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Division of Cancer Epidemiology and Genetics

Linkage

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Energy Balance Link to Cancer Probed in DCEG Research

Energy balance—the sum of energy intake through eating and energy output through physical activity and metabolism—has been implicated in a host of diseases, including cancer. Figure 1 shows the joint evaluation of energy intake, body mass, and physical activity in relation to breast cancer risk in the PLCO (Prostate, Lung, Colorectal, and Ovarian) cancer screening trial. Scientists in DCEG's Nutritional Epidemiology Branch (NEB), led by **Arthur Schatzkin, M.D., Dr.P.H.,** use several approaches, both traditional and innovative, to better understand the relationship between energy balance and cancer. These methods include the use of detailed questionnaires administered to a large number of people in cohort studies that can be tracked for disease outcomes. More cutting-edge approaches involve biomarker studies in which study participants not only respond to questions but also provide blood specimens so that physiologic and biochemical factors associated with obesity and physical activity can be examined. In addition, many studies now include the collection of DNA so that researchers can analyze genetic variation and gene-environment interactions.

From 1995 to 1996, a 16-page questionnaire that requested information on diet, body weight, physical activity, and medical history was sent to 3.5 million members of the American Association of Retired Persons (AARP) in six states and two metropolitan

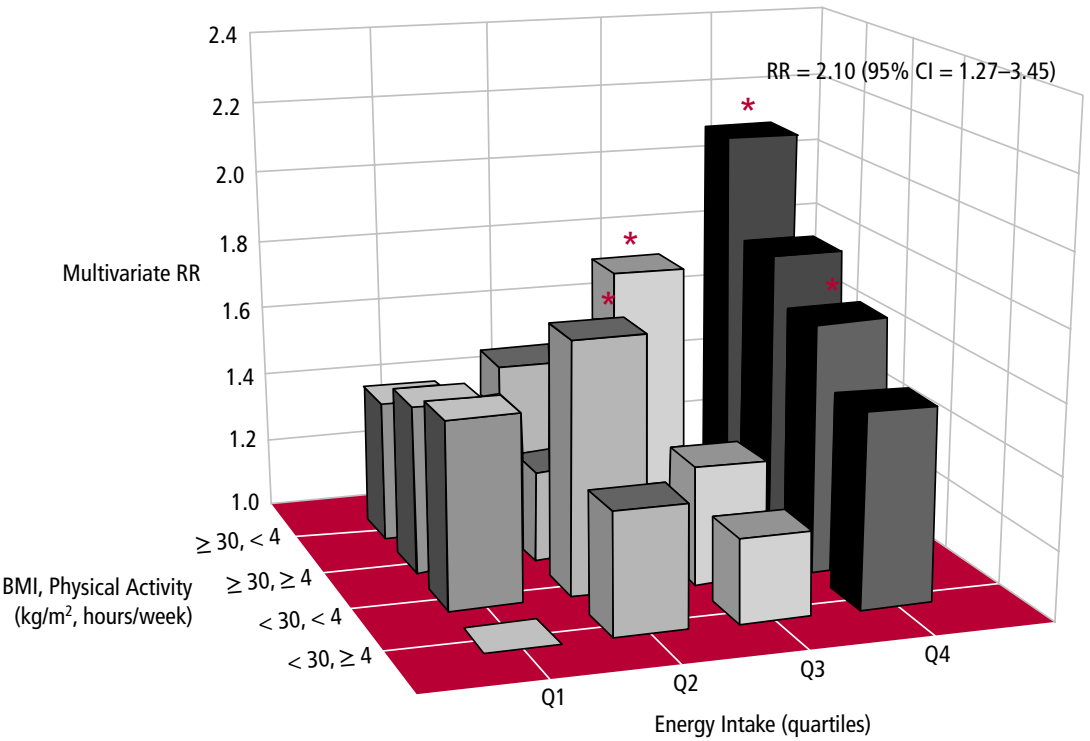

Figure 1: Multivariate relative risk of breast cancer in relation to the joint associations of energy intake, body mass index, and physical activity in the PLCO trial. (Chang SC, et al., submitted)

* Statistically significant

DCEG *Linkage*

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Michael Leitzmann

areas. These areas were chosen because they offered reliable cancer registries, thus enabling researchers to track cancer incidence. The 566,990 respondents established the AARP cohort. This study, which has recently completed collecting information on the participants' cancer experience, will yield a wealth of new insights into the complicated relationship between diet, physical activity, and cancer.

In the past year, a follow-up questionnaire was sent out to request updated information on physical activity, body weight, and disease status. This form included new questions on dietary supplement and menopausal hormone use. According to **Demetrius Albanes, M.D.,** a senior investigator in NEB, "This follow-up questionnaire will improve the specificity of the data for the cohort, and it will permit evaluation of important direct effects and interactions for cancer risk with two highly prevalent population exposures—dietary supplement and hormone use."

The AARP study will serve to confirm past findings that link energy imbalance to risk for certain cancers, such as breast, colon, and prostate. In addition, "It offers a valuable opportunity to elucidate the relationship between energy imbalance and less frequently occurring cancers, such as those of the endometrium, ovary, kidney, pancreas, and liver," says **Michael Leitzmann, M.D., Dr.P.H.,** one of the main researchers on the study and a tenure-track investigator in NEB. The large size of this cohort makes it possible to examine important interactions between certain exposures—menopausal hormone therapy, for example—and obesity in relation to breast, colorectal, and other malignancies.

Today, approximately one-third of the adult U.S. population is considered obese … [and] almost two-thirds are considered overweight or obese.

Dr. Leitzmann is also working to improve the effectiveness of the instruments used in these types of studies. In a 600-person subset of a large study Dr. Leitzmann is performing in Shanghai, China, the participants fill out questionnaires on their physical activity and undergo periodic fitness tests and physical activity monitoring with accelerometers. A few times each year, participants wear these motion sensors for seven consecutive days to measure physical activity during weekdays, weekends, and different seasons. In order to gauge how accurate respondents' recall is, these sensor measurements will be compared to the answers provided in the activity questionnaires. "By correlating objectively measured data with recall data, we can learn how to better pose questions to get more accurate measures of physical activity from the entire cohort," explains Dr. Leitzmann.

This subset of 300 men and 300 women is part of a molecular and metabolic

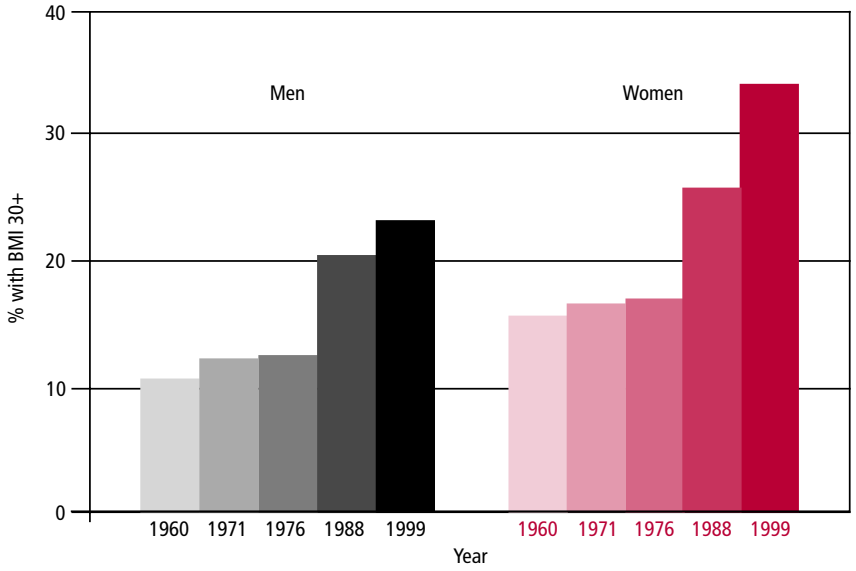


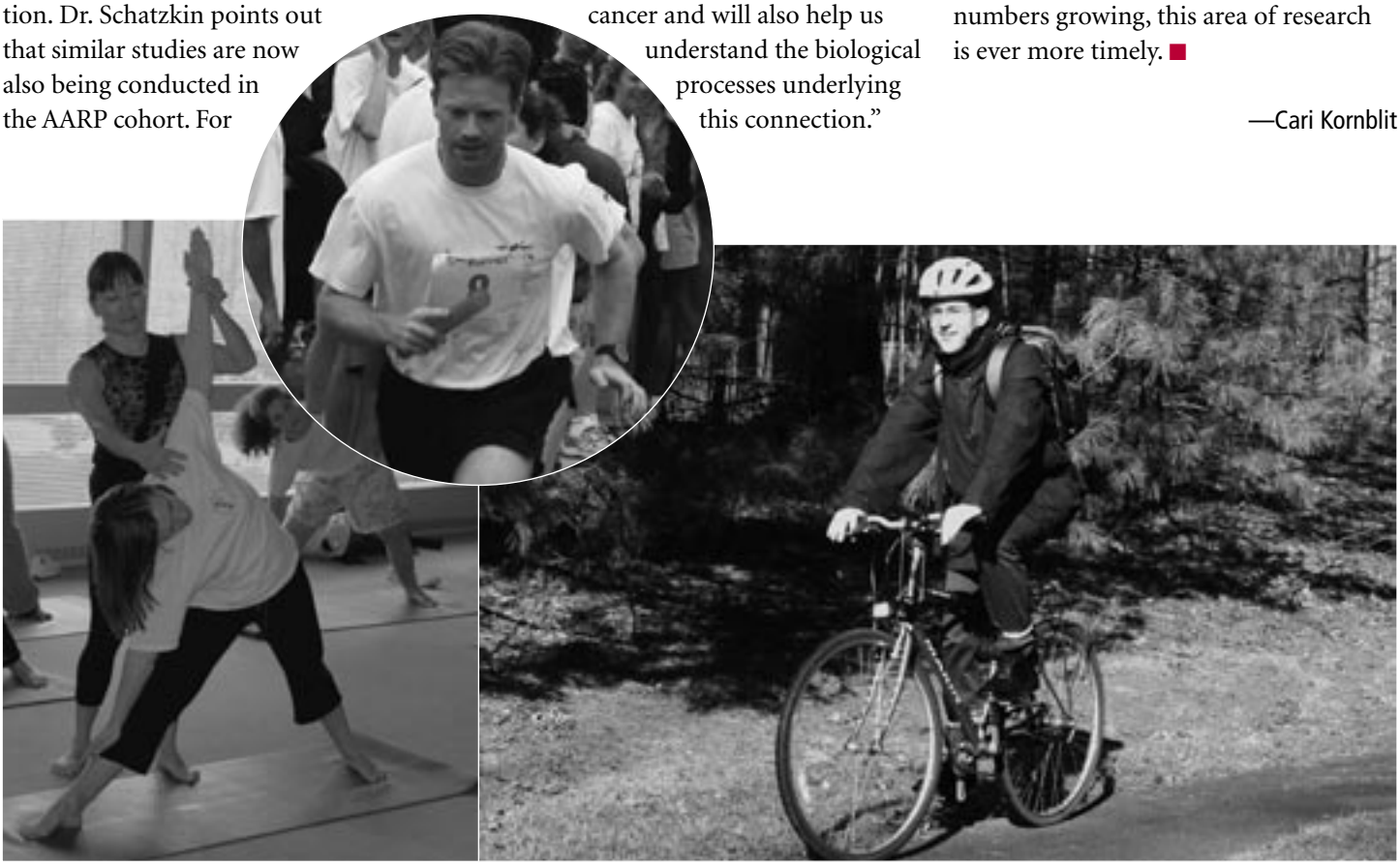
Figure 2: Increasing obesity among men and women, United States, 1960–1999. (Flegal KM, et al., *JAMA* 2002; National Health and Nutrition Examination Survey)

study in which participants' blood will be tested for many biomarkers to examine how they relate to differing levels of physical activity. Key emerging pathways to be studied include insulin resistance, growth factors, and chronic inflammation. Dr. Schatzkin points out that similar studies are now also being conducted in the AARP cohort. For example, some participants donate cheek cells from which DNA can be extracted. "This molecular genetic information," Dr. Schatzkin notes, "will help us establish with even greater certainty a causal connection between energy balance and cancer and will also help us understand the biological processes underlying this connection."

The field of energy balance is vast, and NEB researchers are vigorously investigating many aspects and hypotheses. "We don't yet know, for example, how higher levels of physical activity reduce cancer risk, and whether the mechanisms are different for breast cancer and colon cancer," suggests Dr. Albanes.

DCEG researchers continue to probe such questions by taking advantage of the longitudinal cohorts and other studies that have collected dietary, activity, and anthropometric data. They are improving upon these studies while incorporating novel methods to examine molecular pathways. Also, NEB investigators are involved in NCI and NIH working groups on energy balance to ensure coordination of the DCEG efforts with others across NIH. Today, approximately one-third of the adult U.S. population is considered obese, as shown in Figure 2; almost two-thirds are considered overweight or obese. With these numbers growing, this area of research is ever more timely. ■

—Cari Kornblit



DCEG staff members pursue fitness in many ways: (left) Laura Beane-Freeman with yoga instructor Maggie Rhoades; (inset) James Lacey; and (right) Michael Hauptmann.

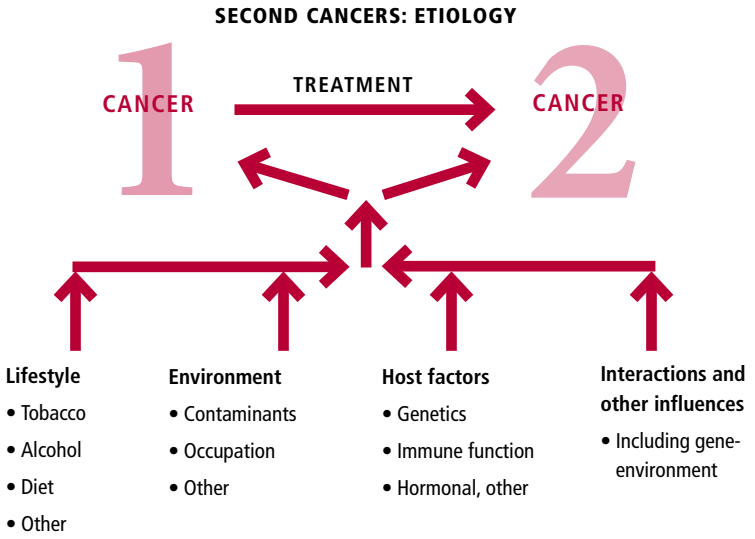
WORKSHOP EXPLORES SECOND CANCERS

On November 8 and 9, 2004, the NCI Division of Cancer Epidemiology and Genetics (DCEG) convened a workshop entitled "Cancer survivorship: Genetic susceptibility and second primary cancers." The goals of the workshop, sponsored by the NIH Office of Rare Diseases, were to identify research issues, priorities, and resources needed to advance the study of genetic susceptibility and second primary cancers; to identify unusual research opportunities that NCI can address in future collaborative endeavors; and to make specific recommendations for implementation by intramural and extramural divisions of NCI. **Lois B. Travis, M.D., Sc.D.,** Radiation Epidemiology Branch (REB), was chair of the Scientific Program Committee, and **Linda Morris Brown, Dr.P.H.,** Biostatistics Branch (BB), served as assistant chair. Other NCI investigators on the committee included **Blanche Alter, M.D., M.P.H.,** Clinical Genetics Branch (CGB), **Neil Caporaso, M.D.,** Genetic Epidemiology Branch (GEB), **Stephen Chanock, M.D.,** NCI Core Genotyping Facility (CGF), Dr. Graca Dores (NCI Division of Cancer Prevention), **Mark H. Greene, M.D.** (CGB), **Michie Hisada, M.D., M.P.H., Sc.D.,** Viral Epidemiology Branch (VEB), **Peter Inskip, Sc.D.** (REB), **Charles Rabkin, M.D.** (VEB), and **Margaret Tucker, M.D.** (GEB). Dr. Mary Gospodarowicz (Princess Margaret Hospital, Toronto), Dr. Alfred Knudson (Fox Chase Cancer Center), and Dr. Peter Shields (Georgetown University Medical Center) served as extramural advisors. Representatives from the NCI Office of Cancer Survivorship (Dr. Julia Rowland, director, and Dr. Noreen Aziz, senior program director, Division of Cancer Control and Population Sciences) participated in the meeting with researchers from the NCI Center for Cancer Research (Dr. William D. Figg) and the NCI Division of Cancer Treatment and Diagnosis (Dr. Barry Anderson). Dr. Michael Thun (American Cancer Society) and Susan Leigh (National Coalition for Cancer Survivorship), who are members of the NCI Board of Scientific Counselors, also participated. **Ursula Leitzmann, M.A.** (REB) served as Administrative Coordinator, and **Jose Reyes** (BB) assisted with travel arrangements and document preparation.

Linda Morris Brown and Lois Travis

Workshop participants were experts from various specialties, including molecular carcinogenesis, epidemiology, pharmacogenomics, statistics, clinical oncology, and radiation oncology. The advocacy community was also well-represented.

There were four sessions that summarized state-of-the-art knowledge. Session 1, "Populations of Cancer Survivors: Description and Overview of Current Work in Primary Cancers and Other Late Effects," was moderated by Dr. Christine Ambrosone (Roswell Park Cancer Institute) and Dr. Rabkin. The speakers were: Dr. Gospodarowicz, Dr. Robert Wittes (Memorial Sloan-Kettering Cancer Center), Dr. Andrea Ng (Brigham and Women's Hospital), Dr. Louise Strong (University of Texas M.D. Anderson Cancer Center), and Dr. Leslie Robison (University of Minnesota). They described multidisciplinary programs at their institutions that have integrated clinical care and research and provided innovative web-based education for patients, including scientific information on late sequelae of treatment. The development of web-based informatics resources to collect long-term follow-up data on large cohorts of patients was emphasized.



Source: Travis LB, *Acta Oncologica* 2002: 323–333.

Session 2, "Inherent Genetic Susceptibility to Second Primary Cancers," was moderated by Drs. Shields and Tucker and featured the following: Dr. David Malkin (Hospital for Sick Children, Toronto), Dr. Ken Offit (Memorial Sloan-Kettering Cancer Center), **Ruth Kleinerman, M.P.H.** (REB), and Dr. Toshi Taniguchi (Fred Hutchinson Cancer Research Center). Participants discussed a number of familial cancer syndromes that have helped elucidate basic carcinogenic mechanisms, such as Li-Fraumeni syndrome and hereditary breast and ovarian cancers. Another central topic was hereditary retinoblastoma, the most prominent example of an inherited mutation that predisposes to radiotherapy-related cancers.

Session 3, "Radiation, Chemotherapy, Genetic Susceptibility and Second Primary Cancers," was moderated by Dr. John Little (Harvard School of Public Health) and Dr. Caporaso, and featured Dr. Eric Hall (Columbia University), Dr. James Allan (University of York, United Kingdom), Dr. Figg, Dr. Ching-Hon Pui (St. Jude Children's Research Hospital), and **Nathaniel Rothman, M.D.** (Occupational and Environmental Epidemiology Branch). Speakers described how the carcinogenic effects of chemotherapy and radiotherapy might be influenced by the level of carcinogen exposure as well as by polymorphisms in genes involved in carcinogen metabolism and DNA repair, and the patient's nutritional status. The discussion also addressed interactions between cytotoxic drugs and radiation.

Drs. Gospodarowicz and Greene moderated a Special Topics session, "At the Intersection of Cancer Survivorship Research," which included Dr. Chanock, Dr. Colin Begg (Memorial Sloan-Kettering Cancer Center), Dr. Angela DeMichele (University of Pennsylvania), and Dr. Carol Kasten-Sportes (NCI Division of Cancer Control and Population Sciences). Speakers discussed current and future tools available for genetic analysis, study-design issues for etiologic investigations of second primary cancers, practical issues regarding multidisciplinary clinical and research programs in cancer survivorship, and research funding opportunities provided by the NCI.

Following the presentations, attendees broke into three workgroups to address the workshop goals and make specific recommendations about the study of second cancers. A full meeting report is being prepared for publication. ■

—Linda Morris Brown, Dr.P.H.

AARON BLAIR LEAVES OEEB LEADERSHIP AFTER 26 YEARS

Aaron Blair

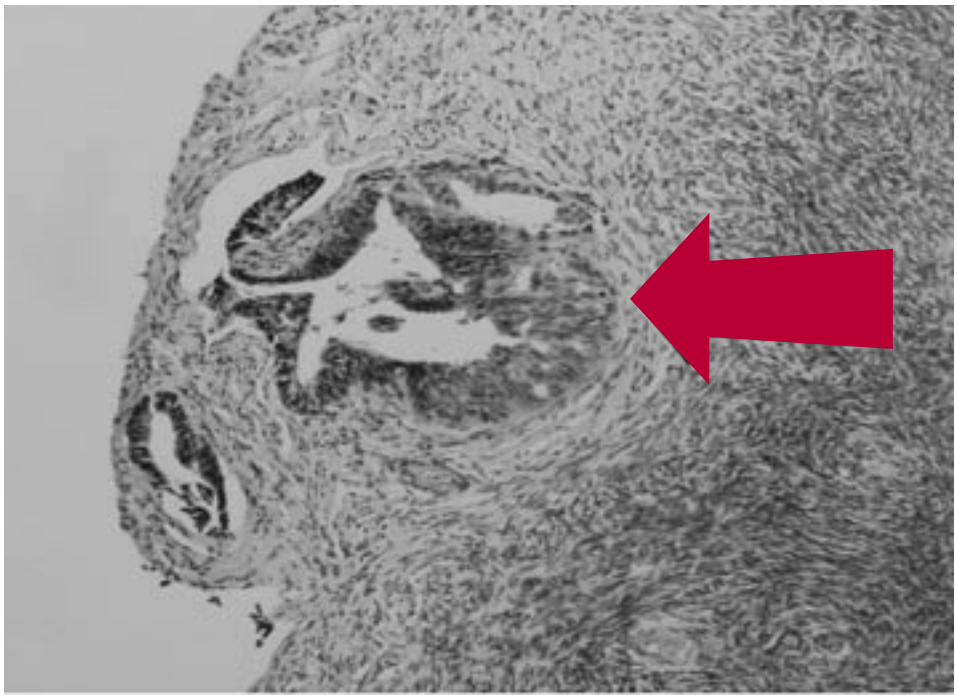
Aaron Blair, Ph.D., has stepped down as Chief of the Occupational and Environmental Epidemiology Branch (OEEB), as of October 2004, to refocus on his research interests as a Principal Investigator. Dr. Blair has developed and led NCI's occupational epidemiology program for 26 years, first as Head of the Occupational Studies Section and later as Branch Chief when the Section was upgraded (originally the Occupational Epidemiology Branch, now the OEEB). Over this period, the staff has grown from 4 professionals to more than 30.

The OEEB has led the way in the incorporation of state-of-the-art industrial hygiene into robust epidemiologic research designs, in the development of biochemical and molecular epidemiology, in the assessment of risks associated with important and widespread industrial exposures, and in pioneering advances in evaluating the risks associated with agricultural exposures. More recently, the Branch has been a leader in demonstrating how these same methods can be developed and used for the difficult but important tasks of studying carcinogenic risks in the general environment. Much of this was accomplished because of Dr. Blair's personal leadership and his development of a supportive and creative environment for the outstanding investigators he has recruited to the program. This same atmosphere has also made the OEEB a highly sought-after opportunity for training a new generation of occupational and environmental epidemiologists. Under Dr. Blair, OEEB has fostered collaborations with some of the most experienced epidemiologists in the world.

Dr. Blair's accomplishments at OEEB have come about through his unique combination of scientific judgment and insight, outstanding administrative and management skills, honesty, integrity, humility, good humor, sincere caring for people, and dedication to the team effort. He will be greatly missed as Branch Chief and, indeed, a hard act to follow. We are very fortunate, however, that he is remaining as a senior investigator and will continue to contribute his talents to the Branch, Division, Institute, and NIH.

MARK GREENE LEADS HEREDITARY OVARIAN CANCER STUDY

DCEG researchers have been studying inherited ovarian and breast cancer for decades, but with the creation of the Clinical Genetics Branch (CGB) five years ago, they are now able not only to study the disease in families, but also to look toward preventing the disease by applying molecular biology advances. A large prospective study led by **Mark H. Greene, M.D.,** in collaboration with the Gynecologic Oncology Group (GOG) and the Cancer Genetics Network (CGN), aims to do just that.



A single focus of highly atypical epithelial cells (arrow) was the only abnormality found in the ovarian tissue removed from a CGB patient at increased genetic risk of ovarian cancer. *(Image courtesy of Dr. Maria Merino)*

As soon as clinical tests to identify *BRCA* mutation carriers became commercially available, concerns arose as to how to manage the care of patients who are at greater genetic risk of breast and ovarian cancers. Retrospective studies from high-risk clinics in tertiary care facilities offered some useful preliminary information, but it was clear that a large prospective study was needed to provide answers that were unbiased, statistically sound, and representative of the diverse population of women at risk. Dr. Greene and his colleagues set out to design a protocol that would not only answer lingering questions, but would also develop data on important issues not yet addressed by prior studies, such as non-cancer morbidity (e.g., heart attack and osteoporosis) and the quality of life experienced by women who undergo premature menopause as a consequence of opting for risk-reducing removal of the ovaries. Dr. Greene has had a career-long interest in ovarian cancer, having worked as a clinician and researcher in NCI's program of studies in familial cancer. He explains that patients with ovarian cancer "are exceptionally motivated and determined to get well. It has been inspirational to be part of the care of these patients."

The study, dubbed GOG 0199, incorporates two arms and is a collaboration between several divisions within NCI, extramural researchers, and more than 100 GOG centers around the world. The first arm of the study offers women at high risk of ovarian cancer the option to undergo an oophorectomy, the surgical removal of the ovaries and fallopian tubes. These women are then monitored every six months for five years. Recruitment and treatment are being carried out at 110 institutions around the United States and, as of the beginning of 2005, at 5 centers in Australia. The Clinical Center on NIH's main campus is also a study site, so that family members who are participating in DCEG's hereditary breast/ovarian cancer family studies program can enroll and benefit from this project.

The second arm of GOG 0199 involves a screening protocol originally devised by the Cancer Genetics Network, an NCI-funded consortium of eight institutions. It offers women the option of regular blood screening for ovarian cancer through an improved version of the CA-125 screening tool that uses a mathematical model, ROCA (Risk of Ovarian Cancer Algorithm), to measure changes in blood levels over time instead of a single measurement.

Since July 2003, when enrollment began, more than 700 subjects have joined both arms of the study. Eventually, study researchers would like to enroll a total of 1,800 women. Because this number is larger than any one center can handle, coordination between all of the clinical sites is necessary if the study is to meet its accrual goals and achieve statistical significance. On getting such an expansive study rolling, Dr. Greene is happy to report: "Well, it is clear that we *can* do the study. Some people thought we'd never get this off the ground, since it is so complicated."

In addition to extramural collaborations, Dr. Greene works with Dr. Jeffery Struewing's laboratory in the Center for Cancer Research to obtain *BRCA*

He explains that patients with ovarian cancer "are exceptionally motivated and determined to get well. It has been inspirational to be part of the care of these patients."

mutation data on all study participants, with Dr. Ted Trimble and others in the Division of Cancer Treatment and Diagnosis to facilitate the relationship with the GOG centers, and with the Division of Cancer Prevention, which is providing major funding support through its Community Clinical Oncology Program.

Both arms of the study are collecting clinical information on all enrolled patients, along with biological samples such as blood and ovarian tissue, which are taken at the time of surgery. Dr. Greene is confident that this study will "yield a treasure trove of data."

Overall, the GOG 0199 trial serves as a model for future intervention studies of genetically at-risk populations because it has managed to successfully incorporate so many centers and such multidisciplinary expertise. Although at times the collaboration has been difficult, Dr. Greene says matter-of-factly, "To bring diverse groups together—instead of being competitors—that is what it will take to move the field forward." And in the process, many women and their families will benefit from these efforts. ■

—Cari Kornblit

DCEG DOUBLES NUMBER OF FARE WINNERS

Eight DCEG fellows were recipients of the 2005 NIH Fellows Award for Research Excellence (better known as FARE), double the number who won the award last year. The FARE program recognizes outstanding scientific research by fellows in the NIH intramural research program. To enter the competition, fellows submit abstracts of their research, which are reviewed by a panel of NIH postdoctoral fellows and tenured/tenure-track investigators. Winners receive a travel stipend to attend a scientific meeting, where they present their research papers. More information about the FARE competition is available at http://felcom.nih.gov/FARE.

DCEG FARE Winners and Abstract Titles

Biostatistics Branch

- Jinbo Chen, Ph.D.: *Haplotype-based test of association using data from cohort and nested case-control epidemiological studies*
- Roxana Moslehi, Ph.D.: *Cigarette smoking, NAT2 alleles, and the risk of advanced colorectal adenoma*

Genetic Epidemiology Branch

- David Ng, M.D.: *Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in BCoR (BCL [B-cell leukemia]-6 interacting CoRepressor) gene*

Hormonal and Reproductive Epidemiology Branch

- Gabriella Andreotti, M.P.H.: *Polymorphism of genes in the lipid metabolism pathway and the risk of biliary tract cancers: A population-based study in Shanghai, China*

Nutritional Epidemiology Branch

- Shih-Chen Chang, Ph.D.: *Association of energy intake, body size, and physical activity with postmenopausal breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial*

Occupational and Environmental Epidemiology Branch

- Jennifer Rusiecki, Ph.D.: *Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study*

Radiation Epidemiology Branch

- Preetha Rajaraman, M.S.: *Occupational exposure to lead, genetic susceptibility and risk of brain tumors in adults*
- Cecile Ronckers, Ph.D.: *Second thyroid cancer among childhood cancer survivors: Evaluation of radiation dose-response and its modifiers*

DCEG FARE Winners: (front) Preetha Rajaraman, Roxana Moslehi, and Gabriella Andreotti; (back) David Ng, Cecile Ronckers, Jennifer Rusiecki, and Shih-Chen Chang (not shown: Jinbo Chen).

NILANJAN CHATTERJEE EARNS TENURE

Although he was originally trained in theoretical statistics, **Nilanjan Chatterjee, Ph.D.,** now works on solving "difficult and interesting" statistical problems in cancer epidemiology. "I try to select problems in which my knowledge of theoretical statistics is strong, but which also have wide application," he says.

Nilanjan Chatterjee

"Not everyone who smokes gets lung cancer; the ones who do [get cancer] not only have the environmental exposure (smoking), but also must have some susceptibility genes. Studying any gene-environment interaction is difficult because it requires so much data. I am coming up with more efficient ways to do these studies."

Dr. Chatterjee, a senior investigator in the Biostatistics Branch, has been with NCI since 1999 and received tenure on November 1, 2004. His first area of research, which he started as a graduate student at the University of Washington, Seattle, involved developing methods to analyze two-phase data, which are often collected in epidemiologic studies.

"Two-phase design reduces expense. We can collect inexpensive data on a large number of people, and then more expensive data on a subsample. There is a complex statistical problem in how to analyze those data. Some of the previous methods proposed in this area utilize only data from phase two subjects who have complete covariate information, thus losing valuable information from phase one subjects who were not selected for phase two," Dr. Chatterjee explains. He developed an analytic method that treats a two-phase study as a missing data problem, in which subjects not selected for phase two have only partial covariate information. "This method combines the phase one and phase two sources of data," he says.

A second area of interest that caught Dr. Chatterjee's attention soon after coming to NCI is the kin-cohort approach in studies of familial cancer risk. He developed methods for estimating disease risks associated with genetic and environmental factors, as well as ways to quantify familial aggregation of disease due to unmeasured risk factors. The methods account for the age at onset of disease as well.

Dr. Chatterjee has also worked on streamlining the analysis of gene-environment interactions. "For example, we did a study looking at *BRCA1* status and oral contraceptive use," he says. "We can assume these two factors are independent, because the women didn't know their *BRCA1* status. Our study showed that if we assume the two factors are independent, we can more precisely measure odds ratios and risk, compared with a standard logistic regression analysis." Dr. Chatterjee and others also showed that the same independent assumption may be made in a matched case-control study.

Those studies led Dr. Chatterjee into the general field of genetic and molecular epidemiology. "Molecular data linked to exposure data is a new thing, and it's generating a lot of new statistical problems," he says. "Not everyone who smokes gets lung cancer; the ones who

do not only have the environmental exposure (smoking), but also must have some susceptibility genes. Studying any gene-environment interaction is difficult because it requires so much data. I am coming up with more efficient ways to do these studies."

The advent of microarrays and other biotechnologies that allow for the collection of huge amounts of data has kept Dr. Chatterjee busy as well. "Today, there are lots of ways to classify cancer. It is feasible, for example, to use gene expression patterns to diagnose cancer and to tailor treatment. However, it's been less clear how to use this information as a component of epidemiologic studies."

Dr. Chatterjee has developed methods for studying whether the environmental exposures are different for different subtypes of cancer. "For example, smoking may increase the risk of only certain types of lung cancer, and we can figure out which types by studying both molecular and exposure data," he suggests. "The method I have developed allows one to simultaneously study multiple disease characteristics that might be related, such as estrogen-receptor (ER) and progesterone-receptor (PR) status in breast cancer," he says. Previously used methods are suitable mainly for analyzing subtypes defined by only single disease characteristics.

"Using my method, one can study whether there is independent variation in the effect of an exposure by ER and by PR status, after adjusting for one another," he says. "Similarly, using my method, one can study whether the variation in the effect of an exposure between ER categories is modified by PR status and vice versa."

Was it challenging for a theoretical statistician to learn genetics? "It really was not a difficult transition," he answers. "Once I started learning about kin-cohort studies, which were originally developed by colleagues in DCEG, that gave me an introduction, and I've gone on from there."

In the future, Dr. Chatterjee has more ideas to investigate. "One topic I think is important is how to analyze genetic data when we are choosing multiple genes in a causal pathway, such that the genes are not independent of one another," he says. "I'm interested in how to analyze those types of data, and also in data mining tools to look at complex interactions." ■

—Nancy Volkers

TEAM CONDUCTS PROSTATE CANCER STUDY IN GHANA

Ann Hsing, Ph.D., Hormonal and Reproductive Epidemiology Branch, is leading a DCEG team that is screening for prostate cancer in Africa in the Ghana Study. The DCEG team is collaborating with scientists at the University of Ghana Medical School (UGMS) and its teaching hospital, Korle-Bu Hospital, led by Professor Edward Yeboah, a leading Ghanaian urologist. Recruiting of subjects is underway for 1,000 healthy men between 50 and 74 years old, randomly selected from the population in Accra, Ghana. NCI researchers spent more than two years planning the study and working with UGMS collaborators to prepare for the data collection effort. Field work should be completed by December 2005.

Ann Hsing (third from left) with Ghana Prostate Cancer Study Team.

LIGIA PINTO HEADS HPV IMMUNOLOGY LABORATORY

As a graduate student in Portugal in 1993, **Ligia Pinto, Ph.D.,** was awarded a fellowship that allowed her to complete her dissertation work in any laboratory in the world. She chose Dr. Gene Shearer's lab in NCI's Experimental Immunology Branch, and she hasn't left NCI since.

Her early work involved HIV infection and AIDS, but today Dr. Pinto is head of DCEG's Human Papillomavirus (HPV) Immunology Laboratory in the Hormonal and Reproductive Epidemiology Branch (HREB), where she works on immunologic responses to vaccines that could one day help treat and prevent cervical cancer. "I'm very much interested in infectious diseases, and HPV is an important public health concern," says Dr. Pinto. "With HIV, most infections progress to AIDS. With HPV, only a small proportion of infected individuals progress to cancer; most people clear the infection. It's been interesting to try to understand why that happens."

There are more than 100 strains of HPV; at least 12 have been associated with cervical cancer, with HPV-16 showing the strongest link. Each year, cervical cancer is diagnosed in almost a half million women worldwide. Approximately 250,000 women die of the disease each year, with higher mortality rates in non-industrialized countries.

One promising HPV vaccine developed at NCI is now being tested in a phase III trial in Costa Rica. This vaccine has been found to induce robust antibody responses and was efficacious in reducing incidence of infection. Although protection is likely conferred through neutralizing antibodies, cell-mediated immune responses may play an important role as regulators of strong and sustained humoral responses. The HPV laboratory has played an important role in monitoring immunogenicity of the vaccine in the NCI-Johns Hopkins University phase II trial. In these studies, the laboratory showed that vaccination induced HPV-specific T-cell responses detectable by proliferation of both $CD4^+$ and $CD8^+$ T cells and *in vitro* production of Th1, Th2, and inflammatory cytokines. To help researchers understand how immunity is induced and how it might change over time, the phase III trial will follow women for several years after vaccination.

Ligia Pinto *(Photograph Credit: Marti Welch)*

Another important function of the lab is to develop and validate immunologic methods that are applicable to field studies and serve to evaluate cellular and humoral immune responses systemically and at the genital tract. These include assays of neutralizing antibodies, whole blood assays for multiplex cytokine detection, preparation of samples in remote sites for flow cytometric analysis, and development of methods to evaluate immune responses at the cervix. The overall aim of these studies is to gain a better understanding of host immunity to HPV through identification of immune determinants of protection from infection and associated disease.

Dr. Pinto works closely with other investigators in HREB, especially **Allan Hildesheim, Ph.D.,** to understand how the HPV vaccine works. "We want to know how it induces protection and the duration of the protection," Dr. Pinto says. "We hope that what we learn from this trial will help us improve HPV vaccines and design better therapeutic strategies."

Dr. Pinto says she has always loved science, biology in particular, and wanted to conduct laboratory research. After graduating with a degree in biology from the Faculty of Sciences and the Faculty of Medicine of Lisbon, Dr. Pinto started her graduate work with the Faculty of Medicine of Lisbon in 1988. In 1993, she was awarded the fellowship that brought her to the United States and to NCI. "My goal with the fellowship was to get solid training in immunology and infectious diseases and return to Portugal. However, I ended up staying at NCI for postdoctoral work in the Experimental Immunology Branch. Now I'm head of a lab working on exciting aspects of HPV research, which shows promise in reducing the burden of cervical cancer around the world." ■

—Nancy Volkers

DCEG STAFF RECEIVE NIH MERIT AWARDS

Congratulations to the following DCEG staff members, who were recognized for their accomplishments over the past year at the annual NIH Awards Ceremony, held on October 28, 2004:

- **Eric Engels, M.D., M.P.H.,** Viral Epidemiology Branch (VEB), for his research providing strong evidence that simian virus 40 infection is not a major cause of human malignancy.
- **Qing Lan, M.D., Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB), for her pioneering research on lung cancer and indoor air pollution, leading to interventions that reduced cancer risk.
- **Stephen Chanock, M.D.,** for exceptional leadership in the development of the NCI's Core Genotyping Facility, which provides high-throughput genotyping and sequencing for NCI's Intramural Research Program.
- **Charles Land, Ph.D.,** Radiation Epidemiology Branch (REB), to honor his innovative scientific leadership in quantifying radiation-related breast cancer risks in the premier radiation epidemiological follow-up study of Japanese atomic bomb survivors.
- **Donna Gellerson Siegle,** recognized by the Office of Management for her excellence and creativity as an ARC manager and for her contributions to the improvement of operations across NCI.
- **Betsy Duane-Potocki,** Office of the Director (OD), honored by the NCI Office of the Director for her part on the team responsible for the *NCI Cancer Bulletin.*

DCEG members of the team responsible for the I-131 dose/risk calculator include: (starting sixth from left) Charles Land, Elaine Ron, Andrew Bouville, and Betsy Duane-Potocki. NCI Director Andrew von Eschenbach is at far left.


Wong-Ho Chow with NCI Director Andrew von Eschenbach


Qing Lan with NCI Director Andrew von Eschenbach

- **Andre Bouville, Ph.D.,** Ms. Duane-Potocki, Dr. Land, **Elaine Ron, Ph.D., Steve Simon, Ph.D.,** and **Bob Weinstock,** recognized by the NCI OD as part of the team responsible for the I-131 dose/risk calculator.
- **Allan Hildesheim, Ph.D.,** and **Mark Schiffman, M.D., M.P.H.,** Hormonal and Reproductive Epidemiology Branch (HREB), honored as part of the team responsible for breakthrough work on HPV/cervical cancer etiology, diagnostics, and therapeutics. ■

—Sandy Rothschild


Donna Siegle with NCI Director Andrew von Eschenbach

RUDOLF KAAKS GIVES SEMINAR AS HREB DISTINGUISHED LECTURER

The Hormonal and Reproductive Epidemiology Branch (HREB) hosted the second seminar in its distinguished lecturer series on January 6, 2005, featuring Dr. Rudolf Kaaks of the International Agency for Research on Cancer (IARC). His seminar was titled "Overweight, physical inactivity, and cancer risk: Hormonal mechanisms."

Dr. Kaaks first summarized data in the literature, which provide sufficient evidence that obesity is associated with cancers of the colon, endometrium, kidney, and esophagus, and with breast cancer in postmenopausal women. He then presented data from his ongoing work, particularly in the European Prospective Investigation into Cancer (EPIC) study, that suggest potential mechanisms by which obesity predisposes to cancer. His research illustrates that the link between obesity and cancer risk is mediated by sex hormone levels and other metabolic pathways, including inflammation, insulin, and insulin-like growth factors. Specifically, he concluded that (1) hyperinsulinemia and alterations in endogenous sex steroid metabolism are the likely underlying mechanisms that link obesity and various cancers; (2) elevated plasma androgens and estrogens are associated with cancers of the endometrium and breast in postmenopausal women, with elevated estrogens resulting from excess weight, though the cause of elevated androgen levels is not entirely clear; (3) among premenopausal women, endometrial cancer risk is increased in those with ovarian androgen excess; and (4) elevated circulating IGF-1 levels are associated with colon, prostate, and postmenopausal breast cancer. He also emphasized the importance of investigating energy balance, exogenous hormones, and genetic susceptibility in future studies to clarify the underlying mechanisms linking obesity to higher cancer risk. During his two-day visit, he met with numerous DCEG investigators to offer his insights on conducting hormone-related epidemiologic studies.

Dr. Kaaks is especially interested in elucidating the relationships between cancer risk and diet, other lifestyle factors, obesity, physical activity, endogenous hormones and growth factors, and gene-environmental interactions.

Rudolf Kaaks and HREB Chief Louise Brinton

Dr. Kaaks, a leader in the field of nutritional epidemiology, was trained at Wageningen University, the Netherlands. He joined IARC in 1988 as a scientist in the Unit of Nutrition and Cancer and became head of the Hormones and Cancer research team in 2002. He directs a laboratory with expertise in measuring serum sex steroids and insulin-like growth factors. As a coinvestigator of the EPIC Study, a multi-center collaboration among 10 European nations to investigate the role of nutrition and other lifestyle risk factors for cancer and other chronic diseases, he is especially interested in elucidating the relationships between cancer risk and diet, other lifestyle factors, obesity, physical activity, endogenous hormones and growth factors, and gene-environment interactions. He serves on a number of important committees, including the Specimen Advisory Board of the American Cancer Society. ■

—Jennifer Connor and Lori Sakoda, M.P.H.

SCIENTIFIC HIGHLIGHTS

BLADDER CANCER

Bladder Cancer and Low-level Arsenic

At high concentrations, inorganic arsenic can cause bladder cancer in humans, but it is unclear whether low exposure in drinking water (< 100 µg/L) is related to risk. Toenail samples provide an integrated measure of internal arsenic exposure and reflect long-term exposure. The authors examined the relationship between toenail arsenic levels and bladder cancer risk among participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a cohort of Finnish male smokers aged 50-69 years. Data for 280 bladder cancer cases and matched controls showed no association between inorganic arsenic concentration and bladder cancer risk (odds ratio [OR] = 1.1, confidence interval [CI] = 0.7–1.8 for the highest vs. lowest quartile). Toenail arsenic concentrations were similar to those reported in U.S. studies (range: 0.02–17.5 µg/g). These findings suggest that low-level arsenic exposure is unlikely to explain a substantial excess risk of bladder cancer. **(Michaud DS, Wright ME, Cantor KP, Taylor PR, Virtamo J, Albanes D. Arsenic concentrations in prediagnostic toenails and the risk of bladder cancer in a cohort study of male smokers. *Am J Epidemiol* 2004;160: 853-859)**

BRAIN TUMORS

Electrical Appliance Use

Electrical appliances produce the highest intensity residential exposures to extremely low frequency electromagnetic fields. The authors investigated whether appliances may be associated with adult brain tumors in a hospital-based case-control study at three centers in the United States from 1994 to 1998. A total of 410 glioma, 178 meningioma, and 90 acoustic neuroma cases and 686 controls responded to a self-administered questionnaire about 14 electrical appliances. There was little evidence of association between brain tumors and the use of curling irons, heating pads, vibrating massagers, electric blankets, heated water beds, sound systems, computers, televisions, humidifiers, microwave ovens, and electric stoves. Use of hair dryers was associated with glioma (OR = 1.7, CI = 1.1–2.5), but there was no evidence of increasing risk with increasing amount of use. In men, meningioma was associated with electric shaver use (OR = 10.9, CI = 2.3–50), and the odds ratio increased with cumulative minutes of use, although based on only two unexposed cases. Despite the potential for recall bias, the results indicate that extremely low frequency electromagnetic fields from commonly used household appliances are unlikely to increase the risk of brain tumors. **(Kleinerman RA, Linet MS, Hatch EE, Tarone RE, Black PM, Selker RG, Shapiro WR, Fine HA, Inskip PD. Self-reported electrical appliance use and risk of adult brain tumors. *Am J Epidemiol* 2005;161:136-14)**

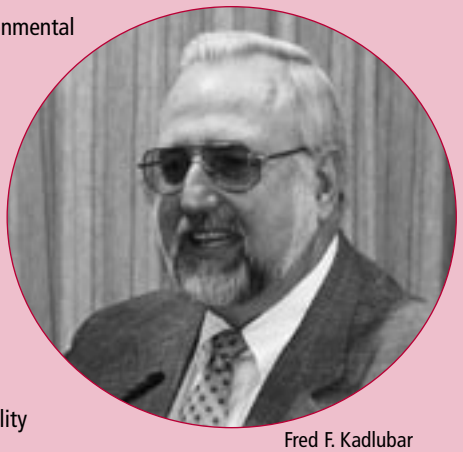
BREAST CANCER

CHEK2:1100delC and Breast Cancer in the United States

The *CHEK2*:1100delC mutation was evaluated in a nested case-control study of female breast cancer from a cohort of radiologic technologists and in 21 probands from *BRCA1/2* mutation-negative breast/ovarian cancer families. The findings suggest that this mutation is a rare allele that approximately doubles a carrier's risk of breast cancer

FRED KADLUBAR DELIVERS OEEB DISTINGUISHED LECTURE

Dr. Fred F. Kadlubar, Director, Division of Molecular Epidemiology, National Center for Toxicological Research, Jefferson, Arkansas, was honored as the DCEG Distinguished Lecturer in Occupational and Environmental Cancer. Dr. Kadlubar presented a seminar on October 7, 2004, entitled "Breast cancer: Biomarkers of carcinogen exposure and treatment efficacy." Dr. Kadlubar received his Ph.D. from the University of Texas at Austin. His research interests include:



Fred F. Kadlubar

- Characterization of human genetic polymorphisms, modulation of drug metabolism and carcinogen activation, and detoxification.
- Metabolic genotyping and phenotyping of human populations and assessment of individual susceptibility to chemical exposures.
- Dietary and environmental risk factors that influence individual differences in human urinary bladder, colon, pancreas, lung, and breast cancer susceptibility.
- Assessment of human exposure to carcinogens by measurement of carcinogen-macromolecular adducts in surrogate and target tissues.

—Dalsu Baris, M.D., Ph.D.

in the population setting and may account for familial aggregation in a small fraction of *BRCA1/2* mutation-negative families. **(Mateus Pereira LH, Sigurdson AJ, Doody MM, Pineda MA, Alexander BH, Greene MH, Struewing JP. CHEK2:1100delC and female breast cancer in the United States. *Int J Cancer* 2004;112:541-543)**

Measuring Urinary Estrogens Simultaneously

A rapid, sensitive, and specific high-performance liquid chromatography-electrospray ionization-multistage mass spectrometry (MS) method for measuring endogenous ketolic estrogen metabolites in human urine has been developed. The method requires a single hydrolysis/extraction/derivatization step and only 2.5 mL of urine, yet it is able to simultaneously quantify estrone and its 2-methoxy and 2-, 4-, and 16-alpha-hydroxy derivatives, 16-ketoestradiol, and 2-hydroxyestrone-3-methyl ether metabolites. The combination of a simple hydrazone derivatization step with multistage MS greatly enhances the sensitivity and specificity of the analysis of endogenous estrogens in human urine. The method provides accurate and specific measurement of estrogen metabolites in biological matrices, thus facilitating future breast cancer research. **(Xu X, Keefer LK, Waterhouse DJ, Saavedra JE, Veenstra TD, Ziegler RG. Measuring seven endogenous ketolic estrogens simultaneously in human urine by high-performance liquid chromatography-mass spectrometry. *Anal Chem* 2004;76(19):5829-5836)**

CERVICAL CANCER

Impact of Adding HPV Types to Screening and Triage Tests

Use of human papillomavirus (HPV) testing in cervical cancer prevention is increasing rapidly. A DNA test for 13 HPV types that can cause cervical cancer is approved in the United States for coscreening with cytology of women 30 years old and older and for triage of women of all ages with equivocal cytology. However, most HPV infections are benign. Trade-offs between specificity and sensitivity for about 40 HPV types in predicting cervical intraepithelial neoplasia 3 and cancer were evaluated in two prospective studies: a population-based screening study that followed 6,196 women from Costa Rica, and a triage study that followed 3,363 women with equivocal cytology in four U.S. centers. For both screening and triage, testing for more than about ten types decreased specificity more than it increased sensitivity. The minimal increases in sensitivity and in negative predictive value achieved by adding HPV types to DNA tests must be weighed against the projected burden to women falsely labeled as being at high cervical cancer risk. **(Schiffman M, Khan MJ, Solomon D, Herrero R, Wacholder S, Hildesheim A, Rodriguez AC, Bratti MC, Wheeler CM, Burk RD, for the PEG Group and the ALTS Group. A study of the impact of adding HPV types to cervical cancer screening and triage tests. *J Natl Cancer Inst* 2005;97:147-150)**

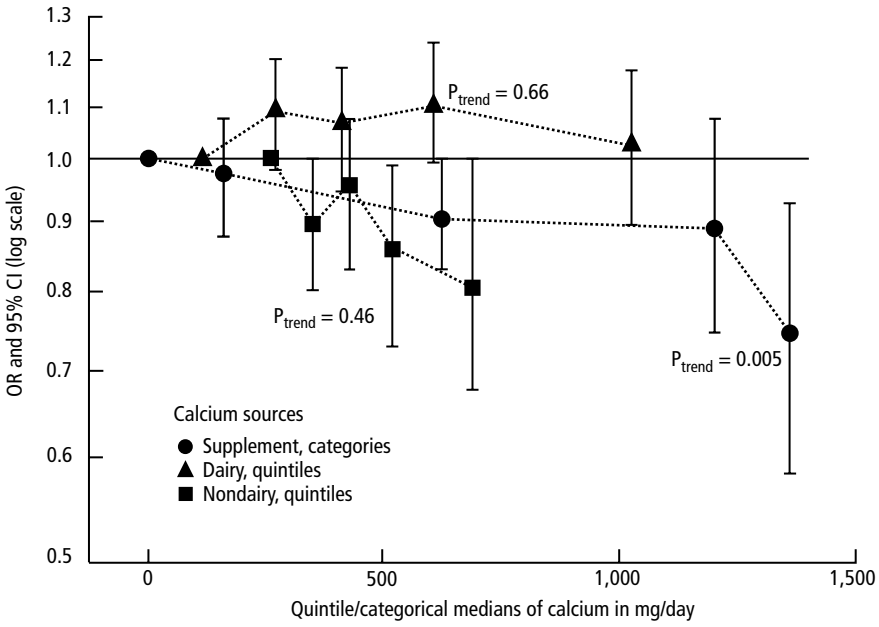


Figure 1: Association between dairy, nondairy, and supplemental calcium intake and distal colorectal adenoma. (Peters U, et al. 2004)

COLORECTAL TUMORS

Physical Activity and Risk of Colon Cancer

Colon cancer incidence has been low historically but has been rapidly increasing in Shanghai, China for reasons still unclear. In a population-based study of 931 incident colon cancer patients and 1,552 controls, risk was reduced among subjects with high commuting physical activity (OR = 0.5, CI = 0.3–0.9 for men; OR = 0.6, CI = 0.2–0.9 for women), particularly among those with high activity for at least 35 years (OR = 0.3, CI = 0.1–0.7 for men; OR = 0.31, CI = 0.1–0.7 for women). Commuting physical activity significantly modified the risk conferred by high body mass index (BMI), with the highest risk observed among those at the highest quintile of BMI and the lowest activity level (OR = 6.4, CI = 1.8–8.5 for men; OR = 7.4, CI = 2.8–10.0 for women). These results suggest that regular and frequent physical activity over a long period of time protects against colon cancer and significantly modifies

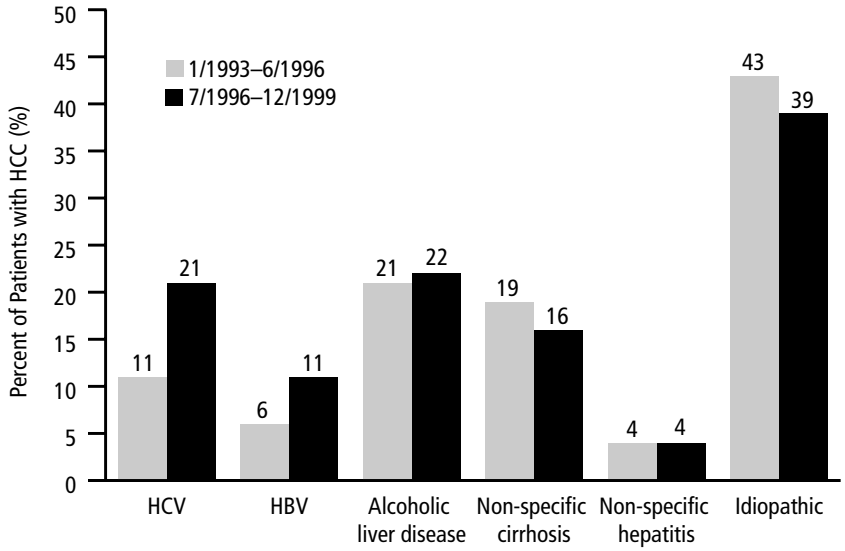


Figure 2: Changes in the proportion of HCV, HBV, alcohol-induced liver disease, non-specific cirrhosis, non-specific hepatitis, and idiopathic among 2,584 patients with HCC over two time periods. (Davila JA, et al. 2004)

the BMI-associated risk. **(Hou L, Ji BT, Blair A, Dai Q, Gao YT, Chow WH. Commuting physical activity and risk of colon cancer in Shanghai, China. *Am J Epidemiol* 2004;160:860-867)**

Colorectal Adenoma and Calcium

Calcium can reduce the risk of colorectal tumors by binding secondary bile and fatty acids, leading to antiproliferative effects in the bowel, or by acting directly on the colonic epithelium, affecting differentiation and apoptosis. Supplemental and dietary calcium intake was evaluated among 3,696 participants with histologically verified adenoma of the distal colon and 34,817 sigmoidoscopy-negative controls in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Adenoma risk was 12% lower for those in the highest quintile of total calcium intake (> 1,767 mg/d) than for participants in the lowest quintile (< 731 mg/d) (OR = 0.8; CI = 0.8–1.0; p for trend = 0.04). The inverse association between total calcium and colorectal adenoma was largely due to calcium supplement use, with a 27% lower risk for participants taking more than 1,200 mg/d than for nonusers of supplements (OR = 0.7; CI = 0.6–0.9; p for trend = 0.005). (Figure 1) **(Peters U, Chatterjee N, McGlynn KA, Schoen RE, Church TR, Bresalier RS, Gaudet MM, Flood A, Schatzkin A, Hayes RB. Calcium intake and colorectal adenoma in a US colorectal cancer early detection program. *Am J Clin Nutr* 2004;80:1358-1365)**

Calcium-Sensing Receptor Variants and Colorectal Adenoma

Evidence suggests that calcium prevents colorectal cancer, possibly mediated through the calcium-sensing receptor (CASR). A relation between CASR gene variants and risk for colorectal adenoma was assessed among individuals with advanced distal adenomas (n = 716) and controls with a negative sigmoidoscopy exam (n = 729), randomly selected from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Three nonsynonymous variants in the intracellular signaling region of CASR (A986S, R990G, Q1011E) were analyzed by TaqMan PCR. Compared with the most common diplotype (haplotype pair), the odds ratios for advanced adenoma were 0.8 (CI = 0.6–1.1), 0.79 (CI = 0.6–1.1), and 0.6 (CI = 0.4–0.9) for the other three common diplotypes (> 5% frequency). Although calcium intake was inversely associated with adenoma risk, CASR diplotypes did not modify this association. **(Peters U, Chatterjee N, Yeager M, Chanock SJ, Schoen RE, McGlynn KA, Church TR, Weissfeld JL, Schatzkin A, Hayes RB. Association of genetic variants in the calcium-sensing receptor with risk of colorectal adenoma. *Cancer Epidemiol Biomarkers Prev* 2004;13:2181-2186)**

HEPATOCELLULAR CARCINOMA

Hepatitis C Infection and Increasing Incidence of Liver Cancer

A significant increase in the incidence of hepatocellular carcinoma (HCC) has been reported in the United States, but underlying risk factors remain unclear. Using Surveillance, Epidemiology, and End Results program (SEER)-Medicare-linked data, a population-based study evaluated changes in risk factors over time (from January 1993 to June 1996 and July 1996 to December 1999). The age-adjusted incidence of HCC among persons 65 years of age and older significantly increased from 14.2 per 100,000 in 1993 to 18.1 per 100,000 in 1999. The proportion of hepatitis C virus (HCV)-related HCC increased from 11% in 1993–96 to 21% in 1996–99, and hepatitis B virus (HBV)-related HCC increased from 6% to 11% ($p < .0001$). In multivariate analyses, the risks for HCV-related HCC and HBV-related HCC increased by 126% and 67%, respectively. Idiopathic HCC decreased from 43% to 39%, which did not fully account for the increases observed for HCV and HBV. No significant changes over time were observed for alcohol-induced liver disease, non-specific cirrhosis, or non-specific hepatitis. (Figure 2) **(Davila JA, Morgan RO, Shaib Y, McGlynn KA, El Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: A population-based study. *Gastroenterology* 2004;127:1372-1380)**

LYMPHOMA

Simian Virus 40 and Non-Hodgkin Lymphoma

Simian virus 40 (SV40) accidentally contaminated U.S. poliovirus vaccines that were widely administered from

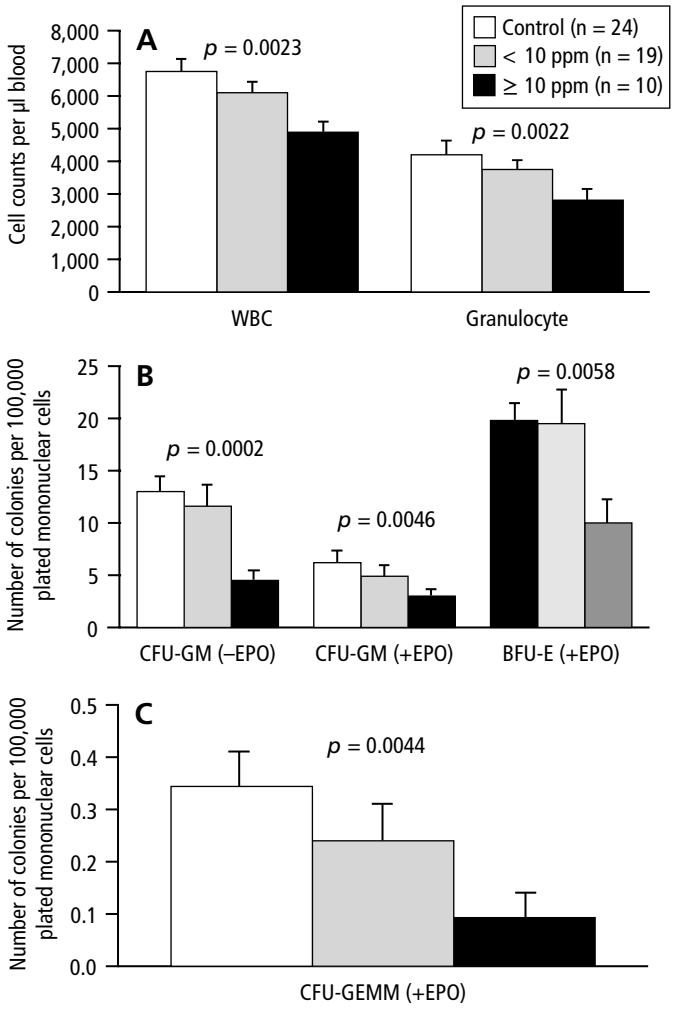


Figure 3: Effect of benzene exposure on (A) white blood cell (WBC) and granulocyte counts; (B) colonies from the colony-forming unit-granulocyte-macrophage (CFU-GM) and burst-forming unit-erythroid (BFU-E); and (C) colonies from the colony-forming unit-granulocyte, erythroid, macrophage, megakaryocyte (CFU-GEMM). There was a greater proportional decrease in colonies in workers exposed to Q10 ppm versus controls for CFU-GM, BFU-E, and CFU-GEMM compared to the decline in WBCs (P G 0.011, 0.048, and 0.0078, respectively) and for CFU-GM and -GEMM compared to the decline in granulocytes (P 0 0.026 and 0.0094, respectively). (Lan Q, et al. 2004)

l955 through 1962. Recent laboratory studies have reported detection of SV40 DNA in tumor tissues from 15%–43% of U.S. non-Hodgkin lymphoma (NHL) patients. Since epidemiologic data are lacking, we examined serum samples from 724 incident NHL case patients and 622 control subjects in a population-based U.S. case-control study. SV40 serostatus was analyzed by two independent laboratories (designated A and B) using similar virus-like particle (VLP) enzyme immunoassays. VLPs for the human polyomaviruses BK and JC were used in competitive inhibition experiments to assess the specificity of SV40 reactivity. SV40 antibody results from the two laboratories were correlated (R = 0.59; $p < 0.001$). Laboratories A and B detected SV40 seropositivity in 7.2% and 9.8% of NHL case patients, respectively, and in 10.5% and 9.6% of control subjects, respectively. SV40 seropositivity was neither associated with increased NHL risk overall, nor for any specific histology or site. In persons born before 1963, the presence of SV40-specific antibodies, although rare, could reflect exposure to SV40-contaminated vaccines. Nevertheless, NHL risk was unrelated to serologic evidence of SV40 exposure or infection. **(Engels EA, Viscidi RP, Galloway DA, Carter JJ, Cerhan JR, Davis S, Cozen W, Severson RK, De Sanjose S, Colt JS, Hartge P. Case-control study of simian virus 40 and non-Hodgkin lymphoma in the United States. *J Natl Cancer Inst* 2004;96:1368-1374)**

OCCUPATION

Hematotoxicity in Benzene-exposed Workers

Benzene is known to have toxic effects on the blood and bone marrow, but its impact at levels below the U.S. occupational standard of 1 part per million (ppm) remains uncertain. In a study of 250 workers exposed to benzene, white blood cell and platelet counts were significantly lower than in 140 controls, even for exposure below 1 ppm in air. Progenitor cell colony formation significantly declined with increasing benzene exposure and was more sensitive to the effects of benzene than was the number of mature blood cells. Two genetic variants in key metabolizing enzymes, myeloperoxidase and NAD(P)H:quinone oxidoreductase, influenced susceptibility to benzene hematotoxicity. (Figure 3) **(Lan Q, Zhang L, Li G, Vermeulen R, Weinberg RS, Dosemeci M, Rappaport SM, Shen M, Alter BP, Wu Y, Kopp W, Waidyanatha S, Rabkin C, Guo W, Chanock S, Hayes RB, Linet M, Kim S, Yin S, Rothman N, Smith MT. Hematotoxicity in workers exposed to low levels of benzene. *Science* 2004;306:1774-1776)**

Pesticides and Cancer Risk

Four reports were published evaluating associations between pesticides and cancer risk in the Agricultural Health Study, a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina. Chlorpyrifos-exposed applicators did not have a higher risk of all cancers combined than unexposed applicators, but the incidence of lung cancer was significantly associated with both lifetime exposure-days and intensity-weighted exposure-days. The herbicide glyphosate was not associated

with increased risk of cancer overall, but there was a suggestive association with multiple myeloma that should be studied as more cases occur in the AHS. Atrazine, the most heavily applied pesticide used on crops in the United States, also showed no association with overall cancer incidence or with specific forms of cancer. The fourth study evaluated the relation between 50 pesticides and lung cancer incidence. Lung cancer was less common among the cohort than expected (standardized incidence ratio = 0.44, CI = 0.39-0.49), due in large part to a low cigarette smoking prevalence. However, two widely used herbicides (metolachlor and pendimethalin) and two widely used insecticides (chlorpyrifos and diazinon) were related to an excess of lung cancer, which could not be explained by known lung cancer risk factors. **(Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, Dosemeci M, Alavanja MC. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *J Natl Cancer Inst* 2004;96:1781-1789. Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MC. Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. *J Natl Cancer Inst* 2004;96:1375-1382. De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 2005;113:49-54. Alavanja MC, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, Barker J, Hoppin JA, Sandler DP, Coble J, Thomas K, Blair A. Pesticides and lung cancer risk in the Agricultural Health Study Cohort. *Am J Epidemiol* 2004;160:876-885.)**

STOMACH AND ESOPHAGEAL CANCER

Interleukin-8 and IL8RB Variants and Risks of Gastric and Esophageal Cancers

Chronic inflammation may contribute to the very high risk of gastric cardia adenocarcinoma (GCC) and esophageal squamous cell carcinoma (ESCC) in Linxian, China. Interleukin-8 (IL8), a potent chemoattractant, has three well-characterized single nucleotide polymorphisms (SNP), one of which (–251) alters transcriptional activity. Four SNPs in the two IL8 receptors, IL8RA and IL8RB, have been associated with inflammation. In a case-cohort study using specimens from the Nutrition Intervention Trials in Linxian, we evaluated the association between these SNPs and incident GCC (n = 90) and ESCC (n = 131). The homozygous variants of IL8 –251 and +396 were associated with twofold increased relative risks for GCC, but variation within IL8 was not associated with ESCC. Variation in IL8 may alter the IL8 expression pattern or interact with environmental factors to increase the risk for inflammatory processes leading to GCC. **(Savage SA, Abnet CC, Mark SD, Qiao YL, Dong ZW, Dawsey SM, Taylor PR, Chanock SJ. Variants of the IL8 and IL8RB genes and risk for gastric cardia adenocarcinoma and esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2004;13:2251-2257)**

Histological Precursors of Esophageal Squamous Cell Carcinoma

Esophageal squamous cell carcinoma (ESCC) has a very poor prognosis, which is largely due to late diagnosis. To identify clinically relevant histological precursors of ESCC that could be targets for early detection and treatment, a cohort of 682 patients from Linxian, China were endoscoped and biopsied at baseline and followed for 13.5 years. A total of 114 (16.7%) patients developed ESCC during the follow-up period. Squamous dysplasia and carcinoma *in situ* were the only histological lesions associated with a significantly increased risk of developing ESCC within 13.5 years after endoscopy. There was no evidence that esophagitis predisposes to this tumor, but increasing grades of dysplasia were strongly associated with increasing risk, indicating that histological grading is clinically meaningful. The follow-up experience of severe dysplasia and carcinoma *in situ* was equivalent, suggesting that this distinction is not clinically relevant. **(Wang GQ, Abnet CC, Shen Q, Lewin KJ, Sun XD, Roth MJ, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Histological precursors of esophageal squamous cell carcinoma: Results from a 13-year prospective follow-up study in a high-risk population. *Gut* 2005;54:187-192)**

BEVERLEY CRANSTON EARNS SPECIAL APPRECIATION AWARD

Beverley Cranston of the University of the West Indies, Jamaica, received a DCEG special recognition award for her 21 years of service as a project manager for the Viral Epidemiology Branch (VEB) research program on human T-cell lymphotropic virus type I (HTLV-I). Endemic in the Caribbean, southern Japan, parts of Africa, the Middle East, and South America, HTLV-I is causally associated with adult T-cell leukemia/lymphoma and a neurologic disease called HTLV-I–associated myelopathy/tropical spastic paraparesis. On behalf of DCEG, **Michie Hisada, M.D., M.P.H., Sc.D.,** a tenure-track investigator in VEB, presented the award to Ms. Cranston during the program site visit in October 2004.

Michie Hisada (left front) presents award to Beverley Cranston (right front).

DCEG PEOPLE IN THE NEWS

Blanche Alter, M.D., M.P.H., Clinical Genetics Branch (CGB), presented invited talks on medical and genetic issues and cancer risk in inherited bone marrow failure syndromes at the Annual Education Conference, National Society of Genetic Counselors in Washington, DC, the NIDCD Clinical Seminar Series, Bethesda, Maryland, the German Fanconi Anemia Family Meeting in Kronach, Germany, the Charite Campus Virchow-Klinikum in Berlin, and the Pediatric Tumor Board Lecture, Loma Linda University Children's Hospital in California.

Aaron Blair, Ph.D., Occupational and Environmental Epidemiology Branch (OEEB), gave an invited talk on "The Agricultural Health Study" at the 14th Annual Meeting of the Pennsylvania Association of Sustainable Agriculture held in State College in February. Dr. Blair also attended, as a board member, a National Toxicology Science Advisory Board meeting in Research Triangle Park, North Carolina in October.


Matthew Bonner

Matthew Bonner, Ph.D. (OEEB), has been appointed as a DCEG representative to the NIH Fellows Committee. He joins **Beth Brown, Ph.D.,** of the Viral Epidemiology Branch (VEB).

Louise Brinton, Ph.D., Hormonal and Reproductive Epidemiology Branch (HREB), gave a talk on "Infertility treatment and breast cancer risk" at the 60th Annual Meeting of the American Society of Reproductive Medicine in Philadelphia in October.

Beth Brown, Ph.D. (VEB), gave a presentation titled "Common variations in immune-mediated genes and risk of B-cell and Hodgkin lymphomas, Epilymph-Barcelona" at the Epilymph Meeting in Lyon, France in November. Dr. Brown also gave an invited presentation on "Human herpesvirus-8 and classic Kaposi sarcoma: Phenotypic and genotypic markers of immunity" at the Rollins School of Public Health, Emory University, Atlanta in December.

Capt. Linda Morris Brown, Dr.P.H., Biostatistics Branch (BB), gave an invited talk on "The role of race/ethnicity in the epidemiology of esophageal cancer" at the NIH Academy, Bethesda, Maryland in December.

Eric Engels, M.D., M.P.H. (VEB), gave a lecture on "Leadership and service for the public's health" to the Jefferson Scholars at the University of Virginia, Charlottesville in August. Dr. Engels later gave an invited talk on "Simian virus 40 and non-Hodgkin lymphoma: Weighing the evidence" at the Harvard School of Public Health in October. In addition, he was invited to talk on "Epidemiology of cancer in persons with HIV/AIDS: A look to the future" at the Planning Meeting for Emerging and Re-emerging Malignancies in HIV/AIDS at NCI and the National Institute of Allergy and Infectious Diseases in Rockville, Maryland

Margaret Wright

SCHOLAR-IN-TRAINING AWARD FOR WRIGHT

Margaret Wright, Ph.D., Nutritional Epidemiology Branch (NEB), won an AACR-AFLAC Scholar-in-Training Award from the American Association for Cancer Research (AACR) at the third annual Frontiers in Cancer Prevention Research Conference in Seattle in October.

in October. Dr. Engels also gave a talk on "Polyomaviruses and childhood cancer: Plenty of smoke, but is there fire?" at the Pediatric Oncology Branch, Center for Cancer Research, NCI in Bethesda, Maryland in November.

Ethel Gilbert, Ph.D., Radiation Epidemiology Branch (REB), gave a talk on "Contributions of new epidemiology studies to radiation risk assessment" in honor of Dr. Gilbert Beebe, who was a scientist in DCEG for more than 30 years. The Third Annual Gilbert W. Beebe Symposium, held in Washington, DC in December, focused on recent developments in radiation risk assessment.

Mark Greene, M.D. (CGB), recently spoke on risk-reducing strategies for hereditary ovarian cancer at: Harrington Cancer Center in Amarillo, Texas; the Ovarian Cancer National Alliance Annual Advocacy Conference in Washington, DC; Holy Cross Hospital in Silver Spring, Maryland; and the Scottsdale HealthCare Symposium on Cancer Genetics in Arizona. He also spoke on familial breast and ovarian cancer and melanoma at Yale University, the Virginia Piper Cancer Center in Scottsdale, Arizona, and North Arundel Hospital, Glen Burnie, Maryland. In addition, Dr. Greene, **Joan Kramer, M.D.** (CGB), and **Mary Lou McMaster, M.D.,** Genetic Epidemiology Branch (GEB), recently gave talks to the Third Investigators' Meeting of the International Testicular Cancer Linkage Consortium, held in November at the United Kingdom Institute for Cancer Research in London. They focused on the CGB-led Familial Testicular Cancer Projects.

Patricia Hartge, Sc.D., Epidemiology and Biostatistics Program (EBP), gave two lectures on cancer epidemiology at George Washington University's School of Public Health and Health Services in Washington, DC in November and December.

Michael Hauptmann, Ph.D. (BB), gave a two-day course in genetic epidemiology for the postgraduate public health training program at the University of Munich, Germany in November.


Michael Hauptmann

Robert N. Hoover, M.D., Sc.D. (EBP), and Dr. Edward Trapido from NCI's Division of Cancer Control and Population Sciences gave an invited briefing on "Advances in molecular science and technology" to NCI's National Cancer Advisory Board in Bethesda, Maryland in November.


Mark Greene, Blanche Alter, Sadie Hutson, and Jennifer Loud of the Clinical Genetics Branch.

Sadie Hutson, Ph.D., R.N., C.R.N.P. (CGB), received her Ph.D. in Nursing from the University of Pennsylvania in May 2004. Her DCEG thesis advisors were **Blanche Alter, M.D., M.P.H.,** and **Mark Greene, M.D.** She is continuing to work as a postdoctoral fellow in the CGB. She gave a talk on the topic of her thesis, "Containment and invisibility: The experiences of siblings of patients with Fanconi's anemia," to the 16th Annual Fanconi Anemia Scientific Symposium in Cambridge, Maine in October. Dr. Hutson and **Jennifer Loud, M.S.N., C.R.N.P.,** also guest edited a special issue on cancer genetics in *Seminars in Oncology Nursing* in August.


Ruth Kleinerman

Ruth Kleinerman, M.P.H. (REB), gave a talk on "Assessment of radiation exposure using biological dosimetry" at the 13th Annual Ionizing Radiation Measurement and Standards Council Meeting in Gaithersburg, Maryland in October. Ms. Kleinerman also spoke on "Genetic susceptibility to second cancers in a cohort of retinoblastoma patients" at the Cancer Survivorship Workshop in Rockville, Maryland in November.

HPV DNA SCREENING STUDY IN MISSISSIPPI DELTA


Philip Castle and Denise Whitby

Philip Castle, Ph.D. (HREB), and colleagues are developing human papillomavirus (HPV) screening strategies for underserved women in the Mississippi Delta region in collaboration with the NCI Center for Reducing Cancer Health Disparities (CRCHD) and the University of Alabama. The team, in collaboration with **Denise Whitby, Ph.D.,** Viral Epidemiology Section (VES), and other NCI-Frederick VES members, will develop a core HPV DNA testing facility. Dr. Castle also recently joined the editorial advisory board of the *Journal of Infectious Diseases.*

Qing Lan, M.D., Ph.D. (OEEB), gave a lecture titled "Hematotoxicity in workers exposed to low levels of benzene" at George Washington University in Washington, DC in December.


Maria Teresa Landi

Maria Teresa Landi, M.D., Ph.D. (GEB), gave the keynote address on "Genetic epidemiology of cutaneous melanoma" at the XLII Italian National Congress of Dermatology in Rimini, Italy in October. Dr. Landi also gave talks on "Epidemiologic studies of the genetic and environmental factors associated with malignant melanoma" at the Symposium on Cancer Biology at the University of Colorado at Boulder in November and the Colorado Cancer Center Symposium Series at the University of Colorado Cancer Center in Denver in November.

Michael Leitzmann, M.D., Dr.P.H. (NEB), gave a talk on "Diet and prostate cancer" at Boston University in December. That month, he also spoke about "Energy balance and cancer" at George Washington University, Washington, DC.

Martha S. Linet, M.D., M.P.H. (REB), gave a Grand Rounds presentation on "Cancer in children: Characteristics and causes" to the American Academy of Pediatrics National Conference & Exhibition in San Francisco in October. Dr. Linet also gave a presentation on "Hematologic malignancies: Patterns, risk factors, and future directions" at the University of Illinois Cancer Center, Chicago in December.


Mary Lou McMaster

Mary Lou McMaster, M.D. (GEB), was recently invited to chair the "Predisposition to Waldenström's macroglobulinemia" session at the Third International Workshop on Waldenström's Macroglobulinemia in Paris, where she also spoke on "Long-term follow-up of familial Waldenström's macroglobulinemia."

Jay Nuckols, Ph.D. (OEEB), gave an invited seminar on "Exposure assessment for environmental epidemiology: Integrating earth and health sciences" to the University of Colorado Health Sciences Center's School of Medicine in Denver in January. Dr. Nuckols also gave an invited talk on "Use of GIS in exposure assessment for environmental epidemiology" at the Bay Area Automated Mapping Association meeting in San Francisco in January.


June Peters

June Peters, M.S. (CGB), gave three talks at professional meetings in October. Two were at the National Society of Genetic Counselors Annual Education Conference in Washington, DC on "Genetic counseling, psychosocial assessment, and empathy" and on "Increased cancer risk in FA, DC, and XP." The third was on "Research opportunities in hereditary cancers" at the annual meeting of the International Society of Nurses in Genetics, Toronto.


Ruth Pfeiffer

Ruth Pfeiffer, Ph.D. (BB), gave a talk titled "Mixed effects models for specially ascertained samples: Statistical issues and examples in epidemiologic studies" at the Statistics Seminar at

CANCER PREVENTION CONFERENCE

DCEG staff members participated in the third international Frontiers in Cancer Prevention Research conference, held by the American Association for Cancer Research (AACR), in Seattle in October. Some of the DCEG presenters and speakers were **Kenneth Adams, Ph.D.** (NEB), **Wen-Yi Huang, Ph.D.** (OEEB), **Marc Gunter, Ph.D.** (NEB), **Daehee Kang, M.D., Ph.D.** (OEEB), **Tanuja Rastogi, Sc.D.** (NEB), and **Margaret Wright, Ph.D.** (NEB).

DCEG staff at the AACR conference: (front) Marc Gunter and Kenneth Adams; (back) Wen-Yi Huang, Daehee Kang, Margaret Wright, and Tanuja Rastogi.

Yale University in September. Dr. Pfeiffer also spoke on "Criteria for evaluating models of absolute risk" at a Statistical Methods in Epidemiology Seminar at Harvard University in January.


Tanuja Rastogi

Tanuja Rastogi, Sc.D. (NEB), gave a talk on "Asian Indians and chronic diseases: Role of lifestyle and diet" to the National University of Singapore Department of Community, Occupational, and Family Medicine in September.

OEEB's **Nathaniel Rothman, M.D., M.P.H., M.H.S., Qing Lan, M.D., Ph.D.,** and **Richard Hayes, D.D.S., Ph.D.,** were invited speakers at the meeting "Recent Advances in Benzene Toxicity" held in Munich, Germany in October. Dr. Hayes was a member of the organizing committee and spoke on "Benzene and cancer in China"; Dr. Rothman chaired a session on epidemiologic studies and spoke on "Use of intermediate endpoints to study the health effects of benzene"; and Dr. Lan spoke on "Benzene exposure and hematotoxicity."

Arthur Schatzkin, M.D., Dr.P.H. (NEB), spoke on "Diet and cancer: A role for molecular epidemiology?" to the United Kingdom Molecular Epidemiology Group meeting in Cumbria, England in September.

Mark Sherman, M.D. (HREB), spoke on "Clinical applications of HPV testing: Today and tomorrow" at the New England Society of Pathologists September meeting in Boston and for the Pathology Grand Rounds at the University of Vermont in Burlington in October. While in Boston, Dr. Sherman also gave a visiting professor talk on "The pathologist as etiologist: Bridging the chasm between population and laboratory science" at the Beth Israel Deaconess Medical Center. In addition, Dr. Sherman has accepted an appointment to serve on the editorial board of *Gynecologic Oncology*.


Rashmi Sinha

Rashmi Sinha, Ph.D. (NEB), spoke on "Diet and cancer" to the Roche Research Chapter of Sigma Xi, the Scientific Research Society, in Nutley, New Jersey in October.

Lois B. Travis, M.D., Sc.D. (REB), presented lectures on second cancer primaries at the Sixth International Symposium on Hodgkin Lymphoma in Cologne, Germany in September and at Georgetown University's Lombardi Comprehensive Cancer Center, Washington, DC in December.


Sophia Wang

Sophia Wang, Ph.D. (HREB), was an invited speaker and discussant on "Genetic markers of cervical cancer risk" for the Early Detection Research Network meeting in New York City in September.


Mary Ward

Mary Ward, Ph.D. (OEEB), gave an invited talk, "Agricultural chemicals and cancer: Evidence from occupational and environmental epidemiology studies," at the Cancer Biology Symposium at the University of Colorado at Boulder in November.


DCEG's Jim Vaught and Marianne Henderson with Robert Hanner.

SPECIMEN MANAGEMENT CONFERENCE

Jim Vaught, Ph.D., Office of the Director (OD), presented an invited lecture on "Specimen management for high throughput genotyping" at the International Society of Biological and Environmental Repositories (ISBER) meeting in Perugia, Italy in October. **Marianne K. Henderson, M.S.,** Office of Division Operations and Analysis (ODOA), also gave an invited lecture, "Challenges of scientific data management for large epidemiology studies," at the meeting. Dr. Vaught and Ms. Henderson are pictured here with Dr. Robert Hanner, past president of ISBER, in front of Perugia's main fountain, which dates from 1278.

COMINGS . . . GOINGS

After more than four years serving as a Visiting Fellow in the Occupational and Environmental Epidemiology Branch (OEEB), **Juan Alguacil, M.D., Ph.D.,** has accepted a position on the faculty of the University of Huelva in Spain. He will be leading the research unit on environmental and occupational epidemiology and teaching epidemiology, preventive medicine, and occupational and environmental health at the medical school. During his stay with the OEEB, Dr. Alguacil made important contributions to the DCEG program, particularly in the areas of pancreatic cancer and bladder cancer epidemiology.

Berit Bakke, Ph.D., a postdoctoral fellow, arrived at the OEEB in October. Dr. Bakke is an industrial hygienist from the National Institute of Occupational Health in Oslo. She recently completed her doctoral dissertation on adverse respiratory effects among construction workers due to exposures generated by tunneling operations. She will be at DCEG for two years. Dr. Bakke will be working on several occupational exposure assessment projects, including case-control and methodologic studies, with **Roel Vermeulen, Ph.D., Joseph Coble, Sc.D.,** and **Patricia Stewart, Ph.D.**


Berit Bakke


Parveen Bhatti

Parveen Bhatti, M.S., has joined the Radiation Epidemiology Branch (REB) as a predoctoral fellow. Mr. Bhatti graduated with a Master of Science degree in 2000 from the University of British Columbia in Vancouver with a major in occupational and environmental hygiene. While at REB, Mr. Bhatti plans to gain experience in molecular epidemiology in a search for underlying genetic susceptibility to the carcinogenic effects of ionizing radiation. He is currently completing his doctoral thesis at the University of Washington, Seattle, on DNA double strand-break repair polymorphisms and breast cancer risk.


Elizabeth Bluhm

Elizabeth Bluhm, M.D., M.P.H., has joined the REB as a Division of Cancer Prevention (DCP) cancer prevention fellow. Dr. Bluhm received an M.D. from the Mount Sinai School of Medicine, New York City, in 2000. She earned an M.P.H. from the University of North Carolina at Chapel Hill, concentrating in epidemiology.

Anil Chaturvedi, Ph.D., has joined the Viral Epidemiology Branch (VEB) as a visiting fellow. In 2004, Dr. Chaturvedi received a Ph.D. in epidemiology from Tulane University School of Public Health and Tropical Medicine in New Orleans. His doctoral dissertation was entitled "Prevalence and impact of multiple infections in HIV+ and HIV– women." Dr. Chaturvedi will work on a number of VEB studies, with a primary focus on immunologic parameters and genetic polymorphisms related to certain infections and their associated malignancies.

Deirdre Hill, Ph.D., who has been a postdoctoral fellow in the REB since 2000, has accepted a position at the University of New Mexico, Albuquerque. During her fellowship at DCEG, Dr. Hill made significant contributions in radiation research. She worked on the risk of glioma, meningioma, and acoustic neuroma associated with diagnostic and therapeutic radiation.

Aimee Kreimer, Ph.D., a DCP cancer prevention fellow, has joined the Hormonal and Reproductive Epidemiology Branch (HREB) and is being mentored by **Diane Solomon, M.D.,** and **Philip Castle, Ph.D.** Dr. Kreimer has an M.S. in health evaluation sciences from the University of Virginia in Charlottesville and a Ph.D. in epidemiology from Johns


Paul Levine (fourth from right) and Roxana Moslehi (third from right) in their GWU classroom.

DCEG SCIENTISTS TEACH AT GWU

Paul Levine, M.D., formerly of VEB and now at George Washington University (GWU), and **Roxana Moslehi, Ph.D.,** Biostatistics Branch (BB), organized and taught a course titled "Current Controversies in Cancer Epidemiology" at GWU's Department of Public Health and Biostatistics from September to December. Invited speakers included **Arthur Schatzkin, M.D., Dr.P.H.,** Nutritional Epidemiology Branch (NEB), **Neil Caporaso, M.D.,** Genetic Epidemiology Branch (GEB), **Michael Leitzmann, M.D., Dr.P.H.** (NEB), **Eric Engels, M.D., M.P.H.** (VEB), and **Ruth Pfeiffer, Ph.D.** (BB).

Hopkins University. She spent last year at the International Agency for Research on Cancer, studying oral HPV and related neoplasias. Dr. Kreimer has continued these studies and is working on HREB cervical cancer projects.

Wonjin Lee, M.D., a visiting fellow in OEEB, has taken an Associate Professor position at the Department of Preventive Medicine, College of Medicine, Korea University, Seoul. Dr. Lee joined the OEEB in 2001. He worked with several DCEG investigators on studies of stomach and esophageal cancer, lymphoma, multiple myeloma, and lung cancer, as well as exposure to occupational and environmental agents, particularly pesticides. In the Agricultural Health Study, he evaluated the incidence of cancer among pesticide applicators exposed to alachlor and chlorpyrifos.


Jolanta Lissowska

Jolanta Lissowska, Ph.D., has joined HREB for one year as a Guest Scientist under sponsorship by the NCI Office of International Affairs. Dr. Lissowska is a senior epidemiologist at the Cancer Center and Institute of Oncology in Warsaw, Poland. She has been collaborating with DCEG investigators and serving as Principal Investigator on a recently completed multidisciplinary study of breast, ovarian, and endometrial cancers in Poland. During her stay at NCI, she will work with **Montserrat Garcia-Closas, M.D., Dr.P.H., Louise Brinton, Ph.D., Mark Sherman, M.D.,** and others on analyses of data from the study.


Panagiota Mitrou

Panagiota Mitrou, Ph.D., has joined the NEB as a postdoctoral fellow. Dr. Mitrou received her Ph.D. from the University of Cambridge in molecular epidemiology. In addition, Dr. Mitrou holds a bachelor's degree in biochemistry and a master's degree in genetics from the University of Sussex, Brighton, United Kingdom. She conducted doctoral research under the supervision of Dr. Sheila Bingham at the Dunn Human Nutrition Laboratory, Cambridge, where she investigated polymorphisms in xenobiotic and folate metabolism genes in relation to colorectal adenoma and cancer risk. She will be working on genetic variation in nutrient metabolism and its impact on cancer risk within the framework of large, epidemiological studies.

Diane Solomon, M.D., of the NCI Division of Cancer Prevention (DCP), recently joined HREB as an Adjunct Investigator. Dr. Solomon has collaborated extensively with **Mark Schiffman, M.D., M.P.H., Mark Sherman, M.D.,** and other HREB staff members on cervical cancer studies. Dr. Solomon is the former Chief of the Cytopathology Section in the NCI Laboratory of Pathology. She transferred to DCP to conduct the ASCUS/LSIL Triage Study, a large randomized trial that established the value of human papillomavirus (HPV) testing to triage equivocal cervical cytology. Dr. Solomon chaired a recent conference that revised the categorization of cervical cytology and an American Cancer Society consensus conference on screening guidelines.


Kay Wanke

Kay Wanke, Ph.D., a cancer prevention fellow, has joined the GEB. Dr. Wanke received her Ph.D. in clinical psychology from Southern Illinois University at Carbondale and an M.P.H. from the Harvard School of Public Health. She is currently leading an analysis of genetic determinants of smoking cessation in heavy smoking men in the Alpha-Tocopheral Beta-Carotene Lung Cancer Prevention Trial. She is also examining the contribution of genetic factors to patterns of behavior in the Polyp Prevention Trial and the relationship of co-morbid psychological conditions to the stages of smoking in NHANES III. Dr. Wanke's major interest is in the smoking phenotype.

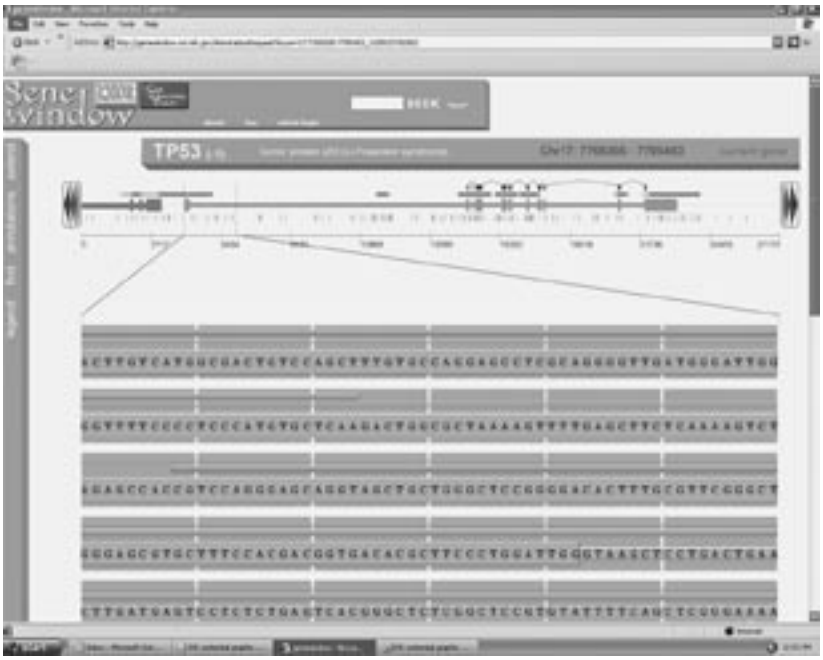
BRUGGE WINS FRANKLIN AWARD

Dr. Joan S. Brugge, Professor of Cell Biology at Harvard Medical School, received the 4th Annual NCI Rosalind E. Franklin Award for Women in Cancer Research and gave an invited lecture on "Probing mechanisms of breast epithelial oncogenesis in a 3D culture model" at the 2005 NCI Principal Investigator Retreat.


Joan Brugge receives the Rosalind E. Franklin Award from NCI Women Scientist Advisors Elise Kohn, Deborah Morrison, Lynn Goldin, Debra Silverman, and Michele Forman.

CORE GENOTYPING FACILITY LAUNCHES GENEWINDOW TOOL

Genetic sequencing technology has come a long way, but unfortunately the computer applications that manage the mounting volumes of data generated have lagged far behind. The current applications are error-prone, because they depend on manual data entry, and their limited visualization capabilities make it difficult for researchers to clearly see what they are looking at. To solve this problem, a team led by **Meredith Yeager, Ph.D.,** at NCI's Core Genotyping Facility (CGF) developed the Genewindow tool for their laboratory. An article announcing Genewindow's public availability appeared in the February issue of *Nature Genetics* (2005;37:109-110).



TP53 (Li-Fraumeni syndrome) gene

Data that used to take CGF staff days to sift through, enter, and analyze now are handled by an automated system that can feed sequences directly into the CGF databases while also linking to other public databases.

CGF staff performs genotyping and DNA sequencing for DCEG and other research groups at NCI, especially the Center for Cancer Research. Over the past year, the CGF has delivered more than four million genotypes to researchers doing genetic analyses. Data that used to take CGF staff days to sift through, enter, and analyze now are handled by an automated system that can feed sequences directly into the CGF databases while also linking to other public databases, such as that of the National Center for Biotechnology Information at the National Library of Medicine. Dr. Yeager explains, "We developed this tool in response to problems we were having in databasing and annotating hundreds of genes used in DCEG-based candidate gene studies. We then realized that Genewindow is useful to outside researchers as well." Researchers from a variety of institutions, such as universities, cancer centers, biotechnology companies, and other institutes and agencies, have visited the Genewindow site (http://genewindow.nci.nih.gov) to explore it as a reference tool.

Genewindow's strength comes not only from its automation and ability to cut workload, but also in its visualization capabilities. It clearly delineates each gene along with its associated data so that a scientist can easily tell which parts of the gene code for a protein, what variations have been found, and how these variations affect protein structure.

Bernice Packer, M.S., manager of bioinformatics at the CGF, compares Genewindow to a land map. Just as a map might display the cities in each country, Genewindow displays publicly known genetic polymorphisms as marked regions along the human genome. Like a cartographer who might add pushpins to a land map when new cities are established, CGF staff adds their own annotations in Genewindow when they find new polymorphisms. Genewindow also contains a legend, complete with diagrams and explanations.

The CGF bioinformatics team has designed the tool to be as intuitive, user-friendly, and helpful as possible. They are constantly adding new features to Genewindow's repertoire. In the works are the incorporation of haplotypes and haplotype tag single nucleotide polymorphisms (htSNPs) and the option to filter information from selected databases. The developers also plan to release the source code so that other laboratories can not only use Genewindow as a reference, but incorporate it into their own operations for data analysis. ■

—Cari Kornblit