkin lymphoma (NHL) among 603,585 subjects who enrolled in the Korean Cancer Prevention Study during 1992–1995 and who had baseline data for serum hepatitis B surface antigen (HBsAg) status. Nine percent of the participants tested positive for HBsAg at baseline, which was regarded as evidence of chronic HBV

infection. During follow-up through 2006, 133 HBsAg-positive and 905 HBsAg-negative individuals developed NHL (HR = 1.74). In adjusted analyses, HBsAg positivity was associated with increased risk of diffuse large B-cell lymphoma (HR = 2.01) and other or unknown subtypes (HR = 1.65), compared with HBsAg negativity. Increased risk also was recorded for malignant immunoproliferation (HR = 3.79). These results suggest that chronic HBV infection promotes lymphomagenesis. (Engels EA, Cho ER, Jee SH. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: A cohort study. *Lancet Oncol* 2010; 11(9):827–834)

Human Leukocyte Antigen Class I and II Alleles

To complement GWAS and candidate gene studies implicating different genetic variants within the 6p21 chromosomal region with NHL subtypes, the authors conducted human leukocyte antigen (*HLA*) class I and II genotyping among 610 NHL cases and 555 controls. Significant associations included *HLA-DRB1*0101* for follicular lymphoma (OR = 2.14), *HLA-DRB1*0401* for diffuse large B-cell lymphoma (DLBCL; OR = 0.45), and *HLA-DRB1*13* and follicular lymphoma (OR = 0.48). The authors also observed significant heterozygote advantage for *HLA* class I alleles and NHL, particularly DLBCL. (Wang SS, Abdou AM, Morton LM, Thomas R, Cerhan JR, Gao X, Cozen W, Rothman N, Davis S, Severson RK, Bernstein L, Hartge P, Carrington M. Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology. *Blood* 2010;115:4820–4823)

PANCREATIC CANCER

Carbohydrates and Glycemic Load

The authors investigated the associations of glycemic load, glycemic index, and carbohydrate intake with pancreatic cancer risk in the PLCO Cancer

Screening Trial. Between 1998 and 2006 (median follow-up = 6.5 years), 266 incident, confirmed pancreatic cancers were identified among 109,175 participants. HRs and confidence intervals (CIs) were adjusted for sex, smoking, body mass index (BMI), and total energy. Overall, elevated risks for pancreatic cancer were observed in the 90th versus 10th percentile of glycemic load (HR = 1.45), available carbohydrate (HR = 1.47), and sucrose intake (HR = 1.37, CI = 0.99–1.89). The positive association for available carbohydrate intake was observed during the first four years of follow-up (HR_{<2 years} = 2.60, HR_{2 to <4 years} = 1.94) but not subsequently (HR = 0.86, CI = 0.52–1.44); the opposite pattern was observed for total fat and saturated fat intake. Rather than being causal, the short-term increase in risk of pancreatic cancer associated with high available carbohydrate and low fat intake may be capturing dietary changes associated with subclinical disease. (Meinhold CL, Dodd KW, Jiao L, Flood A, Shikany JM, Genkinger JM, Hayes RB, Stolzenberg-Solomon RZ. Available carbohydrates, glycemic load, and pancreatic cancer: Is there a link? *Am J Epidemiol* 2010;171:1174–1182)

PROSTATE CANCER

Refining the *JAZF1* Association

In the two-stage Cancer Genetic Markers of Susceptibility (CGEMS) prostate cancer scan, rs10486567, an SNP located within intron 2 of the *JAZF1* gene on chromosome 7p15.2, showed a promising association with prostate cancer overall ($p = 2.14 \times 10^{-6}$), with a suggestion of stronger association with aggressive disease ($p = 1.2 \times 10^{-7}$). In the third stage of GWAS, the authors genotyped 106 *JAZF1* SNPs in 10,286 prostate cancer cases and 9,135 controls of European ancestry. The strongest association was observed with the initial marker rs10486567, which achieved genome-wide significance

($p = 7.79 \times 10^{-11}$; OR_{HET} [OR heterozygous] = 1.19; OR_{HOM} [OR homozygous] = 1.37). The authors did not confirm a previous suggestion of a stronger association of rs10486567 with aggressive disease (in the present study, $p = 1.60 \times 10^{-4}$ for aggressive cancer, $n = 4,597$; $p = 3.25 \times 10^{-8}$ for nonaggressive cancer, $n = 4,514$). Based on a multilocus model with adjustment for rs10486567, no additional independent signals were observed at chromosome 7p15.2. There was no association between risk of prostate cancer and SNPs in *JAZF1* previously associated with height (rs849140), body stature (rs849141, tagged by rs849136), and risk of type 2 diabetes and systemic lupus erythematosus (rs864745, tagged by rs849142). rs10486567 remains the most significant marker for risk of prostate cancer within *JAZF1* in individuals of European ancestry. The authors suggest that future studies identify all variants in high linkage disequilibrium with rs10486567 and evaluate their functional significance for prostate cancer. (Prokunina-Olsson L, Fu YP, Tang W, Jacobs KB, Hayes RB, Kraft P, Berndt SI, Wacholder S, Yu K, Hutchinson A, Spencer Feigelson H, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Schumacher FR, CANCEL-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Haiman CA, Henderson BE, Kolonel L, Le Marchand L, Siddiq A, Riboli E, Travis R, Kaaks R, Isaacs WB, Isaacs SD, Grönberg H, Wiklund F, Xu J, Vatten LJ, Hveem K, Kumle M, Tucker M, Hoover RN, Fraumeni JF Jr, Hunter DJ, Thomas G, Chatterjee N, Chanock SJ, Yeager M. Refining the prostate cancer genetic association within the *JAZF1* gene on chromosome 7p15.2. *Cancer Epidemiol Biomarkers Prev* 2010;19:1349–1355)

RENAL CANCER

Blood Pressure Gene Variants

Researchers examined the risk of renal cell carcinoma (RCC) in relation to 142 SNPs in eight genes having a role in blood pressure control among 777 cases

and 1,035 controls in a multicenter, hospital-based study in Central Europe. Of the eight genes examined, *AGT* (angiotensinogen) was the most strongly associated with RCC (minimum p per a permutation test = 0.02). Of the 17 *AGT* tagging SNPs considered, associations were strongest for rs1326889 (OR = 1.35) and rs2493137 (OR = 1.31), which are both located in the promoter region. The *AGT* SNPs were statistically significant among participants with hypertension or a high BMI (≥ 25 kg/m²) but not among subjects without hypertension and with a normal BMI (< 25). Also, haplotypes with risk-conferring alleles of markers located in the promoter and intron 1 regions of *AGT* were significantly associated with RCC compared with the common haplotype in subjects with hypertension or high BMI (global $p = 0.003$). The findings suggest that common genetic variants of *AGT*, particularly those in the promoter region, increase RCC risk among subjects who are hypertensive or overweight. (Andreotti G, Boffetta P, Rosenberg PS, Berndt SI, Karami S, Menashe I, Yeager M, Chanock SJ, Zaridze D, Matteev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Rothman N, Brennan P, Chow WH, Moore LE. Variants in blood pressure genes and the risk of renal cell carcinoma. *Carcinogenesis* 2010;31:614–620)

Trichloroethylene and Metabolism Gene Variants

Trichloroethylene (TCE) is a suspected renal carcinogen. TCE-associated renal genotoxicity occurs predominantly through glutathione S-transferase (GST) conjugation and bioactivation by renal cysteine beta-lyase (*CCBL1*). In a case-control study in Central Europe (1,097 cases and 1,476 controls), increased risk was observed among subjects ever occupationally exposed to TCE (OR = 1.63), with significant exposure-response trends (below median intensity, OR = 1.38; CI = 0.81–2.35; above median

intensity: OR = 2.34; $p_{\text{trend}} = 0.02$). A significant association was found among TCE-exposed subjects with at least one intact *GSTT1* allele (active genotype; OR = 1.88) but not among subjects with two deleted alleles (null genotype; OR = 0.93; CI = 0.35–2.44; $p_{\text{interaction}} = 0.18$). Similar associations for all exposure metrics including average intensity were observed among *GSTT1*-active subjects but not among *GSTT1* nulls. Further evidence of heterogeneity was seen among TCE-exposed subjects with ≥ 1 minor allele of several *CCBL1*-tagging SNPs: rs2293968, rs2280841, rs2259043, and rs941960. These findings provide the strongest evidence to date that TCE exposure is associated with increased renal cancer risk, particularly among individuals carrying polymorphisms in genes that are important in the reductive metabolism of this chemical. (Moore LE, Boffetta P, Karami S, Brennan P, Stewart PS, Hung R, Zaridze D, Matveev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Gromiec J, Holcatova I, Merino M, Chanock S, Chow WH, Rothman N. Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants. *Cancer Res* 2010;70:6527–6536)

TESTICULAR CANCER

Epigenetic Mechanisms

Although there is a clear familial component to testicular germ cell tumors, no high-penetrance susceptibility gene has been identified. Epigenetic aberrations inherited through the germ line represent an alternative mechanism for cancer susceptibility. The authors performed a study of global methylation at long interspersed nuclear elements-1 (LINE-1) in peripheral blood DNA isolated from 466 family members of 101 multiple-case testicular cancer families. Investigating the correlation of LINE-1 methylation levels among parent-child pairs independent of affection status

($n = 355$) revealed a strong positive association only between mother-daughter ($r = 0.48, p < 0.001$) and father-daughter pairs ($r = 0.31, p = 0.02$), suggesting sex-specific inheritance of methylation. When cancer status was incorporated, a strong correlation in LINE-1 methylation levels was seen only among affected father-son pairs ($r = 0.49, p = 0.03$). In addition, there was a marginally significant inverse association between lower LINE-1 methylation levels and increased risk in a comparison with healthy male relatives ($p = 0.049$). The strong correlation between LINE-1 methylation levels among affected father-son pairs suggests that transgenerational inheritance of an epigenetic event may be associated with testicular cancer susceptibility. (Mirabello L, Savage SA, Korde L, Gadalla SM, Greene MH. LINE-1 methylation is inherited in familial testicular cancer kindreds. *BMC Med Genet* 2010;11:77)

THYROID CANCER

Nitrate Intake

The authors investigated the association of nitrate intake from public water supplies and diet with the risks of thyroid cancer and self-reported hypothyroidism and hyperthyroidism among a cohort of 21,977 women in Iowa who were enrolled in 1986 and had used the same water supply for more than 10 years. Nitrate ingestion from drinking water was estimated using a public database of nitrate measurements, and dietary nitrate intake was estimated using a food frequency questionnaire and levels from the published literature. Cancer incidence was determined through 2004. The authors found an increased risk of thyroid cancer with higher average nitrate levels in public water supplies and with longer consumption of water exceeding 5 mg/L nitrate-N (for five or more years at more than 5 mg/L, the relative risk

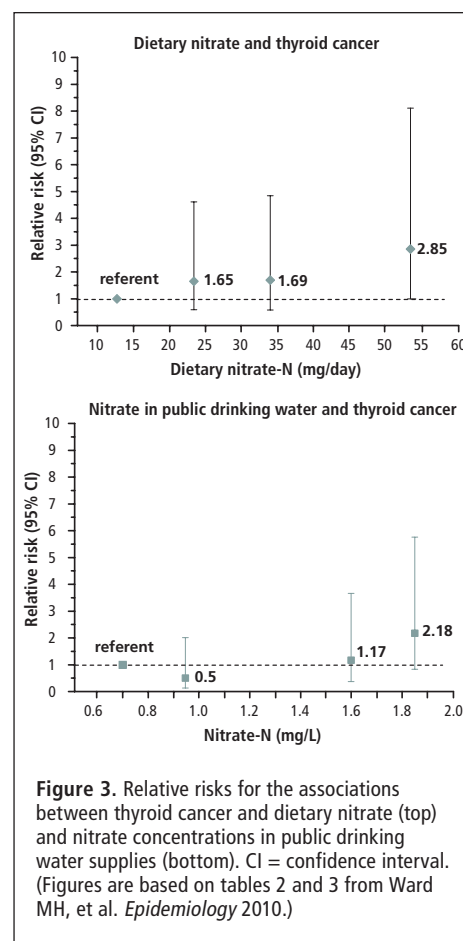


Figure 3. Relative risks for the associations between thyroid cancer and dietary nitrate (top) and nitrate concentrations in public drinking water supplies (bottom). CI = confidence interval. (Figures are based on tables 2 and 3 from Ward MH, et al. *Epidemiology* 2010.)

[RR] = 2.6). Increasing intake of dietary nitrate was associated with an increased risk of thyroid cancer (highest vs. lowest quartile, RR = 2.9 [CI = 1.0–8.1]; p for trend = 0.046) and with the prevalence of hypothyroidism (OR = 1.2) but not hyperthyroidism (see Figure 3). (Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR. Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology* 2010;21:389–395)

UPPER GASTROINTESTINAL CANCER

Polycyclic Aromatic Hydrocarbons

To evaluate the association between polycyclic aromatic hydrocarbon (PAH) exposure and esophageal squamous cell carcinoma (ESCC), a case-control study was conducted in a high-risk population in northeastern Iran. Tissue microarrays (TMAs) of non-tumoral esophageal

biopsies were analyzed from patients with biopsy-proven ESCC and gastrointestinal clinic patient controls. Immunohistochemistry staining was performed using monoclonal antibodies 8E11 and 5D11 raised against benzo[a]pyrene (B[a]P) diol epoxide (BPDE)-I-modified guanosine and BPDE-I-modified DNA, respectively. Sufficient epithelial tissue was available in the TMA cores to analyze 91 cases and 103 controls. Compared with the lowest quintile of 8E11 staining in the controls, adjusted ORs for the 2nd to 5th quintiles were 2.42, 5.77, 11.3, and 26.6, respectively (p for trend < 0.001) (see Figure 4). This finding adds to the evidence for a causal role for PAHs in esophageal cancer in high-risk populations. (Abedi-Ardekani B, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, Taylor PR, Boffetta P, Malekzadeh R, Dawsey SM. Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. *Gut* 2010;59:1178–1183)

Smoking

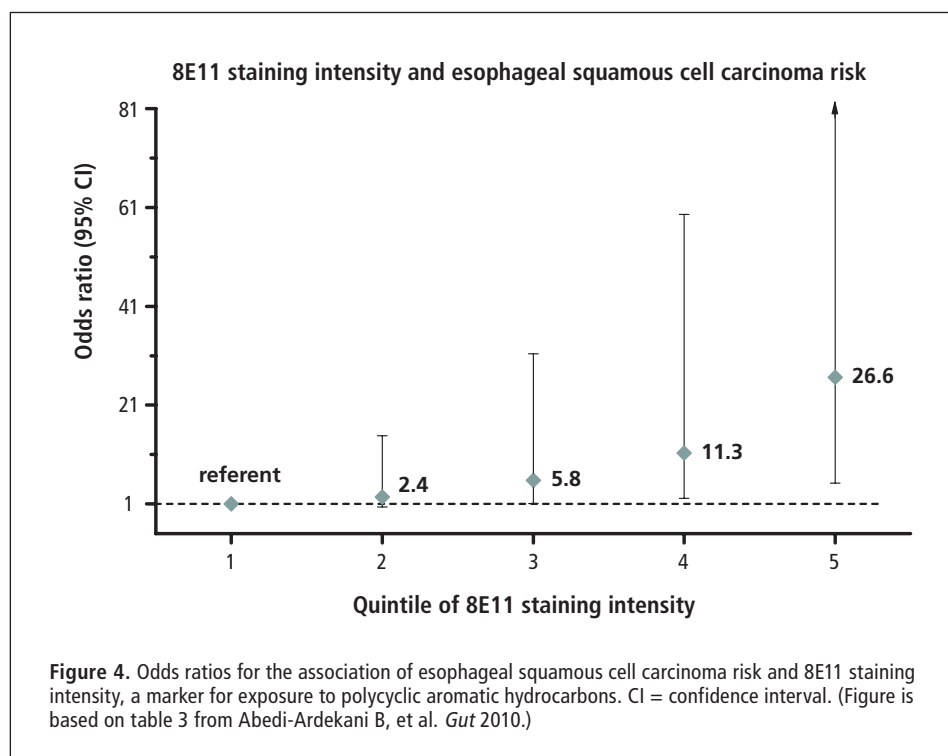
The authors used data from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium to investigate associations with smoking by tumor site, sex, dose, and duration of cessation of cigarette smoking. Subjects were classified as having esophageal adenocarcinoma ($n = 1,540$), esophagogastric junctional adenocarcinoma ($n = 1,450$), or a combination of the two (all adenocarcinoma; $n = 2,990$) or as controls ($n = 9,453$). There were strong associations between cigarette smoking and esophageal adenocarcinoma (OR = 1.96), esophagogastric junctional adenocarcinoma (OR = 2.18), and all adenocarcinoma (OR = 2.08). In addition, there was a strong dose-response association between pack-years of cigarette smoking and each outcome ($p < .001$). Compared with current smokers, those with longer smoking

cessation had a decreased risk of all adenocarcinoma after adjusting for pack-years (< 10 years of smoking cessation: OR = 0.82, CI = 0.60–1.13; and ≥ 10 years of smoking cessation: OR = 0.71). Cigarette smoking is associated with increased risks of adenocarcinomas of the esophagus and esophagogastric junction; compared with current smoking, smoking cessation was associated with reduced risks. (Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Pandeya N, Webb PM, Wu AH, Ward MH, Giffen C, Casson AG, Abnet CC, Murray LJ, Corley DA, Nyrén O, Vaughan TL, Chow WH. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: A pooled analysis from the international BEACON consortium. *J Natl Cancer Inst* 2010;102(17):1344–1353)

Susceptibility Locus at 10q23

The authors conducted a GWAS of 2,240 gastric cancer cases, 2,115 ESCC cases, and 3,302 controls among ethnic Chinese subjects drawn from five

studies. Multiple variants at 10q23 had genome-wide significance for gastric cancer and ESCC independently. A notable signal was found for rs2274223, a nonsynonymous SNP located in *PLCE1*, for gastric cancer ($p = 8.40 \times 10^{-9}$; per-allele OR = 1.31) and ESCC ($p = 3.85 \times 10^{-9}$; OR = 1.34). The association with gastric cancer differed by anatomic subsite. For tumors in the cardia, the association was stronger ($p = 4.19 \times 10^{-15}$; OR = 1.57), and for those in the noncardia stomach, it was absent ($p = 0.44$; OR = 1.05). Findings at 10q23 could provide insight into the high incidence of both cancers in China. (Abnet CC, Freedman ND, Hu N, Wang Z, Yu K, Shu XO, Yuan JM, Zheng W, Dawsey SM, Dong LM, Lee MP, Ding T, Qiao YL, Gao YT, Koh WP, Xiang YB, Tang ZZ, Fan JH, Wang C, Wheeler W, Gail MH, Yeager M, Yuenger J, Hutchinson A, Jacobs KB, Giffen CA, Burdett L, Fraumeni JF Jr, Tucker MA, Chow WH, Goldstein AM, Chanock SJ, Taylor PR. A shared susceptibility locus in *PLCE1* at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat Genet* 2010; 42:764–767)



DCEG PEOPLE IN THE NEWS

Christian C. Abnet, Ph.D., M.P.H., Nutritional Epidemiology Branch (NEB), spoke in May on “Selenoprotein gene variants and risk of esophageal and gastric cancer in a high-incidence Chinese population” at the Selenium 2010 meeting at Kyoto University in Japan. In June, he gave a talk titled “Molecular approaches to dietary exposures” at George Washington University in Washington, DC.

Blanche P. Alter, M.D., M.P.H., Clinical Genetics Branch (CGB), spoke on “Inherited bone marrow failure syndromes” at the Clinical Genetics conferences at the National Human Genome Research Institute in March and June. During the summer, she gave presentations for the Fanconi Anemia, Diamond Blackfan Anemia, and Shwachman-Diamond Syndrome family support meetings.

Samsiddhi Bhattacharjee, Ph.D., a research fellow in the Biostatistics Branch (BB), received a Young Investigator Award from the Statistics in Epidemiology section of the American Statistical Association for his paper titled “Using principal components of genetic variation for robust and powerful detection of gene-gene interactions in case-control and case-only studies,” published in the *American Journal of Human Genetics* in April. The award was presented at the Joint Statistical Meetings in Vancouver, Canada. At the same meeting, **Mitchell H. Gail, M.D., Ph.D.** (BB), gave an invited talk on “Risk models for deciding to take tamoxifen to prevent breast cancer and for allocating public health resources.”

Louise A. Brinton, Ph.D., Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), spoke in May on “Breast cancer in Klinefelter syndrome”

at the International Workshop on Klinefelter Syndrome in Copenhagen, Denmark, and on “Cancer risk following endometriosis” at the Endometriosis Foundation first annual symposium, Advancing the Art and Science of Endometriosis: Stem Cells to Radical Excision Surgery, in New York, New York. In June, she gave a lecture at the Johns Hopkins Summer Institute in Baltimore, Maryland, on “New insights on hormonal relationships for breast cancer risk.”

At the Eurogin 2010 Cervical Cancer Prevention conference held in Monte Carlo, Monaco, in February, **Philip E. Castle, Ph.D., M.P.H.** (HREB), gave several invited talks on cervical cancer screening strategies incorporating human papillomavirus (HPV) testing. At the same meeting, **Nicolas Wentzensen, M.D., Ph.D., M.S.** (HREB), gave invited presentations on host epigenetic changes, biomarkers, and assessment of risk profiles for cervical precancer and cancer. In March, Dr. Castle gave an invited talk on “Risk management: Principles and practice” and spoke on “Practice improvement

in cervical screening and management moving forward: Update from NIH.” He also served on a panel discussing “Cervical cancer: Past, present and future” at the American Society for Colposcopy and Cervical Pathology Biennial Meeting in Las Vegas, Nevada. At the same meeting, Dr. Wentzensen spoke on “NCI studies to improve colposcopy—How many biopsies?”

In June, **Nilanjan Chatterjee, Ph.D.**, Chief of BB, presented a grand rounds seminar at the MD Anderson Cancer Center in Houston, Texas titled Estimating Effect Size Distribution in Genome-wide Association Studies and Implications for Future Discoveries.

In June, **Michael B. Cook, Ph.D.** (HREB), spoke on “Exposure to endocrine disruptors and testis cancer risks” at the Gordon Research Conference on Environmental Endocrine Disruptors in Les Diablerets, Switzerland.

In July, **Eric A. Engels, M.D., M.P.H.**, Infections and Immunoepidemiology Branch, spoke on the Transplant Cancer

STEPHANIE WEINSTEIN WINS MERIT AWARD

Stephanie J. Weinstein, Ph.D., Nutritional Epidemiology Branch (NEB), received the Merit Clinical/Translational Research Award at the Sixth Annual NCI Staff Scientist and Staff Clinician (SS/SC) Retreat in April. The award provides funding for Dr. Weinstein to travel to a scientific conference of her choice. Her abstract, *Serum creatinine and prostate cancer risk in a prospective study*, was coauthored by NEB investigators **Demetrius Albanes, M.D.**, and **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.**

The NCI SS/SC Retreat provides a venue for staff scientists and clinicians from DCEG and the Center for Cancer Research (CCR) to share research findings, secure funding for travel to meetings, forge new collaborations, and obtain career training. DCEG representatives **Dalsu A.N. Baris, M.D., Ph.D.**, Occupational and Environmental Epidemiology Branch, and **Mark J. Roth, M.D.** (NEB), along with CCR staff, helped organize the retreat. **Sharon A. Savage, M.D.**, Clinical Genetics Branch, provided a keynote address to the attendees. Dr. Baris has now handed over her responsibilities to **Amanda Black, Ph.D., M.P.H.**, Epidemiology and Biostatistics Program. As the current DCEG representatives, Drs. Roth and Black are working with CCR colleagues to develop the agenda for the seventh annual retreat in 2011.

Match Study at the Technical Advisory Committee to the U.S. Scientific Registry of Transplant Recipients in Detroit, Michigan. He also spoke on “Infection-related cancers among HIV-infected people” at the International Conference on Emerging Infectious Diseases in Atlanta, Georgia.

Three Occupational and Environmental Epidemiology Branch (OEEB) investigators participated in the Scientific Committee on Epidemiology in Occupational Health (EPICOH) Conference in Taipei, Taiwan in April. **Melissa Friesen, Ph.D.**, gave three presentations on methodologic approaches to understanding and improving expert retrospective assessment of occupational exposures. **Qing Lan, M.D., Ph.D., M.P.H.**, gave presentations on gene-environment interactions and on molecular epidemiology studies of benzene. **Nathaniel Rothman M.D., M.P.H., M.H.S.**, spoke on “Hematotoxicity and risk of leukemia and lymphoma—Implications for cross-sectional molecular epidemiology studies of benzene.”

In May, **Gretchen L. Gierach, Ph.D.** (HREB), gave a talk on “Genetics and breast density” at the Barbara Ann Karmanos Cancer Institute and Wayne State University School of Medicine’s Breast Density, Breast Cancer Risk and Health Disparities Research Retreat in Detroit, Michigan. At the same retreat, **Mark E. Sherman, M.D.** (HREB), spoke on “Human trials in breast cancer: Chemoprevention and nutritional agents.” In June, Dr. Gierach spoke

on “Mammographic density: A tool to study the molecular epidemiology of breast cancer” at the NCI Laboratory of Cancer Biology and Genetics, Center for Cancer Research, in Bethesda, Maryland.

H. Dean Hosgood, III, Ph.D., (OEEB), received the Eric W. Mood New Professional Award from the Yale School of Public Health in New Haven, Connecticut. The award recognizes the career of an alumnus who is a promising new professional in public health. In June, he gave an invited lecture on “The molecular epidemiology of in-home solid fuel use and lung cancer” at the Maine Institute for Human Genetics and Health in Bangor, Maine.

Ann W. Hsing, Ph.D. (HREB), gave an invited talk in March titled “Epidemiology and etiology of biliary tract cancer” at the School of Public Health, University of Pittsburgh.

In June, **Maria Teresa Landi, M.D., Ph.D.**, Genetic Epidemiology Branch (GEB), gave a talk on “Environment and genetics in lung cancer etiology: An integrative approach to the study of lung cancer” at the Oncology Unit, IRCCS Casa Sollievo della Sofferenza, in San Giovanni Rotondo, Italy and on “Pigmentation and skin cancer, a GWAS review” at the GenoMEL meeting in Leeds, United Kingdom.

In May, **Saloni Nayar, M.P.H.**, Office of Communications and Special Initiatives, received the Milford E. Barnes Award

from the University of Iowa for exceptional work in the Department of Community and Behavioral Health.

Sharon A. Savage, M.D. (CGB), gave talks on “Clinical and molecular characterization of dyskeratosis congenita: A cancer predisposition syndrome” at Texas Children’s Cancer Center in Houston, Texas; “Osteosarcoma: Epidemiology and genomic studies” at the Pediatric Cancer Epidemiology: Fundamental Questions and Strategies for Solutions symposium at Texas Children’s Cancer Center/Baylor College of Medicine; and “Genome-wide association studies” at the annual NCI Cancer Prevention Fellowship meeting.

In June, **Mark E. Sherman, M.D.** (HREB), served on the program committee for the American Association for Cancer Research Future of Molecular Epidemiology conference held in Miami, Florida. During the conference, he gave a talk on “Molecular pathology in epidemiologic research: From study designs to data.” He also cochaired with **Montserrat García-Closas, M.D., Dr.P.H.** (HREB), the educational sessions and a session on “Applications of new biomarkers in molecular epidemiology studies.”

In July, **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB), gave a talk on vitamin D and cancer at the Epidemiology Department of Imperial College in London, United Kingdom.

Rashmi Sinha, Ph.D., Deputy Chief of NEB, gave a talk on “Meat intake and risk of colorectal neoplasia: A molecular epidemiology point of view” at the 12th International Congress of Toxicology held in July in Barcelona, Spain.

In May, **Philip R. Taylor, M.D., Sc.D.** (GEB), gave a talk on “Advanced glycation end-products, soluble receptor for advanced glycation end-products, and risk of colorectal cancer” at Digestive Diseases Week in New Orleans, Louisiana.

MARIANNE HENDERSON HONORED BY INTERNATIONAL REPOSITORIES SOCIETY

In May, **Marianne K. Henderson, M.S.**, Chief of the Office of Division Operations and Analysis, was elected President-Elect of the International Society of Biologic and Environmental Repositories at its annual meeting held in Rotterdam, The Netherlands. Ms. Henderson also received a Poster Award for Outstanding Research in BioBanking. The poster was titled *Introducing automation to improve throughput in DNA extraction and sample aliquoting for human biofluids*. Her coauthors were **Karen E. Pitt, Ph.D.**, special assistant for biological resources, Office of the Director, and Dr. Timothy Sheehy and Dr. L. Mark Cosentino, of SAIC-Frederick, Inc.

COMINGS . . . GOINGS

Porcia Bradford, M.D., left the Genetic Epidemiology Branch (GEB), where she had been a fellow since 2007, for a dermatology residency at Duke University Health System in Durham, North Carolina.



Denise Brandenburg

Denise Brandenburg joined DCEG's Administrative Resource Center as a budget administrative officer. Ms. Brandenburg received her

B.S. in business administration from the University of Maryland and her M.B.A. in 2007 from the University of Phoenix. She has been working in the NCI Office of Budget and Finance as a budget analyst since 2005. Ms. Brandenburg has a wealth of experience in managing grants, gift funds, royalty funds, budget mechanisms, and various financial reporting systems.



Dianna Buckett

Dianna Buckett joined the Infections and Immunology Branch (IIB) and the Laboratory of Translational Genomics

(LTG) as a postbaccalaureate fellow. Ms. Buckett graduated from Claremont McKenna College in Claremont, California in May 2010 with a B.A. in chemistry. She will be working with **Thomas R. O'Brien, M.D., M.P.H.** (IIB), and **Ludmila Prokunina-Olsson, Ph.D.** (LTG), on studies of hepatitis viruses and human genetics.



Felipe Castro

his doctorate in epidemiology at the University of Heidelberg, Germany. His doctoral research at the German Cancer Research Center focused on the genetic epidemiology of cervical cancer. Dr. Castro will work with **Aimee Kreimer, Ph.D.**, and **Allan Hildesheim, Ph.D.**, Chief of IIB, to investigate the genetic epidemiology of cervical cancer among women who received (or did not receive) the human papillomavirus (HPV) vaccine and to work on other HPV-related projects.

Felipe Castro, Ph.D., joined IIB as a visiting fellow. Dr. Castro studied veterinary medicine in Manizales, Colombia and obtained

Sarah Coseo, M.P.H., left IIB to start the Sc.D. program in epidemiology at the Harvard School of Public Health in Boston, Massachusetts.

Sonja Dawsey left the Nutritional Epidemiology Branch (NEB) to attend medical school at Marshall University in Huntington, West Virginia.



Sara De Matteis

Sara De Matteis, M.D., M.P.H., joined GEB as a postdoctoral visiting fellow. She received her M.D. and M.P.H. from the University

of Milan in Italy and has collaborated on several epidemiological projects,

DCEG PARTICIPATES IN RADIATION AND HEALTH CONFERENCE

In June, DCEG researchers participated in the 2010 American Statistical Association's Conference on Radiation and Health in Annapolis, Maryland. The conference offered a unique forum for discussing the qualitative aspects of radiation health research in a multidisciplinary setting. DCEG had strong representation at the conference, with 19 of the approximately 80 investigators in attendance coming from the Radiation Epidemiology Branch (REB). Members of the conference's Radiation and Health Planning Committee included **Alice J. Sigurdson, Ph.D.**, cochair, **Alina V. Brenner, M.D., Ph.D.**, and **Ruth A. Kleinerman, M.P.H.**

Dr. Sigurdson helped organize the first session of the conference, titled "Exposure to medical personnel, patients, and the public: Trends & issues." During the session, **Steven L. Simon, Ph.D.**, gave a presentation on "Personnel dose estimation for interventional cardiology and other higher dose procedures." In the second session, titled "Cancer and non-cancer late effects of therapeutic radiation," **Peter D. Inskip, Sc.D.**, presented "Radiation-related second cancers and cardiovascular outcomes in the Childhood Cancer Survivors Study." Another session on "New technologies in radiation medicine" included **Amy Berrington de González, D.Phil.**, discussing "Projected cancer risks from current levels of diagnostic medical imaging in the U.S."

Several REB fellows won New Investigator Travel Awards, including **Deukwo Kwon, Ph.D.**, **Stephanie Lamart, Ph.D.**, **Gila Neta, Ph.D., M.P.P.**, and **Sara Schonfeld, Ph.D., M.P.H.** Dr. Lamart also received an award for Best Poster at the conference.

including the recent analysis of occupational exposures and risk of lung cancer in the Environment And Genetics in Lung cancer Etiology (EAGLE) study. She is pursuing a Ph.D. in occupational and environmental medicine at the University of Milan in Italy, with a focus on epidemiology. While in GEB, Dr. De Matteis will work with **Maria Teresa Landi, M.D., Ph.D.**, and colleagues on the interplay between exposure to asbestos and other man-made fibers and genetic susceptibility in association with lung cancer risk.



Curt DellaValle

Curt DellaValle, Ph.D., M.P.H., joined the Occupational and Environmental Epidemiology Branch (OEEB) as a postdoctoral fellow in

July 2010. Dr. DellaValle received his M.P.H. and Ph.D. in environmental health sciences from Yale University in New Haven, Connecticut. The focus of his dissertation was the development and evaluation of techniques for modeling exposure to ambient allergens. Under the direction of mentor **Mary H. Ward, Ph.D.**, Dr. DellaValle's research

goals are to focus on the improvement and validation of methods for assessing environmental exposures in epidemiological studies of cancer.



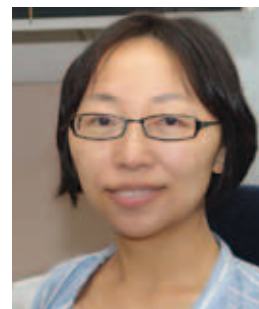
Arash Etemadi

Arash Etemadi, M.D., Ph.D., joined NEB as a postdoctoral fellow. Dr. Etemadi received his medical degree and trained

in epidemiology at Tehran University of Medical Sciences in Iran. For his dissertation, he worked on familial aggregation of myopia and segregation analysis of refractive errors. In NEB, he will work with **Sanford M. Dawsey, M.D.**, and **Christian C. Abnet, Ph.D., M.P.H.**, on esophageal cancer studies, especially in relation to polycyclic aromatic hydrocarbon exposure.

Montserrat García-Closas, M.D., Dr.P.H., left the Hormonal and Reproductive Epidemiology Branch (HREB) for a position as a professor of epidemiology at the Institute of Cancer Research and the Breakthrough Breast Cancer Research Centre in London, United Kingdom.

Meg Gerstenblith, M.D., a postdoctoral fellow, left GEB to take an assistant professor position in the Department of Dermatology at Case Western Reserve University School of Medicine in Cleveland, Ohio.



Fangyi Gu

Fangyi Gu, M.Med., Sc.D., joined GEB as a postdoctoral fellow. Dr. Gu received a master of medicine from Peking Union

Medical College in Beijing, China and a doctorate in epidemiology from the Harvard School of Public Health in Boston, Massachusetts. She has collaborated on several epidemiological projects, including the recent genome-wide association study of smoking behaviors led by DCEG and Harvard investigators and an international multicenter association study of insulin-like growth factor (IGF) pathway genes with circulating IGF1/binding protein-3 (BP3) hormone levels. Dr. Gu will be working with **Neil E. Caporaso, M.D.**, and colleagues on smoking exposure and genetic susceptibility in relation to lung cancer risk.

TODD GIBSON DEFENDS DISSERTATION

In April, **Todd M. Gibson, Ph.D.**, Nutritional Epidemiology Branch (NEB), successfully defended his doctoral dissertation at the Yale School of Public Health in New Haven, Connecticut. He conducted research for his thesis, "Folate, one-carbon metabolism, and risk of colorectal and renal cancers," under the mentorship of Dr. Susan Mayne of Yale University, **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB), **Stephanie J. Weinstein, Ph.D.** (NEB), **Ruth M. Pfeiffer, Ph.D.**, Biostatistics Branch, and **Lee E. Moore, Ph.D.**, Occupational and Environmental Epidemiology Branch. Dr. Gibson will continue his postdoctoral work in DCEG as a member of the Cancer Prevention Fellowship Program. He is joining the Radiation Epidemiology Branch, where he will work with **Lindsay M. Morton, Ph.D.**, to investigate patterns and risk factors for multiple primary cancers and to conduct molecular epidemiology studies of lymphoma.



Wei Hu

Wei Hu, Ph.D., joined OEEB as a postdoctoral fellow. Dr. Hu has a Ph.D. in safety technology and engineering from the University

of Science and Technology in Beijing, China. His doctoral research focused on the interactive effects on respiratory

health of outdoor air pollutants and other factors, such as indoor pollution indicators and historic diseases/symptoms. Dr. Hu will be involved in several OEEB projects, including the Asia Lymph Study (a hospital-based case-control study of lymphoma in Asia) and studies of lung cancer in Xuanwei, China. Under the mentorship of **Qing Lan, M.D., Ph.D., M.P.H.**, Dr. Hu will continue to obtain experience in the design and conduct of molecular epidemiology.



Elizabeth Khaykin

Elizabeth Khaykin, Ph.D., M.H.S., joined the Radiation Epidemiology Branch (REB) as a postdoctoral fellow.

Dr. Khaykin received her M.H.S. in biostatistics and her Ph.D. in epidemiology from Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland and previously earned her S.M. in technology and policy from the Massachusetts Institute of Technology in Cambridge, Massachusetts. Prior to coming to DCEG, she was a postdoctoral fellow in psychiatric epidemiology at Johns Hopkins. Dr. Khaykin is interested in applying her skills to the examination of biomarkers of exposure, polymorphisms in genes potentially related to hormone modulation, genomic integrity, and xenobiotic detoxification. In REB, she will be working with **D. Michal Freedman, Ph.D., M.P.H.**, **Preetha Rajaraman, Ph.D., M.P.H.**, and **Alice J. Sigurdson, Ph.D.**, on several projects within the U.S. Radiologic Technologists (USRT) study.

Huilin Li, Ph.D., left the Biostatistics Branch (BB) to take a tenure-track position at the New York University School of Medicine's Division of Biostatistics in New York, New York.



Mark Little

Mark Little, Ph.D., joined REB as a visiting senior scientist. Dr. Little studied mathematics at Trinity College, Cambridge, United

Kingdom and obtained his doctorate in mathematics at New College, Oxford, United Kingdom. During the past two decades, he has been analyzing the risks of cancer and cardiovascular disease in Japanese atomic bomb survivors and in other irradiated populations and their children. Previously, he worked in the Imperial College Department of Epidemiology and Biostatistics in London. Dr. Little will work on assessing the risk of thyroid cancer in a cohort of persons exposed as a result of the Chernobyl accident and on treatment-related second cancer risks in various populations.

Tamra E. Meyer, Ph.D., previously a Sallie Rosen Kaplan Fellow in HREB, has accepted a position at the Pharmacovigilance Center, Department of the Army, Office of the Surgeon General, in Washington, DC.

Megan Murphy, M.S., left HREB to begin doctoral studies at the Harvard School of Public Health in Boston, Massachusetts.

Elisabetta Petracci, Ph.D., left BB to take a research position in the Department of Statistics at the University of Bologna in Italy.

Laura Sue, M.P.H., a postbaccalaureate fellow in the Office of the Director, Epidemiology and Biostatistics Program, left in July to start medical school at the University of California, San Diego.

Min Tang, M.S., left BB to become a research fellow in the Biostatistics and Computational Biology Department at the Dana-Farber Cancer Institute in Boston, Massachusetts.

DCEG STAFF RECEIVE NIH DIRECTOR'S AWARDS

In July, several members of DCEG received NIH Director's Awards. Radiation Epidemiology Branch members **D. Michal Freedman, Ph.D., M.P.H.**, **Ruth A. Kleinerman, M.P.H.**, **Cari Meinhold Kitahara, M.H.S.**, **Gila Neta, Ph.D., M.P.P.**, **Elaine Ron, Ph.D.**, **Sara Schonfeld, Ph.D., M.P.H.**, and **Alice J. Sigurdson, Ph.D.**, along with **Dilys M. Parry, Ph.D.**, Genetic Epidemiology Branch, **Catherine Schairer, Ph.D.**, Biostatistics Branch, and **Sandhya Xirasagar, Ph.D.**, Office of Division Operations and Analysis, were recognized for participation in the Volunteer Program for English Proficiency. **Donna Siegle**, Chief of the Administrative Resource Center, was recognized for her work on the NIH Long-Term Administrative Support Contract.

The NIH Director's Award recognizes superior performance or special efforts significantly beyond the regular duty requirements and directly related to fulfilling the NIH mission. Nominations are submitted for one of four categories: scientific/medical, technical/clerical/support, administrative, and common fund leadership.

MEMORIAL SLOAN-KETTERING CANCER CENTER HONORS STEPHEN CHANOCK

In June, **Stephen J. Chanock, M.D.**, Director of the NCI Core Genotyping Facility and Chief of DCEG's Laboratory of Translational Genomics, received the Niehaus Southworth Weissenbach Award in Predictive Cancer Genetics from the Memorial Sloan-Kettering Cancer Center in New York, New York. The award is given to an individual who has made a significant contribution to the understanding of the genetic basis of cancer susceptibility, with the prospect of using this knowledge to improve cancer prevention or early detection and screening.

In receiving the award, Dr. Chanock gave the Visiting Professor Lecture in Clinical Cancer Genetics, which was titled "Genome-wide association studies (GWAS) in cancer: Sorting out the nuggets of gold." He outlined the process of investigating markers of susceptibility identified through GWAS, from the initial "hits" to follow-up studies, fine-mapping, sequencing, and evaluating the function of associated variants. He spoke on the abundance of information



Stephen Chanock (right) receives the Niehaus Southworth Weissenbach Award in Predictive Cancer Genetics from Robert and Kate Niehaus along with Kenneth Offit of the Memorial Sloan-Kettering Cancer Center.

generated from GWAS and the promise that these findings hold for gaining a better understanding of the etiology of disease and for risk prediction to inform individual and public health decision-making. He concluded his presentation by remarking on future directions and challenges for GWAS.

Selection for the award is made by a committee of clinicians and researchers at the Memorial Sloan-Kettering Cancer Center. The individual receiving the award is a scientist whose work has substantively advanced the field of cancer genetics. ■



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