

Linkage

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Unraveling Genetic Susceptibility to Melanoma

Tenure-track investigator **Kevin Brown, Ph.D.**, Laboratory of Translational Genomics, has added a new chapter to DCEG's history of discovering the genetic factors that contribute to the risk of melanoma. As reported in a recent *Nature* article, Dr. Brown and colleagues used whole-genome sequencing to identify a novel, recurrent mutation, the E318K variant, in *MITF*. *MITF* is a gene that predisposes people to familial and sporadic melanoma (see Figure 1).

The *MITF* gene, or microphthalmia-associated transcription factor, helps control the development and function of pigment-producing cells called melanocytes. *MITF* has been considered an important gene in melanoma tumors for many years, being somatically amplified or mutated in some subsets of melanoma while strongly over-expressed in others.

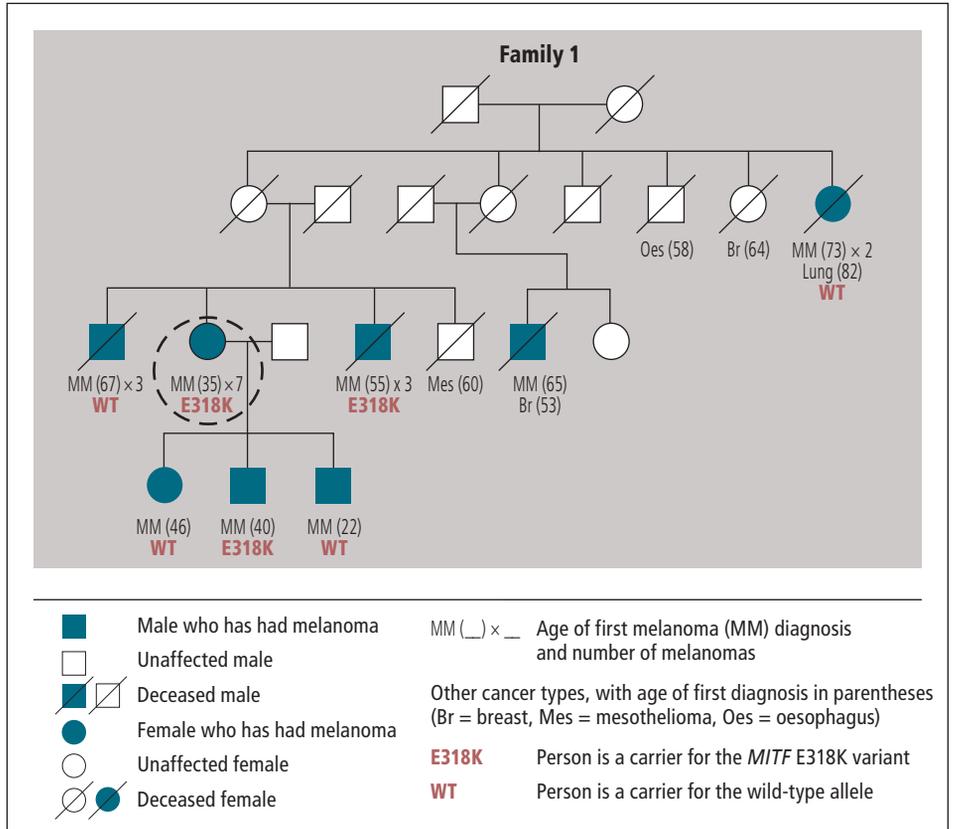


Figure 1. Pedigree of the *MITF* E318K variant in the family in which it was identified. The individual circled is the melanoma case in which the *MITF* E318K variant was discovered through whole-genome sequencing. (Yokoyama S, et al. *Nature* 2011)

DCEG *Linkage*

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Dr. Brown's paper describes the latest in a series of major DCEG findings on the genetics of melanoma. The ultimate goal of this research is the prevention and early detection of melanoma in high-risk individuals. The application of novel research approaches has been enabled by the large body of clinical and epidemiological data, as well as biospecimens, that have been collected over years of family and case-control studies.

A History of Genetic Detective Work

DCEG first began investigating possible genetic linkages to melanoma during the late 1970s under the leadership of **Mark H. Greene, M.D.**, now Chief of the Clinical Genetics Branch. **Margaret A. Tucker, M.D.**, Director of DCEG's Human Genetics Program, was a post-doctoral fellow working with Dr. Greene at the time of the initial investigation, and she later led and expanded the effort in melanoma research. Over time, the Genetic Epidemiology Branch (GEB) evaluated and prospectively followed approximately 80 multigenerational families with more than 1,800 members, some for up to 30 years. The investigators gathered detailed family histories, performed clinical examinations, and phenotyped the families. The goal was to identify high-risk susceptibility genes for melanoma, understand the risk factors for sporadic and familial cases, and provide better guidance for screening and clinical practice.



Past and present melanoma researchers in DCEG: Mark Greene, Margaret Tucker, Maria Teresa Landi, Kevin Brown, Ruth Kleinerman, Rose Yang, Alisa Goldstein, and Lynn Goldin. (Photograph credit: Bill Branson)

One of the first major clinical findings in these families was the identification and characterization of dysplastic nevi, the unusual moles seen in melanoma families. In a large case-control study, Dr. Tucker later showed that dysplastic nevi are precursors to both familial and sporadic melanoma, a finding that has had a significant impact on clinical screening protocols.

Gathering the Pieces of the Melanoma Puzzle

The first linkage analysis of familial melanoma, based on 23 genetic markers, was conducted in 1983 by **Lynn R. Goldin, Ph.D.**, now Deputy Chief of GEB, who found suggestive evidence of linkage on the short arm of chromosome 1. In 1994, **Alisa M. Goldstein, Ph.D.** (GEB), and Dr. Tucker identified the first melanoma susceptibility gene—*CDKN2A*, a tumor suppressor gene found in roughly 40 percent of melanoma-prone families. *CDKN2A* codes for p16 and p14 proteins and also has been found to be associated with pancreatic cancer, although the precise mechanism underlying that association has yet to be understood. The two researchers identified a second melanoma susceptibility gene in 1996—*CDK4*, which encodes cyclin-dependent kinase 4, an oncogene, and

accounts for approximately 2 percent of melanoma-prone families. Dr. Goldstein also demonstrated that another gene, *MC1R*, is a modifier of melanoma risk in American families with *CDKN2A* mutations. Individuals with *MC1R* variants are more likely to have multiple melanomas that start at an earlier age.

Further studies were performed through GenoMEL (the Melanoma Genetics Consortium), which was established in 1997 with initial funding through NCI and is composed of researchers from approximately 20 countries. The creation of GenoMEL provided a larger number of familial melanoma patients in whom mutations in the high-risk melanoma genes could be studied and better characterized. Dr. Goldstein has led multiple analyses within GenoMEL, including a study that identified differences in the risk of melanoma and other tumors associated with mutations in *CDKN2A* across geographic locales. That study also detected a strong association between pancreatic cancer and *CDKN2A* mutations.

In 2006, **Maria Teresa Landi, M.D., Ph.D.** (GEB), reported on data from case-control studies in Italy and San Francisco showing that Caucasians with a germline variant of *MC1R*, the gene encoding the melanocortin-1 receptor, were more likely to develop melanoma with *BRAF* mutations. Following up on her finding by examining the association in a much larger number of subjects in GenoMEL, Dr. Landi and colleagues found three areas of significant association with melanoma: on 16q24 marking *MC1R*, on 11q12-q14 near *TYR*, and on 9p21 near *MTAP*. In subsequent larger studies, four more loci have been identified, in *ATM*, *MX2*, and *CASP8*, as well as on 1q21.3.

Along with **Ruth A. Kleinerman, M.P.H.**, of the Radiation Epidemiology Branch, Dr. Tucker and colleagues found that patients with inherited

retinoblastoma, a rare cancer of the eye that tends to develop in early childhood, had a significantly higher risk of developing melanoma and that a family history of retinoblastoma further increased their risk. This work suggests that the tumor suppressor gene *RB* may play a role in melanoma as well as retinoblastoma.

Harnessing New Technology

In more recent years, investigators have harnessed next-generation DNA sequencing technology to make critical discoveries. For example, exome sequencing has become a common means of interrogating the protein-coding regions of a genome at a relatively low cost. Other new techniques include high-resolution array-based comparative genomic hybridization (array-CGH), which detects genomic copy number variations, or alterations of the DNA of a genome that result in an abnormal number of copies of a section of DNA; chromatin immunoprecipitation (ChIP) sequencing, which is used to analyze protein interactions with DNA; and molecular profiling, which provides a powerful means of classifying tumors based on their underlying biology.

Xiaohong Rose Yang, Ph.D., M.P.H. (GEB), is employing these new techniques in her search for genetic variation and regulation of genes linked to melanoma susceptibility within the American families. In collaboration with Dr. Meg Gerstenblith of the Case Western Reserve University School of Medicine in Cleveland, Ohio, Dr. Yang is launching a study that will identify clinically and etiologically relevant subtypes of melanoma using integrated molecular profiling approaches. She and other scientists are assessing the feasibility of conducting molecular profiling analyses on DNA and RNA extracted from melanoma tissue blocks. “With improved awareness and earlier diagnoses, most

melanoma tumors diagnosed in the U.S. are small,” said Dr. Tucker. “With this pilot study, we will assess whether enough tumor material is available in routinely collected pathology tissue blocks for the molecular analyses.”

Translating Research Into Clinical Practice

The DCEG melanoma research program has always had a strong translational clinical component. Following melanoma-prone families over the long term has enabled investigators to develop recommendations for managing risk factors and has changed clinical practice for screening. Mary Fraser, a former clinical research nurse in GEB, spent considerable time educating members of melanoma-prone families on ways to reduce their risk of the disease and how to recognize dysplastic nevi and other warning signs of early-stage melanoma. GEB also developed a tool to measure exposure to the sun based on lifetime history of residence, and developed a risk prediction model that can be used by primary care providers to plan for screening of individuals not in melanoma-prone families. In addition, to inform study participants, clinicians, and the public, DCEG has published a melanoma atlas, videos, newsletters, and brochures, including a recent award-winning brochure targeting populations of color and their physicians titled *Anyone Can Get Skin Cancer* (see the July 2011 issue of *Linkage*).

Thanks to the long-term investment in these resources, DCEG investigators are poised to apply novel technologies and approaches that will help unlock the complexities of melanoma genetics, including gene-environment interactions, and to translate the findings to facilitate the prevention, early detection, and treatment of this disease. ■

—Victoria A. Fisher, M.P.H., and
Wendy Schneider-Levinson

HORMUZD KATKI'S RESEARCH FEATURED BY ASCO

In June, **Hormuzd A. Katki, Ph.D.**, a tenure-track investigator in the Biostatistics Branch, spoke at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, Illinois, on his research demonstrating the benefits of incorporating human papillomavirus (HPV) testing into cervical cancer screening programs. The study included nearly 332,000 women who underwent combined HPV and Pap testing at Kaiser Permanente Northern California (KPNC). Dr. Katki's research, conducted in collaboration with KPNC researchers and Dr. Philip Castle (formerly of DCEG, now at the American Society for Clinical Pathology), was reported in a paper titled "Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: A population-based study in routine clinical practice" that was published in *Lancet Oncology*. This research also was featured in *Clinical Cancer Advances 2011: Annual Report on Progress Against*

Cancer from the American Society of Clinical Oncology, an annual, independent review of advances in cancer research that have had the greatest impact on patient care.

Dr. Katki found that for women aged 30 and older, a single negative HPV test sufficed to provide strong reassurance against being diagnosed with cervical cancer over five years, supporting current guidelines recommending a three-year screening interval for women older than age 30 who have a negative HPV test and a normal Pap test. HPV testing also resulted in earlier identification of women at high risk of cervical cancer, especially cervical adenocarcinoma, a tumor that is rising in incidence in the United States. Finally, having a normal Pap test and a negative HPV test was associated with about the same cancer risk as a negative HPV test alone. This finding strongly suggests that reserving Pap testing only for HPV-positive women could protect women

while reducing the number of Pap tests by 95 percent within this population.

This paper lays the groundwork for Dr. Katki's ultimate goal of using cervical cancer risk estimates to inform the development of screening guidelines. He is developing a risk model for cervical pre-cancer and cancer that would incorporate HPV vaccination, results of HPV tests and Pap smears, and other clinically available biomarkers to classify women in risk-based management groups. If fully successful, this risk calculator could simplify and improve future screening guidelines. ■



Hormuzd Katki

—Victoria A. Fisher, M.P.H., and Wendy Schneider-Levinson

TWO INVESTIGATORS RECEIVE SCIENTIFIC TENURE

NIH recently awarded scientific tenure to **Amy Berrington de González, D.Phil.**, of the Radiation Epidemiology Branch, and **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.**, of the Nutritional Epidemiology Branch.

Dr. Berrington de González's research is focused primarily on the use of epidemiological data to quantify the cancer risks related to medical radiation exposures, including both low-dose exposures from diagnostic tools, such as computed tomography scans, and high-dose exposures from radiotherapy. She is interested particularly in the cancer risks from



Amy Berrington de González

emerging technologies, such as intensity-modulated radiotherapy and proton therapy. Before joining DCEG, Dr. Berrington de González received her doctoral degree in cancer epidemiology from the University of Oxford in the United Kingdom, and she was a faculty member at both Oxford and the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

Dr. Stolzenberg-Solomon has focused much of her research on understanding the etiology of pancreatic cancer. She has examined dietary, other lifestyle, and genetic factors as well as infectious



Rachael Stolzenberg-Solomon

agents that may help uncover mechanisms of carcinogenesis. Whenever possible, she has utilized biomarkers in cohort and intervention studies of cancer etiology and prevention, paying special attention to aspects of one-carbon metabolism (a biochemical pathway in which folate plays an essential role) in the etiology of gastrointestinal, renal cell, and colorectal cancers. After completing her education and training in nutrition at the University of California, Davis, and at Vanderbilt University in Nashville, Tennessee, Dr. Stolzenberg-Solomon worked for a number of years as a registered dietitian in clinical care and research. She received her M.P.H. in nutrition and epidemiology as well as her Ph.D. in epidemiology from the Johns Hopkins Bloomberg School of Public Health.

2012 INTRAMURAL SCIENTIFIC RETREAT HIGHLIGHTS

In January, DCEG scientists participated in the annual NCI Intramural Scientific Investigators Retreat, where **Shelia Hoar Zahm, Sc.D.**, DCEG Deputy Director, was presented with the 2012 NCI Women Scientist Advisors Mentoring and Leadership Award.

Two DCEG investigators were invited to give short presentations during the retreat's plenary sessions. **Amy Berrington de González, D.Phil.**, of the Radiation Epidemiology Branch, discussed "The burden of cancer from medical radiation exposures: Conventional and emerging technologies." She described the dramatic increase worldwide over the past several decades of exposure to diagnostic radiation and presented data on how increased exposure to ionizing radiation will affect future cancer rates. **Ludmila Prokunina-Olsson, Ph.D.**, of the Laboratory of Translational Genomics (LTG), spoke on "Exploring translational avenues in the post-GWAS era." She noted that in the brief five-year history of cancer genome-wide association studies (GWAS), 216 signals for 17 cancer types have been discovered, and 11 of those signals involved bladder cancer. Dr. Prokunina-Olsson described the steps she has taken to localize the genetic variants and discover their functional mechanisms along with their potential use for clinical and public health applications.

Harold E. Varmus, M.D., NCI Director, presented the 2012 NCI Director's Innovation Awards, which are designed to support the development of novel approaches and technologies for accelerating cancer research. Five tenure-track investigators from DCEG received Principal Investigator Awards: **Sonja I. Berndt, Pharm.D., Ph.D.**, Occupational

and Environmental Epidemiology Branch (OEEB), for her proposal "Mitochondrial DNA copy number and prostate cancer risk"; **Sam M. Mbulaiteye, M.D.**, Infections and Immunoepidemiology Branch (IIB), for "Multiple *Plasmodium falciparum* malaria genotype infections: A link to African Burkitt lymphoma"; Dr. Prokunina-Olsson for "Functional analysis of a novel human protein and its translational application for treatment of hepatitis C virus infection"; **Joshua Sampson, Ph.D.**, Biostatistics Branch, for "Understanding the I179T amino acid change in prostate-specific antigen"; and **Nicolas Wentzensen, M.D., Ph.D.**, Hormonal and Reproductive Epidemiology Branch (HREB), for "Development and evaluation of a human papillomavirus methylation assay to study risk of cervical precancer."

In addition, eight DCEG fellows received Career Development Awards: **Cindy M. Chang, Ph.D.** (IIB), for "Bacterial infection and the risk of cancer in a population-based cohort";

Yi-Ping Fu, Ph.D. (LTG), for a proposal titled "Elucidating the role of SNPs from bladder cancer GWAS through correlation with tumor microarray-based protein expression"; **Wei Hu, Ph.D.**, and **Christopher Kim, M.P.H.**, both of OEEB, for "Urinary F(2)-isoprostane oxidative stress markers and indoor air pollution as risk factors for lung cancer among non-smoking women in China"; **Paula Hyland, Ph.D., M.P.H.**, Genetic Epidemiology Branch, for "Global chromatin accessibility patterns in melanoma-prone individuals with and without *CDKN2A* mutations"; **Indu Kohaar, Ph.D.** (LTG), for "Functional genomic studies of a novel splicing form of the *CCNE1* gene in relation to bladder cancer"; **Wei Tang, Ph.D.** (LTG), for "The integrative annotation and functional characterization of long non-coding RNAs in bladder cancer"; and **Britton Trabert, Ph.D.** (HREB), for "Serological markers of pelvic inflammatory disease and ovarian cancer risk." ■

10TH ANNUAL GILBERT W. BEEBE SYMPOSIUM

In December, members of the Radiation Epidemiology Branch (REB) participated in the 10th Annual Gilbert W. Beebe Symposium, which is conducted by the Nuclear and Radiation Studies Board of the National Academies. This year's symposium, titled *Tracking Radiation Exposure from Medical Diagnostic Procedures*, focused on the need to monitor an individual patient's radiation exposure from diagnostic procedures, such as computed tomography, fluoroscopy, and nuclear medicine exams. These procedures have proven to be clinically beneficial and yet concerns exist regarding the potential health risks resulting from the radiation exposure and increase in utilization of the procedures. Participants in this symposium explored ways to develop a more comprehensive strategy for the collection of data on radiation exposure.

The symposium consisted of four sessions: (1) "National and international efforts in volume and dose tracking," (2) "Appropriate radiation dose metrics and estimation techniques," (3) "Volume—Methods for collecting and evaluating data," and (4) "Risk—What we know and what we need to know." **Amy Berrington de González, D.Phil.**, a senior investigator in REB, moderated Session 4, during which **Kiyohiko Mabuchi, M.D., Dr.P.H.**, Deputy Chief of REB, presented "Non-cancer effects at radiological doses."

For the first time in the 10-year history of the Beebe Symposium, presentations and discussions will be summarized in a National Academies report. The symposium honors the memory of Dr. Gilbert W. Beebe, a distinguished radiation epidemiologist who served as a senior investigator in REB.

THE DES FOLLOW-UP STUDY

In epidemiology, what can be learned from eight cases of an extremely rare tumor observed in the same clinic? Quite a lot, in fact, thanks to an inquisitive mother who asked whether her daughter's tumor was caused by "the medicine" the mother took during pregnancy and to the astute physicians who decided to follow up on her question.

The medicine that the mother referred to was diethylstilbestrol, or DES, a synthetic estrogen manufactured and marketed as a drug that would prevent miscarriage and other complications of pregnancy. DES became clinically available in the United States during the early 1940s and, for the next 30 years, was prescribed to millions of pregnant women. By the late 1950s, a series of clinical trials had been published that showed no efficacy in preventing the adverse events that DES was supposed to keep from occurring. Nonetheless, the drug continued to be prescribed.

Then, in 1971, Dr. Arthur Herbst, Dr. Howard Ulfelder, and Dr. David

Poskanzer published their report of eight clear cell adenocarcinomas (CCA) of the vagina and cervix among young women (aged 14 to 22 years old) in a clinic in Boston and their documented prior exposure to DES. The researchers' findings were noteworthy because CCA

is extremely rare and is usually found in much older women. The seminal paper established the association between *in utero* exposure to DES and a woman's increased risk of cancer. The paper also prompted the U.S. Food and Drug Administration to issue a warning to physicians that the drug should not be prescribed to pregnant women.

Various clinics across the country initiated clinical and follow-up studies of the effects of DES in females and males exposed to the drug *in utero*. However,



Robert Hoover and Rebecca Troisi.

according to **Robert N. Hoover, M.D., Sc.D.**, Director of DCEG's Epidemiology and Biostatistics Program (EBP), "Over time, enthusiasm and funding for these efforts progressively waned, so that by the late 1980s, most of the follow-up work had stopped."

Recognizing the need to continue observing DES-exposed mothers and their offspring, Dr. Hoover reached out to several principal investigators at the various study centers and suggested reviving the cohorts and pooling the



Diethylstilbestrol (DES) was produced for use in pregnancy.

DES was widely prescribed to women for use in threatened miscarriages and was promoted to physicians through medical publications and other communications. It was subsequently prescribed for prophylactic use in normal pregnancies.

Four clinical trials found DES *not* effective, but prescriptions and promotions continued.

1938 1940

1950–1953

DES **Timeline**

data to better answer the many questions that remained. Having the larger cohort would allow sufficient statistical power to find associations for rarer outcomes that otherwise would be missed in the individual cohorts.

In 1992, a combined cohort was assembled and named the “DES Follow-up Study.” It included DES-exposed and non-DES-exposed mothers and their offspring from cohorts that had been enrolled during the 1970s along with clinical and other information from that era. The combined study pooled 5,067 daughters exposed to DES *in utero* and 2,387 non-exposed females. It also included 2,001 DES-exposed sons and 2,111 non-exposed males. Among the mothers, 5,441 were exposed to DES during pregnancy and 4,036 were not exposed, making it the largest follow-up study of DES in the country. Dr. Hoover and **Rebecca Troisi, Sc.D.**, a staff scientist in EBP, have been DCEG’s coprincipal investigators of the study.

Subjects were recontacted and invited to participate in the combined cohort by completing the 1994 baseline questionnaire and subsequent periodic questionnaires. Since that time, numerous key findings have emerged. “DES is an endocrine-disrupting chemical,” Dr. Troisi stated. “From the many laboratory studies that have been done, we know these types of chemicals can cause cancer, birth defects, and other developmental abnormalities in the reproductive tract, and the effects of exposure are most severe when it occurs during fetal development.” The study team explored these leads and confirmed that effects of DES were evident not only in DES-exposed mothers but also in both daughters and sons exposed to the drug *in utero*.

In 2001, the study team found that mothers who had been prescribed DES during pregnancy had a 20 to 30 percent increased risk of breast cancer than non-DES-exposed women in the same age group. A 2009 study of DES-exposed sons found that risks for cryptorchidism, epididymal cyst, and testicular

inflammation or infection were twice those of non-DES-exposed males and were three times as great among sons exposed to DES before the 11th week of gestation. The sons’ abnormalities, however, had no overall adverse effect on their fertility or reproductive outcomes.

Using data from the 1994, 1997, and 2001 follow-up questionnaires, the study team, led by Dr. Hoover, published an article in the October 6, 2011, issue of the *New England Journal of Medicine (NEJM)* that included the most comprehensive analysis of data on women exposed to DES while *in utero*, illustrating the cumulative effects of this exposure over the course of a woman’s lifetime. Among 4,653 DES-exposed and 1,927 non-DES-exposed women, the authors evaluated 12 adverse health and reproductive outcomes—infertility, spontaneous abortion, ectopic pregnancy, loss of second trimester pregnancy, preterm delivery, preeclampsia, stillbirth, neonatal death, early menopause, cervical intraepithelial neoplasia grade 2+, breast cancer, and CCA—all

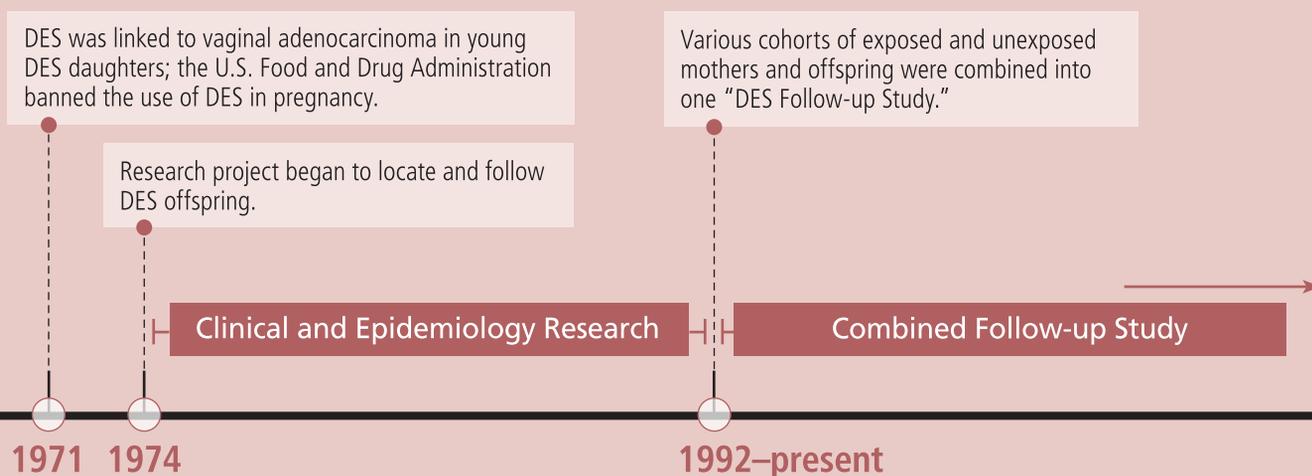


Table 1. Risks for DES-exposed Daughters Compared to Non-DES-exposed Daughters

Outcome	Increased risk
Clear cell adenocarcinoma	40 times higher
Neonatal death	8 times higher
Preterm delivery	4.7 times higher
Loss of second trimester pregnancy	3.8 times higher
Ectopic pregnancy	3.7 times higher
Stillbirth	2.4 times higher
Infertility	2.4 times higher
Early menopause	2.4 times higher
Cervical intraepithelial neoplasia	2.3 times higher
Breast cancer	1.8 times higher
First trimester miscarriage	1.6 times higher
Preeclampsia	1.4 times higher

of which had been linked previously to DES exposure in preliminary reports from the combined study (see Table 1).

Compared with non-DES-exposed women, women exposed to DES *in utero* had eight times the risk of neonatal death, almost five times the risk for preterm delivery, and nearly four times the

risk of having an ectopic pregnancy. In addition, DES-exposed daughters were twice as likely to experience infertility. Risks of breast cancer or neoplastic cervical lesions were approximately doubled and persisted until age 55. Finally, the data showed that the 40-fold increased risk of CCA, the cancer diagnosed in young women exposed to DES *in utero*, remained elevated until at least age 40.

The 2011 paper by Dr. Hoover and colleagues also was the first to assess possible dose-response effects between the amount of DES exposure *in utero* and the risk of all outcomes by using a unique marker called vaginal epithelial changes (VEC), a phenomenon observed particularly in women exposed to high doses of DES early in gestation. These changes appear as red granular patches in the epithelium of the vagina and represent a precursor to CCA. According to the report in *NEJM*, women with VEC experienced even higher risks for 9 of the 12 outcomes evaluated than DES-exposed women without VEC.

Findings from the studies of DES-exposed women have provided the impetus and the laboratory model for the current widespread interest in the biologic impact of endocrine disruptors, particularly from fetal and other early-life exposures. “The DES story has many valuable lessons for clinical medicine, in particular for an entire generation of clinicians who, for the most part, have been unaware of this signal event in medical history,” Dr. Hoover noted. These lessons include the value of clinical trials; the special vulnerability of the fetus; the importance of being alert to unusual events and searching for possible causes; and, perhaps most important, the need for systematic long-term surveillance for adverse outcomes of drug exposures. Dr. Hoover further added, “It is clear that without the startling occurrence of a cluster of a rare cancer in adolescent girls, we would be unaware of the massive burden of multiple common adverse health outcomes ultimately endured by DES-exposed women.”

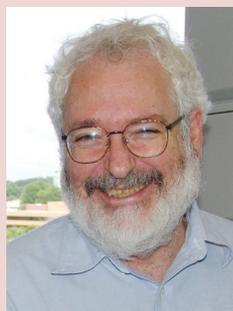
The DES Follow-up Study will continue to follow DES-exposed daughters as they move into the menopausal years and beyond (i.e., the ages when cancers more commonly occur) as well as follow DES-exposed sons. In addition, the study recently has expanded to include granddaughters of DES-exposed and non-DES-exposed women, referred to as the “third generation.” Because of the relatively young age of the research participants, these studies will focus on exploring the basis for biological persistence of DES effects across generations. ■

—Alyssa M. Voss, M.P.H.

NATHANIEL ROTHMAN HONORED BY VANDERBILT-INGRAM CANCER CENTER

In October, **Nathaniel Rothman, M.D., M.P.H., M.H.S.**, a senior investigator in the Occupational and Environmental Epidemiology Branch, was honored as the Orrin Ingram Distinguished Lecturer at the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Dr. Rothman gave a presentation titled “Historical perspectives on studying susceptibility for bladder cancer, lessons learned, and implications for the genomic era.” His research focuses on using biologic markers of exposure, early biologic effect, and genetic susceptibility in epidemiologic studies of occupational and environmental causes of cancer. His study on the health effects of exposure to benzene in China led to a lower occupational standard for benzene exposure in that country. In addition, his findings helped prompt the U.S. Environmental Protection Agency to establish a

rule limiting the benzene content in gasoline and to adopt controls on passenger vehicles and portable fuel containers to reduce the emission of hazardous air pollutants.



Nathaniel Rothman

The Orrin Ingram Distinguished Lecture series features distinguished investigators whose discoveries have contributed to major advances in cancer biology, diagnosis, prevention, and treatment.

DCEG HONOREES AT NCI DIRECTOR'S AWARD CEREMONY

In November, **Margaret A. Tucker, M.D.**, Director of DCEG's Human Genetics Program, received an Outstanding Mentor Award from NCI Director Harold E. Varmus, M.D., for her exemplary mentoring and guidance of trainees in cancer research. Dr. Tucker was recognized during the 2011 NCI Director's Award ceremony. In addition, several DCEG staff members received NIH Merit Awards.

Individual Merit Awards

Steven L. Simon, Ph.D., Radiation Epidemiology Branch (REB), was recognized for his seminal contributions to improving estimates of radiation doses from radioactive fallout from nuclear testing and accidents, thereby clarifying associated cancer risks. **Rebecca Troisi, Sc.D.**, Epidemiology and Biostatistics Program, was recognized for her leadership of the only long-term study of the effects of *in utero* exposure to diethylstilbestrol. **Jill Koshiol, Ph.D.**, Infections and Immunoepidemiology Branch (IIB), was recognized with the 2011 John P. Hartinger Executive Leadership Development Award for her leadership potential, exemplary work ethic, and commitment to public service.

Group Merit Awards

DCEG's Director, **Joseph F. Fraumeni, Jr., M.D.**, Deputy Director, **Shelia Hoar Zahm, Sc.D.**, and members of the Office of Education (OE) staff—**Jackie Lavigne, Ph.D., M.P.H.**, Chief; **Kristin Kiser, M.H.A., M.S.**; and Tess Lee (formerly of OE)—were recognized for creating an outstanding and innovative fellowship training program in epidemiology.

The group responsible for the development of the DNA Extraction and Staging Laboratory, including **Marianne K. Henderson, M.S.**, Chief, Office of Division Operations and Analysis, **Karen E. Pitt, Ph.D.**, Office of the Director, and Mr. Timothy Sheehy, SAIC, was recognized for innovation in process improvements and automation to increase the high-throughput capacity of this NCI and SAIC-Frederick facility in Frederick, Maryland.

DCEG Length of Service Certificates

Several Length of Service certificates were awarded to DCEG staff. Recognized for 30 years of service were: **James J. Goedert, M.D.** (IIB);



Margaret Tucker

Linda K. Ross (retired), Administrative Resource Center (ARC); and **Catherine Schairer, Ph.D.**, Biostatistics Branch.

Recognized for 20 years of service were: **Stephen J. Chanock, M.D.**, Chief of the Laboratory of Translational Genomics and Director of the NCI Core Genotyping Facility; **Peter D. Inskip, Sc.D.** (REB); **Roberto P. Minutillo**, Manager of the ARC; **Nathaniel Rothman, M.D., M.P.H., M.H.S.**, Occupational and Environmental Epidemiology Branch; and **Donna G. Siegle**, Director of the ARC and Director of the Office of Administrative Services for NCI's Office of the Director/Office of Management. ■

NEW SCIENTIFIC REVIEW COMMITTEE LEADERSHIP

In January, **Eric A. Engels, M.D., M.P.H.**, Infections and Immunoepidemiology Branch, was appointed chair of the DCEG Committee for Technical Evaluation of Protocols (TEP). He is replacing outgoing TEP Chair **Shelia Hoar Zahm, Sc.D.**, Deputy Director of DCEG. **Catherine B. McClave, M.S.**, Chief of the Office of Communications and Special Initiatives, serves as executive secretary for TEP.

The purpose of TEP is to evaluate the scientific merit and proposed technical approach for study protocols involving DCEG scientists or resources. TEP serves in an advisory role to the Division Director, who has the final authority for approval of scientific protocols. The TEP review process encompasses a project's rationale, objectives, methods, budget, priority, and relevance to the mission of DCEG.



Catherine McClave and Eric Engels.

DCEG HOSTS VISITING SCHOLAR SILVIA FRANCESCHI



Louise Brinton, Joseph Fraumeni, Silvia Franceschi, and Allan Hildesheim.

In September, DCEG welcomed as a Visiting Scholar Dr. Silvia Franceschi, head of the Section of Infections at the International Agency for Research on Cancer (IARC) in Lyon, France. She is recognized internationally for her research on the link between infectious agents and cancer.

Dr. Franceschi received an M.D. from Milan University in Italy and an M.Sc. in epidemiology from the University of Oxford in the United Kingdom. She also received postgraduate diplomas in obstetrics and gynecology and in medical statistics. Early in her career, she was a research fellow at the Mario Negri Institute for Pharmacological Research in Milan and a fellow at the Division of Epidemiology, Imperial Cancer Research Fund at Oxford. Dr. Franceschi served as Chief of the Epidemiology Unit of the Aviano Cancer Center in Italy for more than 15 years before joining IARC in 2000.

Throughout her distinguished career, Dr. Franceschi has conducted research involving infectious agents and cancer, most notably on the role of human papillomavirus (HPV) in the etiology of cervical and oral cancers, the

associations of HIV and hepatitis C virus with lymphoma, and the relationship of *Helicobacter pylori* to stomach cancer. Her studies have involved broad international collaborations in Latin America, Asia, and Africa, and she has published more than 1,100 peer-reviewed articles. Her collaborations with DCEG date back to the 1980s and include several large pooling projects for cancers of the thyroid, cervix, and head and neck, as well as lymphoma.

Dr. Franceschi's two-day visit, hosted by **Louise A. Brinton, Ph.D.**, Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), and **Allan Hildesheim, Ph.D.**, Chief of the Infections and Immunoepidemiology Branch (IIB), included a seminar titled "HPV infection in women with or without cervical cancer and HIV infection: Update from IARC studies."

Dr. Franceschi explained that more than 85 percent of the global burden of cervical cancer is borne by developing countries. The planning and evaluation of HPV vaccination and HPV DNA test-based screening require population-based data on age- and type-specific

HPV prevalence among women with and without cancer. To this end, IARC has conducted approximately 30 surveys in representative samples of women worldwide, with priority given to countries that lack previous HPV studies or data on cervical cancer. The studies have not only confirmed a high prevalence of HPV in certain areas of sub-Saharan Africa, Latin America, and India but also identified countries where the incidence of cervical cancer was not previously known to be high, including China and Mongolia.

IARC also has investigated HPV prevalence by age group, observing substantial differences in age-specific curves of HPV prevalence between populations. "In some countries, young women do not show higher HPV prevalence than middle-aged women," said Dr. Franceschi. "Western age-specific curves of HPV prevalence should not be taken as the natural history of HPV infection. Women aged 40 years or older living in low-resource countries should not be left out from screening efforts," she said, "because they harbor a large number of precancerous lesions that might be easily treated."

Dr. Franceschi also described work on the distribution of HPV type in cervical cancer by HIV status. Studies from IARC have found no difference in the proportion of cervical cancers associated with HPV 16 and/or HPV 18 between HIV-positive and HIV-negative women. These findings provide reassurance as to the efficacy of current vaccines against HPV 16 and HPV 18, even among populations in which HIV infection is common.

During her visit, Dr. Franceschi participated in several meetings with DCEG scientists. Dr. Brinton led a discussion hosted by the DCEG Africa Working

Group on “Research in low-resource countries, including Africa” that focused on the various opportunities and challenges of conducting epidemiologic studies in developing countries, and Dr. Franceschi emphasized the importance of hiring motivated and capable local staff. **Aimée R. Kreimer, Ph.D.** (IIB), moderated a session on “HPV infection in cancer of the head and neck,” and Dr. Franceschi described her new Study of Human Papillomavirus and Precancerous Lesions in the Tonsil (SPLIT), which she is conducting in France.

Additional meetings focused on cervical cancer, including a session titled “Hormonal influences on cervical cancer” facilitated by **Nicolas Wentzensen, M.D., Ph.D.** (HREB). Dr. Franceschi presented data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study on invasive cervical cancer

and sex hormone levels in premenopausal and postmenopausal women. **Anil K. Chaturvedi, D.V.M., Ph.D.** (IIB), and **Vikrant Sahasrabudhe, M.B.B.S., Dr.P.H.** (HREB), led a session on “Cervical cancer among HIV-infected women: Other research ventures.” A lively discussion ensued on the urgency of preventing cervical cancer in HIV-infected women now that antiretroviral treatment has become available and allows for longer life expectancy, especially in sub-Saharan Africa.

Dr. Franceschi also met with DCEG scientists during informal brown-bag luncheons. **Maria Constanza Camargo, Ph.D.** (IIB), and **Michael B. Cook, Ph.D.** (HREB), hosted a lunch for tenure-track investigators and fellows to discuss opportunities for high-risk innovative research during their early career years. **Mary H. Ward, Ph.D.,**

Occupational and Environmental Epidemiology Branch, and **Katherine A. McGlynn, Ph.D., M.P.H.**, Deputy Chief of HREB, facilitated a lunch hosted by the Women Scientist Advisors to examine how women scientists can best position themselves to succeed in research careers.

“I am very touched by this honor, and I would like to thank Dr. Brinton, Dr. Hildesheim, Dr. Fraumeni, and the entire Division for allowing me to visit,” Dr. Franceschi said. “A substantial portion of what I have done in my career has been conceived through collaborations here, and I greatly admire the creativity and resilience of the Division.” ■

—Victoria A. Fisher, M.P.H.

DCEG INVESTIGATORS PRESENT RESEARCH TO THE NCAB

At its December meeting, the National Cancer Advisory Board (NCAB) performed its annual review of NCI’s Intramural Research Program. **Joseph F. Fraumeni, Jr., M.D.**, Division Director, described the mission and scope of DCEG’s research activities, and four principal investigators from the Division presented the latest findings from their research areas.

Stephen J. Chanock, M.D., Chief of the Laboratory of Translational Genomics and Director of the Core Genotyping Facility, spoke on “The aging genome: Genetic mosaicism and its relationship to cancer.” In a study of nearly 58,000 individuals, he described the surprising frequency of genetic mosaicism in the population and its relationship to aging and to the etiology of certain cancers and other late-onset diseases.

Neal D. Freedman, Ph.D., M.P.H., Nutritional Epidemiology Branch, spoke about “The changing risks of bladder cancer related to tobacco smoking.” In his talk, Dr. Freedman described the increasing risks of bladder and other

tobacco-related cancers, due perhaps to changes in the composition of cigarettes and deeper inhalation. In addition, he discussed the recent introduction of new tobacco products, such as electronic cigarettes and water pipes, and suggested the need for further study.

Robert N. Hoover, M.D., Sc.D., Director of the Epidemiology and Biostatistics Program, discussed “Adverse health outcomes in women exposed *in utero* to diethylstilbestrol (DES).” In 1971, a woman’s exposure to the potent synthetic estrogen DES while she was *in utero* was linked to a high relative risk of vaginal cancer when she reached adolescence. In the early 1990s, DCEG combined several U.S. cohorts of exposed and unexposed women, which had been assembled in the 1970s, into one large cohort that has now been followed for 18 years. This effort linked and quantified 12 adverse reproductive outcomes to DES exposure, including vaginal cancer, cervical dysplasia, and breast cancer. The proportion of women developing each of these outcomes due to DES exposure is unprecedented

in the history of adverse outcomes from drugs given to healthy individuals.

In her presentation “Advancing knowledge on the HPV vaccine: Recent findings from the NCI Costa Rica HPV-16/18 Vaccine Trial,” **Aimée R. Kreimer, Ph.D.**, Infections and Immunoepidemiology Branch, presented evidence that the customary three doses of the human papillomavirus (HPV) vaccine may not be necessary, because similar vaccine efficacies against cervical HPV 16/18 infection were observed among women who received two doses, and even a single dose, of the HPV vaccine after four years of follow-up. Additionally, Dr. Kreimer presented information on the efficacy of the HPV vaccine at anatomic sites beyond the cervix, including the anus and oropharynx.

At the end of the meeting, several NCAB members remarked on the high level of scientific accomplishment that was evident in the presentations.

MALCOLM PIKE VISITS AS AN HREB DISTINGUISHED LECTURER

The Hormonal and Reproductive Epidemiology Branch (HREB) hosted Dr. Malcolm Pike as a Distinguished Lecturer in October 2011. Dr. Pike is widely known for his research on the etiology and chemoprevention of breast, endometrial, and ovarian cancers and has conducted landmark research to clarify our understanding of how pregnancy and oral contraceptives affect these cancers. He is a member of the Epidemiology Service at Memorial Sloan-Kettering Cancer Center in New York, New York, and the Department of Preventive Medicine at the University of Southern California Norris Cancer Center in Los Angeles. He currently is assessing the characteristics of breast tissue in normal nulliparous and parous volunteers to help clarify the biological basis for the effects of various reproductive factors on risk of breast cancer. Dr. Pike's major interest is in designing an oral contraceptive that could reduce the risk of breast cancer without losing the protection offered by these drugs against endometrial and ovarian cancers. To this end, he is studying the effects on the breast tissue of different hormonal contraceptives in volunteers.

During his visit, Dr. Pike gave a seminar titled "Hormonal chemoprevention of breast, endometrial, and ovarian cancer in young women." Beginning around the time of menopause, the incidence of breast, endometrial, and ovarian cancers show a marked slowing in the degree to which their incidence rates increase with age. Dr. Pike proposed that this slowing is the result of the reduction in the cell division of the relevant tissue and that cell division is an important mechanism of carcinogenesis in women. The varying effects of oral contraceptives on different cancers—reductions in ovarian and endometrial cancers but no reduction



Louise Brinton, Malcolm Pike, and Joseph Fraumeni.

in breast cancer—could be explained on this basis. The goal is to use our understanding of the effects of hormones on the breast to help design a hormonal contraceptive that will reduce breast cell division and hence reduce breast cancer risk. Dr. Pike pointed out that the anti-estrogens tamoxifen and raloxifene are very effective in preventing breast cancer in postmenopausal women and that they could become widely used if their significant side effects could be ameliorated.

During his presentation, Dr. Pike discussed the protective effects of oral contraceptives on the risk of ovarian and endometrial cancers and addressed optimal usage regimens. He also discussed an approach to preventing breast cancer that involves giving women a gonadotropin-releasing hormone (GnRH) analog contraceptive with low-dose estrogen. Carriers of the *BRCA1* mutation who are treated with a GnRH agonist have reduced mammographic densities, which would improve the utility of mammographic surveillance and

would help to reduce their breast cancer risk. However, it is likely that such a regimen would not provide any protection against ovarian or endometrial cancer. A progestin is needed to reduce the risk of endometrial and probably ovarian cancer, but the systemic level must be kept very low in order to not affect the breast. A GnRH analog with ultra-low doses of estrogen and progestin may, however, lead to a loss of protection against endometrial and ovarian cancer.

Dr. Pike also participated in a series of roundtable discussions moderated by HREB investigators. **Gretchen L. Gierach, Ph.D.**, led a session titled "Breast tissue age, tissue composition, and breast cancer risk"; **Mark E. Sherman, M.D.**, facilitated a discussion on "Developing novel designs for chemoprevention studies of breast cancer"; and **Nicolas Wentzensen, M.D., Ph.D.**, moderated a session titled "Etiologic heterogeneity of endometrial and ovarian cancers." ■

—M. Patricia Madigan

OEEB HOSTS DISTINGUISHED LECTURER DAVID SAVITZ

In November, the Occupational and Environmental Epidemiology Branch (OEEB) hosted Dr. David Savitz as a Distinguished Lecturer in Occupational and Environmental Cancer. Dr. Savitz is a professor of epidemiology in the Public Health program and a professor of obstetrics and gynecology at Brown University's Alpert Medical School in Providence, Rhode Island. Previously, Dr. Savitz was a professor of community and preventive medicine and Director of the Disease Prevention and Public Health Institute at the Mt. Sinai Medical Center in New York, New York, following a 20-year tenure in the Department of Epidemiology at the University of North Carolina School of Public Health in Chapel Hill.

Dr. Savitz's research has focused on two important and challenging areas in public health—the disease risks from certain environmental exposures and the health problems associated with pregnancy and fertility. He has conducted studies of childhood cancers, adult brain cancer, non-Hodgkin lymphoma, multiple myeloma, breast cancer, and adverse pregnancy outcomes, and he has investigated a wide range of chemical and physical exposures, including perfluorinated chemicals, pesticides, drinking water disinfection by-products, and non-ionizing radiation. His landmark work on disinfection by-products and spontaneous abortion, as well as his research on electromagnetic fields and cancer, has featured carefully designed studies with high-quality assessment of exposures that have made key contributions to the field with real societal impact.

Dr. Savitz has not shied away from difficult and politically charged topics. For example, he chaired Institute of Medicine (IOM) committees evaluating risks associated with exposure to Agent



Debra Silverman, Mary Ward, David Savitz, and Joseph Fraumeni.

Orange among Vietnam veterans and contamination of drinking water at the Marine Corps' Camp Lejeune. Recently, he served on the IOM committee to guide research on the human health effects of the catastrophic oil spill in the Gulf of Mexico.

During his DCEG seminar "From power lines to cell phones: Twenty-five years of epidemiologic evidence on non-ionizing radiation and cancer," Dr. Savitz discussed the major phases of epidemiologic research on magnetic fields—from power lines and radio-frequency radiation to cell phones. His presentation examined the social context and the competing perspectives among scientific disciplines and the public. Dr. Savitz also discussed the evolution of research methods and their challenges, giving particular attention to assessment of exposures.

During his visit, Dr. Savitz also spoke on "The public's love/hate relationship with epidemiology: The burden of being relevant" at a meeting with DCEG staff. He participated in several roundtable discussions, including "Agricultural

exposures and cancer," moderated by **Laura Beane Freeman, Ph.D.** (OEEB); "Exposure assessment," moderated by **Melissa Friesen, Ph.D.** (OEEB); "Environmental exposures and cancer," moderated by **Mary H. Ward, Ph.D.** (OEEB); and "The art of communicating controversial findings to the media, Congress, and the public," moderated by **Martha S. Linet, M.D., M.P.H.**, Chief of the Radiation Epidemiology Branch, and **Jennifer Loukissas, M.P.P.**, Office of Communications and Special Initiatives. In addition, Dr. Savitz held a luncheon meeting with predoctoral and postdoctoral fellows and attended a panel discussion on mentoring with **Wong-Ho Chow, Ph.D.** (OEEB), **Sanford M. Dawsey, M.D.**, Nutritional Epidemiology Branch, and **Patricia Hartge, Sc.D.**, Deputy Director of the Epidemiology and Biostatistics Program. **Jackie Lavigne, Ph.D., M.P.H.**, Chief of the Office of Education, moderated the session. ■

—Mary H. Ward, Ph.D., and
Melissa Friesen, Ph.D.

DCEG CELEBRATES ACCOMPLISHMENTS OF LONGTIME COLLABORATOR

Dr. Yu-Tang Gao, a longtime collaborator with DCEG, was honored in 2011 for his 55 years of dedication to public health research and practice and for his leadership in cancer research. An international symposium, *Frontiers in Global Public Health: Challenges and Opportunities in Cancer Research in Developing Countries*, was held at the Shanghai Jiao Tong University in Shanghai, China, in his honor.

Dr. Gao is a pioneering scientist who has led numerous international collaborative efforts in cancer epidemiology in China since the early 1980s. His vision and leadership in cancer registration efforts in Shanghai paved the way for an in-depth examination of cancer incidence patterns in China and spawned many fruitful leads in cancer etiology and prevention.

Dr. Gao's collaborative research has provided extraordinary opportunities for training a new generation of scientists in China, in the United States, and around the world.

In collaboration with DCEG investigators, Dr. Gao launched a series of case-control studies to systematically investigate the etiology of a variety of cancers in Shanghai. Most notable was a ground-breaking study that examined reasons for the relatively high incidence rates of lung cancer among Chinese women despite their extremely low prevalence of smoking. This study uncovered environmental determinants of lung cancer, notably mutagen-containing vapors from high-temperature wok cooking with rapeseed oil. Dr. Gao's research also



Bu-Tian Ji, Qing Lan, Yu-Tang Gao, Ann Hsing, and Wong-Ho Chow.

has highlighted the importance of nutrition in cancer development, suggesting that certain dietary practices, such as drinking green tea, may lower the risk of certain cancers, whereas obesity increases the risk of other cancers.

Dr. Gao also was instrumental in developing prospective cohort studies with banked biological samples for rapid testing of emerging etiologic hypotheses. Of special interest is an ongoing cohort study of 75,000 Shanghai women that Dr. Gao has been conducting in collaboration with DCEG and Vanderbilt University in Nashville, Tennessee. This study has generated a series of major epidemiological findings and has contributed data and biological samples to countless international consortial efforts. Dr. Gao's collaborative research also has provided extraordinary opportunities for training a new generation of scientists in China, in the United States, and around the world.

Several DCEG investigators helped plan the symposium and gave presentations to mark the celebration. The participants included **Ann W. Hsing, Ph.D.**, of the Infections and Immunoepidemiology

Branch, and Occupational and Environmental Epidemiology Branch investigators **Wong-Ho Chow, Ph.D.**; **Bu-Tian Ji, M.D., Dr.P.H.**; and **Qing Lan, M.D., Ph.D., M.P.H.**

At the plenary session, Dr. Gao was presented with a congratulatory letter from DCEG Director **Joseph F. Fraumeni, Jr., M.D.**, and with a DCEG Special Recognition Award. In his letter, Dr. Fraumeni noted, "Dr. Gao's vision and leadership in cancer epidemiology have paved the way in establishing international partnerships that are continuing to thrive and advance the global agenda in cancer research. We are grateful to him for the friendship and goodwill that have brought our scientists and our nations together in the fight against cancer."

Dr. Zhi-Jie Zheng, Dean of the School of Public Health at Shanghai Jiao Tong University, announced the university's creation of an endowed Professor Yu-Tang Gao lectureship as a tribute to Dr. Gao's monumental contributions to cancer research and education. ■

—Wong-Ho Chow, Ph.D.

DCEG FELLOWS AWARDS FOR RESEARCH EXCELLENCE

The DCEG Fellows Awards for Research Excellence (D-FARE) program provides funding for travel to scientific meetings or conferences to fellows who have made exceptional contributions to research projects. These contributions may include formulating research ideas, developing study designs, conducting fieldwork and analysis, or interpreting results. Each of the recognized fellows also must have played a major role in drafting a manuscript. Special consideration is given to projects in which fellows demonstrate growth beyond the discipline of their previous training.

The D-FARE program was established because scientific meetings are integral to the fellowship experience. The awards enable a greater number of fellows to participate in meetings, where they present their work, hear about new scientific developments, and establish vital connections with other scientists.

This year, eight D-FARE winners were chosen from a record number of 33 applicants, who were judged by members of an ad hoc DCEG committee. The \$1,500 travel awards for this

fiscal year (FY) were announced in October 2011, and funds must be used by the end of FY2012.

The 2011 D-FARE recipients and the titles of their abstracts are:

Arpita Ghosh, Ph.D., Biostatistics Branch: “Leveraging family history in genome-wide association studies.”

H. Dean Hosgood, III, Ph.D., Occupational and Environmental Epidemiology Branch: “Genetic variant in *TP63* on locus 3q28 is associated with risk of lung adenocarcinoma among never-smoking females in Asia.”

Cari Meinhold Kitahara, Ph.D., Radiation Epidemiology Branch (REB): “Early adult weight, subsequent weight change, and cancer incidence in the NIH-AARP Diet and Health Study.”



D-FARE recipients and their mentors: (front) Stephanie Lamart, Lisa Mirabello, Arpita Ghosh, Meredith Shiels, Indu Kohaar, and Joseph Fraumeni; (back) Mark Schiffman, Jonine Figueroa, Gretchen Gierach, Cari Meinhold Kitahara, Laura Linville, Sholom Wacholder, and Jackie Lavigne. (Not shown: Dean Hosgood.)

Indu Kohaar, Ph.D., Laboratory of Translational Genomics: “Strong effect of rs2294008 on mRNA and protein expression of the prostate stem cell antigen in human normal and tumor bladder tissue.”

Stephanie Lamart, Ph.D. (REB): “Analysis of trends in radiation doses to the esophagus from radiotherapy treatment for breast cancer.”

Laura Linville, Hormonal and Reproductive Epidemiology Branch: “Associations between age and parity and morphometry of terminal ductal lobular units in the Komen Tissue Bank Study of healthy women.”

Lisa Mirabello, Ph.D., Clinical Genetics Branch: “Elevated methylation of HPV 16 DNA is associated with the development of high-grade cervical intraepithelial neoplasia.”

Meredith Shiels, Ph.D., Infections and Immunoepidemiology Branch: “The impact of the HIV epidemic on anal cancer rates in the United States.” ■

JUDY SCHWADRON RETIRES

In December, **Judy Schwadron** retired from the Administrative Resource Center after 15 years of service in DCEG. She provided invaluable expertise in the processing of Cancer Research Training Award and Visiting Fellow appointments and in the handling of visa applications. More recently, she served as the tenure-track/tenure search committee coordinator for the Division. During her time at DCEG, Ms. Schwadron worked meticulously to assure a smooth transition for all new scientists, particularly foreign scientists, into the Division, helping them acclimate to their new surroundings while anticipating and answering their questions. She was often the first person that young scientists met when they came on board. Ms. Schwadron will be spending her time enjoying her grandchildren, practicing yoga, and attending the theater.



Judy Schwadron

DCEG TENURE-TRACK RETREAT

In December, DCEG tenure-track investigators gathered for a half-day retreat that was designed to offer tactical and strategic approaches to help them advance in their career paths. The retreat included presentations and guidance from experienced scientists both inside and outside of DCEG.

During the first half of the retreat, Roland Owens, Ph.D., Assistant Director of the NIH Office of Intramural Research, presented new developments in the tenure-track evaluation process, including achievements in mentoring and activities in increasing diversity. Paul Sorlie, Ph.D., Chief of the Epidemiology Branch of the National Heart, Lung, and Blood Institute and chair of the Epidemiology and Biometry Review Panel of the NIH Central Tenure Committee, discussed the process of tenure review at NIH and important points to consider for epidemiologists and biostatisticians. DCEG Director **Joseph F. Fraumeni, Jr., M.D.**, spoke on key criteria for measuring success on the road to tenure in DCEG, while **Robert N. Hoover, M.D., Sc.D.**, Director of DCEG's Epidemiology and Biostatistics Program (EBP), discussed evaluation by the DCEG Promotion and Tenure Review Panel and offered a practical reality check for success in advancing on the tenure track.

The second half of the retreat covered strategies for the three stages of the tenure-track process.

Beginning stage: One to three years (pre-site visit)—**Allan Hildesheim, Ph.D.**, Chief of the Infections and Immunoepidemiology Branch (IIB), spoke on defining a research focus and how to balance “doing” and mentoring.

Middle stage: Four to six years (site visit)—**Patricia Hartge, Sc.D.**, Deputy

Director of DCEG's EBP, presented on various topics, such as developing a research plan and telling a story, the essentials of authorship, and strategic planning by positioning and focusing on elements needed to fill gaps in the research portfolio. **Louise A. Brinton, Ph.D.**, Chief of the Hormonal and Reproductive Epidemiology Branch, then spoke on obtaining guidance in career development and getting the most out of one's mentoring committee and annual reviews.

Final stage: Six to eight years (post-site visit)—**Martha S. Linet, M.D., M.P.H.**, Chief of the Radiation Epidemiology



Roland Owens

Branch, spoke about assembling the tenure package, salary negotiations/determinations, and how to obtain needed information.

The retreat was organized by tenure-track investigators **Melissa Friesen, Ph.D.**, Occupational and Environmental Epidemiology Branch, and **Aimée R. Kreimer, Ph.D.** (IIB). ■

DCEG WELCOMES NEW HHMI-NIH RESEARCH SCHOLAR

In September, **Lindsey Wu** joined the Radiation Epidemiology Branch (REB) as a guest researcher through the Howard Hughes Medical Institute (HHMI)-NIH Research Scholars Program. Ms. Wu received her B.A. in statistics from Williams College in Williamstown, Massachusetts, where she wrote a thesis on heterogeneous ensemble methods in data classification. After graduation, she taught high school mathematics at the Munich International School in Germany for two years before returning to the United States and beginning medical school at Duke University in Durham, North Carolina. She has finished her third year at Duke and is interested in internal medicine as well as research in epidemiology and health services. Under the mentorship of **Amy Berrington de González, D.Phil.** (REB), Ms. Wu plans to work with the SEER (Surveillance, Epidemiology and End Results) database to investigate patterns of sarcomas as second malignancies according to their histology and location and in relation to previous treatment with radiotherapy. Ms. Wu also is evaluating aspects of breast cancer screening among high-risk women under the mentorship of **Mitchell H. Gail, M.D., Ph.D.**, Biostatistics Branch.



Lindsey Wu

The HHMI-NIH Research Scholars Program was established in 1985 to give outstanding students at U.S. medical and dental schools the opportunity to receive research training at NIH.

SCIENTIFIC HIGHLIGHTS

ALL CANCERS

Cancer Studies Among the Elderly

An approach is described for conducting population-based, case-control studies among the elderly by using linked SEER-Medicare data. Cases and controls are drawn from the population of Medicare beneficiaries older than age 65 years who reside in areas with cancer registries that participate in the SEER program. The strength of this type of study is the large size of the population, which allows study of less common cancers. The investigators discuss the cancer risk factors that can be assessed using Medicare claims, the methodology for timing of diagnoses and selecting controls, and the limitations of the approach. (Engels EA, Pfeiffer RM, Ricker W, et al. Use of Surveillance, Epidemiology, and End Results-Medicare data to conduct case-control studies of cancer among the U.S. elderly. *Am J Epidemiol* 2011;174:860–870)

Myotonic Muscular Dystrophy and Cancer Risk

The authors identified 1,658 patients with a myotonic muscular dystrophy (MMD) discharge diagnosis in the Swedish Hospital Discharge Register and Danish National Patient Registry between 1977 and 2008 and linked the patient data to cancer registries. A total of 104 patients developed cancer during follow-up, which corresponds to an observed rate of 73.4 per 10,000 person-years in MMD patients vs. an expected rate of 36.9 in the general Swedish and Danish populations combined (SIR = 2.0). Significant excess risks were observed for cancers of the endometrium (SIR = 7.6), brain (SIR = 5.3), ovary (SIR = 5.2), and colon (SIR = 2.9). Cancer risks were similar among women and men after excluding genital organ tumors. The same pattern of cancer excess was observed first in the Swedish

and then in the Danish cohorts. (Gadalla SM, Lund M, Pfeiffer RM, et al. Cancer risk among patients with myotonic muscular dystrophy. *JAMA* 2011;306:2480–2486)

Solid Organ Transplantation and Cancer Risk

Investigators studied overall patterns of cancer among 175,732 solid organ transplant recipients (kidney: 58.4%, liver: 21.6%, heart: 10.0%, lung: 4.0%) from the U.S. Scientific Registry of Transplant Recipients (1987–2008) with linked data from 13 state and regional cancer registries. During follow-up, transplant recipients were linked to 10,656 malignancy diagnoses, yielding an incidence of 1,375 per 100,000 person-years (SIR = 2.10; excess absolute risk = 719.3 per 100,000 person-years). Compared with the general population, recipients of a kidney, liver, heart, or lung transplant had an increased risk for various infection-related and -unrelated cancers. (Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among U.S. solid organ transplant recipients. *JAMA* 2011;306:1891–1901)

Women Exposed In Utero to Diethylstilbestrol

See article on pages 6–8 of this issue of *Linkage*. (Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *New Engl J Med* 2011;365:1304–1314)

BLADDER CANCER

New Susceptibility Locus on Chromosome 18q12.3

GWAS and candidate gene-association studies of bladder cancer have identified 10 susceptibility loci. The authors conducted a meta-analysis of two published genome-wide scans and followed up the most significant association signals (17 SNPs in 10 genomic regions) in

1,382 cases and 2,201 controls from four studies. A combined analysis identified a novel susceptibility locus that mapped to a region of 18q12.3, marked by rs7238033 and two highly correlated SNPs, rs10775480 and rs10853535. The signal localizes to *SLC14A1*, the gene for a urea transporter that regulates cellular osmotic pressure. The findings suggest that genetic variation in *SLC14A1* may provide new insights into bladder carcinogenesis. (García-Closas M, Ye Y, Rothman N, et al. A genome-wide association study of bladder cancer identifies a new susceptibility locus within *SLC14A1*, a urea transporter gene on chromosome 18q12.3. *Hum Mol Genet* 2011;20:4282–4289)

BREAST CANCER

Gene Variants by Breast Cancer Subtype

A recent multistage GWAS found that SNPs at 1p11.2 and 14q24.1 (*RAD51L1*) were associated with overall risk of breast cancer. To determine risks by tumor subtype, investigators analyzed data from case-control and cohort studies of the Breast Cancer Association Consortium, including 46,036 invasive

GLOSSARY

GWAS	Genome-wide association study
HPV	Human papillomavirus
HR	Hazard ratio
OR	Odds ratio
RCC	Renal cell carcinoma
SEER	Surveillance, Epidemiology and End Results
SIR	Standardized incidence ratio
SNP	Single nucleotide polymorphism

Note: This glossary defines acronyms that occur in more than one summary throughout the Scientific Highlights section.

breast cancer cases and 46,930 unaffected controls. These were evaluated by estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2, grade, node status, tumor size, and ductal or lobular morphology. The SNP at 1p11.2 showed significantly stronger associations with ER+ tumors (per-allele OR for ER+ tumors = 1.13). The association with ER+ tumors was more pronounced for tumors of lower grade and lobular histology. The SNPs at 14q24.1 were associated with risk for most tumor subtypes, including triple-negative breast cancers. (Figueroa JD, García-Closas M, Humphreys M, et al. Associations of common variants at 1p11.2 and 14q24.1 [*RAD51L1*] with breast cancer risk and heterogeneity by tumor subtype: Findings from the Breast Cancer Association Consortium. *Hum Mol Genet* 2011;20:4693–4706)

Physical Activity

In a prospective cohort of 73,049 Chinese women aged 40 to 70 years, the authors studied risk of breast cancer (717 incident cases) in relation to self-reported and work history-related physical activity, including adolescent and adult exercise, household activity, and walking and cycling for transportation. Risk was lower for women in the lowest quartile of average occupational sitting time and in the highest quartile of average occupational energy expenditure (adjusted HR = 0.81 and 0.73, respectively). Adult exercise at or above the recommended level (eight metabolic equivalent hours per week per year) was associated with lower risk (adjusted HR = 0.73) in postmenopausal women. Having both an active job and exercise participation did not confer an additional benefit, but other common daily activities were not associated with lower risk. (Pronk A, Ji BT, Shu XO, et al. Physical activity and breast cancer risk in Chinese women. *Br J Cancer* 2011;105:1443–1450)

CERVICAL CANCER

HPV Screen-and-Treat Strategies

The authors conducted a population-based study in rural Nigeria to identify HPV prevalence and associated cervical abnormalities. Women aged 15 years and older were enrolled, and non-virgins had a cervical exam, including liquid-based cytology and polymerase chain reaction HPV DNA testing. Two-thirds of the invited women participated, and 14.7% had detectable carcinogenic HPV, a proportion that did not decline with age and showed slight peaks in the 15–29 and 60–69 age groups. Among women of the age typically considered for screen-and-treat programs (aged 30–49 years), 12.8% were HPV positive, and the positive predictive value (PPV) for high-grade or worse cytology was 16.4%. Comparatively, women younger than 30 years of age were more likely to be HPV positive (18.9%) with a

lower PPV (4.2%). Among women aged 50 years and older (typically excluded from screening in resource-poor settings because inexpensive treatment is not available), HPV positivity was 14.2% with a PPV of 13.9%. In settings where HPV does not decline with age, HPV-based screen-and-treat programs may be feasible for mid-adult women because prevalence is sufficiently low and positivity predicts elevated risk of more easily treated pre-cancer. (Gage JC, Ajenifuja KO, Wentzensen NA, et al. The age-specific prevalence of human papillomavirus and risk of cytologic abnormalities in rural Nigeria: Implications for screen-and-treat strategies. *Int J Cancer* 2011; May 31 [E-pub ahead of print])

Type-specific HPV Infection

The authors followed a large-scale, community-based cohort in Taiwan for 16 years to investigate the role of genotype-specific HPV persistence in predicting cervical cancer, including

MAJOR EDITORIALS, COMMENTARIES, AND REVIEWS BY DCEG SCIENTISTS

Berrington de González A, Brenner A, Hartge P, et al. Evolving strategies in epidemiologic research on radiation and cancer. *Radiat Res* 2011;176:527–532

Spitz MR, Caporaso NE, Freedman AN. Epidemiology—Found in translation. *Cancer Discovery* 2011;1:21–22

Cook MB. Non-acid reflux: The missing link between gastric atrophy and esophageal squamous cell carcinoma? *Am J Gastroenterol* 2011;106:1930–1932

Gadalla SM, Savage SA. Telomere biology in hematopoiesis and stem cell transplantation. *Blood Rev* 2011;25:261–269

Goldstein AM. Germline *BAP1* mutations and tumor susceptibility. *Nat Gen* 2011;43:925–926

Hartge P, et al. Finding ovarian cancer. *J Natl Cancer Inst* 2012;104:82–83

O'Brien TR. Epidemic-assistance investigations by the Centers for Disease Control and Prevention—The first 60 years (editorial). *Am J Epidemiol* 2011;174:1211–1212

Donnelly RP, Dickensheets H, O'Brien TR. Interferon-lambda and therapy for chronic hepatitis C virus infection. *Trends Immunol* 2011;32:443–450

Sahasrabudde VV, Luhn P, Wentzensen N. Human papillomavirus and cervical cancer: Biomarkers for improved prevention efforts. *Future Microbiol* 2011;6:1083–1098

Schiffman M, Gage JC, Clarke MA. Accepting the universal truths of cervical human papillomavirus epidemiology in pursuit of the remaining mysteries. *Sex Transm Dis* 2011;38:907–908

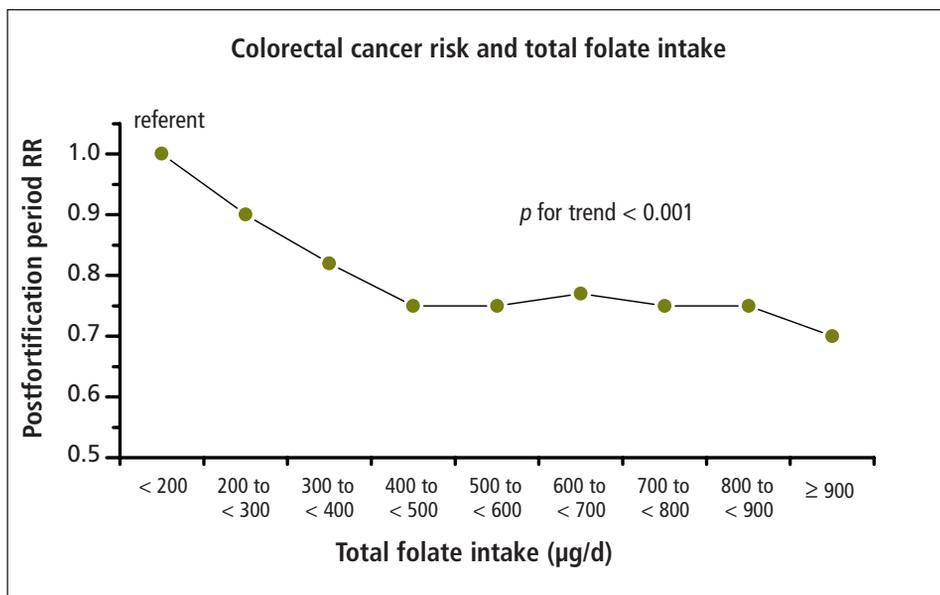


Figure 1. Risk of colorectal cancer by total folate intake (energy-adjusted dietary intake plus unadjusted supplemental intake) during the postfortification period. Total folate intake is in micrograms per day ($\mu\text{g}/\text{d}$). RR = relative risk. (Figure is based on Table 2 from Gibson TM, et al. *Am J Clin Nutr* 2011.)

invasive and *in situ* carcinoma. A total of 11,923 participants consented to HPV testing and cytology at baseline, and women who developed cervical cancer were identified from cancer and death registries. Of 10,123 women who were initially cytologically normal, 68 developed cervical cancer. The 16-year cumulative risks of subsequent cervical cancer for women with HPV 16, HPV 58 (without HPV 16), or other carcinogenic HPV types (without HPV 16 or HPV 58) were 13.5%, 10.3%, and 4.0%, respectively, compared with 0.26% for HPV-negative women. Women with type-specific persistence of any carcinogenic HPV had greatly increased risk compared with women who were HPV negative at both visits (HR = 75.4). The cumulative cervical cancer risks following persistent carcinogenic HPV infections increased with age; the risks were 5.5%, 14.4%, and 18.1% for women aged 30–44 years, 45–54 years, and ≥ 55 years, respectively. Newly acquired infections were associated with a low risk of cervical cancer regardless of age. (Chen HC, Schiffman M, Lin CY, et al. Persistence of type-specific human

papillomavirus infection and increased long-term risk of cervical cancer. *J Natl Cancer Inst* 2011;103:1387–1396)

COLORECTAL CANCER

Folate Intake

The authors examined the association between folate intake and colorectal cancer risk in the NIH-AARP Diet and Health Study, including 8.5 years of postfortification follow-up. During follow-up, 7,212 incident colorectal cancer cases were identified. A higher total folate intake was associated with a decreased risk (HR for ≥ 900 compared with $< 200 \mu\text{g}/\text{d} = 0.70$). The highest intakes specifically from supplements (HR = 0.82) or diet (HR = 0.81) were protective (see Figure 1). The pattern of associations was similar for the pre-fortification period, and no significant differences between time periods were observed. (Gibson TM, Weinstein SJ, Pfeiffer RM, et al. Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. *Am J Clin Nutr* 2011;94:1053–1062)

LIVER CANCER

Association of *IL28B* Genotype with Spontaneous Hepatitis C Virus Clearance

Investigators evaluated alternative genetic models for the association between variation in *IL28B* genotype (SNPs rs12979860 and rs8099917) and hepatitis C virus (HCV) clearance among 1,369 participants in the Urban Health Study, a multi-ethnic cohort of injection drug users. Chronic HCV infection puts infected individuals at risk for cirrhosis and hepatocellular carcinoma. After examining five potential genetic models (general, dominant, recessive, additive, and supra-additive [quadratic]), the investigators found that a quadratic genetic model based on rs12979860 described the association best. If confirmed, these findings may inform *IL28B* genotype-based clinical prediction models for treatment of chronic hepatitis C and the search for *IL28B* variants. (Shebl FM, Pfeiffer RM, Buckett D, et al. *IL28B* rs12979860 genotype and spontaneous clearance of hepatitis C virus in a multi-ethnic cohort of injection drug users: Evidence for a supra-additive association. *J Infect Dis* 2011;204:1843–1847)

LUNG CANCER

Early Gene Expression Signature

The authors measured genome-wide mRNA gene expression from lung tumor and unaffected lung tissue and from peripheral whole blood (PWB) from 73 adenocarcinoma cases and 80 controls in an effort to identify dysregulated genes associated with lung cancer that could be tested in blood to improve identification of at-risk patients. The authors discovered 50 dysregulated genes in stage I adenocarcinoma vs. control PWB samples. Eight of these genes (*TGFBR3*, *RUNX3*, *TRGC2*, *TRGV9*, *TARP*, *ACPI*, *VCAN*, and *TSTA3*) differentiated paired tumor vs. uninvolved lung tissue samples in stage I cases, suggesting a

similar pattern of cancer-related changes in PWB and lung tissue. Results were confirmed in two independent gene expression analyses in a blood-based, case-control study ($n = 212$) and a tumor–non-tumor paired tissue study ($n = 54$). The eight genes discriminated between patients with lung cancer and healthy controls with high accuracy. (Rotunno M, Hu N, Su H, et al. A gene expression signature from peripheral whole blood for stage I lung adenocarcinoma. *Cancer Prev Res [Phila]* 2011;4:1599–1608)

Variation at Chromosome 12p13.33

Although lung cancer is largely caused by tobacco smoking, inherited susceptibility plays an etiologic role. Previous GWAS in European populations have robustly demonstrated three polymorphic variations influencing lung cancer risk. In a GWAS of 5,355 European cases of smoking-related lung cancer and 4,344 smoking controls, the authors conducted a pathway-based analysis based on histologic subtypes of lung cancer, with 19,082 SNPs mapping to 917 genes in the inflammation pathway. A susceptibility locus for squamous cell lung carcinoma (SQ) was identified at 12p13.33 (*RAD52*, rs6489769), and the association was replicated in three independent samples, totaling 3,359 SQ cases and 9,100 controls (OR = 1.20). The combination of pathway-based approaches and information on disease-specific subtypes should improve the identification of susceptibility loci in heterogeneous diseases. (Shi J, Chatterjee N, Rotunno M, et al. Inherited variation at chromosome 12p13.33 including *RAD52* influences squamous cell lung carcinoma risk. *Cancer Discov* 2011; December 7 [E-pub ahead of print])

MELANOMA

Genetic Susceptibility

See article on pages 1–3 of this issue of *Linkage*. (Yokoyama S, Woods SL, Boyle GM, et al. A novel recurrent mutation in *MITF*

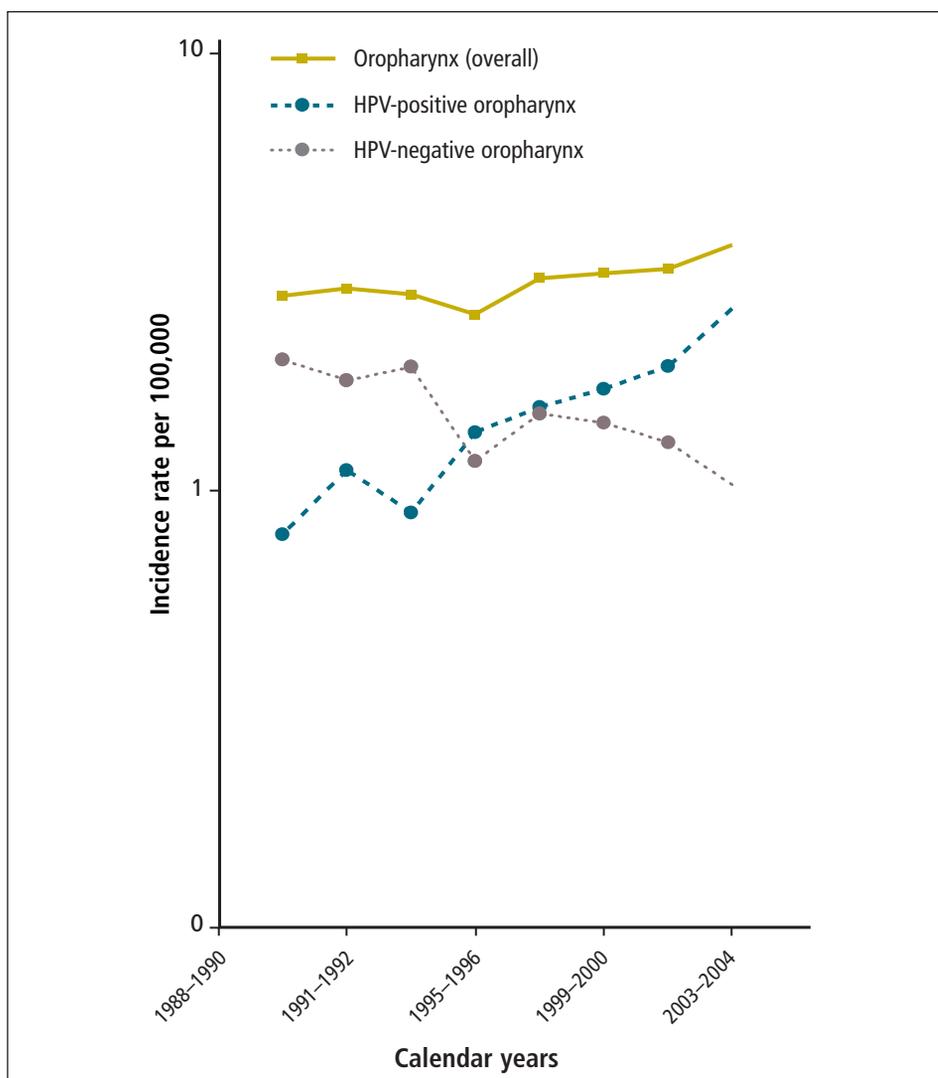


Figure 2. Incidence rates for overall oropharyngeal cancer, HPV-positive oropharyngeal cancer, and HPV-negative oropharyngeal cancer from 1988 to 2004 in Hawaii, Iowa, and Los Angeles. (Chaturvedi AK, et al. *J Clin Oncol* 2011)

predisposes to familial and sporadic melanoma. *Nature* 2011;480:99–103)

NUTRITION

GWAS of Circulating Vitamin E and Retinol Levels

A series of GWAS were conducted to investigate common genetic variants associated with circulating levels of nutrients. The results for vitamin E and retinol are presented here based on data from two studies, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Vitamin E*: Three genomic loci were

found to be associated with vitamin E (alpha-tocopherol) levels. Two were novel SNPs, rs2108622 on 19pter-p13.11 and rs11057830 on 12q24.3, and the authors confirmed a previously reported locus marked by rs964184 on 11q23.3. The three SNPs have been reported to be associated with lipid metabolism and/or regulation. The authors replicated these findings in a combined meta-analysis with two independent samples. (Major JM, Yu K, Wheeler W, et al. Genome-wide association study identifies common variants associated with circulating vitamin E levels. *Hum Mol Genet* 2011;20:3876–3883)

Retinol: Circulating levels of retinol were associated with two independent SNPs, rs1667255 ($p = 2.30 \times 10^{-17}$) and rs10882272 ($p = 6.04 \times 10^{-12}$), located near the transthyretin (*TTR*) and retinol binding protein 4 (*RBP4*) genes, which encode major carrier proteins of retinol. The association was then replicated with rs10882272 in *RBP4* in samples from the Nurses' Health Study and the Invecchiare in Chianti Study, thus suggesting evidence for gender dimorphism (p for interaction = 1.31×10^{-5}). (Mondul AM, Yu K, Wheeler W, et al. Genome-wide association study of circulating retinol levels. *Hum Mol Genet* 2011;20:4724–4731)

OROPHARYNGEAL CANCER

Rising Incidence Associated with HPV Infection

Investigators determined HPV status for all 271 oropharyngeal cancers (1984–2004) collected by the three population-based cancer registries in the SEER Residual Tissue Repositories Program and compared survival of HPV-positive and HPV-negative patients (see Figure 2). Analyses confirmed that increases in the population-level incidence of oropharyngeal cancers in the United States are caused by HPV infection. (Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294–4301)

PANCREATIC CANCER

Mitochondrial DNA Copy Number

To test whether higher mitochondrial DNA (mtDNA) copy number is associated with an increase in incident pancreatic cancer, the authors conducted a nested case-control study in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male smokers aged 50 to 69 years at baseline. During 12 years of follow-up, 203 incident cases of pancreatic adenocarcinoma occurred among participants, and whole blood samples were used for mtDNA extraction. Higher mtDNA

copy number was significantly associated with increased pancreatic cancer risk (highest vs. lowest mtDNA copy number quintile, OR = 1.64) and in continuous models (OR = 1.14), particularly for cases diagnosed during the first seven years of follow-up (OR = 2.14, continuous OR = 1.21), but not for cases occurring after seven years (OR = 1.14, continuous OR = 1.05). The results support the hypothesis that mtDNA copy number is associated with pancreatic cancer and may serve as a biomarker of risk. (Lynch SM, Weinstein SJ, Virtamo J, et al. Mitochondrial DNA copy number and pancreatic cancer in the Alpha-Tocopherol Beta-Carotene cancer prevention study. *Cancer Prev Res [Phila]* 2011;4:1912–1919)

PROSTATE CANCER

Gene Variants and Pesticide Exposure

As part of exploring the role of oxidative DNA damage in the pesticide-associated risk of prostate cancer, the authors studied the interactions between pesticide exposures and genetic variation in base excision repair (BER) pathway genes, the predominant pathway involved in repairing oxidative damage. The authors evaluated interactions between 39 pesticides and 394 tag SNPs for 31 BER pathway genes among 776 prostate cancer patients and 1,444 male controls in a nested, case-control study of pesticide applicators in the Agricultural Health Study. Notable interactions were found between several pesticides and BER gene variants with respect to prostate cancer, but only fonofos \times *NEIL3* rs1983132 showed an interaction fitting an expected biological pattern that remained significant after adjustment for multiple comparisons. Results were consistent with a mechanism of effect involving oxidative stress. (Barry KH, Koutros S, Berndt SI, et al. Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk. *Environ Health Perspect* 2011;119:1726–1732)

New Susceptibility Loci

To identify loci that influence susceptibility to prostate cancer, the authors conducted a GWAS among 2,782 advanced prostate cancer cases and 4,458 controls with 571,243 SNPs. Based on *in silico* replication of 4,679 SNPs in two published GWAS with 7,358 prostate cancer cases and 6,732 controls, the authors identified a new susceptibility locus associated with overall prostate cancer risk at 2q37.3 (rs2292884). They also confirmed a locus suggested by an earlier GWAS at 12q13 (rs902774). The estimated per-allele ORs for these loci (OR = 1.14 for rs2292884 and OR = 1.17 for rs902774) did not differ between advanced and non-advanced prostate cancer. (Schumacher FR, Berndt SI, Siddiq A, et al. Genome-wide association study identifies new prostate cancer susceptibility loci. *Hum Mol Genet* 2011;20:3867–3875)

RENAL CELL CARCINOMA

Fine Mapping Chromosome 2p21

In a follow-up to a recent GWAS that identified a locus in chromosome 2p21 associated with the risk of RCC, a fine mapping analysis was conducted in a region that includes *EPAS1*. The authors genotyped 59 tagged common SNPs in 2,278 cases of RCC and 3,719 controls of European background and observed a novel signal for rs9679290 ($p = 5.75 \times 10^{-8}$, per-allele OR = 1.27). Imputation of common SNPs surrounding rs9679290 yielded two additional signals, rs4953346 ($p = 4.09 \times 10^{-14}$) and rs12617313 ($p = 7.48 \times 10^{-12}$), both highly correlated with rs9679290 but, interestingly, not correlated with the two SNPs reported in the GWAS, rs11894252 and rs7579899. Genotype analysis of rs12617313 confirmed an association with RCC risk ($p = 1.72 \times 10^{-9}$, per-allele OR = 1.28). The authors concluded that chromosome 2p21 harbors a complex genetic architecture for common RCC risk variants. (Han SS, Yeager M, Moore LE, et al. The chromosome 2p21 region harbors a complex

genetic architecture for association with risk for renal cell carcinoma. *Hum Mol Genet* 2011; November 23 [E-pub ahead of print]

Hypertension and Racial Disparities

The authors examined the association between hypertension and risk of RCC in a population-based, case-control study involving 843 whites and 358 blacks with RCC, along with controls that included 707 whites and 519 blacks. After adjustment for demographic characteristics, smoking, body mass index, and family history of cancer, hypertension doubled renal cancer risk overall (OR = 2.0, whites: OR = 1.9, blacks: OR = 2.8). ORs increased with time after hypertension diagnosis, reaching 4.1 for blacks and 2.6 for whites after 25 years (see Figure 3). The findings indicate that hypertension is a risk factor for RCC among both blacks and whites; these results may explain a substantial portion of the higher incidence of RCC among the black population. (Colt JS, Schwartz K, Graubard BI, et al. Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology* 2011;22:797–804)

VHL Gene Inactivation

The authors examined the role of the von Hippel-Lindau gene (*VHL*) and epigenetic inactivation among 507 sporadic RCC, including 470 clear cell renal tumors (ccRCC). Case-only multivariate analyses were conducted to identify associations between genetic alteration subtypes and risk factors. *VHL* inactivation, either through sequence alterations or promoter methylation in tumor DNA, was observed in 86.6% of ccRCC cases. Germline *VHL* SNPs and a haplotype were associated with promoter hypermethylation in tumor tissue. Risk of having genetic *VHL* inactivation was inversely associated among former smokers (OR = 0.70) and current smokers (OR = 0.56). Alteration

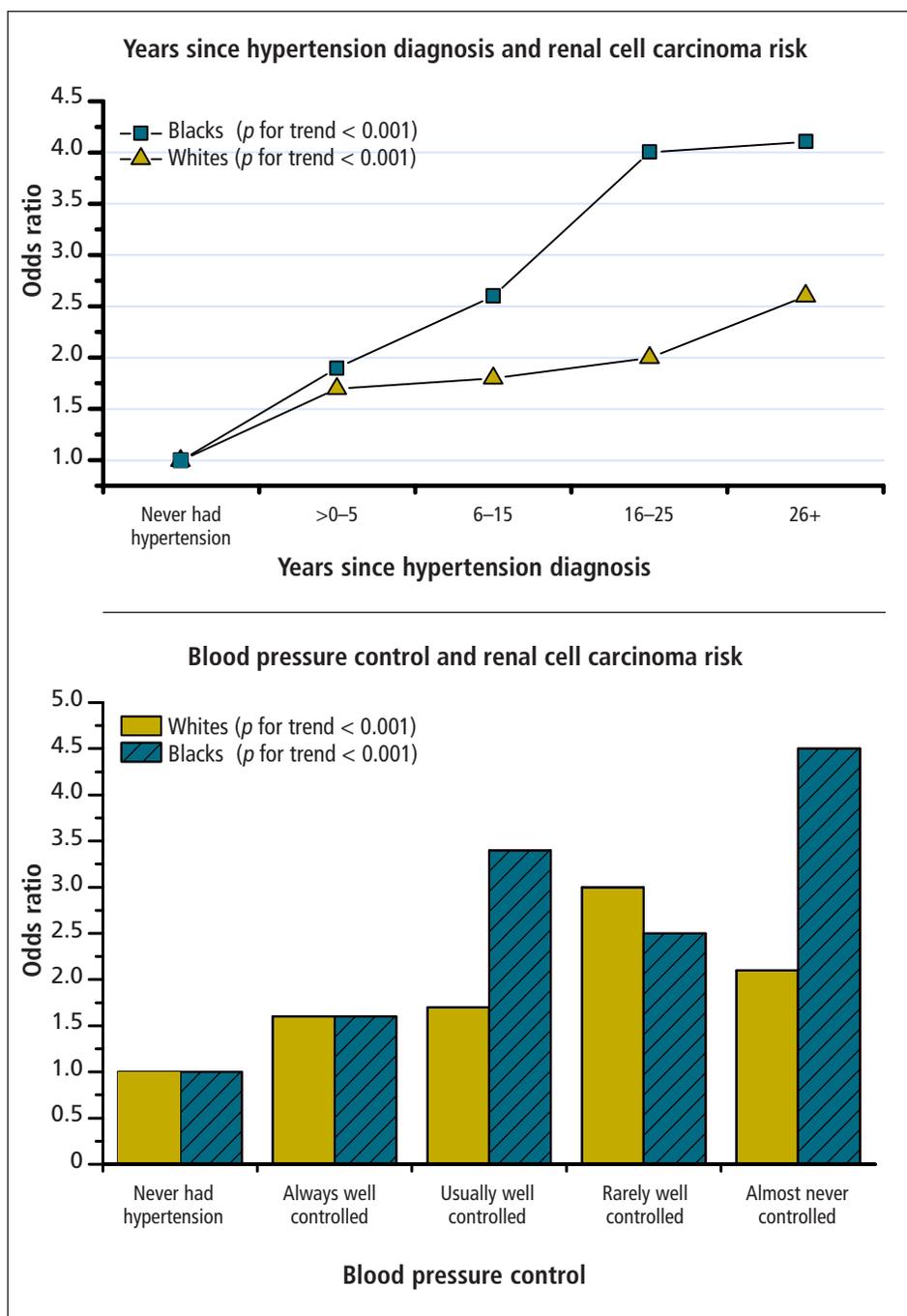


Figure 3. Hypertension and renal cell carcinoma (RCC) risk by race. The top figure shows years since hypertension diagnosis and RCC risk. The bottom figure shows blood pressure control and RCC risk. (Figure is based on Table 2 from Colt JS, et al. *Epidemiology* 2011.)

prevalence did not differ by histopathologic characteristics or occupational exposure to trichloroethylene. ccRCC cases with particular *VHL* germline polymorphisms were more likely to have *VHL* inactivation through promoter hypermethylation than through sequence alterations in tumor DNA, suggesting an inherited propensity to

epigenetic variation in renal tissue. Tumors from current smokers lacking *VHL* alterations may represent an entity distinct from inactivated cases. (Moore LE, Nickerson ML, Brennan P, et al. Von Hippel-Lindau [*VHL*] inactivation in sporadic clear cell renal cancer: Associations with germline *VHL* polymorphisms and etiologic risk factors. *PLoS Genet* 2011;7:e1002312)

DCEG PEOPLE IN THE NEWS

In December, DCEG staff participated in the African Organisation for Research & Training in Cancer (AORTIC) 2011 conference, titled *Entering the 21st Century for Cancer Control in Africa*, in Cairo, Egypt. **Christian C. Abnet, Ph.D., M.P.H.**, Nutritional Epidemiology Branch (NEB), gave a presentation titled “Study of esophageal squamous dysplasia prevalence (the STEP study).” **William F. Anderson, M.D., M.P.H.**, Biostatistics Branch (BB), spoke on “Age-period-cohort models in cancer surveillance research.” **Kishor Bhatia, Ph.D.**, Director of the AIDS Malignancy Program within the NCI Office of HIV and AIDS Malignancy and adjunct investigator in the Infections and Immunoepidemiology Branch (IIB), spoke on “EMBLEM—Molecular and genomic component.” **Benjamin Emmanuel, M.P.H.** (IIB), gave a talk on “Antibodies reactive to *Plasmodium falciparum* serine repeat antigen in children with Burkitt lymphoma in Ghana” and spoke on behalf of Dr. Martin Ogwang of St. Mary’s Hospital Lacor in Uganda on “EMBLEM implementation—Uganda.” **Sam M. Mbulaiteye, M.D.** (IIB), chaired a session on “NCI Intramural Research Program collaborations: EMBLEM and Ghana prostate studies.” He also spoke on “EMBLEM collaboration, objectives, study design, and timeline” and presented “Prostate cancer rates in Africa and the Ghana Study” on behalf of **Ann W. Hsing, Ph.D.** (IIB).

In September, **Christian C. Abnet, Ph.D., M.P.H.** (NEB), spoke on “Esophageal and gastric cancer risk: The contribution of common genomic variants” at the NCI Gastrointestinal Malignancies Retreat in Bethesda, Maryland. He also gave an invited talk

on “Career journey: The etiology of upper gastrointestinal cancers” at the Pathways for Postgraduates and Early Career Researchers Symposium at the University of Sydney in Australia.

In November, **Blanche P. Alter, M.D., M.P.H.**, Clinical Genetics Branch (CGB), presented the Lanzkowsky Lecture, in honor of Dr. Philip Lanzkowsky, at pediatric grand rounds at the Steven and Alexandra Cohen Children’s Medical Center of New York in New Hyde Park. Her lecture was titled “Inherited bone marrow failure syndromes.”

Matthew P. Banegas, a former summer fellow in BB, was selected to present his research at the NIH National Graduate Student Research Conference in October. Mr. Banegas, who was mentored in his research by **Mitchell H. Gail, M.D., Ph.D.**, and **Hormuzd A. Katki, Ph.D.**, both of BB, presented a poster titled “Evaluating and comparing breast cancer risk projections for Hispanic and non-Hispanic white women.”

In November, **Laura Beane Freeman, Ph.D.**, Occupational and Environmental Epidemiology Branch (OEEB), gave a keynote lecture on “Health effects of arsenic in drinking water” at the conference *Arsenic in Iowa’s Water Sources: Surveillance, Research, Education and Policy* held in Des Moines, Iowa.

In October, **Aaron E. Blair, Ph.D., M.P.H.** (OEEB), chaired a meeting of the International Agency for Research on Cancer’s Monograph Working Group on Asphalt in Lyon, France.

In September, **Louise A. Brinton, Ph.D.**, Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), gave a talk on “New insights on hormonal relationships for breast and

gynecologic cancers” for grand rounds at Vanderbilt University School of Medicine in Nashville, Tennessee.

In October, **Louise A. Brinton, Ph.D.**, Chief of HREB, spoke about “The editor’s perspective and effectively responding to reviewer comments” at the NCI Prostate Cancer in Men of African Descent Workshop held in Bethesda, Maryland. **Ann W. Hsing, Ph.D.** (IIB), also gave three presentations at the workshop: “Prostate cancer epidemiology and risk factors in Africa,” “Defining needs for international collaboration for prostate cancer epidemiology,” and “How to choose scientific journals for your publications.”

In September, several DCEG investigators participated in the seventh annual meeting of the International Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON) in Brisbane, Australia. At the meeting, **Michael B. Cook, Ph.D.** (HREB), discussed his pooled analysis of five studies of gastroesophageal reflux disease in relation to esophageal adenocarcinoma. He also presented a pooled analysis of five studies of smoking among women in relation to Barrett’s esophagus. **Linda Liao, Ph.D.** (OEEB), gave an update on an analysis being led by **Christina Persson, Ph.D.** (HREB), on the relationship between telomere length and risk of Barrett’s esophagus and esophageal adenocarcinoma. **Philip R. Taylor, M.D., Sc.D.**, Genetic Epidemiology Branch (GEB), spoke about screening biomarkers from RNA expression analysis in the Barrett’s Esophagus Early Detection Case-Control Study.

In September, **Michael B. Cook, Ph.D.** (HREB), gave a talk at the Peter MacCallum Cancer Centre in

Melbourne, Australia, on “Progress and limitations in our understanding of esophageal adenocarcinoma: Analyses from the international BEACON consortium.” He also spoke about “Elucidation of risk factors and interactions in the international BEACON consortium” at the Cancer Institute New South Wales in Eveleigh, Australia.

In November, **Eric A. Engels, M.D., M.P.H.** (IIB), gave a talk on “Cancer risk in U.S. transplant recipients: The Transplant Cancer Match Study” at Baylor Annette C. and Harold C. Simmons Transplant Institute grand rounds at Baylor University Medical Center in Dallas, Texas.

In November, several DCEG investigators participated in the 13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies held in Bethesda, Maryland. **Eric A. Engels, M.D., M.P.H.** (IIB), moderated a session on “Comorbidities in the era of antiretroviral therapy,” and **Sam M. Mbulaiteye, M.D.** (IIB), moderated a session on “HIV, co-infections, and cancer: Studies from international

settings.” **Vikrant Sahasrabudde, M.B.B.S., Dr.P.H.** (HREB), spoke on “Hepatobiliary cancers in persons with HIV/AIDS in the United States,” and **Meredith Shiels, Ph.D.** (IIB), presented on “The impact of the HIV epidemic on U.S. anal cancer rates, 1980–2007.”

In October, **Mitchell H. Gail, M.D., Ph.D.** (BB), spoke on “The use of risk models in disease prevention” at the Prentice Symposium on Emerging Methodological Issues in Population-Based Chronic Disease Research at the Fred Hutchinson Cancer Research Center in Seattle, Washington. He also gave an invited talk in November on “The value of SNPs (single nucleotide polymorphisms) for decisions based on risk models” at the Fifth Annual Program in Quantitative Genomics Conference at the Harvard School of Public Health in Boston, Massachusetts.

In October, DCEG staff participated in the Conference on Risk Assessment and Evaluation of Predictions, which was organized by the Department of Epidemiology and Biostatistics at the University of Maryland, College Park. **Mitchell H. Gail, M.D., Ph.D.**, and

Ruth M. Pfeiffer, Ph.D., both of BB, were on the conference program committee. **Nilanjan Chatterjee, Ph.D.**, Chief of BB, spoke on “Prediction with scores of tiny effects: Lessons from genome-wide association studies”; Dr. Gail spoke on “Comparative benefits for disease prevention of improved interventions versus more discriminating models of disease risk”; **Stephanie Kovalchik, Ph.D.** (BB), discussed “Absolute risk prediction of second primary thyroid cancer for 5-year childhood cancer survivors based on patient-reported treatment history”; Dr. Pfeiffer presented “Two criteria for evaluating risk prediction models”; **Philip S. Rosenberg, Ph.D.** (BB), spoke on “Age-period-cohort models in cancer surveillance research: Ready for prime time?”; and **David Wheeler, Ph.D., M.P.H.** (OEEB), discussed “Spatial-temporal risk analysis of case-control studies of cancer.”

In September, **Gretchen L. Gierach, Ph.D.** (HREB), delivered a talk on “Breast density: A breast cancer biomarker?” for the NCI Center of Excellence in Integrative Cancer Biology and Genomics Seminar Series in

ADMINISTRATIVE RESOURCE CENTER STAFF PROMOTIONS

In October, DCEG congratulated **Donna Siegle**, Director of the DCEG Administrative Resource Center (ARC), on receiving a well-deserved promotion to a new position as Director of the Office of Administrative Services for the NCI Office of the Director/Office of Management. Ms. Siegle served as Director of the DCEG ARC for the past 12 years, partnering with scientific and administrative staff to ensure that the Division’s endeavors were well supported. In addition to her new position, Ms. Siegle will remain the Director of the DCEG ARC. **Joseph F. Fraumeni, Jr., M.D.**, DCEG Director, said, “Donna’s contributions to DCEG cannot be overestimated. Her expertise, creative problem solving, professionalism, customer service ethic, and staff training have been superb. Without her invaluable contributions, and those

of the entire DCEG ARC, DCEG could not have carried out its mission.”

Roberto Minutillo will serve as the Manager for the DCEG ARC and will oversee its day-to-day administrative activities. Mr. Minutillo has been the Deputy Manager for the DCEG ARC since 2009 and has past experience as a purchasing agent, an Administrative Career Development Intern, and an administrative officer at NCI and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

In addition, **Charlotte Mercanti**, who has served as an administrative officer in DCEG for many years, was selected as a new lead administrative officer for the DCEG ARC. Ms. Mercanti will provide administrative services to the Genetic Epidemiology



Charlotte Mercanti, Roberto Minutillo, and Donna Siegle.

Branch, the Infections and Immunoepidemiology Branch, and the Office of the Director for the Human Genetics Program and will take on supervisory duties as well as special projects.

Bethesda, Maryland. She also spoke on “The ultrasound study of tamoxifen” at the Karmanos Cancer Institute’s Breast Multidisciplinary Team Meeting in Detroit, Michigan.

In October, **James J. Goedert, M.D.** (IIB), gave an “Update on malignancies among people with HIV/AIDS” at the 13th Annual International Meeting of the Institute of Human Virology at the University of Maryland School of Medicine in Baltimore. Also at the conference, **Sam M. Mbulaiteye, M.D.** (IIB), gave a talk on “Virally-associated malignancies in the HIV era.”

In November, **Lynn R. Goldin, Ph.D.**, Deputy Chief of GEB, spoke at the American College of Rheumatology’s (ACR’s) Basic Science Symposium “Mechanisms of lymphoma development in systemic autoimmune disease” at ACR’s 2011 Annual Scientific Meeting in Chicago, Illinois. Her talk was titled “Autoimmunity and lymphomagenesis.”

In September, **Alisa M. Goldstein, Ph.D.** (GEB), gave the President’s Welcome Address at the 20th Annual International Genetic Epidemiology Society Conference in Heidelberg, Germany. She also chaired a scientific session at the meeting on “Multiple phenotypes and other data.” **Xiaohong Rose Yang, Ph.D., M.P.H.** (GEB), spoke at the meeting as well, presenting on “Whole exome sequencing to identify major susceptibility genes in cancer-prone families.”

In October, **Asieh Golozar, M.D., M.P.H.** (GEB), gave a talk on “Change in body size during early adulthood and prevalence of diabetes mellitus” at the American Public Health Association’s 139th Annual Meeting in Washington, D.C.

In September, **Mark H. Greene, M.D.**, Chief of CGB, presented a lecture on

“Screening trials for hereditary ovarian cancer: 2011 status report” at the Second Annual Joint Meeting on Hereditary Breast and Ovarian Cancers: Lessening the Burden held at New York University Medical Center in New York, New York.

In September, **Patricia Hartge, Sc.D.**, Deputy Director of the Epidemiology and Biostatistics Program (EBP), spoke on “Cancer research strategies for public health” at the Fred Hutchinson Cancer Research Center in Seattle, Washington. In October, she gave an invited talk on “Provocative questions in cancer and epidemiology” at the Memorial Sloan-Kettering Cancer Center in New York, New York.

In October, several DCEG investigators gave presentations at the 2011 Annual Meeting of the NCI Cohort Consortium in Boston, Massachusetts. **Robert N. Hoover, M.D., Sc.D.**, Director of EBP, offered opening remarks to the meeting, as did Dr. Robert Croyle, Director of the NCI Division of Cancer Control and Population Sciences. Other DCEG presenters included **Amy Berrington de González, D.Phil.**, Radiation Epidemiology Branch (REB), on “Updates from the Obesity Working Group”; **Patricia Hartge, Sc.D.**, Deputy Director of EBP, on “Brainstorming: Best thing to do next”; **Aimée R. Kreimer, Ph.D.** (IIB), on “HPV and head and neck cancer”; and **Mary H. Ward, Ph.D.** (OEEB), on “Exposure linkage in cohorts: Linking the Agricultural Health Study and the Iowa Women’s Health Study to environmental data.”

In October, **Lindsey M. Hoskins, Ph.D., M.S., LCMFT** (CGB), conducted several focus groups and presented a poster on “*BRCA1/2* gene mutation counseling and testing during emerging adulthood” at the Annual Education Conference of the National Society of Genetic Counselors in San Diego, California. **June A. Peters, M.S., CGC**

(CGB), also presented a poster at the conference on “Familial testicular cancer: Men’s health communications and social supports.”

In November, **Ann W. Hsing, Ph.D.** (IIB), spoke on “Epidemiology of prostate cancer” at the New Perspectives on Prostate Cancer Symposium in Bethesda, Maryland, sponsored by the Washington Adventist Hospital in Takoma Park, Maryland.

In October, **Aimée R. Kreimer, Ph.D.** (IIB), was an invited speaker at the Second Annual Updates on HPV-Associated Head and Neck Cancer, a continuing medical education event hosted by the Department of Otolaryngology—Head and Neck Surgery at the Johns Hopkins Hospital in Baltimore, Maryland. Dr. Kreimer spoke on “Oral HPV infection in healthy people: What do we know?”

In November, **Gabriel Lai, Ph.D.** (NEB), spoke on “Diabetes and micronutrients in the risk of liver and other cancers” at the Division of Health Services and Preventive Medicine, Institute of Population Health Sciences, at the National Health Research Institutes in Zhunan, Taiwan.

In August, **Stephanie Lamart, Ph.D.** (REB), gave a presentation on “Comparison of S values for three classes of adult computational phantoms for I-131 in the thyroid” at the 2011 Joint American Association of Physicists in Medicine/Canadian Organization of Medical Physicists Meeting in Vancouver, Canada.

In November, **Maria Teresa Landi, M.D., Ph.D.** (GEB), gave a presentation on “The interplay of telomere-related genes, nevi and the risk of melanoma” at the meeting of the Society for Melanoma Research Steering Committee in Tampa, Florida.

In October, **Shih-Wen (Wenny) Lin, Ph.D., M.P.H.** (NEB), received an American Association for Cancer Research (AACR) Scholar-in-Training Award funded by Susan G. Komen for the Cure® to present research at the 10th AACR International Conference on Frontiers in Cancer Prevention Research in Boston, Massachusetts. The title of Dr. Lin's project was "Selenoprotein gene variants and risk of esophageal and gastric cancer in a Chinese population." In addition, Dr. Lin was elected to the AACR Associate Member Council and will serve from 2012 to 2015. She will present the needs of early-career scientists to the AACR leadership and will plan professional development sessions for the AACR annual meeting.

In October, **Mark Little, Ph.D.** (REB), spoke on "Epidemiology of non-cancer effects of moderate and low doses" at the International Commission on Radiological Protection Symposium in Bethesda, Maryland. **Alice J. Sigurdson, Ph.D.** (REB), spoke on "Genetic predisposition to radiation-related cancer and potential implications for risk assessments" at the same meeting.

In November, the *Anyone Can Get Skin Cancer* brochure earned a Silver Inkwell Award from the D.C. Metro Chapter of the International Association of Business Communicators. The award, which recognizes high-quality work in business communications, honored the efforts of current and former DCEG staff who contributed to the brochure, including Dr. Porcia Bradford, a former fellow in GEB; Mary Fraser, a retired research nurse specialist, also in GEB; **Jennifer Loukissas, M.P.P.**, Office of Communications and Special Initiatives (OCSI); **Saloni Nayar, M.P.H.** (OCSI); and **Margaret A. Tucker, M.D.**, Director of the Human Genetics Program.

In September, **Ruth M. Pfeiffer, Ph.D.** (BB), gave invited talks on "Two criteria for evaluating risk prediction models" at the Yale School of Public Health in New Haven, Connecticut, and at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

In September, **Mark Purdue, Ph.D.** (OEEB), spoke on "NCI Occupational and Environmental Epidemiology Branch: Setting priorities for occupational cancer research" at the 2011 National Occupational Research Agenda Manufacturing Sector Conference in Cincinnati, Ohio. In October, he gave a presentation on "Molecular epidemiologic investigations of immune dysregulation and non-Hodgkin lymphoma" as part of the Visiting Scholars Seminar Series hosted by the NCI Epidemiology and Genomics Research Program in the Division of Cancer Control and Population Sciences. In November, Dr. Purdue spoke on "Molecular epidemiologic investigations into the etiologies of lymphoma and kidney cancer" at the University of Texas MD Anderson Cancer Center in Houston, Texas.

In August, **Sharon A. Savage, M.D.** (CGB), spoke on "Telomeres, telomerase and cancer" at the NCI 2011 Summer Curriculum in Cancer Prevention/Molecular Prevention in Rockville, Maryland. In November, she gave a presentation on "Epigenetics, genomics, and the environment" for the course Introduction to Children's Health and the Environment at the George Washington University School of Public Health in Washington, D.C.

In October, DCEG investigators participated in the NIH Research Festival in Bethesda, Maryland. **Sharon A. Savage, M.D.** (CGB), gave a talk on "Characterization of human telomere biology disorders," and **Rebecca Troisi,**

Sc.D. (EBP), spoke on "Early life exposures and subsequent cancer risk: The Diethylstilbestrol Project."

In September, **Mark E. Sherman, M.D.** (HREB), gave a lecture on "Where does breast cancer come from? A molecular epidemiological perspective" at the Ohio State University College of Medicine in Columbus. In October, he spoke at the University of Massachusetts Amherst School of Public Health and Health Sciences on "Molecular histology: Gateway to breast cancer prevention."

In July, **Steven L. Simon, Ph.D.** (REB), gave a talk on "The Fukushima disaster: What we know today about the accident and possible health impacts" at the 2011 NASA Occupational Health Meeting in Albuquerque, New Mexico. In August, he spoke on "Dosimetry techniques to support long-term health risk studies" at the 14th International Congress of Radiation Research in Warsaw, Poland. In addition, he chaired a session at the congress on "New developments in radiation dosimetry." In September, Dr. Simon gave a talk on "After the crisis: What next?—Preparing for long-term follow-up of an exposed population" at the 5th International Radiation Emergency Assistance Center/Training Site Symposium: The Medical Basis for Radiation Accident Preparedness in Miami, Florida.

In September, **Philip R. Taylor, M.D., Sc.D.** (GEB), presented "Cancer prevention: A personal odyssey" at the Pathways for Postgraduates and Early Career Researchers Symposium held by the University of Sydney Cancer Research Network and the New South Wales and Australian Capital Territory Cancer Epidemiology Network in Sydney, Australia. Dr. Taylor also gave several talks on selenium, genetics, and cancer prevention at the 14th International Symposium on Trace Elements in Man

and Animals in Enshi, China, and at the Cancer Institute of the Chinese Academy of Medical Sciences in Beijing.

In September, **Rebecca Troisi, Sc.D.** (EBP), chaired a workshop on “Predicting future health” at the 2011 meeting Placenta: Predicting Future Health organized by the International Federation of Placenta Associations in association with the European Placenta Group in Geilo, Norway.

In September, **Mary H. Ward, Ph.D.** (OEEB), gave an invited talk on “Facing and overcoming exposure assessment challenges in studies on water pollution and cancer” at the 23rd Annual Conference of the International Society for Environmental Epidemiology in Barcelona, Spain.

In October, **Nicolas Wentzensen, M.D., Ph.D.** (HREB), spoke on “Biomarkers for cervical cancer screening” at the German Society of Cytology meeting in Mannheim, Germany. Dr. Wentzensen also has been invited to serve on the faculty of the American Society for Colposcopy and Cervical Pathology Biennial Scientific Meeting in March 2012 in San Francisco, California.

In September, **Xiaohong Rose Yang, Ph.D., M.P.H.** (GEB), spoke on “Identifying susceptibility genes for familial cancers using array-CGH and whole exome sequencing” at the German Cancer Research Center in Heidelberg. In October, she gave a presentation on “Differences of breast cancer risk factor associations in breast cancer subtypes” at McGill University in Montreal, Canada.

DCEG PARTICIPATES IN THE INTERNATIONAL PAPILLOMAVIRUS CONFERENCE

In September, DCEG scientists participated in the 27th International Papillomavirus Conference and Clinical Workshop in Berlin, Germany. The meeting was designed to help define future directions of papillomavirus research, with an eye toward transitioning responsibility to the next generation of researchers.

Presentations and other contributions by DCEG members at the meeting included the following:

Felipe Castro, Ph.D., Infections and Immunoepidemiology Branch (IIB): *Prevalence and determinants of anal HPV infection in young women.*

Anil K. Chaturvedi, D.V.M., Ph.D. (IIB): *HPV and rising oropharyngeal cancer incidence in the United States.*

Allan Hildesheim, Ph.D., Chief of IIB, chaired an oral presentation session on “Prophylactic vaccines.”

Hormuzd A. Katki, Ph.D., Biostatistics Branch: *Five-year cervical cancer risk following HPV triage of equivocal cytology and HPV vaccine efficacy against both cervical and anal HPV 16/18 infection.*

Aimée R. Kreimer, Ph.D. (IIB): *Anal HPV 16/18 vaccine efficacy among females in the Costa Rica Vaccine Trial; HPV-associated head and neck cancer; and HPV vaccine efficacy with fewer than the customary three doses.*

Shih-Wen (Wenny) Lin, Ph.D., M.P.H., Nutritional Epidemiology Branch: *HPV 16/18 seropositivity and subsequent infection risk: Comparison of serological assays.*

Patricia Luhn, Ph.D., M.P.H., Hormonal and Reproductive Epidemiology Branch (HREB): *Chromosomal amplifications measured in cytology specimens from women with high-grade cervical intraepithelial neoplasia (CIN).*

Lisa Mirabello, Ph.D., Clinical Genetics Branch (CGB): *Elevated methylation of HPV 16 DNA is associated with CIN 2+ development.*

Mahboobeh Safaeian, Ph.D. (IIB): *Correlation between ELISA, CLIA, and secreted alkaline-phosphatase protein neutralization assays.*

Vikrant Sahasrabudhe, M.B.B.S., Dr.P.H. (HREB): *HPV genotype attribution in anal intraepithelial neoplasia among HIV-infected men who have sex with men.*

Mark Schiffman, M.D., M.P.H. (CGB): *HPV methylation distinguishes CIN 3 from infection: A general phenomenon.* He also chaired an oral presentation session on “Risk factors” and co-organized a workshop on “Improving colposcopy in the era of HPV-based cervical cancer prevention” with **Nicolas Wentzensen, M.D., Ph.D.** (HREB).

Nicolas Wentzensen, M.D., Ph.D. (HREB): *Improved disease ascertainment: More directed biopsies; Ascertainment of cervical disease: Colposcopy-targeted versus random biopsies; Molecular heterogeneity of CIN 3; and The incremental benefit of taking multiple biopsies for detecting high-grade CIN.*

COMINGS...GOINGS



Simina Boca

Simina Boca, Ph.D., joined the Biostatistics Branch (BB) as a postdoctoral fellow. She received her Ph.D. in biostatistics from the Johns Hopkins

Bloomberg School of Public Health in Baltimore, Maryland. For her doctoral dissertation, Dr. Boca developed methodology to analyze high-dimensional data that focuses specifically on the discovery of driver genes and gene sets involved in the pathogenesis of cancer. She will be working with **Nilanjan Chatterjee, Ph.D.**, Chief of BB, and **Joshua Sampson, Ph.D.** (BB), on statistical methods to identify biomarkers that can be used for estimating an individual's risk of cancer.



Laura Burke

Laura Burke, M.P.H., joined the Genetic Epidemiology Branch (GEB) as a predoctoral fellow. She received her B.A. in

quantitative economics from Tufts University in Medford, Massachusetts, and an M.P.H. in epidemiology from George Washington University in Washington, D.C. During her fellowship, she will continue the work she began as a summer student in GEB with **Xiaohong Rose Yang, Ph.D., M.P.H.** (GEB), exploring telomere length, long interspersed nuclear elements-1 (LINE-1) methylation, and their relationships with melanoma, dysplastic nevi, *CDKN2A* mutation status, and germline copy number variation.

David Capo-Ramos, M.D., M.P.H., left GEB after completing his fellowship to become a Preventive Medicine and Public Health Fellow at the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) in Hyattsville, Maryland.



Jiyeon Choi

Jiyeon Choi, Ph.D., joined the Laboratory of Translational Genomics (LTG) as a postdoctoral fellow. Dr. Choi has a Ph.D. in cell and developmental biology from the University of Medicine and Dentistry of New Jersey in Newark, where she pursued functional studies of autism-associated common genetic variants. She also has an M.S. in molecular biology from Korea University in Seoul. In the lab of **Kevin Brown, Ph.D.**, Dr. Choi will work on the functional characterization of common and rare genetic variants contributing to melanoma susceptibility by following up recent genome-wide association studies and work in family resequencing.



Jennifer Drahos

Jennifer Drahos, Ph.D., M.P.H., joined the Hormonal and Reproductive Epidemiology Branch (HREB) as a Cancer Prevention Fellow. Dr. Drahos received her M.A., M.Phil., and Ph.D. in microbiology from Columbia University in New York, New York, where she focused

on the innate immune response in picornavirus-infected cells. She received her M.P.H. from the Harvard School of Public Health in Boston, Massachusetts, concentrating on quantitative methods, and while at Harvard researched treatment-induced acute myeloid leukemia, examining incidence and survival variability by ethnicity among pediatric patients. Dr. Drahos will work with **Michael B. Cook, Ph.D.** (HREB), towards elucidating the etiology of distinct stages of esophageal adenocarcinomas and with **Mahboobeh Safaeian, Ph.D.**, Infections and Immunoepidemiology Branch (IIB), to investigate the serologic response to human papillomavirus (HPV) natural infection and vaccination.



John Fargo

John Fargo, D.O., joined the Clinical Genetics Branch (CGB) as a visiting fellow from the Children's National Medical Center (CNMC) in Washington, D.C. He received his D.O. from the University of New England College of Osteopathic Medicine in Biddeford, Maine, and completed his pediatric residency training at the Phoenix Children's Hospital in Arizona. He is currently a pediatric hematology/oncology fellow at CNMC. Dr. Fargo will work with **Christian Kratz, M.D.** (CGB), to study diagnostic tools for Diamond-Blackfan anemia.

Ashley S. Felix, Ph.D., joined HREB as a Cancer Prevention Fellow. She received an M.P.H. in epidemiology from the University of Michigan in Ann Arbor



Ashley Felix

and a Ph.D. in epidemiology from the University of Pittsburgh in Pennsylvania. She will work with **Louise A. Brinton, Ph.D.**, Chief

of HREB, and others in the Branch, including **Gretchen L. Gierach, Ph.D.**, **Mark E. Sherman, M.D.**, and **Nicolas Wentzensen, M.D., Ph.D.**, to investigate the etiologic heterogeneity of endometrial cancer and to expand her expertise in various tissue markers for gynecologic and breast cancers.



Hisani Horne

Hisani Horne, Ph.D., M.P.H., joined HREB as a Cancer Prevention Fellow. She received her Ph.D. in pathology from

Duke University in Durham, North Carolina, and completed an M.P.H., with a certificate in health disparities and health inequality, at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. Dr. Horne will work with **Jonine D. Figueroa, Ph.D., M.P.H.**, and **Mark E. Sherman, M.D.**, both of HREB, to explore her interests in breast and ovarian cancer biology through molecular epidemiologic studies.

Briseis Kilfoy, Ph.D., left the Occupational and Environmental Epidemiology Branch (OEEB) for a position as assistant research professor in the Department of Health Studies at the University of Chicago in Illinois.



Wendy Kim

Wendy Kim joined LTG as a post-baccalaureate fellow. Ms. Kim graduated from Claremont McKenna College in Claremont,

California, with a B.A. in biology. Previously, she researched partial molar volumes and how these affect structure-making and structure-breaking hydrogen bonds. Under the mentorship of **Kevin Brown, Ph.D.** (LTG), Ms. Kim is currently investigating novel mutations in low-, medium-, and high-penetrance genes that lead to increased susceptibility to melanoma.



Terry Lee

Terrence (Terry) Lee, M.P.H., joined the Radiation Epidemiology Branch (REB) as a pre-doctoral fellow. He received his M.P.H.

in epidemiology from the University of California, Los Angeles, and is currently a Ph.D. candidate in epidemiology at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. Previously, Mr. Lee worked for the U.S. CDC as a surveillance coordinator in China and for the U.S. Army as an epidemiologist. In REB, he will be working with **Martha S. Linet, M.D., M.P.H.**, Chief of REB, **Mark Little, Ph.D.**, and **Alice J. Sigurdson, Ph.D.**, evaluating data from the U.S. Radiologic Technologists Study on the risk of basal cell carcinoma associated with ionizing and ultraviolet radiation, radiation-related cataract risk, and health risks after exposure to I-131.



Pami Lotinsky

Pamela (Pami) Lotinsky joined the Office of Education (OE) as a fellowship program analyst. Ms. Lotinsky, who received her

B.A. in Spanish from the University of Texas at El Paso, previously worked as a travel coordinator in HREB. In her new role, she will be working with **Jackie Lavigne, Ph.D., M.P.H.**, Chief of OE, and **Kristin Kiser, M.H.A., M.S.**, to facilitate OE programs, meetings, and fellow-related activities.

Nora Macklin, M.P.H., left IIB to join the CDC. She will be stationed in Puerto Rico and will assist the local department of health with HPV vaccine implementation.



Morgan Marks

Morgan Marks, Ph.D., joined IIB as a postdoctoral fellow. Dr. Marks received his Ph.D. in molecular epidemiology from the

Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, where he also was a postdoctoral fellow in cancer epidemiology. At Johns Hopkins, he investigated the relationship of HPV infection to immune responses of the cervical mucosa and examined the changing international burden of HPV-related cancers. In DCEG, he will be working with **Anil K. Chaturvedi, D.V.M., Ph.D.** (IIB), on the molecular epidemiology of HPV-related oropharyngeal cancers and the role of host immune responses to HPV infections at multiple anatomic sites.



Kristin Moy

Kristin Moy, Ph.D., M.P.H., joined the Nutritional Epidemiology Branch (NEB) as a postdoctoral fellow. She completed her Ph.D. in epidemiology at the University of Minnesota in Minneapolis. Dr. Moy will work with **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.** (NEB), on the role of diet, nutrition, and genetics in the etiology of pancreatic cancer.



Adam Mumy

Adam Mumy joined LTG as a post-baccalaureate fellow. Mr. Mumy received his B.A. in English and French studies from Western Michigan University in Kalamazoo.

In the lab of **Ludmila Prokunina-Olsson, Ph.D.** (LTG), he is conducting follow-up studies on a single nucleotide polymorphism found in the prostate stem cell antigen gene (*PSCA*) and its connection with bladder cancer.



Leticia Nogueira

Leticia Nogueira, Ph.D., M.P.H., joined IIB as a Cancer Prevention Fellow. Dr. Nogueira received her Ph.D.

in cell and molecular biology at the University of Texas at Austin and her M.P.H. in quantitative methods from the Harvard School of Public Health in Boston, Massachusetts. Her doctoral

dissertation focused on the relationship between energy balance and breast cancer. Under the mentorship of **Jill Koshiol, Ph.D.** (IIB), she plans to investigate the mechanisms by which obesity and inflammation affect the risk of biliary tract cancer.



Colleen Pelser

Colleen Pelser, Ph.D., joined NEB as a Cancer Prevention Fellow.

Dr. Pelser received her Ph.D. in epidemiology from

the University of Maryland in Baltimore, conducting her dissertation under the mentorship of **James J. Goedert, M.D.** (IIB). In NEB, she will be working with **Yikyung Park, Sc.D.**, on dietary and lifestyle factors related to cancer incidence and survival. She will also work with **Lindsay M. Morton, Ph.D.** (REB), on lifestyle factors related to the risk of second cancers.

Preetha Rajaraman, Ph.D., left her position as a tenure-track investigator with REB to relocate to New Delhi, India. Dr. Rajaraman will continue to work on the Glioma Scan Study (a genome-wide association study involving collaborators from 22 international studies) and the U.S. Radiologic Technologists Study, which is investigating the relationships between low-dose radiation and cancer risks.



Carolyn Reyes-Guzman

Carolyn Reyes-Guzman, M.P.H., joined GEB as a predoctoral fellow. She received her M.P.H. from

George Washington University in Washington, D.C., with a focus on epidemiology and biostatistics. Currently, she is studying cancer epidemiology as a doctoral student at George Washington University. She will work with **Neil E. Caporaso, M.D.**, Chief of GEB, to study genomic and biochemical associations with disease among light and intermittent smokers, a group that has not been studied in depth.

Elizabeth Hill Ruder, Ph.D., M.P.H., R.D., left NEB for a new position as assistant professor and Director of the Didactic Program in Dietetics in the Department of Sports Medicine and Nutrition, School of Health and Rehabilitation Sciences, at the University of Pittsburgh in Pennsylvania.



Mindy Sarkisian

Chamindri (Mindy) Sarkisian joined the Administrative Resource Center (ARC) as an administrative technician. She previously worked at the

NIH National Institute of Allergy and Infectious Diseases and has experience in travel planning, oversight of meeting management, and general administrative duties. She will be working with several administrative officers to provide administrative support to HREB, IIB, and the DCEG Office of the Director.

Sara Schonfeld, Ph.D., left REB to become a postdoctoral fellow in the Section of Environment and Radiation at the International Agency for Research on Cancer in Lyon, France.



Marketta Singletary

Marketta Singletary

joined the ARC as an administrative technician. She previously worked at the NIH National Institute of

Allergy and Infectious Diseases. Ms. Singletary is skilled in travel planning, oversight of meeting management, and general administrative duties. She will be working with several administrative officers to provide administrative support to BB, CGB, the Epidemiology and Biostatistics Program, and GEB.



Farzana Walcott

Farzana Walcott, M.D.,

joined CGB as a Cancer Prevention Fellow. Dr. Walcott earned her M.P.H. at the University of

Texas Health Science Center at Houston School of Public Health in international family health with a concentration in epidemiology, and she received her M.D. from the Texas A&M Health Science Center College of Medicine in College Station. She is board eligible in both internal medicine and preventive medicine and has an interest in gynecologic malignancies and chemoprevention. Dr. Walcott will work with **Sharon A. Savage, M.D.** (CGB), on projects related to a multidisciplinary study of Li-Fraumeni syndrome and will help launch a Phase II chemoprevention trial of metformin in carriers of the *TP53* germline mutation. She also will participate in a pilot study of the association between telomere length and genetic variations in selected telomere biology

genes as candidate modifiers of *BRCA1/2*-related breast cancer risk.

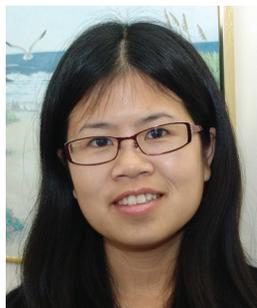
David Wheeler, Ph.D., M.P.H., left OEEB to become assistant professor in the Department of Biostatistics in the School of Medicine at Virginia Commonwealth University in Richmond.



Jincao Wu

Jincao Wu, Ph.D., joined BB as a post-doctoral fellow. She received her Ph.D. in statistics from the University of Michigan in Ann Arbor.

In BB, Dr. Wu will work with **Mitchell H. Gail, M.D., Ph.D.**, and **Ruth M. Pfeiffer, Ph.D.**, on methods for building risk models based on single nucleotide polymorphisms, handling missing data in case-control studies, and building models from high-dimensional data.



Qian Xiao

Qian Xiao, Ph.D., M.P.H., joined OEEB as a Cancer Prevention Fellow. Dr. Xiao received her Ph.D. in biological sciences

from the University of California, San Diego, where her doctoral dissertation focused on the role of muscle-derived molecules in neuronal differentiation. She received her M.P.H. in epidemiology from the University of Michigan in Ann Arbor, where she investigated inflammatory breast cancer in Egypt. She also studied the consumption of cooking fat and childhood growth in Colombian schoolchildren. She will be working with **Wong-Ho Chow, Ph.D.**, and others in

OEEB on a variety of projects examining lifestyle, environmental, and host determinants of cancer risks.



Guoqin Yu

Guoqin Yu, Ph.D., joined GEB and IIB as a postdoctoral fellow. She has an M.S. in genetics from Zhejiang University in Hangzhou,

China, and completed her thesis with faculty at the Institute of Botany, Chinese Academy of Sciences, in Beijing. Dr. Yu received her Ph.D. in evolution, ecology, and population biology from Washington University in St. Louis, Missouri. Dr. Yu's mentors will be **James J. Goedert, M.D.** (IIB), and **Alisa M. Goldstein, Ph.D.** (GEB). During her fellowship, Dr. Yu will evaluate data on human sequencing, microbiomics, and epigenetics to uncover underlying genetic susceptibility variants through the analysis of population and family-based studies.

SHELIA HOAR ZAHM, DCEG DEPUTY DIRECTOR, RETIRES

In December, **Shelia Hoar Zahm, Sc.D.**, DCEG's Deputy Director, retired after 31 years of government service. Throughout her tenure at NCI, Dr. Zahm received numerous awards and accolades for her scientific accomplishments, breadth of scientific vision, and extraordinary organizational skills. She took on the responsibilities of Deputy Director not long after the formation of the Division and, in the words of the Director, **Joseph F. Fraumeni, Jr., M.D.**, she was a "full partner in leading the Division as we grew and changed in response to new scientific opportunities and challenges."

Dr. Zahm received her doctorate in epidemiology from the Harvard School of Public Health, where she created the first job-exposure matrix, which continues to serve as the conceptual underpinning for assessing exposure in occupational studies. In 1980, she joined NCI, where she investigated the etiology of non-Hodgkin lymphoma, the risk of cancer associated with pesticide use, and occupational cancer among women. The author of more than 270 publications, she has served on several editorial boards for leading scientific journals.

Beginning with her appointment as Deputy Director in 1998, Dr. Zahm led strategic planning for budget, personnel, policy, and practice in DCEG. She organized and chaired the Technical Evaluation of Protocols Committee and the Promotion and Tenure Review Panel, and she oversaw virtually all major DCEG initiatives. She served on more than 50 advisory committees, including panels for international research centers in Spain and Canada, the United Auto Workers/General Motors Occupational Health Advisory Board, the U.S. Military Cancer Institute Institutional Review Board, the HHS Interagency Breast Cancer and Environmental Research Coordinating Committee, and the NIH Intramural Clinical Research Steering Committee. She also cochaired the NIH Scientific Directors' Subcommittee on Biorepository Practices and Guidelines for the NIH Intramural Research Program.

Dr. Zahm encouraged junior and senior investigators to pursue opportunities for professional growth and development. Her commitment to innovative and rigorous research as well as the highest ethical standards has earned her universal admiration. Her widespread



Shelia Hoar Zahm (Photograph credit: Bill Branson)

contributions have been recognized by her receipt of numerous honors, including the HHS Secretary's Award for Distinguished Service, the PHS Special Recognition Award, the NIH Director's Award, the NIH Merit Award, the American Occupational Medical Association commendation for research excellence, and the Harvard School of Public Health Alumni Award of Merit.

According to Dr. Fraumeni, "The success of the DCEG research and training enterprise can be traced in so many ways to the inspiring leadership of Shelia Zahm. I can think of few individuals who have made such an impact in furthering the mission of NCI and NIH." ■

