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Invited Commentary: The Value of GWAS

Major advances in genomic science and technology have recently made it possible to analyze the entire human genome through genome-wide association studies (GWAS) designed to find common susceptibility genes associated with a particular disease. Before this breakthrough, researchers were dependent on using promising candidate genes, which are identified and individually assessed based on a gene's location in a chromosomal region with a particular biologic function. After more than 20 years of using candidate gene studies in cancer research, scientists have identified fewer than six cancer susceptibility genes, the exact number depending on the criteria for supporting evidence. However, in less than four years, researchers using GWAS have identified more than 100 genetic regions associated with risk for 18 different cancers.

GWAS represent just the beginning of scientists' efforts at discovering the role of genetics in the origins of disease, which are now moving into subsequent phases, including identification of the causal variants within regions associated with cancer risk and laboratory research to determine the functions and biologic roles of these causal variants in carcinogenesis.

The advent of GWAS has been heralded as a major success story; however, as might be expected of any ambitious effort, concerns have emerged. With few exceptions, studies using GWAS have found comparatively small relative risks for disease associated with the identified risk variants—usually between 1.1 and 1.4 per allele. Some researchers assert that these estimated effects are too low to be clinically useful in characterizing disease risk and are unlikely to have meaningful or even identifiable roles in the underlying

Robert Hoover

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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biology of disease. These assumptions need to be examined to determine the true value of GWAS.

There has long been enthusiasm for characterizing an individual's risk of a variety of diseases based on that individual's profile of high-risk genetic variants. Indeed, some of the first commercial uses of GWAS have been in developing and marketing such tests. For the most part, these risk profiles have not been shown to be clinically relevant at the individual level. For example, susceptibility genes for coronary disease have failed to meaningfully add to the risk stratification provided by the Framingham Risk Score; susceptibility genes for breast cancer also have failed to enhance the predictability provided by the Gail model.[1] The results are thought to be due to the low levels of risk associated with the individual variants and the limited number of people with multiple deleterious variants.

Findings from breast cancer research suggest, however, that these initial impressions may be too simplistic. For example, the model used for genetic susceptibility in the aforementioned study was based on the first 10 single-nucleotide polymorphisms (SNPs) to be identified as risk factors. More variants have been discovered since these 10 were identified, and inevitably more will be discovered in the future; the risks for the identified regions are likely to increase as the true causal SNPs are identified in follow-up studies. As the number of multiple causal SNPs increases, the higher risks may have clinical implications. For example, those in the top 4 percent of women based on the number of deleterious alleles have a threefold increased risk of breast cancer compared to those in the lowest 12 percent—a level of risk that indicates these women might benefit from specialized screening and other interventions currently under evaluation for the 1 percent of the population at high risk for breast cancer because they are *BRCA* carriers.

The value of risk prediction also depends on the criteria for clinical utility. Although the reported SNPs do not greatly enhance the Gail model, the SNP model by itself is slightly superior to the Gail model alone. This is important because the level of risk discrimination provided by the Gail model is thought to have clinical relevance—the Gail model has been used to identify women eligible for clinical trials of chemopreventive agents and to identify levels of breast cancer risk for which the benefit/risk ratios of tamoxifen as a preventive measure might justify its use. It also has been suggested that the individualized risk data from the Gail or SNP models could be used to determine the appropriate age to begin mammography screening.

However, the majority of cancers do not have a risk factor model analogous to breast cancer's Gail model. Consider, for example: with the bonanza of SNPs associated with prostate cancer through GWAS, would a SNP model for this tumor be clinically useful in the absence of an effective risk factor model such as the Gail model? The answer would likely be "yes" if we had an effective screening tool or chemopreventive agent—which as yet we do not. Thus, the clinical utility of SNP-based models will depend on the discovery of clinical screening and intervention tools whose application would benefit from the level of risk-discriminating power commensurate with the SNP models currently emerging from GWAS.

While most of the discussion about risk assessment has focused on personal risk stratification and its clinical utility, little attention has been given to population-level risks. Though the relative risks

found through GWAS are low, the proportion of the population "exposed" (those with one or two copies of the risk allele) is quite high because these are common variants. Thus, the proportion of cases of a particular disease in a population that is explained by, or attributable to, the genetic variants may be quite substantial for a single gene and truly impressive for the combined impact of several variants. For example, the strongest GWAS "hit"—a variant in *FGFR2*—can be attributed to 15 percent of breast cancer in the population, and 37 percent can be attributed to those having more than six of the risk alleles.

One interpretation of an attributable risk is that it represents the proportion of disease in a population that would not occur if that risk factor was removed. Obviously, we cannot remove a common gene variant. However, if a specific step in the pathway through which the gene exerts its carcinogenic effect can be blocked or altered, then the cases of disease prevented may be truly impressive. As the biologic mechanisms of GWAS risk variants start to be elucidated, special efforts should focus on those variants involved in pathways that offer these opportunities.

The claim has been made that the relatively low relative risks reported from GWAS do not provide important etiologic clues to cancer. This reasoning is reminiscent of environmental epidemiology 30 years ago. At that time, few studies were finding risks that approached the high levels associated with tobacco smoking and occupational exposures, and it was speculated that the much lower risks being detected for the exposures might not be useful or even real. Some have used the same logic when the risks for susceptibility genes did not approach those of the rare variants responsible for familial clusters. Fortunately, this logic proved false for environmental epidemiology, and the same may apply for susceptibility genes as well. Many important environmental and lifestyle variables have been causally linked to malignancies at relatively low levels of relative risk; despite these relatively low levels, the population impact and prevention opportunities have been substantial. For example, the initial relative risks for breast cancer associated with both obesity and hormone therapy, and the risks for lung cancer associated with passive smoking and small particulate air pollution, were in the range of 1.1 to 1.3. In all these instances, the associations have been established as causal, and interventions have resulted in reduced risks.

The challenge ahead is to pursue the most promising of these leads in order to dissect the underpinnings of cancer susceptibility and provide insights into causal mechanisms that will inform new strategies for cancer prevention, detection, and therapy.

This sequence of events that happened in the field of environmental epidemiology also could potentially happen with the risk factors identified by GWAS. So far, the associations reported are only the markers for a genetic variant directly responsible for disease risk; and when that causal variant is identified, it too will only be a marker—a marker of a pathway that is much more directly also and meaningfully related to disease risk. In time, the combination of a gene's product with those of other genes, along with their substrates from metabolic and environmental sources, will help to uncover proximal causal mechanisms with much broader ranges in risk than those attributed to any single gene by itself. The reverse sequence in the discovery process is illustrated by the increased bladder cancer risk associated with occupational and tobacco-related aromatic amine exposures. It was later found that people identified as slow metabolizers of these chemicals had somewhat higher risks than those identified as rapid metabolizers. Subsequently, variants in the *NAT2* gene that influence this metabolic process were associated with a relative risk of 1.4 for bladder cancer. Thus, it is easy to see how the identification of a susceptibility gene could progress to elucidation of an entire carcinogenic pathway, resulting in the discovery of important disease risk factors and the potential for effective interventions. Our task now is to take advantage of the opportunity to determine the pathways that are identified by GWAS and the products of these pathways that more directly impact disease risk. Along the way, we hope that research findings will point to metabolic and environmental components of these pathways that may be more easily manipulated.

It has been said, "Each success only buys an admission ticket to a more difficult problem." Although there has been an explosion of exciting etiologic leads from GWAS, the challenge ahead is to pursue the most promising of these leads in order to dissect the underpinnings of cancer susceptibility and provide insights into causal mechanisms that will inform new strategies for cancer prevention, detection, and therapy. ■

—Robert N. Hoover, M.D., Sc.D.

[1] Wacholder S, et al. Performance of common genetic variants in breast-cancer risk models. *N Engl J Med* 2010;362:986–993.

DRS. PROKUNINA-OLSSON AND AMUNDADOTTIR INVESTIGATE GWAS HITS

DCEG's Laboratory of Translational Genomics (LTG) is busy exploring the abundance of new data being made available through large-scale genome-wide association studies (GWAS), which assess hundreds of thousands of single nucleotide polymorphisms (SNPs) in large epidemiologic studies. Once a GWAS signal is detected, follow-up studies are critical for analyzing the contribution of identified regions to the risk of disease and investigating whether SNPs discovered by GWAS represent a functional genetic variant. LTG tenure-track investigators **Laufey Amundadottir, Ph.D.,** and **Liudmila Prokunina-Olsson, Ph.D.,** are vigorously pursuing genomic variants identified in GWAS that may alter an individual's risk of developing cancer.

Dr. Prokunina-Olsson explained the process this way: "Imagine a room full of telephone books, and we are trying to find a tiny but significant error in one book. We need a way to limit the search to one or just a few books. GWAS enable us to do that. They narrow down the number of 'books'—sections of DNA in many people's genomes—that we have to comb through using advanced analytical tools, such as fine mapping, deep sequencing, and functional analysis. That's how we can identify genetic variants that affect the risk of developing cancer. Then, we have to learn whether variants are functional and if they correlate with phenotypes, such as a particular cancer."

Some of the identified SNPs can affect coding sequence and lead to disease-causing changes in proteins. However, the majority of disease-associated markers are non-coding SNPs that may have regulatory functions and affect DNA-protein interactions and expression

Liudmila Prokunina-Olsson

Laufey Amundadottir

of mRNA, miRNA, proteins, and so forth. Using a wide variety of methods, Dr. Prokunina-Olsson aims to identify molecular underpinnings of the genomic associations with phenotypes relevant to human disease.

Dr. Prokunina-Olsson believes it may be possible to develop therapies or diagnostic tests based on the molecular biomarkers and pathways associated with cancer risk. Such approaches could benefit public health by leading to personalized medicine for groups of patients based on the genetic landscape.

The new genome-wide associations generated by NCI's Cancer Genetic Markers of Susceptibility (CGEMS) initiative have been essential for the LTG research program. Dr. Prokunina-Olsson has been analyzing some of the variants identified in studies of breast, prostate, and bladder cancers and connecting them to phenotypes in a measurable and reproducible way. Results are sometimes surprising. Dr. Prokunina-Olsson observed, "There is no such thing as a 'typical' cancer gene. For example, we found one gene, *JAZF1,* that is associated not only with prostate cancer but also with type 2 diabetes, systemic lupus erythematosus, and height/body stature—several seemingly unrelated conditions."

Working in the field of genetics comes naturally for Dr. Prokunina-Olsson. As a child in Russia, she tagged along to the laboratory with her parents, both of whom were agricultural geneticists. She earned a master's degree in molecular genetics from Moscow State University in 1993 and a Ph.D. in medical genetics from Uppsala University in Sweden in 2004. From 2005 to 2008, she was a visiting fellow with Dr. Francis Collins at the National Human Genome Research Institute. She subsequently joined LTG as a research fellow in June 2008 and became a tenure-track investigator in April 2010.

Dr. Prokunina-Olsson plans to continue her work investigating the genetic underpinnings of human diseases. When she is not in the laboratory, she enjoys spending time with her husband and children. The family has a particular interest in traditional Scandinavian music and dance, and her hobbies include knitting and Russian cooking.

After GWAS, it is critical to identify the functional risk variants and the genes

affected. Dr. Amundadottir commented, "We already have identified a number of common germline susceptibility variants, but we are not yet at the point where we can use the information for developing diagnostics. Each variant increases risk by only 10 to 20 percent, and most people have both 'good' and 'bad' variants that decrease and increase risk, respectively. That's why we need to understand the biology behind the GWAS-identified variants: to see how their effects are mediated."

Dr. Amundadottir's background spans two worlds—genetics and functional molecular biology—making her particularly well suited for investigating risk variants. A native of Iceland, Dr. Amundadottir earned an advanced degree in genetics from the University of Iceland and a Ph.D. in cell biology from Georgetown University in Washington, DC. After a postdoctoral fellowship at Harvard University, she led the cancer department at deCODE Genetics in Reykjavik for eight years. In 2007, she interviewed with **Stephen J. Chanock, M.D.,** Director of the Core Genotyping Facility and Chief of LTG. She accepted a position as senior scientist and, with her family, moved across the Atlantic. She became a tenure-track investigator in 2008.

Working at the interface of GWAS and functional biology, Dr. Amundadottir and her laboratory team are trying to understand how SNPs identified by GWAS influence the risk of prostate and pancreatic cancers. She explained, "We are building a repository of genome-wide transcriptome and epigenome data that can be consulted whenever we find a new region of interest. Then, we apply a more targeted approach in each of the different regions to try to correlate molecular phenotypes with the risk variants identified through GWAS. We are looking at gene expression and regulation thereof, analyzing how proteins bind DNA and DNA methylation. The common goal is to elucidate the biology of the association signal and the genes affected."

Dr. Amundadottir described two of her most exciting recent achievements: finding risk variants on chromosome 8q24 that are associated with prostate cancer risk and, through a team effort, discovering four genetic regions that influence risk for pancreatic cancer. She hopes to determine how some of the germline variants mediate risk. Her accomplishments have been possible, according to Dr. Amundadottir, "because the leadership of DCEG has been working for decades to assemble large epidemiologic studies with biospecimens that provide the basis for conducting GWAS in multiple cancers. This amazing interdisciplinary orientation allows good science to flourish, not only in cancer, but in other disease areas as well."

Dr. Amundadottir thrives in the collaborative environment of NCI and NIH. She explained, "There is always someone available who is an expert in the gene or the technology in which you are interested. Everything is open, and information flows easily." Although searching for germline susceptibility factors is now relatively easy and straightforward, the downstream biology to understand the genes and pathways affected by these variants takes time. Dr. Amundadottir said she persists because "it is a privilege to work in this exciting area of research. I see my future here at LTG, following paths where the data lead me."

In her spare time, Dr. Amundadottir enjoys being outdoors with her family. "In Iceland, we liked to travel to remote areas of the country, climb mountains, hike across glaciers, and sleep in rustic huts," she recalled. ■

—Karen Eddleman

SECOND ROBERT A. WELCH FELLOW

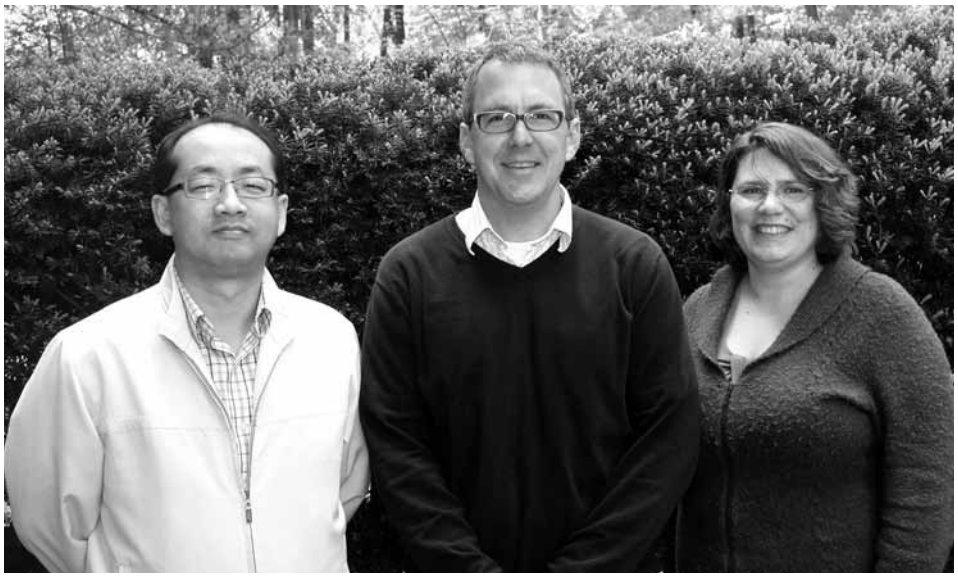
Hemang Parikh

Hemang Parikh, Ph.D., Laboratory of Translational Genomics (LTG), has been selected as the second Robert A. Welch Fellow. Dr. Parikh joined LTG in 2009 and has been working with his mentor, **Laufey Amundadottir, Ph.D.** (LTG), to identify the functional causal variants of pancreatic cancer through follow-up analyses of data from genome-wide association studies (GWAS) using several high-throughput genomic approaches. Dr. Parikh's focus involves biostatistical and bioinformatical analyses of next-generation sequencing data, including deep DNA sequencing, chromatin immunoprecipitation (ChIP) sequencing, and RNA and microRNA sequencing. He will conduct his research in the context of large-scale case-control and cohort studies. In addition to a stipend, the award provides Dr. Parikh with funding for additional training and travel to a scientific conference focusing on genetic technology.

The Robert A. Welch Fellowship is a competitive postdoctoral award within DCEG that supports mentored research in molecular epidemiology, with special emphasis on the application of emerging genomic technology. The fellowship was established in honor of the late Robert A. Welch, M.S., founding Director of Operations at the NCI Core Genotyping Facility (CGF). Mr. Welch played a key role in developing and managing the CGF and its large-scale studies of the cancer risks associated with common genetic variations. His commitment and leadership inspired his colleagues at both the CGF and elsewhere and were central to the success of the CGF, which continues to work toward his vision.

DRS. FRIESEN, LEE, AND MATTHEWS TACKLE EXPOSURE ASSESSMENT

Accurate exposure assessment is critical as cancer epidemiologists strive to clarify exposure-disease relationships. To further advance this field, three new DCEG tenure-track investigators are using their unique skills to improve exposure assessment in occupational, radiation, and physical activity epidemiology.



Choonsik Lee, Charles Matthews, and Melissa Friesen.

Opening the "Black Box" in Assessing Workplace Exposure

Melissa Friesen, Ph.D., joined the Occupational and Environmental Epidemiology Branch in June 2009 after completing a postdoctoral research fellowship in environmental health sciences at the University of California, Berkeley. "It was my interest in the methods for estimating workplace exposures that drew me to DCEG," Dr. Friesen said. "The resources here provide a great place to test assessment methods because you can look at many occupational exposures across many different studies."

Dr. Friesen, who received an M.Sc. and Ph.D. from the University of British Columbia's School of Occupational and Environmental Hygiene—now called the School of Environmental Health—in Vancouver, Canada, initially wanted to be a practitioner in industrial hygiene. "I entered the field because of my family, many of whom work in environments where they might experience harmful exposures, and I wanted to protect them," she explained. "However, a month after starting my graduate program, I fell in love with research and changed my plans."

According to Dr. Friesen, the biggest challenge in the field of occupational cancer is "the long latency period between exposure and the development of disease." Another major challenge is evaluating questionnaire responses to make decisions about exposure. In population-based case-control studies, the current best practice is to use experts to review occupational histories and job- or industry-specific modules completed by the study subjects and to assign exposure estimates. This approach, however, creates a "black box effect" in terms of the decision process.

Improving expert assessments is a key research interest for Dr. Friesen. "For production jobs, we have pretty good agreement across multiple assessors," she stated. "But for non-production jobs, there tends to be less agreement." Making more assessments and averaging them in non-production jobs might be a way to improve accuracy. To sort this out, Dr. Friesen is studying the use of statistical models and machine-learning approaches to uncover the latent decision rules used in expert assessments.

"Although these decision rules tend not to be transparent, it may be possible to create models that can improve accuracy," Dr. Friesen noted. Such models also may greatly improve efficiency because assessments tend to be time-consuming. For example, in a 10,000-person study, if each subject reports an average of 8 to 10 jobs over a working lifetime, that can mean 100,000 job records. The task becomes even more labor-intensive when the specific exposures of interest are considered. As part of her interest in exposure assessment, Dr. Friesen has been a member of the Occupational and Environmental Exposure Advisory Group for the Canadian Partnership against Cancer since 2009.

Human Phantoms: Creating Models of Radiation Exposure

With the widespread use of radiation in medical diagnosis and therapy, exposure to radiation and the subsequent risk for developing cancer remains a high-priority research area in cancer epidemiology.

In May 2009, **Choonsik Lee, Ph.D.,** joined the Radiation Epidemiology

Branch, bringing expertise in improving the precision of estimating exposures from medical radiation. Dr. Lee, who has an M.S. and Ph.D. in health physics from Hanyang University in Seoul, South Korea, focuses on computational human phantom development and advanced dosimetry applications.

"This is a really wonderful field," Dr. Lee reflected. "It's an area of research where I can apply my interests in methodology and computer modeling to something really important."

Dr. Lee is currently working on estimating radiation doses from computed tomography scans, especially in children; quantifying the risk of second cancers following therapeutic radiation for a first cancer; and developing better methods to quantify exposures from x-rays.

One way to enhance these areas is through anthropomorphic modeling, which uses computational models of human anatomy (called human phantoms) and the simulation of radiation behavior to investigate the way the human body responds to radiation. Dr. Lee is an emerging leader in developing the third generation of human phantoms, which employ advanced mathematical representations wherein body height and weight can be adjusted. "These newer phantoms allow a great deal of flexibility in modeling, which helps us increase the accuracy of radiation exposure assessment," Dr. Lee noted.

Working with his advisor, Dr. Wesley Bolch, Dr. Lee and other team members at the University of Florida in Gainesville developed a series of 12 phantoms for males and females, representing newborns to adults. Data from three databases were incorporated into the model: reference organ mass from the International Commission on Radiological Protection and Measurements (ICRP), anthropomorphic data from the Centers for Disease Control and Prevention, and body composition data from the International Commission on Radiation Units and Measurements.

"The matching to three reference databases provides adaptability that we haven't had before in these types of phantoms," Dr. Lee said. ICRP recently adopted this model as the basis for the international reference phantom standard. Dr. Lee serves as a corresponding member of the Dose Calculation Task Group of the ICRP.

Although the model represents a significant advance in the field, "the biggest challenge is to validate the computer models in humans. If we succeed, it will give epidemiologists great confidence in the accuracy of the models."

Although the model represents a significant advance in the field, "the biggest challenge is to validate the computer models in humans," Dr. Lee said. "If we succeed, it will give epidemiologists great confidence in the accuracy of the models."

Self-reported Physical Activity: Improving Precision and Ease of Use

The role of physical activity as it relates to cancer prevention and control is a fairly new but rapidly expanding field of research. In 1996, the U.S. Surgeon General issued the first report on physical activity and health. After extensive analysis of the scientific information on physical activity and health, the Department of Health and Human Services issued the *2008 Physical Activity Guidelines for Americans.*

Charles E. Matthews, Ph.D., a physical activity epidemiologist who joined the Nutritional Epidemiology Branch (NEB) in June 2009, believes that the timing was fortuitous in his entry into the field. "I started out in exercise physiology, but physical activity epidemiology was taking off just as I was doing my training," Dr. Matthews noted. He has an M.S. in exercise science from the University of South Carolina in Columbia and a Ph.D. in epidemiology from the University of Massachusetts in Amherst. "I was exposed to the idea of combining exercise and public health early in my training," he explained.

Dr. Matthews has been working on updating ACT24 (Activities Completed over Time in 24 hours), a Web-based, automated, self-administered recall system developed by scientists in DCEG and the NCI Division of Cancer Control and Population Sciences (DCCPS). ACT24 walks individuals through the previous 24-hour period to gather information about how and where they spent their time. These data can be translated into time spent sleeping, time performing sedentary behaviors (i.e., sitting), and energy expended on physical activity.

"Our new measurement tools are helping us refine our understanding of how people spend their time and the risks and benefits associated with different physical activity behaviors," Dr. Matthews explained. "And what we've found is that people spend the majority of their time sitting—up to 8 to 10 hours per day at

their computers, in their cars, in front of their televisions… and this much sitting may be more harmful than we previously thought, even for very active individuals." Dr. Matthews added that a major impediment to advancing our understanding of the health risks associated with prolonged sitting, or the potential benefits of participating in lower-intensity activities at home or work, has been the limited ability to measure these exposures in etiologic studies.

"Although we gained a lot of insight into the benefits of moderate-intensity activity during the 1990s, it's been much harder to measure sitting time and the many light-intensity activities we do each day." For example, household activities may be difficult to recall. "You may be thinking about 12 other things while you are cleaning the house, so you don't necessarily remember how much you did," he explained.

The hope is that the previous-day reporting approach used in ACT24 will improve recall data. Additionally, administering ACT24 via the Web will greatly reduce the cost of using such an instrument in large cohort studies and will facilitate gathering repeated measures over time that can be used to estimate habitual levels of behavior. "One of the great things about being here is being able to work closely with the biostatisticians at NCI," Dr. Matthews noted. "This is helping us use cutting-edge measurement error models to optimize the information we gather from ACT24."

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Dr. Matthews and his colleagues will soon implement ACT24 in a feasibility study within the NIH-AARP Diet and Health Study and in large-scale methodological studies that will help determine the measurement properties of the instrument. Dr. Matthews, along with colleagues in NEB and DCCPS, plans to make ACT24 available to the extramural community.

Dr. Matthews is a Fellow of the American College of Sports Medicine (ACSM) and is associate editor for ACSM's journal *Medicine & Science in Sports & Exercise*. Since 2003, he has worked on the NIH Special Emphasis Panel for Improving Diet and Physical Activity Assessment and is a Planning Workgroup member on the ACSM Roundtable on Exercise Guidelines for Cancer Survivors. ■

—Maria Sgambati, M.D.

JOURNAL SECTION FOCUSES ON BIOSPECIMENS AND BIOMARKERS IN EPIDEMIOLOGY

The April issue of *Cancer Epidemiology, Biomarkers & Prevention* includes a special section on the latest advances in technology and research in biomarkers and biospecimens. The section was co-edited by **Ann W. Hsing, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), and Dr. Jimmie B. Vaught, Deputy Director of NCI's Office of Biorepositories and Biospecimen Research and former DCEG Special Assistant for Biological Resources. "High-quality assays with good sensitivity, specificity, and reproducibility are essential to the validity of molecular epidemiologic investigations," Dr. Hsing explained. "Our aim is to share important findings on assay quality, as well as the impact of biospecimen collection, processing, and storage on the integrity of the specimens, with the hope of facilitating the application of novel biomarker tools in molecular epidemiology," Dr. Vaught stated. Several DCEG investigators coauthored articles for the section, including **Kelly L. Bolton,** Laboratory of Translational Genomics; **Jonine D. Figueroa, Ph.D., M.P.H.** (HREB); **Montserrat Garcia-Closas, M.D., Dr.P.H.,** Office of the Director (OD); **Allan Hildesheim, Ph.D.,** Chief of the Infections and Immunoepidemiology Branch (IIB); **Jonathan N. Hofmann, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB); **Wen-Yi Huang, Ph.D.** (OEEB); **Jill Koshiol, Ph.D.** (IIB); **Maria Teresa Landi, M.D., Ph.D.,** Genetic Epidemiology Branch (GEB); **Petra Lenz** (OEEB); **Tamra E. Meyer, Ph.D.** (HREB); **Lee E. Moore, Ph.D.** (OEEB); **Ruth M. Pfeiffer, Ph.D.,** Biostatistics Branch (BB); **Ligia A. Pinto, Ph.D.** (IIB); **Karen E. Pitt, Ph.D.** (OD); **Carolina Porras, M.Sc.** (IIB); **Mark P. Purdue, Ph.D.** (OEEB); **Sabah M. Quraishi, M.P.H.** (HREB); **Mark Schiffman, M.D.,** Clinical Genetics Branch; **Fatma M. Shebl, M.D., Ph.D.** (IIB); **Mark E. Sherman, M.D.** (HREB); **Xiaohong Rose Yang, Ph.D.** (GEB); and **Kai Yu, Ph.D.** (BB).

ANNUAL NCI INTRAMURAL SCIENTIFIC RETREAT HELD

The 14th Annual NCI Intramural Scientific Retreat was held in January to recognize the outstanding research being conducted in NCI's Intramural Research Program. The retreat opened with welcomes from John E. Niederhuber, M.D., NCI Director; Dr. Robert Wiltrout, Director of the Center for Cancer Research (CCR); and **Joseph F. Fraumeni, Jr., M.D.,** DCEG Director. Participants included more than 650 NCI scientists and administrators along with members of the Board of Scientific Counselors, the Board of Scientific Advisors, the Clinical Trials Advisory Committee, and the National Cancer Advisory Board. The retreat featured three award lectures, scientific presentations, and poster sessions.

Dr. Leslie Bernstein from the City of Hope National Medical Center received the NCI Rosalind E. Franklin Award for Women in Science, given annually to a woman scientist for excellence in cancer research. She presented a lecture on "Reducing breast cancer risk through biology, epidemiology, and serendipity."

Dr. Stephen Baylin, Deputy Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, received the 14th annual Alfred G. Knudson Award in Cancer Genetics and presented "Dissecting the cancer epigenome: From biology to the patient."

Michael Gottesman, M.D., NIH Deputy Director for Intramural Research and Chief of the CCR Laboratory of Cell Biology, accepted the sixth annual Alan S. Rabson Award for Intramural Research. He spoke on "New ways to think about multidrug resistance in cancer."

The NCI Women Scientist Advisors sponsored a tenure-track networking breakfast and a career development luncheon. During the luncheon, the group presented its first annual Mentoring and Leadership Awards to Dr. Fraumeni and Dr. Maria Merino of CCR.

DCEG Winners of the NCI Director's Intramural Innovation Awards: Jill Koshiol, Melissa Rotunno, and Lisa Mirabello. (Not shown: Jonine Figueroa.) *(Photograph credit: Bill Branson)*

Dr. Niederhuber presented the 2010 NCI Director's Intramural Innovation Awards, which are designed to support the development of novel approaches and technologies for accelerating cancer research. The awards offer one-time research funding at two levels: (1) the Principal Investigator (PI) Award for tenure-track investigators and scientists tenured within the past five years and (2) the Career Development Award for postdoctoral fellows, staff scientists, staff clinicians, and senior scientists.

Jonine D. Figueroa, Ph.D., M.P.H., Hormonal and Reproductive Epidemiology Branch, received a PI Award for her proposal "Integrating *TP53* somatic alterations, autoantibodies, and risk factors in estrogen receptor-negative breast cancer."

In addition, three DCEG fellows received Career Development Awards: **Jill Koshiol, Ph.D.,** Infections and Immunoepidemiology Branch, for "Stromal infiltrates associated with molecular subtypes of breast cancer: Etiologic and prognostic significance"; **Lisa Mirabello, Ph.D.,** Clinical Genetics Branch, for her proposal "Promoter methylation of susceptibility genes in familial testicular cancer"; and **Melissa Rotunno, Ph.D.,** Genetic Epidemiology Branch, for her proposal "Gene expression signatures for early-stage lung adenocarcinoma from peripheral blood samples." ■

Leslie Bernstein receives the Rosalind E. Franklin Award for Women in Science from Ann Hsing. *(Photograph credit: Bill Branson)*

—Jacqueline Feenster and Marianne K. Henderson, M.S.

DCEG HOSTS VISITING SCHOLAR LOUISE STRONG

DCEG welcomed Dr. Louise C. Strong as a Visiting Scholar in February. Dr. Strong is a tenured professor and the Sue and Radcliffe Killam Chair of the Department of Genetics as well as a professor of cancer genetics in the Department of Breast Medical Oncology, Division of Cancer Medicine, at The University of Texas M.D. Anderson Cancer Center in Houston, Texas. She also is an adjunct professor at the university's School of Public Health.

Dr. Strong is best known for her work in the fields of cancer genetics and epidemiology, where she has shown strong scientific leadership and vision in pursuing studies of the genetic components and late effects of childhood cancer. After receiving her medical degree from The University of Texas Medical Branch at Galveston, she began a postdoctoral fellowship with Dr. Alfred Knudson at the university's Graduate School of Biomedical Sciences at Houston. She describes this "fortunate partnership" as the catalyst that allowed her to pursue her interest in childhood cancer genetics at an early stage of her career. Dr. Strong has since been a pioneer in advancing our understanding of cancer-prone disorders, with seminal discoveries into the genetic basis of Wilms tumor, retinoblastoma, and Li-Fraumeni syndrome (LFS). Her collaborative efforts contributed to the discovery of *p53* germline mutations in individuals with LFS. Dr. Strong is currently involved in studies exploring the role of genetic susceptibility and treatment effects as contributors to the risk of second cancers following various childhood tumors.

Louise Strong

Dr. Strong began her two-day visit by presenting a seminar titled "Li-Fraumeni syndrome: Cancer risk and risk modifiers." **Sharon A. Savage, M.D.,** Clinical Genetics Branch (CGB), opened the seminar, remarking, "It is a great honor to introduce Dr. Strong; she has been a good friend and collaborator with DCEG for several decades."

Dr. Strong outlined the progression of her research into the genetic aspects of childhood cancers, describing the "rich resource of patients" at M.D. Anderson and highlighting the collaborative study that linked *p53* germline mutations to LFS. "Once you have the gene, that's just the beginning of the story. That's when it gets fun," Dr. Strong said.

In her presentation, Dr. Strong described her research that clarified the phenotypic manifestations of LFS. This research also shed light on the risk modifiers of LFS, including gender; *p53* mutation type; radiation exposure; and genotypes of MDM2, a negative regulator of *p53*. She also touched on current studies investigating the link between telomere length and cancer risk. Dr. Strong wrapped up the seminar by discussing the clinical implications of continued research in the field,

FALL 2009 INTRAMURAL RESEARCH AWARDS

DCEG Intramural Research Awards (IRAs) are competitive funding opportunities designed to foster creative, interdisciplinary research by fellows and tenure-track scientists. The IRA program includes spring and fall cycles, with up to three proposals funded per cycle.

Fall 2009 IRA Winners: Lisa Mirabello, Melissa Rotunno, and Gwen Murphy.

The winners of the fall 2009 competition were **Lisa Mirabello, Ph.D.,** Clinical Genetics Branch, for her proposal "Human papillomavirus-16 methylation patterns associated with risk of disease progression in a prospective population-based cohort"; **Gwen Murphy, Ph.D., M.P.H.,** Nutritional Epidemiology Branch, for "Evaluation of serum antibodies to *Helicobacter pylori* proteins and risk of upper gastrointestinal and pancreatic cancers"; and **Melissa Rotunno, Ph.D.,** Genetic Epidemiology Branch, for "Candidate gene expression signature of early-stage lung cancer from peripheral blood samples."

Members of the Board of Scientific Counselors judge the proposals based on their potential for significant scientific or public health impact, innovation, interdisciplinary nature, ability to achieve the objectives within the proposed time frame and resources, and relevance to the mission of the Division and Institute.

emphasizing the importance of patient and physician education for earlier diagnosis and effective treatment.

Following the seminar, **Joseph F. Fraumeni, Jr., M.D.,** Division Director, presented Dr. Strong with the DCEG Visiting Scholar Award for her major achievements in the field of cancer genetics and epidemiology.

Dr. Strong then participated in a luncheon meeting sponsored by the Women Scientist Advisors and the DCEG Committee of Scientists, discussing issues and challenges related to being in a tenure-track position. Topics included the importance of time management and the need for focused energy to reach certain career and scientific goals.

Later that afternoon, Dr. Strong met with DCEG investigators for a discussion of cancer predisposition syndromes. Participants in the meeting included Dr. Savage, **Christian Kratz, M.D.** (CGB), and **Lynn R. Goldin, Ph.D.,** and **Xiahong Rose Yang, Ph.D., M.P.H.,** both of the Genetic Epidemiology Branch (GEB). DCEG investigators discussed their research, including gene discovery efforts in familial lymphoid malignancies, familial chordoma, dyskeratosis congenita, and *DICER1*-related pleuropulmonary blastoma tumor syndrome.

The next morning, Dr. Strong attended a group discussion led by Radiation Epidemiology Branch investigators **Lindsay M. Morton, Ph.D.,** and **Chu-Ling Yu, Sc.D.,** who presented their research on cause-specific mortality in retinoblastoma patients and the radiation-related risk of esophageal cancer among breast cancer survivors. **Alisa M. Goldstein, Ph.D.** (GEB), also discussed her work on melanoma and pancreatic cancer in relation to the *CDKN2A* gene. Dr. Strong posed questions and offered feedback throughout the discussion.

CGB fellows hosted the final session, which was open to all DCEG fellows. The group discussed a wide variety of topics, including Dr. Strong's background, her early career working with Dr. Knudson, the changing field of cancer epidemiology and genetics, and maintaining a work-life balance. Dr. Strong's advice to the fellows was to "take advantage of the many opportunities within DCEG and have fun along the way. You'll be challenged during your fellowship, but I think you'll find it's very fulfilling."

Discussing her visit to DCEG, Dr. Strong expressed that it was a "treat to be here." She commented, "There are so many opportunities and resources within DCEG, and for me, it's always been a special place." ■

—Victoria McCallum, M.P.H.

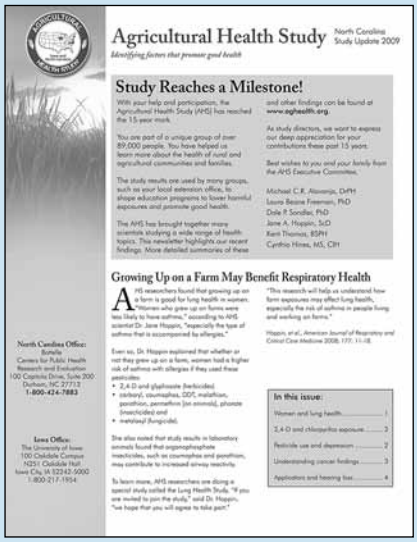
STUDY NEWSLETTER INFORMS AHS PARTICIPANTS

The Agricultural Health Study (AHS), a prospective cohort study of more than 89,000 pesticide applicators and their spouses, recently celebrated its 15th anniversary as a collaborative effort of NCI, the National Institute of Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), the National Institute for Occupational Safety and Health (NIOSH), and extramural investigators. The 2009 AHS newsletter announced the 15-year milestone and thanked participants for their ongoing support.

AHS field stations and Iowa agricultural extension offices distribute the AHS newsletter to cohort members and agricultural communities of Iowa and North Carolina. The newsletter, published annually since 2002, provides information about study results and helps maintain participant awareness, interest, and a sense of common purpose in identifying factors that promote good health.

The AHS newsletter updates participants on recent study results, such as the relation between imazethapyr (an aromatic amine) and bladder and colon cancers as well as the link between two other widely used herbicides (pendimethalin and EPTC) and pancreatic cancer. Recent articles have discussed the cancer evaluation of 25 other pesticides estimated to be used occupationally by more than one billion people worldwide. The newsletter also may include safety tips for reducing pesticide exposure when working with pesticides or when re-entering a home.

In addition to discussing study findings in language understandable to the general public, the AHS newsletter serves as a vehicle to announce new AHS initiatives involving the study population. For example, an article described in plain language the use of buccal cell DNA for studies of gene-environment interactions. Other articles have described the purpose of add-on studies,


Agricultural Health Study
North Carolina Study Update 2009
Identifying factors that promote good health

Study Reaches a Milestone!

Growing Up on a Farm May Benefit Respiratory Health

In this issue:

The Agricultural Health Study newsletter

such as the NIEHS study of respiratory diseases and the exposure assessment measurements used by the EPA and NIOSH.

—Michael C.R. Alavanja, Dr.P.H.

COMPUTED TOMOGRAPHY SCANS AND CANCER RISK

During February, the U.S. Food and Drug Administration (FDA) announced moves to regulate the medical radiation used in computed tomography (CT) scans, nuclear medicine studies, and fluoroscopies. The evidence backing the development of these new standards flows in part from the research of **Amy Berrington de González, D.Phil.,** an investigator in the Radiation Epidemiology Branch, whose estimates of cancer risk from CT radiation exposure were published in the December 2009 issue of *Archives of Internal Medicine.*

Dr. Berrington de González came to the United States from Great Britain four years ago with a D.Phil. in cancer epidemiology from the University of Oxford. Her doctoral work examined the potential cancer risks from diagnostic x-rays. In work published in *Lancet* in 2004, she reported findings suggesting that about 1 percent of cancers diagnosed in the United States during the 1990s could be attributed to x-ray exposure.

The findings that appeared last winter are a natural extension of this work. Dr. Berrington de González and her colleagues reported estimates of the number of additional cases of cancer that could result from current levels of CT use. They also documented wide variations in radiation levels used at four California facilities, often for the same procedure. Dr. Berrington de González's published work has coincided with the issue's rising public profile, following a 2009 National Council on Radiation Protection and Measurements report suggesting that the U.S. population's exposure to ionizing radiation has nearly doubled during the past two decades.

Since the publication of her article, she noted, "I have received a large number of e-mails from individuals who are concerned about risks from CT scans that they or their family members had in the past."

The backdrop for these latest findings is the tremendous growth in the use of CT scans since their introduction during the early 1970s. Between 1993 and 2007, CT scans in the United States tripled to more than 70 million annually. Physicians now have the benefit of higher resolution, but the tradeoff is that more detailed images require higher doses of radiation. The typical radiation dose from a CT scan starts at 2 millisieverts, about 100 times the dose from a standard chest x-ray. The rising use of scans, examinations with higher radiation levels, and multiple-scan series have focused greater attention on the cumulative exposure that patients receive.

Based on a 2005 report on the biological effects of radiation and an FDA quality assurance survey by the National

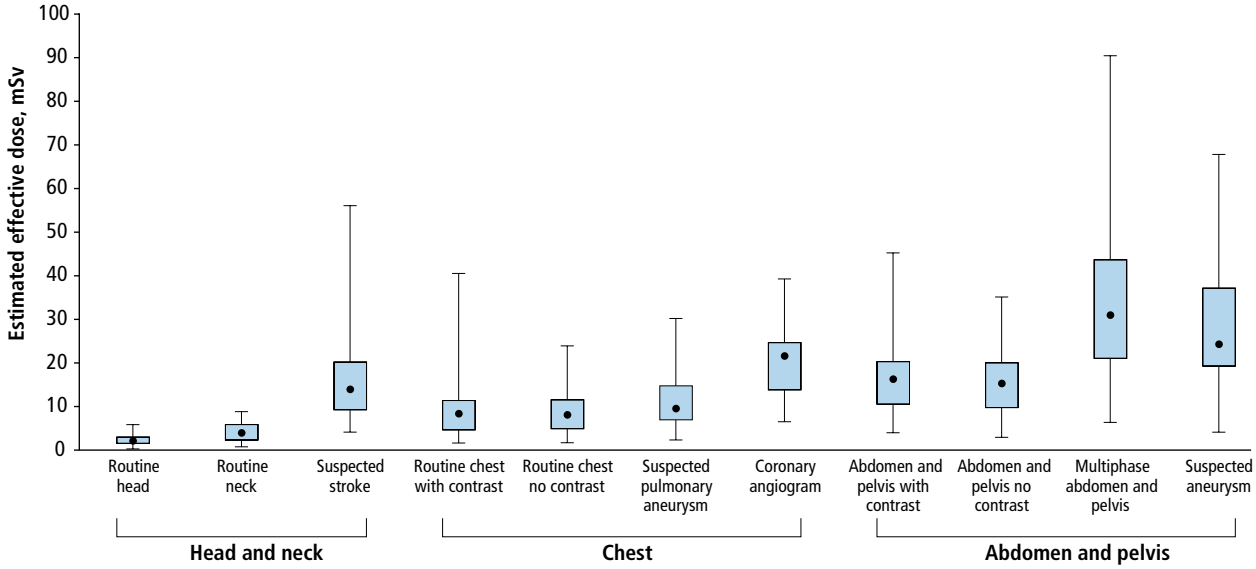


Figure 1. Distribution of median (interquartile range) estimated effective dose by computed tomography study type. The "whiskers" show the minimum and maximum observed values. mSv = millisievert. (Smith-Bindman R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;160:2081)

Research Council, Dr. Berrington de González calculated that current CT scan use could be related to about 29,000 future cases of cancer and, ultimately, 14,500 deaths. Despite typical figures indicating a cancer risk of 1 in 2,000 from CT scans, Dr. Berrington de González and her colleagues found that in scans at the high end of the radiation dose range, a multiphase abdomen and pelvis scan could be associated with a cancer risk as high as 1 in 80 for a 20-year-old woman. In a separate report, the research team estimated that 5 percent of 20-year-old patients undergo CT imaging each year. During 2008, the study documented typical diagnostic exposures at four San Francisco area medical facilities. After examining the 11 most common scanning procedures at these facilities, it was found that, on average, doses for the same procedure varied 13-fold (see Figure 1). This variability indicated that no dose standards were in place for the use of scans.

The research team has proposed solutions for reducing risk, including establishing standards, eliminating overuse, and recording the cumulative exposure of patients. The higher dose scans, such as those examining the abdomen, pelvis, or chest, among patients 35 to 54 years old could have the biggest impact. The studies pointed to the need for establishing standard scanning protocols to limit multiple scans, reduce doses, and encourage accreditation.

As a result of the studies, Dr. Berrington de González said, "I think there will be increasing pressure on equipment manufacturers to improve safety and increase training of the medical staff who operate the machines. I hope these steps will also reduce inappropriate use. Indeed, manufacturers and radiological societies are working on new equipment features, user training, and quality assurance." Already she and her colleagues have seen change close to home; in February, NIH announced a new policy mandating that its facilities use scanners that display radiation exposure levels. This information also will be incorporated into patients' medical records and used to track their cumulative exposure.

The breadth of Dr. Berrington de González's work continues to expand. Her current research estimates the cancer risk resulting from cardiac stress tests using radioactive tracers and analyzes the risks and benefits of CT screening, or virtual colonoscopy, for colorectal cancer. In addition, Dr. Berrington de González serves in an advisory role on a U.K. government committee examining radiation-related cancer risks among the U.K. population. No matter which side of the Atlantic, her work is likely to remain a prominent part of the public conversation. ■

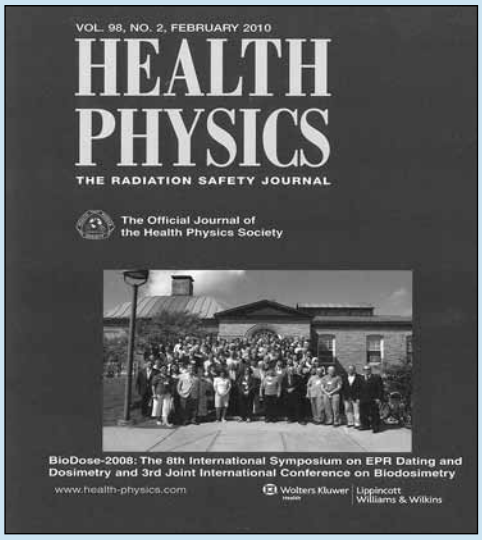
—Sara Harris

STEVEN SIMON LEADS BIODOSE MONOGRAPH

The February 2010 issue of *Health Physics* was a special volume discussing the latest advances in biodosimetry based on presentations from the BioDose-2008 international conference. As guest editor for the volume, **Steven L. Simon, Ph.D.,** of the Radiation Epidemiology Branch, explained, "biodosimetry is the science of coaxing residual radiation-induced signals stored in the human body into revealing themselves in a quantitative way in order to determine the degree of past exposure."

Unlike occupational dosimetry—in which radiation doses for workers are routinely estimated using measurements obtained from personal monitoring devices (e.g., a film badge)—biodosimetry carries with it the challenge of estimating radiation doses for people who do not carry any kind of conventional radiation monitoring device but who might be accidentally or unknowingly exposed to radiation; this can include exposure from accidents or terrorist actions. In such situations, there may be tens of thousands of people who want a dose assessment and some whose exposure may warrant treatment within a very short time frame, ranging from a few hours to a few days. Those working in the field of biodosimetry consider this mass exposure scenario as their greatest challenge.

The national concern about nuclear terrorism has given Dr. Simon opportunities for unique scientific collaborations. He contributes his dosimetry expertise through his work with Medical Countermeasures Against Radiological and Nuclear Threats, a national intra-agency program coordinated by the National Institute of Allergy and Infectious Diseases. He also collaborates with investigators from Oklahoma State University on a method that uses laser light to measure the radiation-induced signal stored in the enamel of human teeth. Dr. Simon stated that "while the possibility of nuclear terrorism is a somber thought, it also challenges us to contribute our knowledge of exposure assessment in cancer risk studies to this larger national issue."



The February issue of *Health Physics*

THYROID CANCER WORKING GROUP

In 2007, the DCEG Senior Advisory Group established a series of working groups to enable strategic planning in areas that are central to the Division's research. Some of the groups focus on specific tumors that are highly lethal or rising in incidence. Toward that end, a working group was established to plan studies of thyroid cancer, whose incidence rates have increased about 6 percent per year over the past decade. The increase in thyroid cancer has been greater among women than men, such that thyroid cancer is now the seventh most common female cancer. These upward trends are not limited to localized tumors, suggesting that the increasing rates cannot be explained entirely by improvements in detection.

The Thyroid Cancer Working Group was created to foster strategic collaborations in several areas of research, including descriptive epidemiology, environmental and radiation exposures, lifestyle and nutritional exposures, molecular tumor markers, pathway-based candidate gene studies, and genome-wide association studies (GWAS). Since the group was established nearly one year ago, almost 20 manuscripts related to thyroid cancer have been submitted for publication, with many more in progress. The sidebar (right panel) details efforts undertaken by members of the group.

Cochaired by **Elaine Ron, Ph.D.,** and **Alice J. Sigurdson, Ph.D.,** both of the Radiation Epidemiology Branch (REB), the working group includes scientists from DCEG, the Center for Cancer Research (CCR), and the extramural community. Recent observations from descriptive epidemiology studies in the United States have clarified temporal, gender, racial, and age patterns by cell type and size (see Figure 1).

Internationally, the incidence rates vary widely by country, but they have generally increased—except in Sweden, where, surprisingly, the rates for men and women have decreased. In age-period-cohort analyses, birth cohort and time period effects have contributed to the rising incidence in the United States, suggesting that surveillance and screening have improved, although lifestyle and environmental exposures may be responsible as well. **Briseis Kilfoy, Ph.D.,** and **Mary H. Ward, Ph.D.,** both of the Occupational and Environmental Epidemiology Branch, along with **William F. Anderson, M.D., M.P.H.,** and **Susan S. Devesa, Ph.D.,** both of the Biostatistics Branch (BB), conducted these descriptive analyses.

Lifestyle and body mass index (BMI) were investigated in two cohorts. A major finding was the association of high BMI with excess risk of papillary and follicular thyroid cancers, with risks up to 1.7-fold in the highest level of adiposity. Consistent with previous findings, a reduced risk of thyroid cancer was associated with smoking and alcohol consumption. DCEG investigators involved in this research have included **Amy Berrington de González, D.Phil., Alina V. Brenner, M.D., Ph.D.,** and **Cari Meinhold, M.H.S.,** all of REB, as well as **Yikyung Park, Sc.D.,** of the Nutritional Epidemiology Branch (NEB). In addition, Drs. Kilfoy and Ward found in the Iowa Women's Cohort an increased risk of thyroid cancer associated with higher nitrate levels in public water supplies and with intake of dietary nitrate.

External ionizing radiation is one of the few established risk factors for thyroid cancer, but much less is known about the effects of exposure to radioiodines.

Elaine Ron and Alice Sigurdson.

Using data from the Surveillance, Epidemiology, and End Results (SEER) Program, **Ethel S. Gilbert, Ph.D.** (REB), and colleagues have analyzed thyroid cancer incidence rates for counties according to the estimated level of radioactive fallout from atmospheric tests conducted in Nevada during the 1950s. Counter to expectation, this ecologic analysis confirmed an earlier finding of excess risk associated with exposure occurring before the age of 1, but not for exposure occurring between ages 1 and 15. Despite the uncertainties in dose estimation and case ascertainment due to migration, the study somewhat supports the role of radioactive fallout in the rising incidence of thyroid cancer. The findings are noteworthy because radioiodines have been linked to thyroid cancer and benign thyroid nodules in DCEG-led studies of populations exposed to nuclear weapons testing in Kazakhstan, the Chornobyl accident in Ukraine, and emissions from the Mayak nuclear weapons plant in Russia. Most recently, **Maureen C. Hatch, Ph.D.** (REB), along with Drs. Brenner and Ron, analyzed thyroid cancer occurrence in children who were exposed *in utero* to radioiodine from the Chornobyl accident and found an elevated risk,

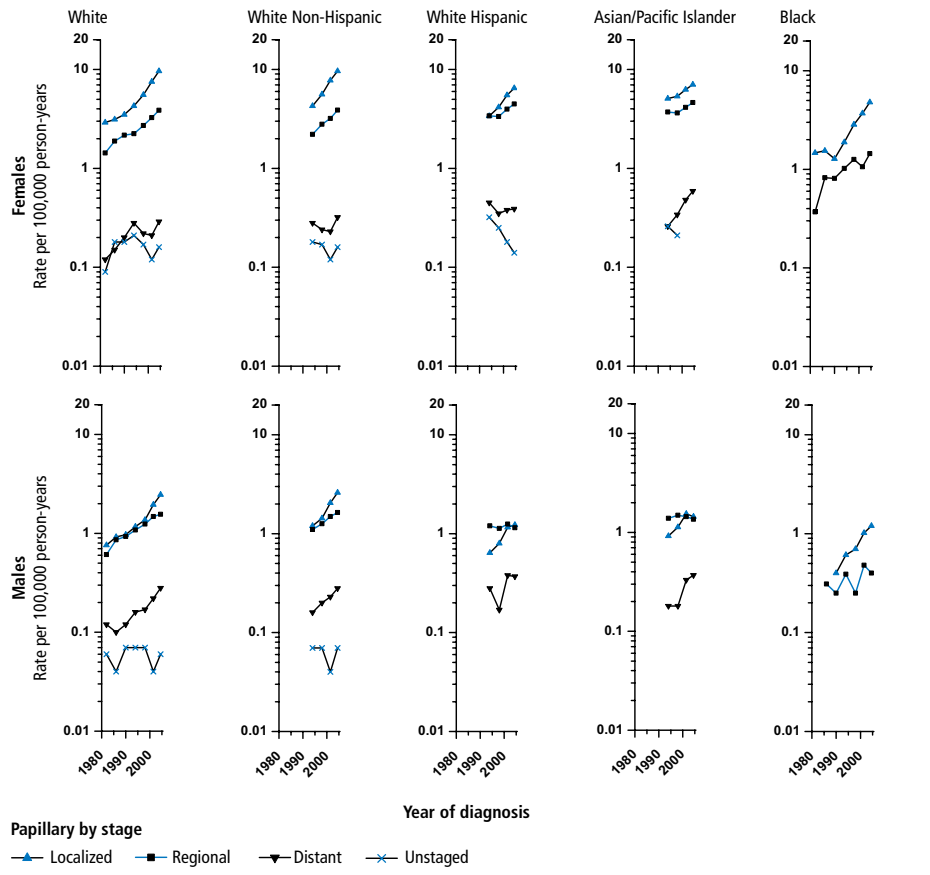


Figure 1. Stage-specific rates of papillary thyroid cancer incidence diagnosed between 1980–1983 and 2003–2005 by sex and race/ethnicity.

suggesting the need for caution in the medical use of radioiodine among pregnant women.

Ongoing projects for the Thyroid Cancer Working Group include the identification of molecular and genetic biomarkers of thyroid cancer (including tumors that are radiation related) and studies on the impact of various chemicals (including persistent organochlorines), the effects of nitrate and nitrite in drinking water and food, and the role of dietary and nutritional factors. Racial-linkage studies are also under way to evaluate associations with various medical conditions, including other cancers. Because thyroid cancer is relatively rare, DCEG investigators are collaborating with extramural colleagues to conduct pooled studies of several cohorts to increase statistical power.

Other members of the working group include Dr. Sanjeeve Balasubramaniam (CCR); Dr. Parveen Bhatti of the Fred Hutchinson Cancer Research Center; Dr. Florent De Vathaire of the Institute for Health and Medical Research (INSERM); Dr. Lindsey Enewold of the U.S. Military Cancer Institute; **Joseph F. Fraumeni, Jr., M.D.,** Division Director; **Jay H. Lubin, Ph.D.** (BB); **Kiyohiko Mabuchi, Ph.D.,** and **Gila Neta, Ph.D.** (both of REB); **Ruth M. Pfeiffer, Ph.D.** (BB); **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB); **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of the Genetic Epidemiology Branch; and **Lene Veiga, Ph.D.** (REB). ■

—Alice Sigurdson, Ph.D., and Elaine Ron, Ph.D.

Areas of Research Concentration by the DCEG Thyroid Cancer Working Group

Descriptive Epidemiology

- Determine reasons for increased thyroid cancer rates
  - Geographic comparisons and international patterns
  - Gender, age, birth cohort, histology, and tumor size
  - Risk factor differences by gender

Ionizing Radiation Exposure

- Environmental
  - Radioactive fallout from the Nevada test site
  - Nuclear weapons testing in Kazakhstan
  - Effects from Chornobyl exposure among young adults and *in utero*
  - Thyroid microcarcinomas among atomic bomb survivors
- Workplace
  - Occupational exposure to radiologic technologists
- Therapeutic
  - Childhood cancer survivors
    - Radiation and chemotherapy for a childhood malignancy
    - Pooled study of childhood cancer survivors in the United States and Europe
  - Diagnostic medical procedures

Nutrition, Lifestyle, and Health Habits

- Body mass index
- Weight change and central adiposity
- Alcohol consumption
- Cigarette smoking
- Reproductive factors
- Fruit and vegetable consumption
- Nitrites and nitrates in the diet
- Health care utilization and screening patterns

Molecular and Genetic

- Changes over time for *RET/PTC*, *RAS*, and *BRAF* in thyroid tumors
- Rare Cancer iSelect for pathway-based genotyping
  - Includes 25,000 single-nucleotide polymorphisms in multiple genes of interest

Environmental Contaminants

- Nitrates and nitrites in drinking water
- Effect of nitrates and nitrites on thyroid-stimulating hormone
- Serum levels of polychlorinated biphenyls and polybrominated diphenyl ethers

SALLIE ROSEN KAPLAN FELLOWS LUNCHEON

Current and former Sallie Rosen Kaplan Fellows, including **Nicole Deziel, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB), **Linda Dong, Ph.D.** (OEEB), **Tamra Meyer, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), **Mahboobeh Safaeian, Ph.D.,** Infections and Immunoepidemiology Branch (IIB), **Meredith Shiels, Ph.D.** (IIB), and **Britton Trabert, Ph.D.** (HREB), along with **Louise A. Brinton, Ph.D.,** Chief of HREB and Chair of the DCEG Office of Education Advisory Group, attended a luncheon in April with Sallie Rosen Kaplan's nephew, Dr. Jeffrey M. Rosen of the Baylor College of Medicine in Houston, Texas. The Sallie Rosen Kaplan Fellowship for Women Scientists in Cancer Research is a competitive program for female postdoctoral fellows applying to train in any of NCI's intramural research settings, including basic, clinical, and population sciences.

DCEG Sallie Rosen Kaplan Fellows (front row) Nicole Deziel and Mahboobeh Safaeian with Jeffrey Rosen (middle); (back row) Britton Trabert, Meredith Shiels, Tamra Meyer, and Linda Dong. *(Photograph credit: Ernie Branson)*

Dr. Rosen opened the luncheon by welcoming the fellows and discussing the origins of the fellowship, which was established in 2000 through the estate of Sallie Rosen Kaplan. Mrs. Kaplan was deeply committed to education, especially for women, based on her own experiences growing up in the early 20th century when educational opportunities for women were limited. When creating the terms of her bequest, Mrs. Kaplan's intent was to help support biomedical research at NIH. As her next of kin, Dr. Rosen was charged with the task of deciding how the funds would be used; his wife, Madeline, suggested this endowment could best be used to support women entering the field of cancer research.

At the luncheon, Dr. Rosen took great interest in each fellow, asking each one to discuss her academic history, research interests, and career aspirations. He also fielded questions and gave career advice, emphasizing the critical roles played by mentors and colleagues, the importance of choosing an environment rich in resources, the value of effective communication skills, and the growing need for multidisciplinary research.

Dr. Rosen stated, "I am happy to see that the Sallie Rosen Kaplan Fellowship has been successful in supporting women scientists. My aunt would have been really pleased with the diversity of research and the multitude of places from where each fellow comes." ■

NEW SALLIE ROSEN KAPLAN FELLOW

Nicole Deziel, Ph.D., DCEG's most recent Sallie Rosen Kaplan Fellow, joined the Occupational and Environmental Epidemiology Branch in February. Dr. Deziel received her master's degree in industrial hygiene in 2000 and her doctorate in environmental health sciences in 2008, both from the Johns Hopkins Bloomberg School of Public Health. Her master's project evaluated the performance of a personal particulate sampler, and her doctoral thesis compared standard methods for assessing exposure to dietary carcinogens, including diet diaries, questionnaires, and biological markers. While at Johns Hopkins, she worked with the Environmental Protection Agency, comparing inhalation and dermal exposure measurements with biomonitoring markers in pesticide handlers. Prior to coming to NCI, she worked at Westat, where she developed environmental sampling procedures for pesticide exposures for the National Children's Study. During her fellowship at DCEG, she will work with **Mary H. Ward, Ph.D.,** and **Melissa Friesen, Ph.D.,** on research to improve and validate methods for assessing environmental and occupational exposures in epidemiological studies.

Nicole Deziel

SECOND ANNUAL FELLOWS' TRAINING SYMPOSIUM

March marked the Second Annual DCEG Fellows' Training Symposium, titled "New Decade, New Directions." The event was sponsored by DCEG's Office of Education (OE) and organized by a group of DCEG fellows, including committee chair **Britton Trabert, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), **Cindy M. Chang, Ph.D.,** Infections and Immunoepidemiology Branch (IIB), **Cher Dallal, Ph.D.** (HREB), **Mercy Guech-Ongey, Ph.D.** (IIB), **Shih-Wen (Wenny) Lin, Ph.D., M.P.H.,** Nutritional Epidemiology Branch (NEB), **Jacqueline Major, Ph.D.** (NEB), **Tamra Meyer, Ph.D.** (HREB), **Fatma Shebl, M.D., Ph.D.** (IIB), and **Laura Sue, M.P.H.,** Epidemiology and Biostatistics Program (EBP), with support from OE Chief **Jackie Lavigne, Ph.D., M.P.H.,** and OE members **Kristin Kiser, M.H.A., M.S.,** and **Tess Lee.** More than 60 predoctoral and postdoctoral fellows, representing all of the DCEG units, participated in the event.

Fellows' Symposium Organizing Committee: (front) Laura Sue, Cher Dallal, Jackie Lavigne, Britton Trabert, Mercy Guech-Ongey, and Cindy Chang; (middle) Jacqueline Major and Shih-Wen Lin; (back) Tamra Meyer, Kristen Kiser, and Fatma Shebl. (Not shown: Tess Lee.) *(Photograph credit: Bill Branson)*

Patricia Hartge, Sc.D. (EBP), began the symposium with the lecture "The people's epidemiologist: Yesterday, today, and tomorrow." Dr. Hartge spoke on the history of epidemiologic research at NCI and provided examples of how classic epidemiologic methods are being integrated with technological advances. In "Cancer epidemiology research: Challenges and opportunities," Dr. Paolo Boffetta, professor and Deputy Director of the Tisch Cancer Institute at Mount Sinai School of Medicine in New York City, discussed obstacles in cancer epidemiology research and provided insight into ways to advance the field. Dr. Roberta Ness, Dean of the University of Texas Health Science Center, discussed "The future of epidemiology: Innovative thinking." She focused on the concept of "lateral thinking" as a way to more creatively analyze epidemiologic research questions and explore new and innovative ideas that may not have been considered previously. The morning concluded with a spirited panel discussion in which speakers responded to a variety of questions, providing valuable scientific explanations and career advice.

Two poster sessions featuring the work of more than 30 fellows were held during the afternoon. The sessions provided the attendees with an opportunity to present information about their research projects and scientific findings. Three fellows were chosen to give oral presentations selected by the planning committee for scientific merit, originality, design, and overall quality. The presenters were **Yi-Ping Fu, Ph.D.,** Laboratory of Translational Genomics, who spoke on "NOTCH2 in breast cancer: Association of SNP rs11249433 with gene expression in ER-positive breast tumors without *p53* gene mutations"; **Barbara J. Fuhrman, Ph.D.** (HREB), who spoke on "Sunlight, polymorphisms in vitamin D-related genes, and risk of breast cancer: A case-control study in the U.S. Radiologic Technologists cohort"; and **Hannah P. Yang, Ph.D., Sc.M.** (HREB), who spoke on "Evaluation of common genetic variations in 1,300 cancer-related candidate genes and endometrial cancer risk."

Joseph F. Fraumeni, Jr., M.D., Division Director, concluded the symposium with a presentation titled "DCEG: Where are we going?" He described the Division's future research priorities and approaches to training the new generation of interdisciplinary scientists. Dr. Fraumeni emphasized that the evolving research agenda of the Division will depend to a considerable extent on the creativity and vision of scientists who are in the early stages of their careers.

All participants agreed that the day was a great success, having learned more about their peers' research and gained perspective from leading epidemiologists about future scientific opportunities in cancer epidemiology and genetics. ■

—Britton Trabert, Ph.D.

DCEG PARTICIPATES IN THE ANNUAL AACR MEETING

In April, DCEG members participated in the 101st Annual Meeting of the American Association for Cancer Research (AACR) in Washington, DC. This five-day event provided a forum to highlight the latest scientific advances in basic, clinical, and epidemiologic cancer research. The theme of this year's meeting was "Conquering cancer through discovery research."

Stephen J. Chanock, M.D., Chief of the Laboratory of Translational Genomics (LTG) and Director of the Core Genotyping Facility (CGF), gave a plenary presentation titled "Genome-wide association studies (GWAS) in cancer: What have we found and what next?" **Eric A. Engels, M.D., M.P.H.,** Infections and Immunoepidemiology Branch (IIB), cochaired the symposium Infection, Inflammation, and Immunity: Crossroads to Cancer and presented "Cancer in immunosuppressed populations: Epidemiologic clues to causation." **Montserrat Garcia-Closas, M.D., Dr.P.H.,** Office of the Director, cochaired the symposium Building Upon Genome-wide Association Studies and gave an introductory talk on "How tumor characterization can help." During this symposium, **Meredith Yeager, Ph.D.** (CGF), presented "Comprehensive cataloging of regions identified in GWAS."

Other meeting presentations included **Neil E. Caporaso, M.D.,** Genetic Epidemiology Branch, "Genome-wide and candidate gene associations with smoking behaviors"; **Charles Chung, Ph.D.** (LTG), "Fine mapping and comprehensive resequencing analysis of a region of chromosome 11q13 reveals multiple independent loci associated with prostate cancer"; **Jill Koshiol, Ph.D.** (IIB), "Little evidence of human papillomavirus in lung cancer tissue"; **Jackie Lavigne, Ph.D.,** Chief of the Office of Education, "NCI funding and training opportunities in cancer research"; **Jacqueline Major, Ph.D.,** Nutritional Epidemiology Branch (NEB), "Insulin-like growth factors and kidney cancer risk in men"; and **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB), "The role of vitamin D in cancer prevention: What do we really know?"

DCEG scientists presented more than 44 posters featuring their work. **Yi-Ping Fu, Ph.D.** (LTG), received the AACR-Susan G. Komen for the Cure Scholar-in-Training Award for her poster "NOTCH2 in breast cancer: Association of SNP rs11249433 with gene expression in ER-positive breast tumors without *p53* gene mutations." Abstracts selected for press attention included: **Katherine A. McGlynn, Ph.D.,** Hormonal and Reproductive Epidemiology Branch, "Attributable risks for hepatocellular carcinoma in the United States"; **Charles S. Rabkin, M.D.** (IIB), "Circulating cytokine levels, Epstein-Barr viremia and risk of AIDS-related non-Hodgkin lymphoma"; and **Laura Sue, M.P.H.,** Epidemiology and Biostatistics Program, "Body mass index (BMI), changes in BMI, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)."

DCEG investigators also led or participated in approximately 15 meetings of collaborative research groups held in conjunction with the AACR meeting. For example, **Phuong Mai, M.D., M.S.,** and **Sharon A. Savage, M.D.,** both of the Clinical Genetics Branch, organized and hosted a meeting of international collaborators on Li-Fraumeni syndrome. Several other groups met to review progress and plan future projects, including the African American Prostate Cancer Consortium, the Asia Cohort Consortium, the Epidemiology of Endometrial Cancer Consortium (E2C2), the Hodgkin Lymphoma Consortium, Inter-Lymph, the International Lung Cancer Consortium (ILCCO), the Liver Cancer Pooling Project, the Mammographic Density Working Group, the Multiple Myeloma Research Consortium, the non-Hodgkin Lymphoma GWAS Project, the Ovarian Cancer Cohort Consortium, the SYNERGY joint session with ILCCO, and the Testicular Cancer Consortium. ■

A MULTIDISCIPLINARY CONFERENCE ON MALE BREAST CANCER

In the April 20 issue of the *Journal of Clinical Oncology* (2010;28:2114–2122), **Larissa Korde, M.D., M.P.H.,** a former staff clinician and current adjunct investigator in the Clinical Genetics Branch, and colleagues summarized the presentations from a multidisciplinary international meeting on male breast cancer (MBC). DCEG, the Division of Cancer Treatment and Diagnosis, and the NIH Office of Rare Diseases organized the meeting to foster collaborative research into this rare tumor, which accounts for less than 1 percent of breast cancer diagnoses worldwide. The meeting brought together representatives from the fields of epidemiology, genetics, pathology, clinical oncology, molecular biology, and health services research as well as the advocacy community. Presentations contrasted the epidemiologic, clinical, and biological aspects of male and female breast cancer as well as the limited data available from clinical trials of MBC. In view of the rarity of this tumor, participants formed an international consortium to expedite the planning of therapy trials by pooling epidemiologic and clinical data as well as tumor specimens.

SCIENTIFIC HIGHLIGHTS

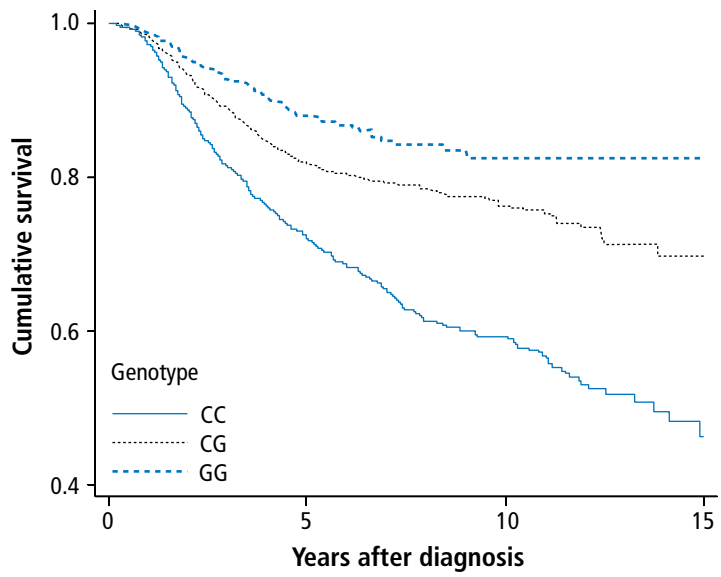
BREAST CANCER

Performance of Genetic Variants in Risk Models

The authors used information on traditional risk factors and results from genome-wide association studies (GWAS) to determine the extent to which identified genetic variants can increase the clinical value of existing risk-assessment models of breast cancer. The study looked at 10 common genetic variants associated with breast cancer in 5,590 case subjects and 5,998 control subjects, 50–79 years of age, from four U.S. cohort studies and one Polish case-control study. Using receiver operating-characteristic curve analysis, the authors calculated the area under the curve (AUC) as a measure of discrimination. By definition, random classification of case and control subjects provides an AUC of 50%; perfect classification provides an AUC of 100%. The authors calculated the fraction of case subjects in quintiles of estimated absolute risk after the addition of genetic variants to the traditional risk model. The AUC for a risk model with age, study, entry year, and four traditional risk factors was 58.0%; with the addition of data on 10 genetic variants for breast cancer, the AUC was 61.8%. About half of the case subjects (47.2%) were in the same quintile of risk as in a model without genetic variants; 32.5% were in a higher quintile, and 20.4% were in a lower quintile. Thus, the inclusion of data on newly discovered genetic factors modestly improved the performance of risk models for breast cancer. The level of predicted breast cancer risk among most women changed little after the addition of currently available genetic information. **(Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, Thun MJ, Cox DG, Hankinson SE, Kraft P, Rosner B, Berg CD, Brinton LA, Lissowska J, Sherman ME, Chlebowski R, Kooperberg C, Jackson RD, Buckman DW, Hui P, Pfeiffer R, Jacobs KB, Thomas GD, Hoover RN, Gail MH, Chanock SJ, Hunter DJ. Performance of common genetic variants in breast-cancer risk models. *N Engl J Med* 2010;362:986–993)**

Survival Associated with Genetic Polymorphism

Using genotype data from a two-stage breast cancer susceptibility GWAS called Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH), the authors evaluated possible associations between overall survival after a breast cancer diagnosis and 10,621 germline single-nucleotide polymorphisms (SNPs) from up to 3,761 patients with invasive breast cancer. To validate putative associations, they used patient genotype and overall survival information for up to 14,096 patients with invasive breast cancer from 15 international case-control studies. In the hypothesis-generating dataset, SNP rs4778137 (for C = common, G = rare; C > G) of the *OCA2* gene at 15q13.1 was associated with overall survival among patients with estrogen receptor–negative tumors, with the rare G allele being associated with increased overall survival (hazard ratio [HR] of death per rare allele carried = 0.56, p for trend = 9.2×10^{-5}). This association was also observed in the validation dataset (HR = 0.88, $p = 0.03$) and in the combined dataset (HR = 0.82, $p = 5 \times 10^{-4}$) (see Figure 1).



Genotype	Total at risk	Patients at risk; study site–adjusted survival rate		
CC	1,615	772; 0.73	199; 0.60	19; 0.48
CG	1,247	642; 0.81	195; 0.76	25; 0.69
GG	292	161; 0.88	46; 0.83	2; 0.83

Figure 1. Predicted cumulative survival adjusted for study site for patients in the combined hypothesis-generating and validation datasets, adjusted to the baseline hazard function of the Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH) study. C = common; G = rare. (Azzato EM, et al. 2010)

(Azzato EM, Tyrer J, Fasching PA, Beckmann MW, Ekici AB, Schulz-Wendtland R, Bojesen SE, Nordestgaard BG, Flyger H, Milne RL, Arias JI, Menendez P, Benitez J, Chang-Claude J, Hein R, Wang-Gohrke S, Nevanlinna H, Heikkinen T, Aittomki K, Blomqvist C, Margolin S, Mannermaa A, Kosma VM, Kataja V, The Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, Beesley J, Chen X, Chenevix-Trench G, Couch FJ, Olson JE, Fredericksen ZS, Wang X, Giles GG, Severi G, Baglietto L, Southey MC, Devilee P, Tollenaar RA, Seynaeve C, Garcia-Closas M, Lissowska J, Sherman ME, Bolton KL, Hall P, Czene K, Cox A, Brock IW, Elliott GC, Reed MW, Greenberg D, Anton-Culver H, Ziogas A, Humphreys M, Easton DF, Caporaso NE, Pharoah PD. Association between a germline *OCA2* polymorphism at chromosome 15q13.1 and estrogen receptor-negative breast cancer survival. *J Natl Cancer Inst* 2010;102:650–662)

CERVICAL CANCER

Association of Age with HPV Persistence and Progression

Using data from 9,175 women screened for cervical neoplasia in the Guanacaste Natural History Study, the authors assessed whether a woman's age and duration of carcinogenic human papillomavirus (HPV) infection influenced subsequent persistence of infection and risk of cervical intraepithelial neoplasia grade 2 (CIN 2) or worse disease. A total of 6,029 participants at low risk of CIN 2 or worse were rescreened at five to seven years, whereas higher-risk participants (n = 2,115), subsets of low-risk women (n = 540), and initially sexually inactive women (n = 410) were rescreened annually or semiannually (actively followed) for up to seven years. Regardless of the woman's age, newly detected infections were associated with very low absolute risks of persistence, CIN 2, or worse disease (CIN 2+). For newly detected infections, the rate of progression to CIN 2+ or CIN 3+, after three years of follow-up, was not higher for women over age 33 than for younger women. Among prevalent infections, persistent infections among women over age 41 were more common than persistent infections among younger age groups and more common than new infections at any age (see Figure 2). Most cases of CIN 2 or worse (66 of 85) detected during follow-up were associated with prevalent infections. Only 25 of 1,128 prevalent infections persisted throughout follow-up without an apparent case of CIN 2 or worse. The rate of new infections declines with age, and new infections typically do not progress to CIN 2 or worse in older women; thus, the potential benefit of prophylactic vaccination or frequent HPV screening to detect new infections at older ages is low. (Rodríguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, Solomon D, Guillén D, Alfaro M, Morales J, Hutchinson M, Katki H, Cheung L, Wacholder S, Burk RD. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: Critical role of duration of infection. *J Natl Cancer Inst* 2010;102:315–324)

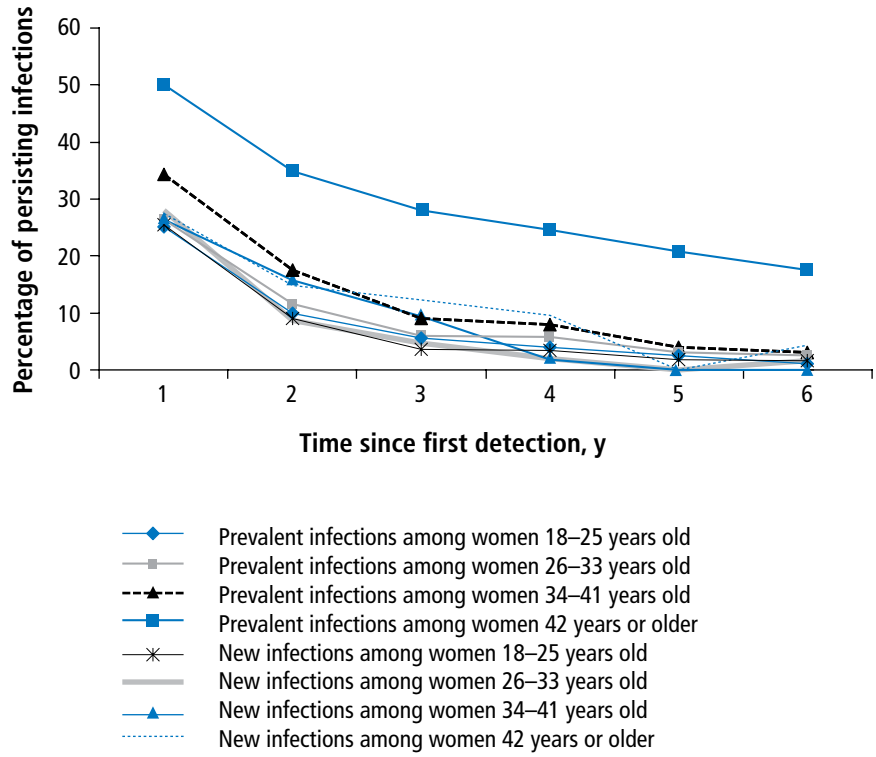


Figure 2. Persistence of baseline-detected and newly detected carcinogenic genotypes of human papillomavirus infection by age group. (Rodríguez AC, et al. 2010)

Carcinogenic HPV Variant Lineages

The authors used a nested case-control design to explore whether the oldest evolutionary branches within each carcinogenic HPV type predicted different risks of viral persistence lasting longer than two years, or precancer and cancer (CIN 3+). Infections were assigned to a variant lineage determined by phylogenetic parsimony methods based on URR/E6 sequences. The authors used Fisher's combination test to evaluate significance of the risk associations, cumulating evidence across

types. Globally, for HPV types including HPV 16, the *p* value was 0.01 for persistence and 0.07 for CIN 3+. Excluding HPV 16, the *p* values were 0.04 and 0.37, respectively. For HPV 16, non-European viral variants were more likely than European variants to cause viral persistence (odds ratio [OR] = 2.6) and CIN 3+ (OR = 2.4). HPV 35 and HPV 51 variant lineages also predicted CIN 3+. HPV variants generally differ in risk of viral persistence. For some HPV types, particularly HPV 16, variant lineages differ in their risk of CIN 3+. Findings indicate that continued evolution of HPV types has led to even finer genetic discrimination linked to HPV natural history and cervical cancer risk. Larger viral genomic studies are warranted, particularly with an emphasis on identifying the genetic basis for the unique carcinogenicity of HPV 16. **(Schiffman M, Rodríguez AC, Chen Z, Wacholder S, Herrero R, Hildesheim A, Desalle R, Befano B, Yu K, Safaeian M, Sherman ME, Morales J, Guillen D, Alfaro M, Hutchinson M, Solomon D, Castle PE, Burk RD. A population-based prospective study of carcinogenic human papillomavirus variant lineages, viral persistence, and cervical neoplasia. *Cancer Res* 2010;70:3159–3169)**

MAJOR EDITORIALS, COMMENTARIES, AND REVIEWS PUBLISHED BY DCEG SCIENTISTS

Anderson WF, et al. Qualitative age interactions in breast cancer studies: Mind the gap. *J Clin Oncol* 2009;27:5308–5311

Caporaso NE, et al. Evolution of a precursor. *Cytometry B Clin Cytom* 2010;78:1–3

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

Chung CC, et al. Genome-wide association studies in cancer: Current and future directions. *Carcinogenesis* 2010;31:111–120

Hartge P. Designing early detection programs for ovarian cancer. *J Natl Cancer Inst* 2010;102:3–4

Sherman ME, et al. Molecular pathology in epidemiologic studies: A primer on key considerations. *Cancer Epidemiol Biomarkers Prev* 2010;19:966–972

Simon SL, et al. Current use and future needs of biodosimetry in studies of long-term health risk following radiation exposure. *Health Phys* 2010;98:109–117

Risk of Miscarriage Following HPV Vaccination

In order to assess whether vaccination against HPV increases the risk of miscarriage, the authors conducted a pooled analysis of two multicenter, phase III masked, randomized controlled trials on several continents and in Costa Rica. The study included 26,130 participants aged 15–25 years at enrollment among whom 3,599 pregnancies were eligible for analysis. Participants were randomly assigned to receive three doses of bivalent HPV 16/18 VLP vaccine with AS04 adjuvant (*n* = 13,075) or hepatitis A vaccine as a control (*n* = 13,055) over six months. The estimated rate of miscarriage was 11.5% among pregnant women receiving the HPV vaccine and 10.2% among pregnant women receiving the hepatitis A vaccine in the control arm, a nonsignificant difference. In secondary descriptive analyses, miscarriage rates were 14.7% in the group receiving the HPV vaccine and 9.1% in the control group among pregnancies estimated to have begun less than 90 days after the most recent vaccination. There was no evidence overall for an association between HPV vaccination and risk of miscarriage, but further analyses were recommended. **(Wacholder S, Chen BE, Wilcox A, Macones G, Gonzalez P, Befano B, Hildesheim A, Rodríguez AC, Solomon D, Herrero R, Schiffman M, for the CVT group. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: Pooled analysis of two randomised controlled trials. *BMJ* 2010;340:c712)**

Susceptibility to HPV Persistence and Progression

The authors examined host genetic factors hypothesized to play a role in oncogenic HPV infection persistence and its progression to cervical precancer or cancer. They evaluated 7,140 tag SNPs from 305 candidate genes suggested to be involved in DNA repair, viral infection, and cell entry in 416 cases of CIN 3/cancer, 356 women with persistent HPV infection (median = 25 months), and 425 random control subjects from the 10,049 women who participated in the Guanacaste Natural History Study in Costa Rica. Genes and regions associated with CIN 3 progression to cancer include the viral infection and cell entry genes 2',5' oligoadenylate synthetase gene 3 (*OAS3*), sulfatase 1 (*SULF1*), and interferon gamma (*IFNG*); the DNA repair genes deoxyuridine triphosphate (*DUT*), dosage suppressor of mck 1 homolog (*DMC1*), and general transcription factor IIH, polypeptide 4 (*GTF2H4*); and the *EVER1* and *EVER2* genes. From each region, the single most significant SNPs associated with CIN 3/cancer were *OAS3* rs12302655, *SULF1* rs4737999, *IFNG* rs11177074, *DUT* rs3784621, *DMC1* rs5757133, *GTF2H4* rs2894054, and *EVER1/EVER2* rs9893818. SNPs for *OAS3, SULF1, DUT,* and *GTF2H4*

were associated with HPV persistence, whereas *IFNG* and *EVER1/EVER2* SNPs were associated with progression to CIN 3 or cancer. Results require replication but suggest that different genes may modulate risk of HPV persistence and disease progression. **(Wang SS, Gonzalez P, Yu K, Porras C, Li Q, Safaeian M, Rodríguez AC, Sherman ME, Bratti C, Schiffman M, Wacholder S, Burk RD, Herrero R, Chanock SJ, Hildesheim A. Common genetic variants and risk for HPV persistence and progression to cervical cancer. *PLoS ONE* 2010;5:e8667)**

COLORECTAL CANCER

Risk Associated with Red and Processed Meat Intake

This study examined potential mechanisms for increased colorectal cancer risk associated with greater red and processed meat intake in a large U.S. prospective cohort. Researchers used a detailed questionnaire on meat types and meat cooking methods linked to databases estimating intake of mutagens formed in meats cooked at high temperatures (including heterocyclic amines and benzo(a)pyrene), heme iron, nitrate, and nitrite. During seven years of follow-up, 2,719 colorectal cancer cases were ascertained from a cohort of 300,948 men and women. The HRs comparing the fifth to the first quintile for red (HR = 1.24) and processed meat (HR = 1.16) intakes indicated elevated risks for colorectal cancer. The factors potentially responsible for this relationship include heme iron (HR = 1.13, confidence interval [CI] = 0.99–1.29, $p = 0.022$), nitrate from processed meats (HR = 1.16), and heterocyclic amine intake [HR = 1.19 for 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MeIQx) and HR = 1.17 for 2-amino-3,4,8-trimethylimidazo[4,5-f] quinoxaline (DiMeIQx)]. In general, the elevated risks were higher for rectal cancer than for colon cancer with the exception of MeIQx and DiMeIQx, which were only associated with colon cancer. The effects of heme iron, nitrate or nitrite, and heterocyclic amines from meat may explain red and processed meat associations with colorectal cancer risks. **(Cross AJ, Ferrucci LM, Risch A, Graubard BI, Ward MH, Park Y, Hollenbeck AR, Schatzkin A, Sinha R. A large prospective study of meat consumption and colorectal cancer risk: An investigation of potential mechanisms underlying this association. *Cancer Res* 2010;70:2406–2414)**

ENDOMETRIAL CANCER

Risk after Endometrial Hyperplasia

The severity of endometrial hyperplasia (EH)—described as simple, complex, or atypical (AH)—influences clinical management, but valid estimates of the absolute risk of clinical progression to carcinoma are lacking. The authors conducted a case-control study nested in a cohort of 7,947 female members of one prepaid health plan who were diagnosed with EH during 1970–2002 and who remained at risk for at least one year. Subjects included women diagnosed with carcinoma on average six years later ($n = 138$) and a control group ($n = 241$). For nonatypical EH, the cumulative progression risk increased from 1.2% (CI = 0.6%–1.9%) through 4 years to 1.9% through 9 years to 4.6% through 19 years after EH diagnosis. For AH, cumulative risk increased from 8.2% through 4 years to 12.4% through 9 years to 27.5% through 19 years after AH diagnosis. Cumulative 20-year progression risk among women who remained at risk for at least one year was less than 5% for nonatypical EH and 28% for AH. **(Lacey JV Jr, Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, Glass AG, Richesson DA, Chatterjee N, Langholz B. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol* 2010;28:788–792)**

GASTRIC CANCER

An Upturn in Incidence

To examine the effects of age at diagnosis on noncardia gastric cancer incidence trends in the United States, the authors conducted a descriptive study with age-period-cohort analysis of cancer registration data from NCI's Surveillance, Epidemiology, and End Results (SEER) Program. During 1977–2006, there were 83,225 adults with incident primary gastric cancer, including 39,003 noncardia cases. Per 100,000 population, overall age-standardized annual incidence declined during the study period from 5.9 to 4.0 in whites, from 13.7 to 9.5 in blacks, and from 17.8 to 11.7 in other races. Age-specific trends among whites varied significantly between older and younger age groups ($p < 0.001$ for interaction by age): incidence per 100,000 declined significantly from 19.8 to 12.8 for ages 60–84 years and from 2.6 to 2.0 for ages 40–59 years but increased significantly from 0.27 to 0.45 for ages 25–39 years (see Figure 3). Conversely, rates for all age groups declined or were stable among blacks and other races. Age-period-cohort analysis confirmed a significant increase in whites among younger cohorts born since 1952 ($p < 0.001$). Additional surveillance and analytical studies are warranted to identify risk factors that may explain this unfavorable trend. **(Anderson WF, Camargo CM, Fraumeni JF, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA* 2010;303:1723–1728)**

GENETICS

Tools for Detecting Gene-Gene Interaction

Many popular methods for exploring gene-gene interactions, including the case-only approach, rely on the assumption that physically distant loci are in

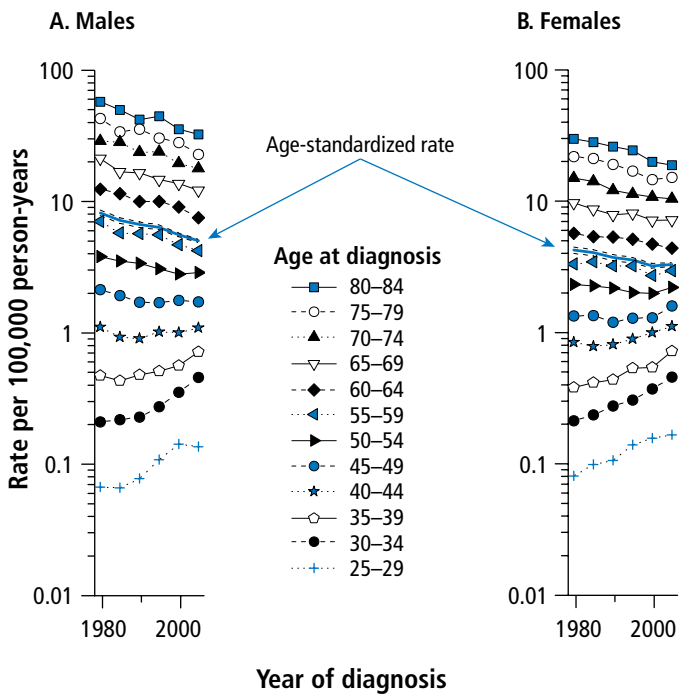


Figure 3. Rates over time of noncardia gastric carcinoma among whites by 12 five-year age groups from NCI's Surveillance, Epidemiology, and End Results (SEER) Program 1977–2006. (Anderson WF, et al. 2010)

linkage equilibrium in the underlying population. These methods utilize the presence of correlation between unlinked loci in a disease-enriched sample as evidence of interactions among the loci in the etiology of disease. The authors used data from the Cancer Genetic Markers of Susceptibility (CGEMS) project's case-control GWAS of breast cancer to demonstrate empirically that the case-only approach and related methods can potentially create large-scale false positives because of the presence of population stratification (PS) that creates long-range linkage disequilibrium in the genome. They show that the bias can be removed by considering parametric and nonparametric methods that assume gene-gene independence between unlinked loci, not in the entire population, but only conditional on the presence of a population substructure that can be uncovered based on the principal components of a suitably large panel of PS markers. The proposed methods are robust to the presence of PS. **(Bhattacharjee S, Wang Z, Ciampa J, Kraft P, Chanock SJ, Yu K, Chatterjee N. Using principal components of genetic variation for robust and powerful detection of gene-gene interactions in case-control and case-only studies. *Am J Hum Genet* 2010;86:331–342)**

LUNG CANCER

Effects of Alcohol Consumption

The authors investigated the relationship between alcohol consumption and lung cancer risk in the Environment And Genetics in Lung cancer Etiology (EAGLE) study. Alcohol consumption during adulthood was assessed among 1,855 subjects with primary lung cancer and 2,065 population-based subjects in a control group; data on lifetime tobacco smoking, diet, education, and anthropometric measures were collected. Overall, both nondrinkers (OR = 1.42) and very heavy drinkers (≥ 60 grams per day, OR = 1.44) were at greater risk than very light drinkers (0.1–4.9 grams per day). The alcohol effect was modified by smoking behavior, with no excess risk observed in never smokers. **(Bagnardi V, Randi G, Lubin J, Consonni D, Lam TK, Subar AF, Goldstein AM, Wacholder S, Bergen AW, Tucker MA, Decarli A, Caporaso NE, Bertazzi PA, Landi MT. Alcohol consumption and lung cancer risk in the Environment and Genetics in Lung Cancer Etiology (EAGLE) study. *Am J Epidemiol* 2010;171:36–44)**

Effects of Chronic Obstructive Pulmonary Disease

Researchers assessed in the EAGLE study whether chronic obstructive pulmonary disease (COPD), defined as chronic bronchitis and/or emphysema, was associated with lung cancer risk among 1,934 lung cancer cases and 2,108 control subjects who reported diagnoses of chronic bronchitis, emphysema, COPD, or asthma more than one year before enrollment. After adjustment for smoking, other previous lung diseases, and study design variables, lung cancer risk was found to be elevated among individuals with a history of chronic bronchitis (OR = 2.0), emphysema (OR = 1.9), or COPD (OR = 2.5). Among current smokers, association between chronic bronchitis and lung cancer was strongest among lighter smokers. Asthma was associated with a decreased risk of lung cancer in men (OR = 0.48). Results suggest that the associations of personal histories of chronic bronchitis, emphysema, and COPD with increased risk of lung

cancer are not entirely due to smoking. Inflammatory processes may contribute to COPD and lung carcinogenesis. **(Koshiol J, Rotunno M, Consonni D, Pesatori AC, De Matteis S, Goldstein AM, Chaturvedi AK, Wacholder S, Landi MT, Lubin JH, Caporaso NE. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. *PLoS One* 2009;4:e7380)**

Role of Metabolic Genes

In the EAGLE study, investigators analyzed 25 SNPs from six phase I metabolic genes, including cytochrome P450s, microsomal epoxide hydrolase, and myeloperoxidase, in relation to lung cancer risk. Two haplotypes in *EPHX1* were associated with lung cancer risk in the overall population. In addition, *CYP1B1* and *CYP2A6* polymorphisms were inversely associated with adenocarcinoma and squamous cell carcinoma risk, respectively. Moreover, the association between *CYP1A1* rs2606345 genotype and lung cancer was modified by the intensity of cigarette smoking, suggesting an underlying dose-response mechanism. Finally, an increased number of variants in *CYP1A1/A2* genes revealed significant protection among never smokers and significant risk in ever smokers. These results were supported by differential gene expression in non-tumor lung tissue samples with down-regulation of *CYP1A1* in never smokers and up-regulation of *CYP1A1/A2* SNPs in smokers. The significant haplotype associations emphasize that the effect of multiple SNPs may be important despite null single SNP-associations and warrant consideration in GWAS. **(Rotunno M, Yu K, Lubin JH, Consonni D, Pesatori AC, Goldstein AM, Goldin LR, Wacholder S, Welch R, Burdette L, Chanock SJ, Bertazzi PA, Tucker MA, Caporaso NE, Chatterjee N, Bergen AW, Landi MT. Phase I metabolic genes and risk of lung cancer: Multiple polymorphisms and mRNA expression. *PLoS One* 2009;4:e5652)**

LYMPHOHEMATOPOIETIC MALIGNANCIES

Diet, Lifestyle, and Risk of Acute Myeloid Leukemia

The relationships between diet, lifestyle, and acute myeloid leukemia were assessed in a cohort of 491,163 people from the NIH-AARP Diet and Health Study, including 338 incident cases of acute myeloid leukemia. The study compared never smokers with former smokers who smoked no more than one pack per day (HR = 1.29, CI = 0.95–1.75) and more than one pack per day (HR = 1.79), and current smokers who smoked no more than one pack per day (HR = 2.42) and more than one pack per day (HR = 2.29). Higher meat intake was associated with increased risk of acute myeloid leukemia (for the fifth vs. first quintile, HR = 1.45); however, there were no clear effects of meat-cooking method or doneness level. Individuals who did not drink coffee appeared to have a higher risk of acute myeloid leukemia than those who drank various quantities of coffee. Neither fruit nor vegetable intake was associated with acute myeloid leukemia. **(Ma X, Park Y, Mayne ST, Wang R, Sinha R, Hollenbeck AR, Schatzkin A, Cross AJ. Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. *Am J Epidemiol* 2010;171:312–322)**

Free Light Chains and AIDS-related Lymphoma

Serum immunoglobulin (Ig) proteins were evaluated as predictors of non-Hodgkin lymphoma (NHL) risk among HIV-infected individuals. By using three cohorts of HIV-infected people from 1982 to 2005, the researchers identified 66 individuals who developed NHL and 225 matched (by cohort, sex, ethnicity, age, and CD4 count) HIV-infected, lymphoma-free control subjects. Serum/plasma samples obtained zero to two years and two to five years before diagnosis/selection were assayed for IgG, IgM, and IgA levels; monoclonal (M) Igs; and kappa and lambda free light chain (FLC) levels. The kappa and lambda FLCs were significantly higher in patients than controls (e.g., in the two-to-five-year window: median kappa FLC level = 4.24 vs. 3.43 mg/dL; median lambda FLC level = 4.04 vs. 3.09 mg/dL) and strongly predicted NHL in a dose-response manner up to two to five years before diagnosis/selection. NHL risk was 3.76-fold higher with kappa FLC concentrations at least two times the upper limit of normal levels and 8.13-fold higher with lambda FLC concentrations at least two times the upper limit of normal levels. In contrast, IgG, IgM, and IgA levels were similar in patients and controls. M proteins were detected in only two patients with NHL and in nine control subjects, and they were not associated with NHL risk. Elevated FLC levels may represent sensitive markers of polyclonal B-cell activation and dysfunction and could be useful for identifying HIV-infected persons at increased NHL risk. **(Landgren O, Goedert JJ, Rabkin CS, Wilson WH, Dunleavy K, Kyle RA, Katzmann JA, Rajkumar SV, Engels EA. Circulating serum free light chains as predictive markers of AIDS-related lymphoma. *J Clin Oncol* 2010;28:773–779)**

Immune System Genes and Non-Hodgkin Lymphoma

In an International Lymphoma Epidemiology (InterLymph) Consortium pooled analysis of 7,999 cases and 8,452 control subjects, polymorphisms in two immune system–related genes—tumor necrosis factor (*TNF*) and interleukin-10 (*IL10*)—were associated with NHL risk. Consistent with previous findings, ORs were increased among 8,847 "new" participant *TNF* -308A (rs1800629) carriers (NHL: $OR_{allelic}$ = 1.10; diffuse large B-cell lymphoma [DLBCL]:

$OR_{allelic}$ = 1.23). In the combined population, ORs were increased for *TNF* -308A carriers (NHL: $OR_{allelic}$ = 1.13, p = 0.0001; DLBCL: $OR_{allelic}$= 1.25, $p = 3.7 \times 10^{-6}$; marginal zone lymphoma: $OR_{allelic}$ = 1.35, p = 0.004) and *LTA* 252G carriers (DLBCL: $OR_{allelic}$ = 1.12; mycosis fungoides: $OR_{allelic}$ = 1.44). The *LTA* 252A>G (rs909253)/*TNF* -308G>A haplotype containing the *LTA/TNF* variant alleles was strongly associated with DLBCL ($p = 2.9 \times 10^{-8}$). The results suggested associations between *IL10* -3575T>A (rs1800890, rs1800896) and DLBCL (p = 0.02) and *IL10* –1082A>G and mantle cell lymphoma (p = 0.04). These findings strengthen previous results for DLBCL and the *LTA* 252A>G/*TNF* -308A locus and provide robust evidence that these *TNF/LTA* gene variants, or others in linkage disequilibrium, are involved in NHL etiology. **(Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjosé S, Hughes AM, Cerhan JR, Skibola DR, Purdue M, Kane E, Lan Q, Foretova L, Schenk M, Spinelli JJ, Slager SL, De Roos AJ, Smith MT, Roman E, Cozen W, Boffetta P, Kricker A, Zheng T, Lightfoot T, Cocco P, Benavente Y, Zhang Y, Hartge P, Linet MS, Becker N, Brennan P, Zhang L, Armstrong B, Smith A, Shiao R, Novak AJ, Maynadie M, Chanock SJ, Staines A, Holford TR, Holly EA, Rothman N, Wang SS. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. *Am J Epidemiol* 2010;171:267–276)**

Mechanisms Relating Formaldehyde Exposure to Leukemia

The authors examined the potential ability of formaldehyde to disrupt hematopoiesis in a study of 94 workers in China; 43 workers were exposed to formaldehyde, and 51 workers were frequency-matched control subjects. Among exposed workers, peripheral blood cell counts were lowered in a manner consistent with toxic effects on the bone marrow (see Figure 4), and leukemia-specific chromosome changes were elevated in myeloid blood progenitor cells, the target for leukemogenesis. Findings suggest that formaldehyde exposure can have an adverse effect on the hematopoietic system and that leukemia induction by formaldehyde is biologically plausible. **(Zhang L, Tang X, Rothman N, Vermeulen R, Ji Z, Shen M, Qiu C, Guo W, Liu S, Reiss B, Freeman LB, Ge Y, Hubbard AE, Hua M, Blair A, Galvan N, Ruan X, Alter BP, Xin KX, Li S, Moore LE, Kim S, Xie Y, Hayes RB, Azuma M, Hauptmann M, Xiong J, Stewart P, Li L, Rappaport SM, Huang H, Fraumeni JF Jr, Smith MT, Lan Q. Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. *Cancer Epidemiol Biomarkers Prev* 2010;19:80–88)**

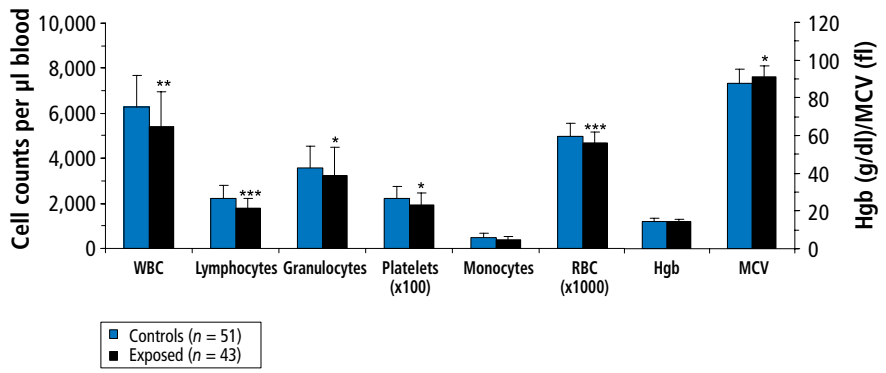


Figure 4. Myeloid, erythroid, and lymphocyte blood cell counts in formaldehyde-exposed and unexposed workers. Data shown as mean ± standard deviation. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Hgb = hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell. (Zhang L, et al. 2010)

Risks Associated with Formaldehyde Exposure

The authors studied the relationships of work practices and formaldehyde exposure levels to cancer mortality among funeral industry professionals. Subjects who died in 1960–1986 from lymphohematopoietic malignancies (n = 168) or brain tumors (n = 48) were compared with deceased matched control subjects (n = 265) by lifetime work practices and exposures assessed by interviews with next of kin and coworkers and by estimated levels of formaldehyde exposure. Mortality from myeloid leukemia increased with increasing number of years of embalming (p = 0.020) and with increasing peak formaldehyde exposure (p = 0.036). Compared with subjects who performed fewer than 500 lifetime embalmings, mortality from myeloid leukemia was elevated among those who performed embalmings for more than 34 years (OR = 3.9), who performed more than 3,068 embalmings (OR = 3.0, CI = 1.0–9.2, p = 0.057), and whose estimated cumulative formaldehyde exposure exceeded 9,253 parts per million-hours (OR = 3.1, CI = 1.0–9.6, p = 0.047). These exposures were not related to other lymphohematopoietic malignancies or brain cancer. **(Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, Hoover RN, Fraumeni JF Jr, Blair A, Hayes RB. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst* 2009;101:1696–1708)**

PANCREATIC CANCER

GWAS Identifies Several Risk Loci

GWAS of 3,851 individuals with pancreatic cancer and 3,934 control subjects drawn from 12 prospective cohort studies and 8 case-control studies identified eight SNPs that map to three loci on chromosomes 13q22.1, 1q32.1, and 5p15.33. Two correlated SNPs, rs9543325 ($OR_{per\ allele}$ = 1.26) and rs9564966 ($OR_{per\ allele}$ = 1.21), map to a nongenic region on chromosome 13q22.1. Five SNPs on 1q32.1 map to *NR5A2,* and the strongest signal was at rs3790844 ($OR_{per\ allele}$ = 0.77). A single SNP, rs401681 ($OR_{per\ allele}$ = 1.19), maps to the *CLPTM1L-TERT* locus on 5p15.33, which is associated with multiple cancers. **(Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M, Helzlsouer K, Holly EA, Jacobs EJ, Klein AP, LaCroix A, Li D, Mandelson MT, Olson SH, Risch HA, Zheng W, Albanes D, Bamlet WR, Berg CD, Boutron-Ruault MC, Buring JE, Bracci PM, Canzian F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Gaziano JM, Giovannucci EL, Goggins M, Hallmans G, Hankinson SE, Hassan M, Howard B, Hunter DJ, Hutchinson A, Jenab M, Kaaks R, Kooperberg C, Krogh V, Kurtz RC, Lynch SM, McWilliams RR, Mendelsohn JB, Michaud DS, Parikh H, Patel AV, Peeters PH, Rajkovic A, Riboli E, Rodriguez L, Seminara D, Shu XO, Thomas G, Tjønneland A, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wang Z, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Fraumeni JF Jr, Hoover RN, Hartge P, Chanock SJ. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet* 2010;42:224–228)**

PROSTATE CANCER

Variants in the Phosphatidylinositol 3-kinase Pathway

Data from the NCI Breast and Prostate Cancer Cohort Consortium were examined for associations between 89 SNPs in phosphatidylinositol 3-kinase genes (*PIK3C2B, PIK3AP1, PIK3C2A, PIK3CD,* and *PIK3R3*) and prostate cancer risk in 8,309 cases and 9,286 control subjects. SNP rs7556371 in *PIK3C2B* was associated with prostate cancer risk ($OR_{per\ allele}$ = 1.08) after adjustment for multiple testing. Simultaneous adjustment of rs7556371 for nearby SNPs strengthened the association ($OR_{per\ allele}$ = 1.21). The adjusted association was stronger for men who were diagnosed before the age of 65 years ($OR_{per\ allele}$ = 1.47) or had a family history ($OR_{per\ allele}$ = 1.57); it was strongest in men with both characteristics ($OR_{per\ allele}$ = 2.31, p for interaction = 0.005). Increased risks were observed among men in the top tertile of circulating insulin-like growth factor-I (IGF-I) levels ($OR_{per\ allele}$ = 1.46). No differences were observed in relation to disease aggressiveness. The association between *PIK3C2B* and prostate cancer risk was more pronounced for familial, early-onset disease, which may be attributable to IGF-dependent PI3K signaling. **(Koutros S, Schumacher FR, Hayes RB, Ma J, Huang WY, Albanes D, Canzian F, Chanock SJ, Crawford ED, Diver WR, Feigelson HS, Giovanucci E, Haiman CA, Henderson BE, Hunter DJ, Kaaks R, Kolonel LN, Kraft P, Le Marchand L, Riboli E, Siddiq A, Stampfer MJ, Stram DO, Thomas G, Travis RC, Thun MJ, Yeager M, Berndt SI. Pooled analysis of phosphatidylinositol 3-kinase pathway variants and risk of prostate cancer. *Cancer Res* 2010;70:2389–2396)**

THYROID CANCER

Non-radiation Risk Factors

The associations of thyroid cancer risk with self-reported medical history, anthropometric factors, and behavioral factors were prospectively examined among 69,506 female and 21,207 male U.S. radiologic technologists followed from 1983 through 2006. Cases of thyroid cancer were reported in 242 women and 40 men. Among women, elevated risks were observed with benign thyroid conditions (HR = 2.35), benign breast disease (HR = 1.56), asthma (HR = 1.68, CI = 1.00–2.83), and body mass index of 35.0 or more versus 18.5–24.9 kg/m^2 (HR = 1.74); current smoking was inversely associated with thyroid cancer risk (HR = 0.54). No clear associations with thyroid cancer risk emerged for reproductive factors, other medical conditions, alcohol intake, or physical activity. Despite few cases of thyroid cancer in men, those with benign thyroid conditions had an increased risk of thyroid cancer (HR = 4.65), and results for other risk factors were similar to those for women. Consistent with prior studies, obesity and benign thyroid conditions increased the risk of thyroid cancer, whereas current smoking decreased the risk. The novel findings for benign breast disease and asthma warrant further investigation. **(Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, Berrington de González A. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* 2010;171:242–252)**

DCEG PEOPLE IN THE NEWS

Christian C. Abnet, Ph.D., M.P.H., Nutritional Epidemiology Branch (NEB), spoke on "The role of oral health in the etiology of upper gastrointestinal cancer" at the University of New Mexico Cancer Center in March and at Morgan State University in Baltimore, Maryland in April.

In March, **Blanche P. Alter, M.D., M.P.H.,** Clinical Genetics Branch (CGB), gave talks on inherited bone marrow failure syndromes at the NIH DNA Repair Interest Group in Bethesda, Maryland; the 11th Annual Diamond Blackfan Anemia International Consensus Conference in New York City; and the American Society of Pediatric Hematology/Oncology 23rd Annual Meeting in Montreal, Canada.

Amy Berrington de González, D.Phil., Radiation Epidemiology Branch (REB), gave an invited talk on "Modeling the risk of radiation-related lung cancer" in January at the annual Cancer Intervention and Surveillance Modeling Network meeting in Bethesda, Maryland.

In March, **Eric A. Engels, M.D., M.P.H.,** Infections and Immunoepidemiology Branch (IIB), presented "Trends in cancer incidence and attributable mortality among people with AIDS in the U.S." at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland; "Knowing where to look: Epidemiology and immune status" at an NCI Think Tank on "Rethinking the role of infectious agents in cancer" in Arlington, Virginia; and "HIV, aging, and cancer" at the Office of AIDS Research Advisory Committee meeting in Rockville, Maryland.

Stephanie M. George, Ph.D. (NEB), successfully defended her doctoral dissertation on energy balance in relation to the risk and prognosis of breast cancer and received her Ph.D. in epidemiology from the Yale School of Public Health. Dr. George joined NEB in 2008 as a predoctoral fellow under the mentorship of Dr. Susan Mayne and Dr. Melinda Irwin from the Yale School of Public Health, **Demetrius Albanes, M.D.** (NEB), and **Mitchell H. Gail, M.D., Ph.D.,** Biostatistics Branch (BB). She will continue in NEB as a postdoctoral fellow working with **Charles E. Matthews, Ph.D.,** on developing better ways to measure and model physical activity and sedentary behavior patterns and investigating the relationship between energy balance and cancer.

Asieh Golozar, M.D., M.P.H., Genetic Epidemiology Branch (GEB), was selected for the Harvey M. Meyerhoff Fellowship in Cancer Prevention. The fellowship is awarded to a doctoral student in the Department of Epidemiology at the Johns Hopkins Bloomberg School of

PHILIP CASTLE RECEIVES TENURE AND ASCCP AWARD

Based on a recommendation by the NIH Central Committee, Dr. Michael Gottesman, NIH Deputy Director for Intramural Research, awarded scientific tenure to **Philip E. Castle, Ph.D., M.P.H.,** Hormonal and Reproductive Epidemiology Branch (HREB). After receiving his Ph.D. in biophysics from Johns Hopkins University in 1995, Dr. Castle completed a postdoctoral fellowship in the Laboratory of Cellular and Developmental Biology at the National Institute of Diabetes and Digestive and Kidney Diseases. He joined HREB as part of the NCI Cancer Prevention Fellowship in 1999 and received his M.P.H. from the Johns Hopkins Bloomberg School of Public Health in 2000. In 2003, he became a principal investigator in HREB.

ASCCP Leadership and Award Recipients: Thomas Wright (ASCCP President), Walter Kinney (who also received an ASCCP Distinguished Scientific Achievement Award), J. Thomas Cox (ASCCP Immediate Past President), and Philip Castle with his father John Castle.

Dr. Castle's research focuses on the natural history of human papillomavirus (HPV) infection and cervical cancer and evaluation of screening and diagnostic technologies for HPV infection, cervical precancer, and cervical cancer. This work includes the development and validation of low-cost strategies for resource-limited countries. In recognition of his work on cervical cancer, the American Society for Colposcopy and Cervical Pathology (ASCCP) recently presented Dr. Castle with the Distinguished Scientific Achievement Award, the highest honor conferred by the Society.

Public Health whose research focuses on the epidemiology of cancer and cancer prevention.

In March, **Mark H. Greene, M.D.,** Chief of CGB, gave a talk titled "Hereditary breast/ovarian cancer: What about the ovaries?" at the 20th Annual National Interdisciplinary Breast Cancer Conference in Las Vegas, Nevada.

In March, **Hormuzd A. Katki, Ph.D.** (BB), **June A. Peters, M.S., C.G.C.** (CGB), **Mark Schiffman, M.D., M.P.H.** (CGB), and **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of GEB, co-moderated a panel on "Cancer risk assessment: New paradigms, old controversies" at the American College of Medical Genetics Annual Clinical Genetics Meeting in Albuquerque, New Mexico. At the same meeting, **Lisa Mirabello, Ph.D.** (CGB), gave a poster presentation titled "A comprehensive candidate gene approach identifies genetic variation in *HSD17B2* and *TDP1* associated with osteosarcoma," and Dr. Schiffman presented "Penetrance of acquired genomic alterations and cancer risk assessment."

Christian Kratz, M.D. (CGB), spoke on "Myeloid malignancies in individuals with underlying genetic predispositions" at the NCI Center for Cancer Research (CCR) Pediatric Oncology Branch in February and at Johns Hopkins University in March. He also presented "Recent advances in the genetics of testicular cancer" at the NCI Genitourinary Malignancies Center of Excellence in Bethesda, Maryland in March.

Elisabetta Petracci, Ph.D. (BB), successfully defended her doctoral thesis, "The effect of risk factor modifications on projections of absolute breast cancer risk." She received her Ph.D. in biomedical statistics from the Institute of Medical Statistics and Biometry at the University of Milan. Dr. Petracci joined BB in February 2009 as a predoctoral fellow working under the supervision of **Mitchell H. Gail, M.D., Ph.D.**

In March, **Melissa Rotunno, Ph.D.** (GEB), gave a talk titled "A gene expression signature from peripheral whole blood with prognostic implications for lung adenocarcinoma" at the CCR Fellows and Young Investigators Colloquium held in Hershey, Pennsylvania.

Sharon A. Savage, M.D. (CGB), spoke on telomeres in inherited and sporadic cancer at the Aplastic Anemia & MDS (Myelodysplastic Syndrome) International Foundation Bone Marrow Failure Disease Scientific Symposium in Bethesda, Maryland in March and at Children's National Medical Center in Washington, DC and the 6th Annual NCI Staff Scientist and Staff Clinician Retreat in Bethesda, Maryland in April. Dr. Savage also gave an invited talk on "Using epidemiology and genomics to understand osteosarcoma etiology" at the Third Jishuitan Orthopedics Forum in Beijing, China in April.

In April, **Alice J. Sigurdson, Ph.D.** (REB), gave an invited talk on "Radiation-related human cancer susceptibility: Progress and puzzles in the genome-wide studies era" at the Low Dose Radiation Research Investigators' Workshop sponsored by the U.S. Department of Energy's Office of Biological and Environmental Research.

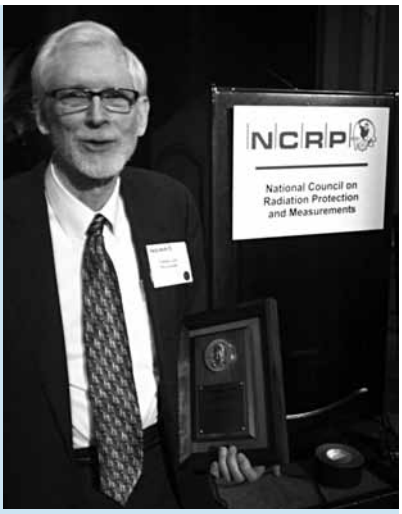
Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D. (NEB), gave invited talks on pancreatic cancer at Westat in Rockville, Maryland in February; at Pennsylvania State University in State College, Pennsylvania in March; and at the Mayo Clinic in Rochester, Minnesota and the University of Minnesota in Minneapolis, Minnesota in April.

In March, **Philip R. Taylor, M.D., Sc.D.** (GEB), gave a talk on "Alcohol intake and cancer prevention" at the NCI Nutrition and Cancer Prevention Research Practicum held in Bethesda, Maryland.

In March, **Rebecca Troisi, Sc.D.,** Epidemiology and Biostatistics Program, gave an invited talk on "Practical issues in international research studies" at the Dartmouth Medical School Department of Community and Family Medicine in Hanover, New Hampshire.

CHARLES LAND GIVES LAURISTON S. TAYLOR LECTURE

Dr. Charles E. Land, who recently retired from the Radiation Epidemiology Branch, gave the 34th Lauriston S. Taylor Lecture at the annual meeting of the National Council on Radiation Protection & Measurements (NCRP) held in March in Bethesda, Maryland. The lecture series honors the late Dr. Lauriston S. Taylor, the NCRP founding president. Dr. Land spoke on "Radiation protection in an uncertain world."



Charles Land

COMINGS . . . GOINGS

Elizabeth Azzato, Ph.D., Genetic Epidemiology Branch (GEB), successfully defended her thesis, "Common germline genetic variation and outcome after diagnosis of breast cancer." Dr. Azzato will return to Duke University, where she will complete her fourth year of medical school. She was supervised by **Neil E. Caporaso, M.D.,** and Dr. Paul Pharoah under the NIH-OxCam program.

Francesco Barone-Adesi

Francesco Barone-Adesi, M.D., Ph.D., has joined the Occupational and Environmental Epidemiology Branch (OEEB) as a visiting fellow. He received an M.D. from the Catholic University of the Sacred Heart in Rome, Italy and a Ph.D. in occupational health from the University of Bari in Italy. His doctoral dissertation involved the use of biologically based models to study temporal trends of lung cancer and mesothelioma in cohorts of asbestos workers. At DCEG, Dr. Barone-Adesi will work on occupational risk factors for lung cancer and leukemia.

Maria-Constanza Camargo

Maria-Constanza Camargo, M.S., M.H.A., joined the Infections and Immunoepidemiology Branch (IIB) as a predoctoral visiting fellow. She received an M.S. from the School of Public Health in Mexico and an M.H.A. from the Pontificia Universidad Javeriana in Bogota, Colombia. She is currently a Ph.D. candidate in epidemiology at the University of Illinois at Chicago. For her dissertation project, Ms. Camargo is working with **Charles S. Rabkin, M.D.,** on the role of Epstein-Barr virus infection in gastric carcinogenesis.

Ashley Corum

Ashley Corum joined the Administrative Resource Center as an administrative technician. She previously worked at the NIH Office of AIDS Research, the National Library of Medicine, and the National Institute of Neurological Disorders and Stroke. Ms. Corum is skilled in travel planning, meeting management oversight, and general administrative duties. She will be working with **Joan Starr** and **Linda Littlejohn** to provide administrative support to the Epidemiology and Biostatistics Program and OEEB.

Jecholia Gallagher

Jecholia Gallagher joined the Office of Division Operations and Analysis as a scientific program specialist. She received a B.A. from George Mason University in Fairfax, Virginia. She is working on data compilation and analysis for reporting and budget activities and is maintaining systems and databases used by DCEG and NIH. Previously, she worked at Global Solutions Network, Inc., in Alexandria, Virginia and at Ariel Research/3E Company in Bethesda, Maryland, where she was the regulatory services coordinator and served on the integrative content team compiling and integrating chemical regulation information.

LINDSEY HOSKINS RECEIVES AWARD

The University of Maryland President's Commission on Women's Issues selected **Lindsey M. Hoskins, Ph.D., M.S., L.G.M.F.T.,** Clinical Genetics Branch, as the 2010 Outstanding Graduate Student. This award honors a female graduate student for her exemplary contributions to women and women's issues in higher education. Students are selected based on their accomplishments in four areas: initiative and approach, communication, problem solving, and service to the campus and broader community. Dr. Hoskins' dissertation is titled "Risk-management decision-making among young female *BRCA1/2* mutation carriers: A qualitative investigation." She received her doctoral degree from the University of Maryland, College Park in May.

Lindsey Hoskins (on right) with University of Maryland President C.D. Mote.

Paula Hyland

Paula Hyland, Ph.D., M.P.H., joined GEB as a postdoctoral fellow. Dr. Hyland received her Ph.D. in biomedical sciences from the University of Ulster at Coleraine in Northern Ireland in 1998 and her M.P.H. from Queen's University Belfast in Northern Ireland in 2009. Her Ph.D. research involved examining the effect of dNTP pool imbalances on DNA replication and repair fidelity in erythroleukemic cells. In GEB, Dr. Hyland will be working with **Philip R. Taylor, M.D., Sc.D.,** on molecular epidemiologic studies of upper gastrointestinal cancers.

Clara Kim

Clara Kim, M.P.H., joined the Radiation Epidemiology Branch (REB) as a predoctoral fellow. Ms. Kim earned her M.P.H. in epidemiology from The George Washington University School of Public Health and Health Services in 2009. She is currently working toward her doctoral degree in epidemiology under the mentorship of **Lindsay M. Morton, Ph.D.** Her research will focus on risk factors for multiple primary cancers among patients with at least one hematopoietic malignancy.

Stephanie Lamart

Stephanie Lamart, Ph.D., joined REB as a postdoctoral visiting fellow. Dr. Lamart received her doctorate in physics in 2008 from the University of Paris XI in France and obtained the French certification in medical physics in 2009. Her doctoral thesis was in the field of internal dosimetry and focused on the influence of biokinetics of radionuclides on whole-body measurements using numeric voxel phantoms. At REB, she will work in radiation dosimetry research and will be mentored by **Choonsik Lee, Ph.D.,** and **Steven L. Simon, Ph.D.** Dr. Lamart is interested in the estimation of organ doses related to external radiotherapy procedures.

Mark O'Doherty

Mark O'Doherty, Ph.D., joined the Nutritional Epidemiology Branch (NEB) as a guest researcher. Dr. O'Doherty received his Ph.D. in nutrition from Queen's University Belfast in Northern Ireland in 2008. For his dissertation, he studied the link between classical and novel cardiovascular risk factors and whether nutritional status affected these factors. In NEB, he is working with **Christian C. Abnet, Ph.D., M.P.H.,** on the role that antioxidants and iron status may play in the development of esophageal adenocarcinoma and its precursor states.

BENCH-TO-BEDSIDE AWARD

Congratulations to **Christian Kratz, M.D.,** Clinical Genetics Branch (CGB), who won a 2010 NIH Bench-to-Bedside Award for his proposal "Phenotype definition and etiologic investigation of cancer susceptibility in patients with pleuropulmonary blastoma (PPB) or associated neoplasms: A natural history study." Dr. Kratz will be working with **Blanche P. Alter, M.D., M.P.H.** (CGB); **Mark H. Greene, M.D.,** Chief of CGB; **Philip S. Rosenberg, Ph.D.,** Biostatistics Branch; Dr. Dana A. Hill from Children's National Medical Center; Dr. Yoav Messinger and Dr. Kris Ann Schultz from the Children's Hospital & Clinics of Minnesota; and Dr. Paul Goodfellow and Ms. Jennifer Ivanovic from the Washington University School of Medicine.

PPB is a rare and aggressive childhood neoplasm of the lung that arises during fetal development. More than 20 percent of patients with PPB have a family history of neoplasia. It has recently been shown that familial PPB is caused by germline mutations of *DICER1*, which is involved in the generation of microRNAs (miRNAs) and small interfering RNAs (siRNAs). miRNAs modulate mRNA levels of their target genes and are known to play a key role in oncogenesis. The proposed study aims to define the clinical phenotype and cancer spectrum associated with this *DICER1*-related familial cancer syndrome, which represents the first known cancer susceptibility syndrome caused by impaired miRNA processing.

The NIH Bench-to-Bedside Award Program fosters collaborations among laboratory, clinical, and population scientists in areas of research that have potential for improving the understanding of important disease processes or for leading investigators to a new therapeutic, preventive, or diagnostic intervention.

Christina Persson

Christina Persson, Ph.D., joined the Hormonal and Reproductive Epidemiology Branch (HREB) as a visiting fellow. Dr. Persson received her M.S. in biology from the Institute of Technology at Linköping University in Linköping, Sweden and her Ph.D. in medical epidemiology and biostatistics from the Karolinska Institute in Stockholm, Sweden. For her doctoral dissertation, she assessed the relationships of host genetic factors and *Helicobacter pylori* infection to the risk of gastric cancer. While in HREB, she will work with **Katherine A. McGlynn, Ph.D., M.P.H.,** on liver cancer projects.

Edgar Simard, Ph.D. (IIB), successfully defended his dissertation, "Cancer incidence and cancer-attributable mortality among persons with AIDS in the United States: 1980–2006," in December and received his Ph.D. in epidemiology from the University of Medicine and Dentistry of New Jersey School of Public Health in January. He has accepted a postdoctoral research fellow position in the Columbia University Mailman School of Public Health Department of Epidemiology.

Nataša Tasevska, M.D., Ph.D., left NEB in February to join the Office of the Associate Director of the Applied Research Program at NCI's Division of Cancer Control and Population Sciences (DCCPS).

Huei-Ting Tsai, Ph.D., a visiting fellow in GEB, has taken a position in the Cancer Control Program at Georgetown University Medical Center.

DR. CHATTERJEE RECEIVES SPIEGELMAN AWARD

Nilanjan Chatterjee, Ph.D., Chief of the Biostatistics Branch, received the prestigious Mortimer Spiegelman Award from the Statistics Section of the American Public Health Association. This award is given annually to a public health statistician under age 40 who has made outstanding contributions to the field.

Nilanjan Chatterjee

Jorge Toro, M.D., has left GEB to become Chief of the Dermatology Department at the Washington, DC Veterans Affairs Medical Center.

Lene Veiga, Ph.D., left REB after a two-year postdoctoral fellowship and returned to her post as a researcher at the Institute of Radioprotection and Dosimetry at the National Nuclear Energy Commission in Rio de Janeiro, Brazil.

Alessandro Villa

Alessandro Villa, D.D.S., joined IIB as a postdoctoral visiting fellow. Dr. Villa received his D.D.S. in 2008 from the University of Milan in Italy, where he collaborated on epidemiologic projects related to the prevention and early diagnosis of oral cancers. He is currently pursuing an M.P.H. While in IIB, Dr. Villa will work with **Anil K. Chaturvedi, Ph.D.,** and **Aimee Kreimer, Ph.D.,** on oral cancer screening methods and biomarkers and will conduct analyses of oral human papillomavirus (HPV) infection using data from the HPV in Males study.

Joanne Watters, Ph.D., M.P.H., has left NEB to work as a program director with the Clinical and Translational Epidemiology Branch of DCCPS's Epidemiology and Genetics Research Program.

OUTSTANDING YOUNG ALUMNUS AWARD

Laura Beane Freeman, Ph.D., Occupational and Environmental Epidemiology Branch, was selected as the 2010 Outstanding Young Alumnus by the University of Iowa College of Public Health, in honor of her exceptional career achievements and for her work on cancer and the environment. Dr. Beane Freeman received an M.S. in preventive medicine in 1999 and a Ph.D. in epidemiology in 2003 from the University of Iowa College of Public Health. Dr. Beane Freeman's research focuses on cancer risks associated with occupational and environmental exposure to pesticides, formaldehyde, and other agents.

Laura Beane Freeman (on right) with Sue Curry, Dean of the University of Iowa College of Public Health.

SAMANTHA NHAN DEPARTS DCEG

In April, DCEG bid a fond farewell to **Samantha Nhan,** who had been the managing editor of *Linkage* since 2004. Ms. Nhan joined DCEG as an epidemiology program specialist in 1997. Over the ensuing 13 years, she assumed positions of increasing responsibility within the Office of the Director. Under her leadership, *Linkage* gained national recognition and received numerous awards for its organization, visual appeal, and presentation of complex information to a wide and diverse scientific and lay audience. In 2006, Ms. Nhan received an NIH Merit Award for her efforts in managing the *Linkage* publication process.

Samantha Nhan and Joseph Fraumeni.

In addition to her work with *Linkage,* Ms. Nhan served as executive secretary for the DCEG Senior Advisory Group (SAG), which advises the Director on Division-wide policy issues and scientific priorities, including the review of scientific concepts for proposed research initiatives. She also managed logistics for the annual SAG retreats. These off-site meetings provide an opportunity for key Division staff to discuss research priorities and new directions.

Ms. Nhan played the lead role in organizing the DCEG Annual Town Meetings. She worked closely with the DCEG Deputy Director, **Shelia Hoar Zahm, Sc.D.,** to invite the featured guest speaker, develop the agenda, distribute flyers and programs, and prepare a slide summary of the previous year. She also coordinated the entire award process, from the submission of nominations to the preparation of individualized plaques for multiple categories of award winners. Her assistance was critical at meetings of the Board of Scientific Counselors and the National Cancer Advisory Board, where she managed the logistics for presentations by the Division Director and other DCEG speakers.

In addition to her enormous contributions to the Division over the years, Ms. Nhan's meticulous attention to detail, cheerful demeanor, and unfailing willingness to help others have been deeply appreciated. We extend our best wishes to Ms. Nhan as she relocates with her family to St. Louis, Missouri. She will be sorely missed. ■

—Catherine B. McClave, M.S.

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