National Cancer Institute

DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS

Linkage

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IN THIS ISSUE:

Training the Next Generation

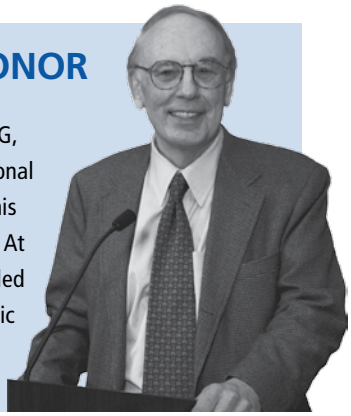
DCEG has a long-standing history of providing high-quality training to the next generation of cancer epidemiologists. More than ever, epidemiologists must be well poised to utilize the emerging molecular technologies and powerful new analytical tools that will maximize the scientific opportunities now available in interdisciplinary, population-based cancer research. Capitalizing on the expertise of DCEG and other NIH investigators and local colleagues from academia, recent innovative training activities within the Division have been embraced not only by tenure-track investigators and postdoctoral fellows, but also by staff at all levels.

The DCEG Molecular Epidemiology Course is a 12-week, 50-hour course, offered biennially from January to April. Begun in 2000 by DCEG's Office of Education (OE), the course was developed to train new researchers, including tenure-track investigators, staff scientists, and fellows, about the principles of design, implementation, management, and analysis of molecular epidemiologic studies. This year, 31 DCEG staff members participated in the third offering of the course, led by organizers **Nathaniel Rothman, M.D., M.H.S., M.P.H.,** Occupational and Environmental Epidemiology Branch (OEEB), **Jim Vaught, Ph.D.,** Office of the Director (OD), **Demetrius Albanes, M.D.,** Nutritional Epidemiology Branch (NEB) and Chief of OE, and **Kristin Kiser, M.H.A.** (OE). Additional assistance was provided by **Erin Toops** (OE) and **Elyse Wiszneauckas**, Office of Division Operations and Analysis (ODOA).

Comprehensive in design, the course is a key element of the Division's education program in molecular epidemiology and serves as a model for other training activities. The curriculum begins with a review of the various molecular studies currently underway in DCEG, and over the course of several weeks, participants learn about designs, methods, and analytic approaches in detail, including the validation

DIRECTOR AWARDED MEDAL OF HONOR

On May 17, **Joseph F. Fraumeni, Jr., M.D.,** Director of DCEG, was presented with the Medal of Honor from the International Agency for Research on Cancer in Lyon, France, in recognition of his outstanding accomplishments in the field of cancer epidemiology. At the same time, he delivered the annual Richard Doll Lecture, entitled "Genes and the environment in cancer causation: An epidemiologic perspective."



Joseph Fraumeni

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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DCEG *Linkage*

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and use of biomarkers (including tumor biomarkers), microarrays, proteomics, genotyping, pharmacogenetics, and strategies for identifying susceptibility genes in large-scale population studies. Participants also learn about the special considerations that must be made in the acquisition and processing of biological specimens and use of specimen data. Participants attend in-class sessions as well as lectures and tours at nearby NCI laboratories. At the completion of the course, participants are asked to integrate methodologic and analytic concepts into viable research biospecimen-based proposals suitable for review and funding. This year, four proposals received the Molecular Epidemiology Course Award, a competitive funding mechanism that was initiated for the purpose of supporting exceptional proposals generated from this course.

An important feature of the course has been the continued investment of several DCEG scientists as faculty members, including: **Neil Caporaso, M.D.,** Genetic Epidemiology Branch; **Montserrat Garcia-Closas, M.D., Dr.P.H., Mark Schiffman, M.D., M.P.H., Mark Sherman, M.D.,** and **Sophia Wang, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB); **Richard Hayes, D.D.S., Ph.D.** (OEEB); **Arthur Schatzkin, M.D., Dr.P.H.** (Chief of NEB); and **Sholom Wacholder, Ph.D.,** Biostatistics Branch (BB).

New to the faculty this year were DCEG's **Allan Hildesheim, Ph.D.** (HREB), **Qing Lan, M.D., Ph.D., M.P.H.** (OEEB), **Sanford Dawsey, M.D.** (NEB), and **Mark Roth, M.D.** (NEB). Guest lecturers included Dr. Timothy Veenstra, Director of the Laboratory of Proteomics and Analytical Technologies and the NCI-Frederick Biomedical Proteomics Program, Dr. Richard Paules, Director of the National Institute of Environmental Health Sciences Microarray Group, Dr. Mark Cosentino and Dr. Kathleen Groover from the Wedgewood Biorepository/SAIC, and Dr. Attila Lörincz from the Digene Corporation.

Also new this year was the advance online availability of course materials, facilitated by **Chitra Mohla, M.S.** (ODOA), which participants felt was particularly helpful in preparing for the sessions and their successful completion of the course.

The course sparked enthusiasm and lively discussion among participants, who ranged from newly appointed fellows to senior investigators and Branch Chiefs.

The popularity of the Molecular Epidemiology Course and the increasing generation of genotyping data in DCEG studies prompted a new course offering this year. NCI and SAIC staff at the Core Genotyping Facility (CGF) held a two-day Course in Genetic Analysis in January at the Natcher Building on the NIH campus. The course provided more than 100 attendees from DCEG and the Center for Cancer Research (CCR) intensive instruction on the basic tenets of human population genetics and germline variation, as well as sophisticated methodologies of SNP selection, haplotype construction, and data analysis. "We placed special emphasis on the state-of-the-art tools, techniques, and services developed by CGF for conducting genomic research and analyzing CGF data," stated **Meredith Yeager, Ph.D.,** Scientific Director of the CGF, who co-organized the event with CGF Director **Stephen Chanock, M.D.** "It is important that investigators are aware of these resources so they can incorporate

relevant, high-quality strategies into their studies."

The course sparked enthusiasm and lively discussion among participants, who ranged from newly appointed fellows to senior investigators and Branch Chiefs.

The faculty consisted of scientists from CGF, DCEG, SAIC, CCR, the National Human Genome Research Institute (NHGRI), and academia. DCEG presenters included Dr. Chanock, Dr. Wacholder, and **Nilanjan Chatterjee, Ph.D.** (BB). Faculty members Dr. Yeager, **Michael Smith, Ph.D.** (CGF), **Robert Welch, M.S.** (CGF), and **Kevin Jacobs** (CGF) also presented, as did Dr. Lisa Brooks (NHGRI), Dr. Dani Fallin (Johns Hopkins University), and Dr. Peter Kraft (Harvard University). Invaluable support was provided by CGF staff members **Jeff Yuenger,** course coordinator, and **Tammy Bell**.

DCEG Director **Joseph F. Fraumeni, Jr., M.D.,** commended the coordinators and contributors of the course, stating that "organizing this course was above and beyond the everyday mission of the CGF and warrants our thanks. This kind of offering helps make the Division such a great place for training and career development."

A similar demand for advanced training in radiation epidemiology was fulfilled when, in 2004, **Peter Inskip, Sc.D.,** Radiation Epidemiology Branch, developed a 10-day training course for scientists interested in learning about the health effects of radiation exposure.

The course gathered an audience of approximately 80 individuals from DCEG, other parts of NIH, and scientists from Europe, the Middle East, and Asia. The course was facilitated by world-renowned experts who first introduced participants to fundamental concepts in radiation physics, dosimetry, chemistry, radiobiology, and radiation oncology. Lecturers then incorporated these principles into later sessions, where participants learned about and discussed radiation epidemiology studies within the Division involving distinct exposure groups: Japanese atomic bomb survivors, medically irradiated populations, and persons with occupational or environmental radiation exposures. Methods for quantifying radiation risks, setting radiation protection standards, and risk communication were also presented. Ultimately, attendees gained insight into the unique challenges posed to radiation scientists, such as accounting for uncertainty in risk and dose estimation and measuring the effects of multiple low-dose exposures over time.

Materials for each of these courses are available online. The Molecular Epidemiology and Genetic Analysis Course materials are available on the DCEG intranet (http://intranet.dceg.cancer.gov/news/molepicourse); the Radiation Epidemiology course materials are available on the Radiation Epidemiology Branch web site (http://dceg.cancer.gov/radia/epicourse/overview.html). ■

—Alyssa Minutillo, M.P.H.

AMERICAN SOCIETY OF PREVENTIVE ONCOLOGY CELEBRATES 30 YEARS

Sandy Rothschild at DCEG exhibit booth (above); Melinda Butsch Kovacic (inset).

At the 30th American Society of Preventive Oncology (ASPO) conference, held in February in Bethesda, Maryland, DCEG Director **Joseph F. Fraumeni, Jr., M.D.,** a founding member and past president of ASPO, and Dr. David Schottenfeld (University of Michigan) gave keynote presentations. Dr. Fraumeni spoke on international consortia that are facilitating epidemiologic research into the genetic and environmental causes of cancer, including the NCI Consortium of Cohorts, case-control consortia of specific cancers, and familial cancer consortia.

ASPO is an active and growing organization that promotes the exchange and dissemination of information and ideas, identifies and stimulates research, and fosters the implementation of programs in cancer prevention and control. The annual meetings provide a forum for multidisciplinary approaches to cancer prevention and control. This year's conference included several workshops, symposia, poster sessions, and an exhibit program.

Melinda Butsch Kovacic, Ph.D., M.P.H., a postdoctoral fellow in the Hormonal and Reproductive Epidemiology Branch, was selected as a participant in the New Investigators Workshop.

—Sandy Rothschild

JAMES LACEY EXAMINES HORMONE THERAPY AND CANCER RISK

James V. Lacey, Jr., Ph.D., came to DCEG under a Cancer Research Training Award in 1998, after studying with Dr. David Schottenfeld at the University of Michigan. Following three years of postdoctoral training in the Hormonal and Reproductive Epidemiology Branch (HREB), Dr. Lacey was converted to a tenure-track investigator in 2001.

Our studies are snapshots of what is happening at a given time. The link between estrogen plus progestin and increased breast cancer risk emerged more fully in the late 1990s and early 2000s. But endometrial and ovarian cancers are less common than breast cancer, so it has taken longer to determine how estrogen plus progestin affects gynecologic cancer risk.

His main research focus has been on the links between menopausal hormone therapy and risk of gynecologic cancers.

What got you interested in hormone therapy and cancer?

My dissertation focused on the role of reproductive factors and hormone therapy on the etiology of systemic

James Lacey

sclerosis, but I was eager to explore hormone therapy and cancer risk. HREB was home to influential studies on the topic, so I looked for ways to build on that legacy.

When I arrived in 1998, studies consistently showed a relationship between hormone therapy and endometrial cancer. The relationship with breast cancer was an unknown yet important issue, and ovarian cancer was not on many people's radar screens because a number of studies had suggested no link. Working with **Catherine Schairer, Ph.D.,** Biostatistics Branch, **Arthur Schatzkin, M.D., Dr.P.H.,** Chief of the Nutritional Epidemiology Branch, and **Louise Brinton, Ph.D.,** Chief of HREB, I led an effort to expand the Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Study analyses to include ovarian cancer. In a study reported in *JAMA* in 2002, we found that long-duration unopposed estrogen use increased ovarian cancer risk twofold. The absolute risk is low, but ovarian cancer mortality is quite high, so any relative risk greater than about 1.5 is notable.

Did that resolve the ovarian cancer question?

Not completely. The BCDDP study collected data through the mid-1990s, and during that period, hormone therapy use increased dramatically, and formulations were changing. A real challenge for this field is to determine risk in relation to changing hormone therapy. Over the past 30 years, indications for use, dosages, and formulations have all changed.

How have those changes affected your research?

In the mid-1970s, reports on the increased endometrial cancer risks among unopposed estrogen users led to a decline in its use and to the development of estrogen-plus-progestin regimens (see Figure 1). By the late 1980s, estrogen plus progestin became the norm for women who had not had a hysterectomy. In the 1990s, research showed that estrogen plus progestin appeared to reduce heart disease risk, so even more women took it. But after 2002, when the Women's Health Initiative (WHI) demonstrated that estrogen plus progestin taken after menopause produced more harm than benefit, hormone therapy use fell by at least a third.

Our studies are snapshots of what is happening at a given time. The link between estrogen plus progestin and increased breast cancer risk emerged more fully in the late 1990s and early 2000s. But endometrial and ovarian cancers are less common than breast cancer, so it has taken longer to determine how estrogen plus progestin affects gynecologic cancer risk.

The new generation of DCEG cohort studies is ideally positioned to capture recent changes in use. For example, the NIH-AARP Diet and Health Study collected extensive data on hormone therapy use among more than 130,000 postmenopausal women in 1996 and 1997. That, it turns out, was exactly the right time to be asking about estrogen plus progestin, because more and more women were using it—almost every set of clinical guidelines then was encouraging hormone therapy use in postmenopausal women. My most recent analysis of NIH-AARP study data shows that estrogen plus progestin appears to increase ovarian cancer risk. Having a portfolio of older and newer DCEG datasets that capture these dynamic exposures is a real asset.

Have the recent studies changed perceptions about hormone therapy?

Definitely, although sometimes I worry that we might forget where we started. The WHI data showed that unopposed estrogen causes fewer breast cancers and coronary events than estrogen plus progestin does, and therefore, despite the known endometrial cancer risks, one could return to prescribing unopposed estrogen for women who have not had a hysterectomy. However, not everyone agrees with that idea. Our 2005 paper in *Cancer Epidemiology, Biomarkers & Prevention* from the BCDDP study showed that endometrial cancer risk remains elevated for years after women stop taking unopposed estrogen, even if it was used for only a few years, and that estrogen plus progestin might increase risk in some women. As with the ovarian cancer findings, we're currently pursuing those questions in other studies across the Division.

Has your work on hormone therapy opened up new avenues of research for you?

Yes, in 2001, I launched a study to better understand endometrial hyperplasia, which is a potential endometrial cancer precursor that often develops in women taking hormone therapy. Not much is known about its natural history or its risk of progressing to cancer, but it is a diagnosis that often leads to hysterectomy.

Mark Sherman, M.D. (HREB), and I are collaborating with Kaiser Permanente in Portland, a large health maintenance organization with a network of linked databases and archived tissues. We combed through 30 years of data to find women diagnosed with hyperplasia who later developed cancer, and we're comparing them with women diagnosed with hyperplasia who didn't develop cancer during the same time frame. Our aim is to produce more accurate estimates of endometrial cancer risk among women diagnosed with hyperplasia. We'll evaluate histopathologic classifications, clinical characteristics, reproductive factors, and molecular markers such as the *PTEN* tumor suppressor gene. I'm excited about the project—understanding this progression should lead to more efficient early detection.

It sounds like what started as hormone therapy work keeps expanding.

It has certainly led me to areas that I had not considered originally. Biologically, it points to what might occur in the endometrium and ovaries during the menopausal transition: Can those changes predict cancer risk over the next five or ten years? And how might hormone therapy use affect those risks?

You're not discouraged by all of the controversy surrounding hormone therapy and cancer risk?

Not yet, at least. These are complex issues that have become even more confusing and emotional for many women because they have heard different messages over the years. But our multidisciplinary studies now have so many tools with which to understand these connections. I'm optimistic that we can identify the risks and express them in terms that women can understand. ■

—Nancy Volkers

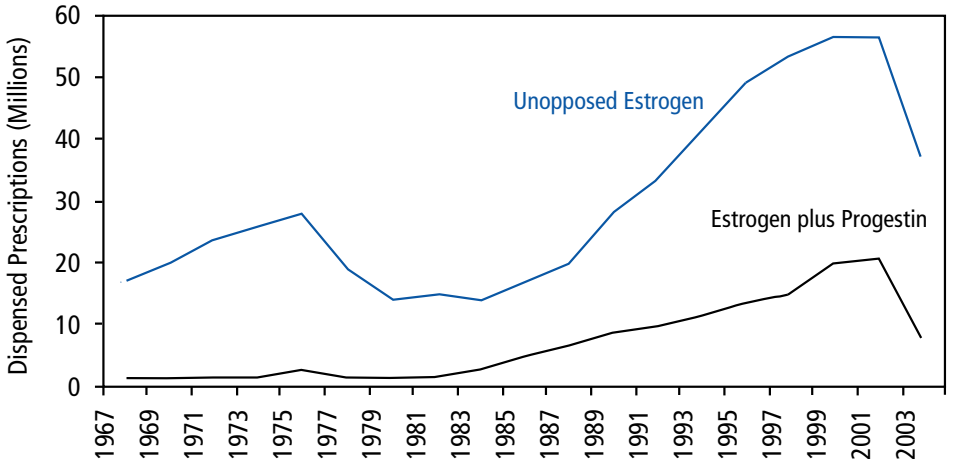


Figure 1. Trends in menopausal hormone therapy use in the U.S.A., 1967–2003. (Adapted from Beral V, et al. 1999 and Hersch AL, et al. 2004)

DCEG STAFF RECOGNIZED AT ANNUAL TOWN MEETING

John E. Niederhuber, M.D., NCI Acting Director, was the featured speaker at the 2006 annual town meeting held in April. Following his introduction by **Joseph F. Fraumeni, Jr., M.D.,** Dr. Niederhuber noted that since his arrival in August 2005, he has gained a true appreciation of NCI as a very special place where outstanding research is being conducted. He emphasized his strong support for the work being carried out by DCEG investigators, as well as his overall commitment to the NCI Intramural Research Program. He noted that, despite the fiscal constraints currently facing the Institute, there are still tremendous opportunities to pursue excellent science by leveraging NCI's existing resources and promoting team science through partnerships with the extramural community. He reiterated his belief in team science and expressed the view that the strength of the Institute resides in its talented and dedicated staff.

Following Dr. Niederhuber's remarks, **Patricia Hartge, Sc.D.,** Deputy Director of the Epidemiology and Biostatistics Program, served as emcee of the annual awards ceremony to recognize outstanding service and scientific contributions over the course of the past year. **Elyse Wiszneauckas,** Office of Division Operations and Analysis (ODOA), was recognized for her leadership in coordinating the Division's contributions to the 2005 Combined Federal Campaign (CFC). DCEG received its eighth consecutive CFC Presidential Award for meeting 175 percent of its dollar goal, contributing approximately $44,000, and 88 percent of its participation goal. Branch key workers were **Holly Brown,** Biostatistics Branch (BB), **Patricia Chandler** (ODOA), **Jennifer Connor,** Hormonal and Reproductive Epidemiology Branch (HREB), **Sadie Holmes-Lillie,** Genetic Epidemiology Branch (GEB), **Ursula Leitzmann, M.A.,** Radiation Epidemiology Branch (REB), **Phyllis Nimeroff,** Occupational and Environmental Epidemiology Branch (OEEB), **José Reyes,** Clinical Genetics Branch (CGB), **Tawanda Roy,** Nutritional Epidemiology Branch (NEB), **Julie Russell-Grey,** Viral Epidemiology Branch (VEB), and **Debbie Schoenberg,** DCEG Administrative Resource Center.

This year, two winners tied for the award for the Outstanding Research Paper by a Fellow, which recognizes a publication during the past calendar year that demonstrated impact, innovation, and clarity of thought and language. The awards were presented to **Amanda Cross, Ph.D.** (NEB), for her paper on "A prospective study of meat and meat mutagens and prostate cancer risk," which was published in *Cancer Research,* and **Lindsay Morton, Ph.D.** (HREB), for her paper on "Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001," which was published in *Blood*. **Rochelle Curtis, M.A.** (REB), received the award for the Outstanding Research Paper by a Staff Scientist, entitled "Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: An international case-control study," which was also published in *Blood*.

DCEG Intramural Research Awards (IRAs) (up to $50,000 in research funds) for tenure-track investigators or postdoctoral fellows support innovative and interdisciplinary collaborative research projects that cross the usual organizational boundaries. Each application is reviewed by a member of the NCI Board of Scientific Counselors or another scientist outside DCEG with appropriate expertise, as well as senior DCEG scientists. Winners of the 2005 IRAs were **Christian Abnet, Ph.D., M.P.H.** (NEB), for his proposal entitled "Is iodine deficiency associated with the etiology of gastric cancer?"; **Anil Chaturvedi, Ph.D.** (VEB), for his project on "Chlamydia pneumoniae infection,

John Niederhuber

Joseph Fraumeni and John Niederhuber with (left to right) Patricia Hartge, José Reyes, and Rochelle Curtis.




Joseph Fraumeni and John Niederhuber with (left to right) Nilanjan Chatterjee, Demetrius Albanes, Patricia Stewart, and Jay Lubin.

chronic inflammation, and risk of lung cancer"; **James Lacey, Ph.D.** (HREB), for his proposal on "PTEN tumor suppressor gene alterations in the progression from endometrial hyperplasia to carcinoma"; **Ola Landgren, M.D., Ph.D.** (GEB), for his project on "Familial, epidemiological, and biological features of over 5,000 cases with monoclonal gammopathy of undetermined significance in Sweden"; Dr. Morton for her proposal entitled "Defining molecular subtypes of lymphoma for relevance to etiology, diagnosis, and survival"; **Christine Mueller, D.O.** (CGB), for her proposal on "Pilot study to develop a method for collecting histologically normal ovarian surface epithelium cells and analyzing them for the presence of molecular abnormalities in relation to ovarian cancer epidemiologic risk factors"; and **Mark Purdue, Ph.D.,** and **Qing Lan, M.D., Ph.D., M.P.H.** (OEEB), for their joint proposal entitled "A nested case-control study of plasma cytokines, other immunologic markers, and lymphoid malignancies in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial."

Dr. Chaturvedi won the DCEG Fellowship Achievement Award for outstanding accomplishments; he will receive a two-step annual increase in his fellowship stipend.

Tammy Bell, Core Genotyping Facility (CGF), **Stephen Chanock, M.D.** (CGF Director), **Nilanjan Chatterjee, Ph.D.** (BB), **Kevin Jacobs** (CGF), **Gilles Thomas, M.D., Ph.D.** (CGF), **Sholom Wacholder, Ph.D.** (BB), **Robert Welch, M.S.** (CGF), **Meredith Yeager, Ph.D.** (CGF), and **Jeff Yuenger** (CGF) received DCEG Certificates of Appreciation for their contributions to the highly successful Genetic Analysis Course.

Demetrius Albanes, M.D. (NEB and OE), **Neil Caporaso, M.D.** (GEB), **Sanford Dawsey, M.D.** (NEB), **Roni Falk, M.S.** (HREB), **Montserrat Garcia-Closas, M.D., Dr.P.H.** (HREB), **Richard Hayes, D.D.S., Ph.D.** (OEEB), **Marianne Henderson, M.S.** (ODOA), **Allan Hildesheim, Ph.D.** (HREB), **Kristin Kiser, M.H.A.** (OE), Dr. Lan, **Mark Roth, M.D.** (NEB), **Nathaniel Rothman, M.D., M.P.H., M.H.S.** (OEEB), **Arthur Schatzkin, M.D., Dr.P.H.** (Chief of NEB), **Mark Schiffman, M.D., M.P.H.** (HREB), **Mark Sherman, M.D.** (HREB), **Erin Toops** (OD), **Jim Vaught, Ph.D.** (OD), and **Sophia Wang, Ph.D.** (HREB), received DCEG Certificates of Appreciation for their contributions to the three-month Molecular Epidemiology Course.

Mr. Reyes was honored with a DCEG Special Recognition Award for outstanding and sustained contributions that advance the mission of the Division and Institute. He developed or revamped several administrative reporting systems that have been adopted across the Division. He also helped train and provide expertise to support staff in their daily activities. The town meeting attendees enthusiastically applauded Mr. Reyes for his talent and generosity in helping others.

Based on nominations from the Division fellows, Dr. Chatterjee, **Patricia Stewart, Ph.D.** (OEEB), and Dr. Albanes received DCEG Outstanding Mentoring Awards. As mentors, they have provided invaluable scientific advice and direction to junior scientists as well as important career guidance.

Jay Lubin, Ph.D. (BB), and Dr. Hartge were recognized by DCEG Exemplary Service Awards. Dr. Lubin was honored for his outstanding contributions to biostatistics, radiation epidemiology, statistical software development, mentoring, and national and international advisory committees. Dr. Hartge was honored for her leadership in epidemiologic research, policy development, strategic planning, conflict resolution, mentoring, and many other areas at the Division, Institute, and national levels. She has focused on the bioinformatics challenges of molecular epidemiology data and the development of intramural/extramural collaborations to answer critical questions in cancer causation and prevention, biorepository policies, risk prediction, and training. ■

WORKSHOP EXPLORES PRESENT AND FUTURE OF KIDNEY CANCER

In April, DCEG and the NIH Office of Rare Diseases co-sponsored an international workshop entitled "Kidney Cancer—Current Perspectives, Future Directions" in Rockville, Maryland. **Lee Moore Ph.D.,** a tenure-track researcher in the Occupational and Environmental Epidemiology Branch (OEEB), co-chaired the event with **Wong-Ho Chow, Ph.D.** (OEEB) and Dr. Paolo Boffetta (International Agency for Research on Cancer).

Paolo Boffetta, Lee Moore, and Wong-Ho Chow.

The goals of the workshop were to share preliminary results from ongoing kidney cancer studies and to stimulate ideas for future research. Conference attendees consisted of population, clinical, and laboratory scientists, including collaborators on the Central and Eastern European Kidney Cancer Study from Russia, Poland, Romania, Czech Republic, and France and the U.S. Kidney Cancer Study from Chicago and Detroit. Together, these two studies represent 2,500 cases and 3,000 controls. Other participants were from Australia, the Netherlands, and the United States.

The first part of the meeting was dedicated to the presentation of new results from studies based on questionnaires, genetic susceptibility, and tumor markers. Dr. Boffetta presented data on obesity, hypertension, smoking, and diet. Dr. Moore presented results from the occupational exposure analysis on trichloroethylene, pesticide, and lead exposures, followed by a presentation on preliminary results from genetic susceptibility and ongoing tumor marker studies using high-throughput methods to detect mutations and promoter hypermethylation in the von Hippel-Lindau gene. The following day, Dr. Berton Zbar (retired from NCI-SAIC), Dr. Maria Merino (NCI Center for Cancer Research [CCR]), **Jorge Toro, M.D.** (Genetic Epidemiology Branch), Dr. Laura Schmidt (CCR), and Dr. Frederic Waldman (University of California, San Francisco Cancer Center) described ongoing research identifying genes and protein pathways involved in familial and sporadic kidney cancers. In addition, Dr. Marston Linehan (CCR) described how these pathways can be targeted in novel kidney cancer treatment strategies being evaluated at NCI.

The second half of the workshop focused on future research ideas for genotyping particular pathways, pooling biological samples across studies, and piloting efforts to identify the determinants of survival. The group plans to meet again in October 2006 to review survival pilot studies in Central and Eastern Europe and the status of ongoing and new collaborative studies. ■

—Lee Moore, Ph.D.

Mitchell Gail

MITCHELL GAIL RECEIVES HARVARD'S MARVIN ZELEN LEADERSHIP AWARD

In June, **Mitchell H. Gail, M.D., Ph.D.,** Chief of the Biostatistics Branch, received the 2006 Marvin Zelen Leadership Award in Statistical Science from the Department of Biostatistics at the Harvard School of Public Health. This award recognizes an individual in government, industry, or academia who by virtue of outstanding leadership has contributed greatly to the theory and practice of statistical science. The most distinguishing criterion for the Zelen Award is the awardee's contribution to the creation of an environment in which statistical science and its applications have flourished. Dr. Gail's award lecture, entitled "Absolute risk: Clinical applications and controversies," illustrated the clinical applications of a model for absolute breast cancer risk, often referred to as the Gail Model.

DCEG PARTICIPATES IN AACR ANNUAL MEETING

Many DCEG researchers participated in the 97th Annual American Association for Cancer Research (AACR) meeting at the Washington Convention Center in Washington, DC, during the first week of April. The events included award lectures, workshops, symposia, and poster sessions.

More than 45 posters and 7 mini-symposia involving DCEG staff were selected for presentation. At a Late-breaking Poster Session, **Sarah Daugherty, M.P.H.,** Occupational and Environmental Epidemiology Branch (OEEB), spoke on "Variants in the α-methylacyl-CoA racemase (AMACAR) gene and the association with advanced distal colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)." During a scheduled press conference on infection and inflammation, she also discussed her research showing that variants in AMACAR might play a role in increasing risk for advanced colorectal adenomas in the general population and that certain polymorphisms may enhance the chemopreventive effect of ibuprofen.

Another key presentation in molecular epidemiology was made by **Jim Vaught, Ph.D.,** DCEG Office of the Director (OD), who spoke on "Sample collection, processing, and storage for large-scale studies: Biorepositories to support cancer research."

Several DCEG staff presented during the Susceptibility Genes Mini-symposium, which was co-chaired by **Maria Teresa Landi, M.D., Ph.D.,** Genetic Epidemiology Branch (GEB), including: **Montserrat Garcia-Closas, M.D., Dr.P.H.,** Hormonal and Reproductive Epidemiology Branch (HREB), on "Large-scale evaluation of candidate genes for bladder cancer susceptibility"; **Lee Moore, Ph.D.** (OEEB), on "Polymorphisms in 1-C metabolism genes and susceptibility to bladder cancer"; **Rose Yang, Ph.D., M.P.H.** (GEB), on "Construction and validation of tissue microarrays of noninvasive breast carcinoma"; **Sophia Wang, Ph.D.** (HREB), on "Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma"; and **Mark Purdue, Ph.D.** (OEEB), on "Polymorphisms in cytokine genes and risk of non-Hodgkin lymphoma."

Unhee Lim, Lindsay Morton, and Melinda Butsch Kovacic.

At the Gene Regulation and Transcription Factors: Gene and RNA Networks Mini-symposium, **Andrew Bergen, Ph.D.** (GEB), gave a presentation entitled "Phylogenetic analysis of *cis* sequence effects on cancer gene transcription."

This year, three DCEG fellows received AACR Scholar-in-Training Awards. **Melinda Butsch Kovacic, Ph.D., M.P.H.** (HREB), was recognized for her abstract on "Immune cells and the natural history of cervical HPV infections." **Unhee Lim, Ph.D.,** Nutritional Epidemiology Branch, presented her research on "Prospective study of aspartame-containing beverages and risk of hematopoietic and brain cancers" in a mini-symposium on Diet and Cancer Risk. **Lindsay Morton, Ph.D.** (HREB), presented "Hepatitis C virus infection and risk of post-transplant lymphoproliferative disorder after liver transplantation." These awards support young investigators who present a paper selected for its scientific merit.

The large attendance at AACR also provided an opportunity for many DCEG researchers participating in international consortia to meet and plan collaborative research projects in molecular epidemiology. Special workshops were devoted to non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, bladder cancer, childhood cancer, and renal cancer. ■

—Nicole Keesecker, M.A.

HORMUZD KATKI RECEIVES HOPKINS' MERRELL AWARD

Hormuzd Katki

Hormuzd Katki, Ph.D., a mathematical statistician in the Biostatistics Branch, successfully completed the doctoral program in the Department of Biostatistics at the Johns Hopkins Bloomberg School of Public Health and received the 2006 Margaret Merrell Award. The award, established in 1995 by friends, colleagues, and former students of the late faculty member Dr. Margaret Merrell, recognizes outstanding research by a biostatistics doctoral student. Dr. Katki's thesis, "Extending Mendelian mutation prediction models that predict if one has a disease-causing mutation based on family history of disease," was completed under the guidance of his advisor, Dr. Giovanni Parmigiani.

INTERNATIONAL LYMPHOMA EPIDEMIOLOGY CONSORTIUM MEETS

The International Lymphoma Epidemiology Consortium (InterLymph) held its fifth annual meeting on March 30 in Washington, DC. The meeting, attended by 90 lymphoma researchers, was hosted by **Patricia Hartge, Sc.D.,** Deputy Director of the Epidemiology and Biostatistics Program (EBP), and Dr. Carol Kasten (NCI Division of Cancer Control and Population Sciences). The meeting opened with results from ongoing projects, including recent pooled publications on increased risk linked to TNF and *IL10* variants and decreased risk linked to alcohol. Since these studies showed distinct histologic patterns, InterLymph pathologist Dr. Jenny Turner (St. Vincent's Hospital, New Zealand), **Lindsay Morton, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), and **Martha Linet, M.D., M.P.H.,** Chief of the Radiation Epidemiology Branch, developed a new "collapsible" pathology classification scheme tailored to pooled analysis. **Sophia Wang, Ph.D.** (HREB), presented a pooled analysis on family history, with overall relative risks of 1.5 for non-Hodgkin lymphoma (NHL), 1.6 for Hodgkin lymphoma, and 1.4 for leukemia. Dr. Anne Kricker (University of Sydney, Australia) presented an ultraviolet radiation analysis, and Dr. Silvia de Sanjose (Catalan Institute of Oncology, Spain) reported on the role of hepatitis C virus. Plans for an immunology pooling project were outlined by Dr. Wendy Cozen (University of Southern California); for an occupational project by Dr. Paolo Boffetta (International Agency for Research on Cancer); and for the next genotype project by Dr. Alexandra Nieters (German Cancer Research Center), Dr. Christine Skibola (University of California, Berkeley), and **Nathaniel Rothman, M.D.,** Occupational and Environmental Epidemiology Branch (OEEB).

Geoffrey Tobias, Executive Secretary for InterLymph, received the 2006 Outstanding Service Award from Wendy Cozen, co-chair of the InterLymph Executive Committee.

Dr. Martyn Smith (University of California, Berkeley) and Dr. Hartge organized and moderated a half-day workshop on NHL and environmental exposures, especially chemicals. Dr. Boffetta highlighted occupational risks, and Dr. Rothman examined emerging data implicating organochlorines. Dr. Gareth Morgan (Institute of Cancer Research, United Kingdom) spoke on the lymphoma risks of chemotherapy as a model system, and Dr. Smith highlighted conflicting data on benzene. A second panel focused on lifestyle factors, with presentations on diet and obesity (Dr. Skibola), ultraviolet light (Dr. Bruce Armstrong, University of New South Wales, Australia), oncogenic viruses (**Eric Engels, M.D., M.P.H.,** Viral Epidemiology Branch), and a complex emerging pattern for altered immunity (Dr. Andrew Grulich, University of New South Wales, Australia). Proceedings of the workshop, co-sponsored by NIEHS, will be published in *Cancer Epidemiology, Biomarkers & Prevention* later this year.

In conjunction with InterLymph, **Dalsu Baris, M.D., Ph.D.** (OEEB), along with Dr. Brenda Birmann (Harvard University), Dr. Anthony Staines (University of Dublin, Ireland), and Dr. Cozen, convened the first meeting of the Multiple Myeloma Consortium, with more than 30 researchers from nine different countries, and established six working groups. In addition, the recently formed Hodgkin lymphoma consortium met, co-chaired by Dr. Cozen, Dr. Henrik Hjalgrim (Statens Serum Institut, Denmark), and Dr. Sally Glaser (Northern California Cancer Center).

InterLymph meeting participants

To conclude the meeting, Dr. Cozen, the executive committee chair, presented an Outstanding Service Award to **Geoffrey Tobias** (EBP) in recognition of his contributions as Executive Secretary for InterLymph, which include establishing a web-based portal for exchange of information, organizing monthly conference calls of the steering committee and working groups, coordinating the annual meeting, and overseeing the exchange of data and report preparation for the first pooled analysis of genotyping data.

The 2007 annual meeting of InterLymph will be hosted by Dr. de Sanjose in Barcelona, Spain. Further information on InterLymph can be found at http://epi.grants.cancer.gov/InterLymph. ■

—Patricia Hartge, Sc.D.

WORKSHOP PROBES PHYSICAL ACTIVITY–BREAST CANCER LINK

For some time, researchers have suspected an association between body weight, physical activity, and the development of cancer—a belief now supported by extensive epidemiologic evidence of the adverse effects of physical inactivity and obesity on cancer risk, prognosis, and quality of life. On March 15 and 16, an NCI-sponsored workshop brought together more than 60 experts from a variety of fields, including nutrition, breast cancer, biometrics, behavioral science, cancer prevention, survivorship, epidemiology, and clinical trials, to review the evidence and debate the feasibility and utility of conducting a randomized, controlled trial to assess the effects of physical activity and weight control on breast cancer risk as well as to consider possible trial designs. The workshop was chaired by Dr. Rachel Ballard-Barbash (NCI Division of Cancer Control and Population Sciences) and **Arthur Schatzkin, M.D., Dr.P.H.,** Chief of the Nutritional Epidemiology Branch, and organized by a trans-NCI working group.

Workshop participants discussed the timeliness of such a trial in light of promising evidence from small intervention trials testing the effects of physical activity and weight loss on potential mechanisms, evidence of larger-than-anticipated benefit from comprehensive lifestyle interventions for other chronic diseases, and surprising evidence that such interventions are more cost-effective than drug therapy. Participants debated the weight of this evidence and observed that while observational studies have provided surprisingly consistent and convincing data, they are limited in terms of implicating the effect of volitional weight loss or increases in physical activity (see Figure 1). Two studies published in 2003 provided important results: an American Cancer Society study suggested that 20 percent of cancer deaths in women can be attributed to obesity, while a study conducted in the Kaiser Permanente Medical Care Program of Northern California and the State of Utah found that the risk of developing colon cancer for persons with high body mass indices and limited physical activity was two to three times the risk of developing colon cancer for others. Also compelling are the growing public health problems of obesity, physical inactivity, and poor diet in the U.S. population. Recent National Health and Nutrition Examination Survey data showed that almost 95 percent of the U.S. population does not get sufficient regular physical activity to realize health benefits, 66 percent is overweight, and 60 percent eats fewer than five half-cup servings of fruits and vegetables per day.

A primary goal of the workshop was to form working groups to plan the next steps in trial design; debate the most relevant study population and appropriate endpoints; define parameters of the behavioral interventions; and integrate trial mechanisms across basic, clinical, and population sciences. These working groups will develop recommendations for action plans, which will be published later this year.

—Arthur Schatzkin, M.D., Dr.P.H.

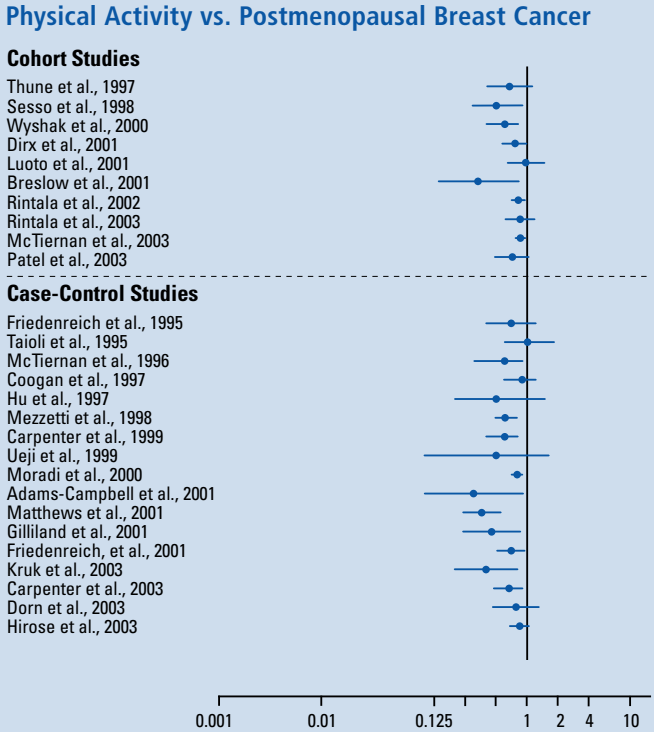


Figure 1. Increased physical activity and reduced risk of breast cancer among 27 studies of postmenopausal women. (Friedenreich C, et al. 2004)

VISITING SCHOLAR VALERIE BERAL HOLDS SEMINAR

Dr. Valerie Beral, Professor of Epidemiology and Director of the Cancer Research U.K. Epidemiology Unit at the University of Oxford, came to DCEG for two days in April as the latest DCEG Visiting Scholar.

Renowned for her work in hormonal and reproductive epidemiology, Dr. Beral first studied medicine in her native Australia and later received training in epidemiology at the London School of Hygiene and Tropical Medicine. There, she began investigating the role of exogenous hormones in mortality and disease trends in several large U.K. cohorts and remained on the faculty for nearly 20 years.

As Director of the Epidemiology Unit at Oxford since 1988, Dr. Beral oversees an extensive cancer research program. She convened the international Collaborative Group on Hormonal Factors and Breast Cancer in 1992 to examine the effects of hormonal and reproductive events on breast cancer risk by combining data from 54 epidemiologic studies. Since that time, a number of similar collaborative groups have been established within the unit to conduct systematic, combined evaluations of risk factors associated with breast, prostate, and AIDS-related cancers.

Dr. Beral is a fellow in both the Royal College of Physicians' Faculty of Public Health and the Royal College of Obstetricians and Gynaecologists, and she has received an honorary doctorate from Aberdeen University in Australia. She has served on numerous working groups and committees advising such organizations as the World Health Organization, the International Agency for Research on Cancer, and the International Atomic Energy Agency.

In her seminar, entitled "Hormones and cancer," Dr. Beral summarized the long history of complex, interrelated, and sometimes conflicting research on how

Valerie Beral

hormones, specifically estrogen and progesterone, influence risk of cancers of the breast, endometrium, cervix, and ovary. She further illustrated how cancer risk changes over time in response to such reproductive variables as parity and breastfeeding. Throughout the seminar, Dr. Beral integrated data and lessons learned from her most recent project, the Million Women Study, a population-based cohort study launched in 1996 that recruited more than 1.3 million women aged 50 to 64. Initial results, published in 2003, showed that current use of hormone replacement therapy (HRT) (either estrogen-only or combined estrogen-plus-progestin regimens) was associated with an increased risk of breast cancer incidence and mortality, with the highest risk in users of combined therapy. The study also showed that cancer risk dropped to expected levels within five years of HRT cessation. Dr. Beral concluded her presentation by stating, "through epidemiologic research, it has been shown that hormones involved in reproduction play a central role in the development of certain female cancers and are key to prevention," and recommending that biochemical approaches be employed to further characterize mechanisms of hormonal carcinogenesis.

After her presentation, Division Director **Joseph F. Fraumeni, Jr., M.D.,**

DCEG COSPONSORS RADIATION WORKSHOP

In February, the Radiation Epidemiology Branch (REB) and the NIH Office of Rare Diseases cosponsored the As Low as Reasonably Achievable (ALARA) Workshop in Pediatric Interventional and Fluoroscopic Imaging in Orlando, Florida. The workshop addressed a range of topics concerning the critical need to minimize radiation doses to pediatric patients undergoing interventional radiologic procedures. Experts in the fields of radiation epidemiology, pediatric radiology, and clinical imaging from hospitals, universities, government, and industry participated in a scientific exchange on radiation dose reduction to children, an issue that has been identified as a critical need by the Society for Pediatric Radiology. **Martha Linet, M.D., M.P.H.,** Chief of REB, Dr. Isabelle Thierry-Chef (International Agency for Research on Cancer), and **Ruth Kleinerman, M.P.H.** (REB), discussed a variety of topics, including the role of NCI in radiation exposure assessment, equipment strategies to reduce pediatric radiation doses, and management of radiation exposures encountered in interventional cardiology and radiology and general fluoroscopy. The goals of the workshop were to promote greater awareness and to stimulate discussion of improving pediatric medical care through radiation imaging while limiting radiation doses to children. Proceedings of the workshop will be available in a special issue of *Pediatric Radiology* in fall 2006.

—Ruth Kleinerman, M.P.H.

presented Dr. Beral with the Visiting Scholar Award in recognition of her leadership and vision in cancer epidemiology and public health.

Dr. Beral has long been a collaborator and friend to many DCEG investigators. She spent the remainder of her time at DCEG visiting a number of scientists and fellows to discuss various works in progress, while providing personal insights and lessons from her own experience.

James Lacey, Ph.D., a tenure-track investigator in the Hormonal and Reproductive Epidemiology Branch (HREB), moderated a session on hormones and cancer risk and further discussed the research presented in Dr. Beral's lecture, public response to findings from the Women's Health Initiative and the Million Women Study and how HRT use changed as a result, and areas where evidence is lacking or inconsistent about the risk of cancer. In a session moderated by **Regina Ziegler, Ph.D., M.P.H.,** Epidemiology and Biostatistics Program, Dr. Beral shared her experience using a dietary assessment survey in the Million Women Study. Dr. Beral concurred with session participants from the Nutritional Epidemiology Branch that accurate measurements are difficult to obtain in cohort studies using simple, standardized tools and discussed the various surveys and instruments currently being used in large-scale nutritional epidemiology studies.

Dr. Beral also participated in several roundtable sessions on the effects of viruses on cancer risk, another area in which she has conducted important research. In a dynamic session led by **Mark Schiffman, M.D., M.P.H.** (HREB), DCEG investigators shared highlights from projects investigating the effects of the human papillomaviruses on cervical cancer across the continuum from screening to diagnosis, treatment, and prevention. Moderator **Robert Biggar, M.D.,** Viral Epidemiology Branch, hosted Dr. Beral in a stimulating session on studies of cancers related to HIV/AIDS and other infectious agents.

Dr. Beral also met with DCEG fellows and with women scientists to discuss timely issues regarding career advancement and mentoring and touched on the differences between European and American work cultures. She encouraged junior researchers to broadly explore their interests early in their careers and ultimately focus on the area that they find most interesting, adding that mentors should help guide them to areas of high impact. "It is more important to write one or two really important papers that advance the field than it is to publish a great number of papers about small findings."

Dr. Beral concluded her visit with meetings with **Demetrius Albanes, M.D.,** Chief of the Office of Education, to discuss international training partnerships, and Dr. Kishor Bhatia, Director of the NCI AIDS Malignancy Program. ■

—Alyssa Minutillo, M.P.H.

DISTINGUISHED LECTURER DALE SANDLER AT DCEG

Dr. Dale Sandler, Chief of the Epidemiology Branch at the National Institute of Environmental Health Sciences (NIEHS), visited NCI in March as an invited speaker for the DCEG Distinguished Lectures in Occupational and Environmental Cancer series. A leader in the field of environmental epidemiology, Dr. Sandler received her Ph.D. from the Johns Hopkins Bloomberg School of Public Health. Her research interests have focused on environmental determinants of chronic diseases, including passive smoking, indoor radon, pesticides and other agricultural exposures, and gene-environment interactions. She has served on many prestigious scientific advisory boards and is a past president of the American College of Epidemiology. She currently serves as an editor for the journal *Epidemiology*. Dr. Sandler is the lead NIEHS investigator for the Agricultural Health Study, a collaborative study with DCEG, and has spearheaded research on non-cancer outcomes in relation to pesticide exposures within the study.


Dalsu Baris, Dale Sandler, and Joseph Fraumeni.

During her lecture, "The Sister Study: Environmental and genetic risk factors for breast cancer in a risk-enriched cohort," Dr. Sandler spoke on another major prospective cohort study that she codirects with Dr. Clarice Weinberg. The Sister Study examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Dr. Sandler illustrated how studying sisters will enhance the ability to assess the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. Following a successful pilot phase in 2003 and 2004, the Sister Study began national recruitment in October 2004. More than 26,000 women were already enrolled by early 2006. During her two-day visit, Dr. Sandler also met with investigators and fellows across the Division and gave a second seminar on a study of uranium miners to members of the Occupational and Environmental Epidemiology Branch.

—Dalsu Baris, M.D., Ph.D.

THE PROMISE OF GLOBAL CERVICAL CANCER PREVENTION

The two major determinants of cervical cancer are chronic infection with oncogenic types of human papillomavirus (HPV) and the lack of effective screening to detect treatable cervical precancers. Although cytology screening by means of Papanicolaou (Pap) smears has significantly reduced cervical cancer rates in many developed countries, it is an expensive program to implement and maintain. For this reason, cervical cancer remains the second leading cancer among women worldwide, taking its greatest toll among women in developing regions of the world. Clinical trials of promising prophylactic vaccines against HPV infection are currently underway. While effective in preventing HPV infection, these vaccines are not useful for the millions of women who have already been infected with HPV. Along with the development of a prophylactic vaccine, HPV-based screening and diagnostic regimens must be implemented that promise effective global cervical cancer prevention strategies at a cost that can be borne by developing nations.

More effective preventive strategies, based on a growing understanding of cervical carcinogenesis, are on the horizon. In the early 1980s, **Louise Brinton, Ph.D.,** Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), coauthored the first case-control study supporting Harald zur Hausen's hypothesis that HPV infection was the long-sought sexually transmissible cause of cervical cancer. This work led to a series of studies over the past 20 years in which DCEG scientists helped to prove that persistent cervical infections with one of approximately 15 carcinogenic HPV genotypes cause virtually all cases of cervical cancer and its precursor lesions. The finding that there is a single cause of cervical cancer paved the way for efforts in primary prevention via prophylactic HPV vaccination among younger women and in secondary prevention using carcinogenic HPV screening among older women.

The current standard of cytology-based cervical cancer prevention is based on three clinical visits: an initial screening, magnified biopsy using a colposcope for women with abnormal screening results, and treatment of precancers. Successive cycles of testing may be required for cancer prevention in cases where one round of cytology, colposcopy, and treatment is not sufficient for the detection and cure of lesions (see Figure 1). This screening regimen is too expensive to implement in third world nations. Cervical cancer prevention in the United States alone costs about $6 billion annually.

In contrast to the traditional approach, new cervical cancer prevention models will almost certainly emphasize virologic and molecular techniques rather than traditional cytologic and colposcopic methods. HPV DNA testing has been shown to be more reproducible and sensitive than cytology/colposcopy for the detection of prevalent and incipient cervical precancer and cancer. For this reason, a negative HPV test provides greater reassurance than any other diagnostic method. Understanding the natural history of carcinogenic HPV types (for example, how their prevalence

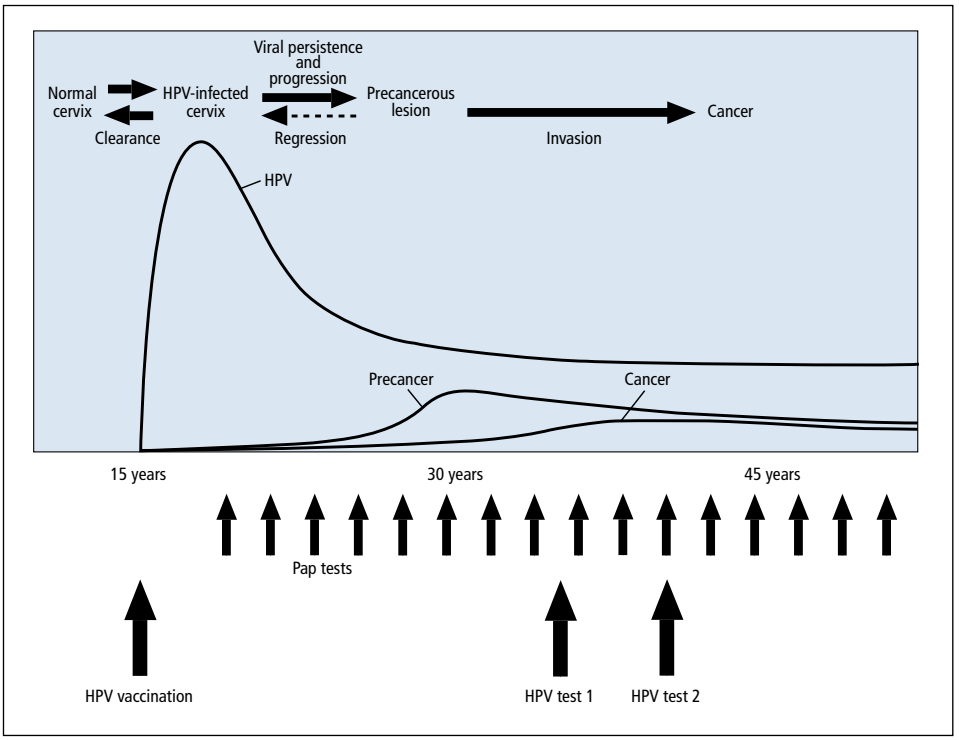


Figure 1. Natural history of HPV infection and cervical cancer. (Schiffman M, Castle P. *N Engl J Med* 2005; 353:2101–2104)

Top panel: The peak prevalence of transient infections with carcinogenic types of HPV occurs in teens and twenties following the initiation of sexual activity. The peak prevalence of cervical precancer occurs approximately 10 years later, and peak prevalence of invasive cancers occurs at ages 40–50.

Bottom panel: The conventional model of cervical cancer prevention is based on repeated rounds of cytology and colposcopy. Alternative strategies include HPV vaccination of adolescents and/or one or two rounds of HPV screening at the peak ages of treatable precancer and early cancer.

rises and falls at young ages) and their relation to cervical cancer development makes it possible to determine which groups of women to target first for screening efforts. For example, in developing nations, where resources are limited, screening efforts should first be directed toward women at the peak ages (~30–45) for precancers and curable early cancers that result from persistent infection. HPV screening is not as valuable for women at younger ages, when viral prevalence is high but cancer risk is very low, or at older ages, when any cancers found are more likely to be advanced.

HPV16 and HPV18 vaccines cover 70 percent of subsequent cervical cancer risk and have demonstrated very high efficacy. Because these vaccines are not designed to treat infection once it has occurred, young women should be vaccinated to achieve maximum impact. Like screening tests, HPV vaccines will need to be adapted for low-cost, single-dose immunizations. NCI Center for Cancer Research investigators Dr. John Schiller and Dr. Doug Lowy, who co-invented the current prophylactic HPV vaccines, are now working toward the development of a second-generation vaccine that is less expensive and easier to administer.

At present, it is unclear how long the protection from HPV vaccines will last. Determining duration of protection is a goal of DCEG's ongoing vaccine trial in Costa Rica. Protection by the current vaccine against the remaining HPV types, which cause 30 percent of cervical cancers, is unlikely to be as complete. Even with rapid implementation of improved, multivalent vaccines, cervical cancer screening will continue to be vital for decades to come.

Ideally, HPV testing and treatment should be compressed into the fewest possible gynecologic visits in order to reduce cost and loss to follow-up. DCEG collaborators are now developing HPV tests that are rapid, robust, and easy to use. The goal is one-visit "screen and treat" strategies, which would be extremely beneficial in low-resource settings. HPV-negative women would be viewed as low-risk and discharged, while HPV-positive women would undergo further assessment by visualization of the cervix to determine the appropriate management strategy. Most HPV-positive women could be treated as outpatients by nurses, midwives, or local generalists. Only women with severe or extensive precancer or obvious cancer, untreatable by outpatient techniques, would require referral to a hospital for management by a gynecologist.

To complete the "screen and treat" strategies, researchers are seeking to validate an inexpensive, safe, and reliably effective treatment comparable in performance to the electrosurgical excision procedures used in developed nations. Although CO_2 cryotherapy is low-cost and ubiquitous, it has undependable performance, and better-performing forms of cryotherapy are often not locally available. There is a critical need for an inexpensive treatment that can be used in low-resource settings in order to translate improved screening efforts into effective prevention.

Faced with the challenge of global cervical cancer prevention, DCEG investigators are currently working to translate HPV vaccines and screening/diagnostic advances into rational cervical cancer prevention programs that fit both low- and high-resource settings. Each senior member of the HREB team leads one of the interlocking priorities. **Mark Schiffman, M.D., M.P.H.** (HREB), and **Ana Cecilia Rodriguez, M.D.** (HREB), concentrate on natural history studies that seek to extend our understanding of multistage carcinogenesis using the cervical HPV model. **Allan Hildesheim, Ph.D.** (HREB), directs the major HPV prophylactic vaccine trial in Costa Rica, managed by **Pamala Gahr, M.P.H.** (HREB). The supporting HPV immunology laboratory is led by **Ligia Pinto, Ph.D.** (HREB), along with Dr. Alfonso Pineres (Universidad de Costa Rica) and **Troy Kemp** (HREB). **Philip Castle, Ph.D., M.P.H.** (HREB), a molecular epidemiologist, and **Jose Jeronimo, M.D.** (HREB), a gynecologic oncologist, combine their complementary skills to lead the screening, diagnostic, and health disparities efforts, assisted by postdoctoral fellow **Mahboobeh Safaeian, Ph.D.** (HREB), and predoctoral fellow **Julia Gage, M.P.H.** (HREB). Two gynecologic pathologists, **Mark Sherman, M.D.** (HREB), and **Diane Solomon, M.D.,** of NCI's Division of Cancer Prevention (DCP) and an adjunct investigator in HREB, add diagnostic rigor and biologic insight to all efforts, while **Sholom Wacholder, Ph.D.,** Biostatistics Branch, serves as the statistician. **Sophia Wang, Ph.D.** (HREB), is searching for the next generation of improved biomarkers, such as germline and somatic changes that could indicate increased risk of cervical cancer among HPV-infected women. Two DCP Prevention Fellows, **Melinda Butsch Kovacic, Ph.D., M.P.H.** (HREB), and **Aimee Kreimer, Ph.D.** (HREB), work on both etiologic and clinical issues.

As our understanding of cervical carcinogenesis increases, it will lead to the development of new tools to improve cervical cancer screening and to restrict the spread of its viral cause. Because it is truly an achievable goal, cervical cancer prevention deserves high priority among global cancer prevention efforts. ■

—Mark Schiffman, M.D., M.P.H.

DCEG AND CCR WIN BENCH-TO-BEDSIDE AWARD

Congratulations to **Sophia Wang, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), **Stephen Chanock, M.D.,** Director of the Core Genotyping Facility, and others in DCEG and the NCI Center for Cancer Research (CCR) who received an NIH Bench-to-Bedside Award for their project entitled "High-density genotyping in lymphoma: Translating etiologic clues into prognostic relevance."

Drs. Wang and Chanock are leading a multidisciplinary collaboration that combines epidemiology, molecular pathology, genetics, and clinical response to understanding non-Hodgkin lymphoma (NHL). Specifically, the project is aimed at identifying genetic predictors of lymphoma survival in two major lymphoma subtypes—diffuse large B-cell lymphoma and follicular lymphoma. In light of the completion of Phase II of the International HapMap Project, Drs. Wang and Chanock will thoroughly interrogate genetic variations within genes, chromosomal regions, and biologic pathways of highest interest and relevance for survival outcomes with high-density genotyping. The project will be conducted within the NCI-SEER (Surveillance, Epidemiology, and End Results) NHL case-control study, in which **Patricia Hartge, Sc.D.,** Deputy Director of the Epidemiology and Biostatistics Program, and the SEER investigators, Dr. James Cerhan, Dr. Scott Davis, Dr. Wendy Cozen, and Dr. Rick Severson, have linked the population-registry case-control study to survival outcomes. The NCI-SEER study is also the first to incorporate survival-based molecular pathology delineations, as recently defined by collaborator Dr. Louis Staudt (CCR), in a population study. This component of the study is being led by **Lindsay Morton, Ph.D.** (HREB). Team members on the survival study also include **Nathaniel Rothman, M.D.,** Occupational and Environmental Epidemiology Branch, and **Sholom Wacholder, Ph.D.,** Biostatistics Branch, who play critical roles in the design and analysis of high-density genotyping data within the Division. The combination of these collaborations and study elements makes the project uniquely poised to quickly translate findings from etiology and molecular pathology into clinical relevance for prognosis and survival outcomes.

The NIH Bench-to-Bedside Award Program fosters collaborations among laboratory, clinical, and population scientists in areas of research that have potential for improving the understanding of an important disease process or leading to a new therapeutic, preventive, or diagnostic intervention. Projects involving extramural partners are encouraged. The awards are funded with contributions from the Office of Rare Diseases, Office of AIDS Research, Office of Research on Women's Health, National Center for Research on Minority Health and Health Disparities, National Center for Research Resources, and matching Institute funds. ■

FAMILY STUDY OF CHRONIC LYMPHOCYTIC LEUKEMIA

For more than two decades, the Genetic Epidemiology Branch (GEB) has been studying families with two or more members diagnosed with chronic lymphocytic leukemia (CLL). The clinical data and biospecimens from these families have been an enormous resource for scientific discovery. The increasing knowledge of the human genome and availability of high-throughput technology have accelerated the pace of research on familial CLL.

In 2002, GEB and other researchers formed an international consortium for familial CLL (IFCLL) and have had three subsequent annual meetings. An IFCLL subgroup submitted a grant to NCI for collection of a large number of CLL families from several centers, including GEB. This project is funded as a cooperative agreement. **Neil Caporaso, M.D.** (GEB), is a coinvestigator for this U01 along with Dr. Susan Slager at the Mayo Clinic. Other coinvestigators include **Lynn Goldin, Ph.D.** (GEB); Dr. Jim Cerhan, Dr. Neil Kay, Dr. Tim Call, and Dr. Celine Vachon (Mayo Clinic); Dr. Logan Spector (University of Minnesota); Dr. Sara Strom (M.D. Anderson Cancer Center); Dr. Laura Rassenti (University of California, San Diego); and Dr. Gerald Marti (Center for Biologics Evaluation and Research, FDA). The study will apply new technology and use linkage and association methods to discover susceptibility genes. A unique aspect of the study is Dr. Marti's flow cytometry studies on first-degree relatives of CLL cases, which can detect monoclonal B-cell lymphocytosis, a possible preclinical stage of CLL.

To communicate the increasing understanding of the underlying causes of CLL and to describe the critical contributions made by the participating families to the study, GEB distributes a newsletter. Recent articles describe the lymphoproliferative cancers that aggregate with CLL in families, evidence suggesting that CLL has a stronger genetic than environmental etiology, and descriptive data from NCI's Surveillance, Epidemiology, and End Results Program about the risk factors that predict variation in CLL incidence rates. There is also a question and answer section on gene discovery and genetic testing.

—Lynn Goldin, Ph.D.

SCIENTIFIC HIGHLIGHTS

ALL CANCERS

Cancer Spectrum in HIV-infected Africans

Records of 12,607 human immunodeficiency virus (HIV)–infected persons attending the AIDS Support Organization in Kyadondo County, Uganda, from 1988 through 2002 were linked to the Kampala Cancer Registry. Standardized incidence ratios (SIRs) were calculated to identify increased cancer risks in the early (4–27 months after registration), late (28–60 months), or combined (4–60 months) incidence periods; 378 cancers (181 prevalent, 197 incident) were identified. Of incident cancers, 137 (70%) were AIDS-defining cancers. Risk was increased in the early-incident period, compared to the general population, for the AIDS-defining cancers: Kaposi sarcoma (SIR = 6.4; CI = 4.8–8.4), non-Hodgkin lymphoma (SIR = 6.7; CI = 1.8–17), and cervical carcinoma (SIR = 2.4; CI = 1.1–4.4). These cancers were also increased in the combined periods. Risk was increased in the combined periods for five non-AIDS-defining cancers: Hodgkin lymphoma (SIR = 5.7; CI = 1.2–17) and cancers of the conjunctiva (SIR = 4.0; CI = 1.5–8.7), kidney (SIR = 16; CI = 1.8–58), thyroid (SIR = 5.7; CI = 1.1–16), and uterus (SIR = 5.5; CI = 1.5–14). Cancers of the breast, nasopharynx, and lung were increased in either the early or late incident periods only. Among 407 children, seven cancers were observed, of which five were Kaposi sarcoma. **(Mbulaiteye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, Workneh M, Coutinho A, Engels EA. Spectrum of cancers among HIV-infected persons in Africa: The Uganda AIDS-Cancer Registry Match Study. *Int J Cancer* 2006;118:985–990)**

Herbicides and Cancer

The incidence of cancer among pesticide applicators exposed to herbicides was evaluated in two reports from the Agricultural Health Study (AHS), a prospective cohort study of over 50,000 licensed pesticide applicators in Iowa and North Carolina. Metolachlor, one of the most widely used herbicides in the United States, was not clearly associated with any cancer subtype. A decreased relative risk (RR) was found for prostate cancer in the highest category of lifetime days exposure (RR = 0.59; CI = 0.39–0.89) and in the second highest category of intensity-weighted lifetime days exposure (RR = 0.66; CI = 0.45–0.97); however, the trends were not significant. A non-significantly increased risk was found for lung cancer with lifetime days exposure in the highest category (RR = 2.37; CI = 0.97–5.82, p for trend = 0.03) but not with intensity-weighted lifetime days. Overall cancer incidence also did not increase with increasing lifetime use of pendimethalin. The risk for rectal cancer rose with increasing lifetime exposure when using nonexposed as the reference (rate ratio = 4.3; CI = 1.5–12.7 for the highest exposed subjects; p for trend = 0.007), but the association was attenuated when using the low-exposed as the referent group (p for trend = 0.08). There was some evidence for an elevated risk for lung cancer, but the excess occurred only in the highest exposure category for lifetime exposure. The trends for lung cancer risk were inconsistent for different exposure metrics. **(Rusiecki JA, Hou L, Lee WJ, Blair A, Dosemeci M, Lubin JH, Bonner M, Samanic C, Hoppin JA, Sandler DP, Alavanja MC. Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. *Int J Cancer* 2006;118:3118–3123. Hou L, Lee WJ, Rusiecki J, Hoppin JA, Blair A, Bonner MR, Lubin JH, Samanic C, Sandler DP, Dosemeci M, Alavanja MC. Pendimethalin exposure and cancer incidence among pesticide applicators. *Epidemiology* 2006;17:302–307)**

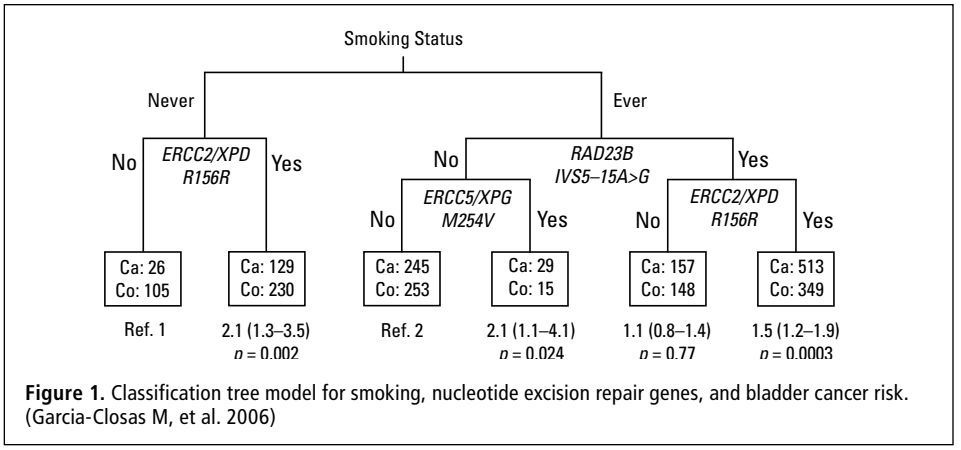


Figure 1. Classification tree model for smoking, nucleotide excision repair genes, and bladder cancer risk. (Garcia-Closas M, et al. 2006)

BLADDER CANCER

Nucleotide Excision Repair Pathway

The effect of genetic variation in the nucleotide excision repair (NER) pathway on bladder cancer risk was evaluated by analyzing 22 single nucleotide polymorphisms (SNPs) in seven NER genes (*XPC, RAD23B, ERCC1, ERCC2, ERCC4, ERCC5,* and *ERCC6*). The study population included 1,150 patients with transitional cell carcinoma of the urinary bladder and 1,149 control subjects from Spain. Subjects with the variant genotypes for SNPs in four of the seven genes evaluated had small increases in bladder cancer risk compared to subjects with the homozygous wild-type genotypes: *RAD23B IVS5-15A>G* (odds ratio [OR] = 1.3; CI = 1.1–1.5), *ERCC2 R156R* (OR = 1.3; CI = 1.1–1.6), *ERCC1 IVS5+33A>C* (OR = 1.2; CI = 1.0–1.5;

p for trend = 0.04), and *ERCC5 M254V* (OR = 1.4; CI = 1.0–2.0). A global test for pathway effects indicated that genetic variation in NER characterized by the 22 SNPs predicts bladder cancer risk ($p = 0.04$). Pairwise comparisons suggested that carrying variants in two genes could result in substantial increases in risk. Classification tree analyses also suggested substantial increases in risk among subgroups of individuals defined by smoking and NER genotypes (see Figure 1). **(Garcia-Closas M, Malats N, Real FX, Welch R, Kogevinas M, Chatterjee N, Pfeiffer R, Silverman D, Dosemeci M, Tardón A, Serra C, Carrato A, Garcia-Closas R, Castaño-Vinyals G, Chanock S, Yeager M, Rothman N. Genetic variation in the nucleotide excision repair pathway and bladder cancer risk. *Cancer Epidemiol Biomarkers Prev* 2006;15:536–542)**

BREAST CANCER

Prophylactic Oophorectomy and *BRCA1* Penetrance

Breast cancer penetrance estimates in *BRCA1* mutation carriers have varied from 40% to 85%; no study has taken oophorectomy status into account in estimating penetrance. Because prophylactic oophorectomy reduces breast cancer risk by about 50%, population differences in oophorectomy prevalence might significantly influence penetrance estimates. Within a cohort of multiple-case breast/ovarian cancer families that segregate deleterious *BRCA1* mutations, 33 cases of breast cancer developed in 98 women with deleterious *BRCA1* mutations, yielding a cumulative lifetime breast cancer risk of 80%. This estimate increased to 94% when the participants were censored at the time of oophorectomy. Six of the 33 mutation-positive women who underwent oophorectomy during follow-up developed breast cancer, compared with 27 of 65 mutation carriers with intact ovaries (hazard ratio [HR] = 0.38; CI = 0.15–0.97). The protective effect of oophorectomy was strongest among women who were premenopausal at the time of surgery. When surgical status was ignored, the strong protective effect of oophorectomy, coupled with the high prevalence of the procedure in these families, led to a significantly lower estimate of the breast cancer penetrance in mutation carriers. **(Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of *BRCA1* mutation carriers. *J Clin Oncol* 2005;23:8629–8635)**

HSD17B1 Gene: Early Results from the Cohort Consortium

The 17beta-hydroxysteroid dehydrogenase 1 gene (*HSD17B1*) encodes 17HSD1, which catalyzes the final step of estradiol biosynthesis. As part of a study of candidate hormone-related genes for 5,370 breast cancer cases and 7,480 controls from five large cohorts in the Breast and Prostate Cancer Cohort Consortium, variation in *HSD17B1* was characterized by resequencing and dense genotyping, and haplotype-tagging single nucleotide polymorphisms (htSNPs) that capture common variation within a 33.3-kb region around *HSD17B1* were identified. No evidence of association between common *HSD17B1* haplotypes or htSNPs and overall risk of breast cancer was found. The ORs for each haplotype relative to the most common haplotype ranged from 0.98 to 1.07 (omnibus test for association: X2 = 3.77, $p = 0.58$, 5 degrees of freedom). However, when cases were subdivided by estrogen receptor (ER) status, two common haplotypes were associated with ER-negative tumors (p for trend = 0.0009 and 0.0076; n = 353 cases). **(Feigelson HS, Cox DG, Cann HM, Wacholder S, Kaaks R, Henderson BE, Albanes D, Altshuler D, Berglund G, Berrino F, Bingham S, Buring JE, Burtt NP, Calle EE, Chanock SJ, Clavel-Chapelon F, Colditz G, Diver WR, Freedman ML, Haiman CA, Hankinson SE, Hayes RB, Hirschhorn JN, Hunter D, Kolonel LN, Kraft P, LeMarchand L, Linseisen J, Modi W, Navarro C, Peeters PH, Pike MC, Riboli E, Setiawan VW, Stram DO, Thomas G, Thun MJ, Tjonneland A, Trichopoulos D. Haplotype analysis of the *HSD17B1* gene and risk of breast cancer: A comprehensive approach to multicenter analyses of prospective cohort studies. *Cancer Res* 2006;66:2468–2475)**

CERVICAL CANCER

Age-related Cervical Changes and HPV Type

Approximately 15 human papillomavirus (HPV) types cause virtually all cervical cancer, whereas other HPV types are unrelated. Whether noncarcinogenic types differ in affinity for the cervical transformation zone, where most HPV-induced cancers occur, was examined by testing cervical specimens from 8,374 women without cervical precancer or cancer participating in a population-based study in Guanacaste, Costa Rica. Age-specific prevalences of HPV types of the alpha9 species, which are mainly carcinogenic and include HPV16, were compared to the genetically distinct types of the alpha3/alpha15 species (e.g., HPV71), which are noncarcinogenic. Prevalence of alpha9 types (7.6%) peaked in the youngest women, declined in middle-aged women, and then increased slightly in older women. By contrast, prevalence of alpha3/alpha15 types (7.6%) tended to remain invariant or to increase with age. Detection of alpha9 infections increased (p for trend < 0.0005) but alpha3/alpha15 infections decreased (p for trend < 0.0005) with increasing exposure of the columnar epithelia. Older age and decreasing cervical ectopy were independently positively associated with having an alpha3/alpha15 infection compared with having an alpha9 infection. These distinct groups of HPV types appear to differ in tissue preferences, which may contribute to their differences in carcinogenic potential. **(Castle PE, Jeronimo J, Schiffman M, Herrero R, Rodriguez AC, Bratti MC, Hildesheim A, Wacholder S, Long LR, Neve L, Pfeiffer R, Burk RD. Age-related changes of the cervix influence human papillomavirus type distribution. *Cancer Res* 2006;66:1218–1224)**

COLORECTAL NEOPLASMS

Iron Intake

Whether dietary intake of iron is associated with colorectal cancer was assessed in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort. Based on 130 colorectal cancer cases (73 colon cancers and 57 rectal cancers) and 260 controls, there was an inverse association between serum ferritin and colorectal cancer risk (OR = 0.4; CI = 0.2–0.9) and a suggestion of an inverse association between dietary iron and colorectal cancer risk (OR = 0.4; CI = 0.1–1.1). In addition, serum ferritin, serum iron, and transferrin saturation were all inversely associated with colon cancer risk (OR = 0.2; CI = 0.1–0.7; p for trend = 0.02, OR = 0.2; CI = 0.1–0.9; p for trend = 0.05, OR = 0.1; CI = 0.02–0.5; p for trend = 0.003, respectively), whereas serum unsaturated iron binding capacity was positively associated with colon cancer risk (OR = 4.7; CI = 1.4–15.1; p for trend = 0.009). **(Cross AJ, Gunter MJ, Wood RJ, Pietinen P, Taylor PR, Virtamo J, Albanes D, Sinha R. Iron and colorectal cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Int J Cancer* 2006;118:3147–3152)**

Inflammation and C-reactive Protein

Serum C-reactive protein (CRP), a marker of inflammation, was examined in relation to colorectal cancer incidence in a nested case-control study of 130 cases and 260 controls within the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study's cohort of 29,133 Finnish males. Baseline median CRP levels were approximately 25% higher among cases (3.4 mg/L) than controls (2.6 mg/L; $p = 0.04$). Relative to men in the lowest quartile of CRP concentration, men in the highest quartile had an OR of 2.9 (CI = 1.4–6.0; p for trend = 0.006) (see Figure 2). The relation between CRP and colorectal cancer was stronger among lean individuals than heavier individuals (p for interaction = 0.018). **(Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Weinstein S, Wood RJ, Virtamo J, Taylor PR, Albanes D, Sinha R. A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res* 2006;66:2483–2487)**

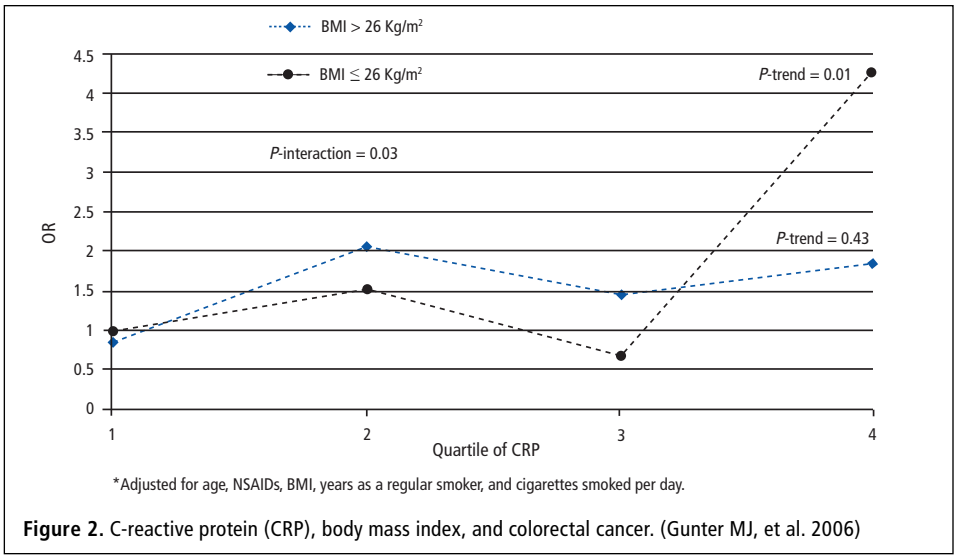


Figure 2. C-reactive protein (CRP), body mass index, and colorectal cancer. (Gunter MJ, et al. 2006)

Nucleotide Excision Repair Genes

Nucleotide excision repair enzymes remove bulky damage caused by environmental carcinogens, including polycyclic aromatic hydrocarbons found in cigarette smoke, a risk factor for colorectal adenoma. Among participants randomized to the screening arm of the PLCO Cancer Screening Trial, the risk of advanced colorectal adenoma in relation to cigarette smoking and 15 SNPs in seven nucleotide excision repair genes [*XPC, RAD23B (hHR23B), CSB (ERCC6), XPD (ERCC2), CCNH, XPF (ERCC4),* and *XPG (ERCC5)*] was studied. Cases (n = 772) had left-sided advanced adenoma (>1 cm in size, high-grade dysplasia, or villous characteristics). Controls (n = 777) were screen-negative for left-sided polyps by sigmoidoscopy. None of the SNPs were associated with advanced adenoma risk. Smoking was related to adenoma risk, and *XPC* polymorphisms ($_{R}492_{H}$, $_{A}499_{V}$, $_{K}939_{Q}$) modified these effects (p for interaction from 0.03 to 0.003). Although the three XPC variants were in linkage disequilibrium, a multivariate logistic regression tended to show independent protective effects for $XPC\ 499_{V}$ (p for trend = 0.06), a finding supported by haplotype analysis (covariate-adjusted global permutation $p = 0.03$). **(Huang WY, Berndt SI, Kang D, Chatterjee N, Chanock SJ, Yeager M, Welch R, Bresalier RS, Weissfeld JL, Hayes RB. Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. *Cancer Epidemiol Biomarkers Prev* 2006;15:306–311)**

ESOPHAGEAL AND GASTRIC CANCERS

Goiter and Gastric Adenocarcinoma

Iodine is concentrated by the gastric mucosa, where it may act as an antioxidant. Thus, iodine deficiency and its sequela, goiter, may be associated with an increased risk of gastric cancer. In a Chinese cohort of 29,584 adults, self-reported goiter was associated with an increased risk of gastric noncardia adenocarcinoma (hazard ratio [HR] = 2.04; CI = 1.01–4.11) and nonsignificantly associated with gastric cardia adenocarcinoma (HR = 1.45; CI = 0.91–2.30). Also, a borderline increased risk of esophageal squamous cell carcinoma (HR = 1.37; CI = 0.97–1.94) was found. Findings are consistent with the hypothesis that iodine deficiency is associated with an increased risk of gastric cancer. **(Abnet CC, Fan JH, Kamangar F, Sun XD, Taylor PR, Ren JS,**

Mark SD, Zhao P, Fraumeni JF Jr, Qiao YL, Dawsey SM. Self-reported goiter is associated with a significantly increased risk of gastric noncardia adenocarcinoma in a large population-based Chinese cohort. *Int J Cancer* 2006; Apr 26 [Epub ahead of print])

GENETICS

Genetic Counseling

Predisposition genetic testing is routinely accompanied by genetic counseling, which addresses many issues related to the implications of testing, including the confidentiality of test results and the appropriateness of sharing test results with family members. This paper reports the case of a 55-year-old woman who tested positive for a *BRCA1* mutation and then lied to her family about her test result in the presence of research team members. This act created an ethical dilemma for the patient's caregivers, who must balance respect for patient privacy against the benefit of disclosing clinically relevant information to at-risk family members. Ultimately, the confidentiality of this patient's genetic information was maintained. Researchers maintained contact with the patient over two years, encouraging her to share the true results with her daughter, which she eventually did. The authors recommend that health care professionals: (a) encourage patients to share genetic information with close family members; (b) strongly encourage patients to be truthful in communication with family members. With prior warning to the patient of the expectation that the patient will be truthful in the communication of test results to family members, the authors suggest that it is acceptable for a clinician to publicly disagree with a patient who lies to family members in the presence of that clinician. (Loud JT, Weissman NE, Peters JA, Giusti RM, Wilfond BS, Burke W, Greene MH. Deliberate deceit of family members: A challenge to providers of clinical genetics services. *J Clin Oncol* 2006;24:1643–1646)

LEUKEMIA

Autoimmune Disorders and CLL

A population-based case-control study was conducted to evaluate risk of developing chronic lymphocytic leukemia (CLL) associated with personal and/or family history of autoimmune and related diseases. Data were obtained for all (n = 7,764) CLL cases diagnosed in Sweden and Denmark over a 40-year period and with linkable relatives, 16,658 matched controls, and first-degree relatives of cases (n = 17,991) and controls (n = 39,388). The risk of CLL was significantly increased among subjects with a personal history of pernicious anemia (OR = 1.94; CI = 1.18–3.18), mainly in the 0–1-year latency period. A significantly decreased risk of CLL was found among individuals with a personal history of chronic rheumatic heart disease (OR = 0.55; CI = 0.33–0.93), particularly persons with a long latency (10+ years) between the two conditions. No associations between personal or familial occurrence of other autoimmune or related disorders and CLL were found. (Landgren O, Engels E, Caporaso NE, Gridley G, Mellemkjaer L, Hemminki K, Linet MS, Goldin LR. Patterns of autoimmunity and subsequent chronic lymphocytic leukemia in nordic countries. *Blood* 2006; Mar 9 [Epub ahead of print])

Genetic Susceptibility to Familial CLL

A subset of chronic lymphocytic leukemia (CLL) shows familial aggregation. A genome-wide scan of 18 CLL families in 2003 detected LOD or non-parametric linkage scores of at least 1.0 on chromosomes 1, 3, 6, 12, 13, and 17. A follow-up study with 28 families showed no evidence of linkage at 1p22.1–p21.2, 3q22.1, 3q26.2, 6q22.31–q23.2, 12q24.23, 14q32.13, or 17p13.3. Chromosome 13q21.33 remains a region of interest with a p-value of 0.013 (marker D13S1291) and warrants additional study as a susceptibility region for CLL. (Ng D, Marti GE, Fontaine L, Toro JR, Caporaso N, Goldin LR. High-density mapping and follow-up studies on chromosomal regions 1, 3, 6, 12, 13 and 17 in 28 families with chronic lymphocytic leukaemia. *Br J Haematol* 2006;133:59–61)

LYMPHOMA

Insecticide Use

In a population-based, multi-center case-control study, non-Hodgkin lymphoma (NHL) risk and use of insecticides in the home and garden were examined using interview data on insecticide use at each home occupied since 1970 (1,321 cases and 1,057 controls) and measures of insecticide levels in dust taken from used vacuum cleaner bags (682 cases and 513 controls). People whose homes were treated for termites had elevated NHL risk (OR = 1.3; CI = 1.0–1.6). Risk was modestly, but not significantly, elevated in all but one study center and in all sexes and races. The elevation in risk was restricted to persons from homes treated before the 1988 chlordane ban. There was a trend of increasing risk with increasing levels of alpha-chlordane residues in dust (p for trend = 0.04) and a suggested trend for gamma-chlordane (p for trend = 0.06). (Colt JS, Davis S, Severson RK, Lynch CF, Cozen W, Camann D, Engels EA, Blair A, Hartge P. Residential insecticide use and risk of non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev* 2006;15:251–257)

Oxidative Stress Genes

Variations within genes mediating oxidative stress were investigated to determine whether they alter risk for NHL. Thirteen SNPs from ten oxidative stress genes *(AKR1A1, AKR1C1, CYBA, GPX, MPO, NOS2A, NOS3, OGG1, PPARG, SOD2)* were genotyped in 1,172 NHL cases and 982 population-based controls from a U.S. multi-center case-control study. Overall, the oxidative stress pathway was associated with the diffuse large B-cell type of NHL (global p = 0.003). Specifically, for nitric oxide synthase (*NOS2A* Ser608Leu, rs2297518) Leu/Leu homozygotes, there was a twofold risk increase

for NHL (OR = 2.2; CI = 1.1–4.4; referent = Ser/Ser and Ser/Leu). This risk increase was consistent by cell lineage (B- and T-cell NHL) and pronounced for the two most common subtypes, diffuse large B-cell (OR = 3.4; CI = 1.5–7.8) and follicular lymphoma (OR = 2.6; CI = 1.0–6.8). In an analysis of manganese superoxide dismutase (*SOD2* Val16Ala, rs1799725) Ala/Ala homozygotes, moderately increased risk for B-cell lymphomas (OR = 1.3; CI = 1.0–1.6; referent = Val/Val and Val/Ala) was consistent across subtypes. Further evaluation of oxidative stress in the context of inflammation, DNA repair, and the induction of the NF-kB pathway may reveal important clues for lymphomagenesis. **(Wang SS, Davis S, Cerhan JR, Hartge P, Severson RK, Cozen W, Lan Q, Welch R, Chanock SJ, Rothman N. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. *Carcinogenesis* 2006; Mar 16 [Epub ahead of print])**

Th1/Th2 Cytokines

SNPs in 20 candidate Th1/Th2 genes were analyzed in a population-based case-control study of NHL ($n = 518$ cases, 597 controls) of women in Connecticut. Analyses of four SNPs in the *IL10* promoter (−3575T >A, −1082A >G, −819C >T, and −592C >A) revealed that both the AGCC haplotype (OR = 1.54; CI = 1.21–1.96; $p < 0.001$) and the TATA haplotype (OR = 1.37; CI = 1.05–1.79; $p = 0.02$) were associated with increased risk for B-cell lymphoma. In contrast, the *IL4*-1098G allele was associated with increased risk of T-cell lymphoma (OR = 3.84; CI = 1.79–8.22; $p < 0.001$). Thus, SNPs in Th2 cytokine genes may be associated with risk of NHL. **(Lan Q, Zheng T, Rothman N, Zhang Y, Wang SS, Shen M, Berndt SI, Zahm SH, Holford TR, Leaderer B, Yeager M, Welch R, Boyle P, Zhang B, Zou K, Zhu Y, Chanock S. Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. *Blood* 2006;107:4101–4108)**

METHODS

Combining Methods to Analyze Genotype and Family Data

In case-control studies of inherited diseases, participating subjects (probands) are often interviewed to collect detailed data about disease history and age-at-onset information for their family members. Genotype data are typically collected from the probands but not from their relatives. In this article, an approach is introduced that combines case-control analysis of data on the probands with kin-cohort analysis of disease history data on relatives to estimate relative risk, cumulative risk, and residual familial aggregation. A variation of the methodology that can be used for kin-cohort analysis of the family history data from a sample of genotyped cases only is also described. Simulation studies to assess performance of the proposed methodologies with correct and misspecified models for familial aggregation are also conducted. The proposed methodologies are illustrated by estimating the risk of breast cancer from *BRCA1/2* mutations using data from the Washington Ashkenazi Study. **(Chatterjee N, Kalaylioglu Z, Shih JH, Gail M. Case-control and case-only designs with genotype and family history data: Estimating relative risk, residual familial aggregation, and cumulative risk. *Biometrics* 2006;62:36–48)**

OCCUPATIONAL EXPOSURES

Polymorphisms and Hematotoxicity of Benzene

SNPs in 20 cytokine and cellular adhesion molecule genes that regulate hematopoiesis were analyzed in a study of 250 workers exposed to benzene and 140 unexposed controls in China. SNPs in five genes were associated with a significant decrease in total WBC counts among exposed workers [*IL-1A* (−889C>T), *IL-4* (−1098T>G), *IL-10* (−819T>C), *IL-12A* (8685G>A), and *VCAM1* (−1591T>C)], and one SNP [*CSF3* (Ex4−165C>T)] was associated with an increase in WBC counts. The adhesion molecule *VCAM1* variant was particularly noteworthy as it was associated with a decrease in B cells, natural killer cells, CD4+ T cells, and monocytes. Further, *VCAM1* (−1591T>C) and *CSF3* (Ex4−165C>T) were associated, respectively, with decreased ($p = 0.041$) and increased ($p = 0.076$) CFU-GEMM progenitor cell colony formation in 29 benzene-exposed workers. **(Lan Q, Zhang L, Shen M, Smith MT, Li G, Vermeulen R, Rappaport SM, Forrest MS, Hayes RB, Linet M, Dosemeci M, Alter BP, Weinberg RS, Yin S, Yeager M, Welch R, Waidyanatha S, Kim S, Chanock S, Rothman N. Polymorphisms in cytokine and cellular adhesion molecule genes and susceptibility to hematotoxicity among workers exposed to benzene. *Cancer Res* 2005;65:9574–9581)**

PROSTATE CANCER

Interleukin-1B (IL-1B), IL-6, IL-8, and IL-10

Polymorphisms in cytokine genes can influence inflammation and immune response and may be related to the risk of prostate cancer. Four common SNPs in the genes encoding interleukin-1B (IL-1B), IL-6, and IL-8 were assessed in 503 prostate cancer cases and 652 controls, and three SNPs in *IL-10* were assessed in 1,320 cases and 1,842 controls from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. No associations were detected between the seven polymorphisms in the four cytokine genes and prostate cancer risk. Use of nonsteroidal anti-inflammatory drugs and stage of disease did not modify the associations. No association between the major *IL-10* haplotypes and the risk of prostate cancer was observed. **(Michaud DS, Daugherty SE, Berndt SI, Platz EA, Yeager M, Crawford ED, Hsing A, Huang WY, Hayes RB. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. *Cancer Res* 2006;66:4525–4530)**

Vitamin E, Beta-carotene, and Vitamin C

Intake of the antioxidants vitamin E, beta-carotene, and vitamin C from foods and supplements and the risk of prostate cancer were studied among 29,361 men in the screening arm of the PLCO Cancer Screening Trial. Based on 1,338 prostate cancer cases, there was no overall association between risk and dietary or supplemental intake of vitamin E, beta-carotene, or vitamin C. However, among current and recent smokers, decreasing risks of advanced prostate cancer were associated with increasing dose (RR = 0.29; CI = 0.12–0.68; *p* for trend = .01) and duration (RR for ≥ 10 years of use vs. none = 0.30; CI = 0.09–0.96; *p* for trend = .01) of supplemental vitamin E use. Supplemental beta-carotene intake at a level of at least 2,000 µg/day was associated with decreased risk in men with low dietary beta-carotene intake (RR = 0.52; CI = 0.33–0.81). Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100,000 person-years in those who did not take supplemental vitamin E, 153 per 100,000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100,000 person-years in those who took supplemental vitamin E for 10 or more years. Among men with low dietary beta-carotene intake, the age-adjusted rate of prostate cancer was 1,122 per 100,000 person-years in those who did not take supplemental beta-carotene and 623 per 100,000 person-years in those who took at least 2,000 µg/day of supplemental beta-carotene. **(Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, Albanes D, Andriole GL, Urban DA, Peters U. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst* 2006;98:245–254)**

SECOND CANCERS

AML after Hodgkin Lymphoma

Treatments for Hodgkin lymphoma are associated with large relative risks of acute myeloid leukemia (AML), but there are few estimates of the excess absolute risk (EAR), a useful measure of disease burden. One-year Hodgkin lymphoma survivors (n = 35,511) were identified within 14 population-based cancer registries in Nordic countries and North America from 1970 through 2001. A total of 217 Hodgkin lymphoma survivors were diagnosed with AML (10.8 expected; unadjusted EAR = 6.2; CI = 5.4–7.1). Excess absolute risk for AML was highest during the first ten years after Hodgkin lymphoma diagnosis but remained elevated thereafter. The EAR was significantly (p < .001) larger in patients diagnosed with Hodgkin lymphoma at age 35 years and older than in those diagnosed before 35 years of age (see Figure 3). The EAR of AML declined significantly after 1984 (from 7.0 to 4.2 and 16.4 to 9.9 in the younger [<35] and older [≥35] age groups, respectively), which may be associated with modifications in chemotherapy. **(Schonfeld SJ, Gilbert ES, Dores GM, Lynch CF, Hodgson DC, Hall P, Storm H, Andersen A, Pukkala E, Holowaty E, Kaijser M, Andersson M, Joensuu H, Fosså SD, Allan JM, Travis LB. Acute myeloid leukemia following Hodgkin lymphoma: A population-based study of 35,511 patients. *J Natl Cancer Inst* 2006;98:215–218)**

Breast Cancer after Hodgkin Lymphoma

Data from a breast cancer case-control study (105 cases, 266 controls) conducted among 3,817 survivors of Hodgkin lymphoma (HL) diagnosed at age 30 years or younger in six population-based cancer registries were analyzed. Women who received radiotherapy (RT) exposure of at least 5 Gy to the breast had a 2.7-fold increased breast cancer risk (CI = 1.4–5.2), compared with those given less than 5 Gy. RT exposure of at least 5 Gy was associated with an OR of 0.8 (CI = 0.2–3.4) among women with a first- or second-degree family history of breast or ovarian cancer and 5.8 (CI = 2.1–16.3) among all other women (p for interaction = 0.03). History of a live birth appeared to increase the breast cancer risk associated with RT among women not treated with ovary-damaging therapies. The additional increased relative risk of breast cancer after RT for HL is unlikely to be larger among women with a family history of breast or ovarian cancer than among other women. **(Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer M, Storm H, Pukkala E, Stovall M, Curtis RE, Allan JM, Boice JD, Travis LB. Breast cancer risk following radiotherapy for Hodgkin**

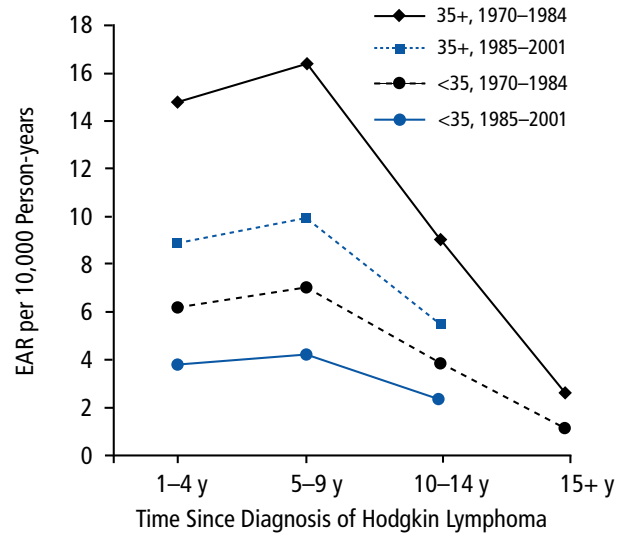


Figure 3. Excess absolute risk (EAR) of acute myeloid leukemia by time since diagnosis of Hodgkin lymphoma. (Schonfeld SJ, et al. 2006)

lymphoma: Modification by other risk factors. *Blood* 2005;106:3358–3365)

VIRUSES

In Utero and Perinatal HIV Infection Risk

This study analyzed mother-to-child HIV transmission rates by gender and exposure time for babies born to HIV-infected, untreated African women. Among 1,394 singleton births, girls were more likely to become infected than boys. For *in utero* transmission (infected in umbilical cord blood), the OR was 1.4 (CI = 0.9–2.2). For transmission during "early life," the OR was 2.7 (CI = 1.5–4.9). However, transmission risks in the perinatal (infected in first postnatal blood) and postnatal (later postnatal infection) periods did not differ in boys and girls. Among 303 tested twin-birth pairs, girls were at higher risk than boys for *in utero* (OR = 2.6; CI = 1.2–5.8) and perinatal (OR = 1.9; CI = 1.0–3.7) infection. Recognized mother-to-child transmission risk factors did not explain the higher risk of infection in girls. It is proposed that minor histocompatibility reactions between maternal lymphocytes and infant Y chromosome-derived antigens reduce the risk of HIV transmission in boys. **(Biggar RJ, Taha TE, Hoover DR, Yellin F, Kumwenda N, Broadhead R. Higher in utero and perinatal HIV infection risk in girls than boys. *J Acquir Immune Defic Syndr* 2006:41:509–513)**

Host Immunogenetics and HHV-8 Infection Control

Kaposi sarcoma (KS) is primarily caused by human herpesvirus 8 (HHV-8) infection, and the risk is increased with high HHV-8 lytic or latent antibody titers or the detection of HHV-8 DNA in peripheral blood mononuclear cells (PBMCs). In 172 HHV-8 latent nuclear antigen (LANA)–seropositive adults in Italy without KS, the authors examined correlations of common variants in host immune genes with the detection of HHV-8 DNA in PBMCs and with high lytic and latent antibody titers. Detection of HHV-8 DNA in PBMCs was not significantly related to any variant examined. In contrast, a 3-locus haplotype of *IL4,* which contains the *−1098G* allele (rs2243248), was overrepresented among subjects with high lytic titers (OR = 2.8; CI = 1.1–6.7) compared with those with low titers, as was the functional promoter variant of *IL6,* C-236C (rs1800795) (OR = 3.7; CI = 1.1–12.8). Compared with subjects with low HHV-8 latent antibody titers, analysis of inferred haplotypes for *IL12A* revealed an overrepresentation of −798T/277A in subjects with high HHV-8 latent antibody titers (OR = 2.4; CI = 1.1–5.2). Thus, common variants in key host immune genes may influence the control of HHV-8 infection. **(Brown EE, Fallin MD, Goedert JJ, Hutchinson A, Vitale F, Lauria C, Giuliani M, Marshall V, Mbisa G, Serraino D, Messina A, Durum S, Whitby D, Chanock SJ. Host immunogenetics and control of human herpesvirus-8 infection. *J Infect Dis* 2006;193:1054–1062)**

Risk Factors for HHV-8 Seropositivity

Factors associated with human herpesvirus 8 (HHV-8) seropositivity were evaluated in 2,795 participants (132 with Kaposi sarcoma [KS]) in the NCI AIDS Cancer Cohort, including 1,621 men who have sex with men (MSM), 660 heterosexual men, and 514 women. Among non-KS subjects, HHV-8 seropositivity was 6%, 13%, and 29% among women, heterosexual men and MSM, respectively. HHV-8 seropositivity was decreased in heavier (at least one-half pack/day) compared to lighter smokers among women (5% vs. 8%; OR = 0.4; CI 0.2–0.8) and MSM (27% vs. 32%; OR = 0.7; CI = 0.6–1.0), but not among heterosexual men (12% vs. 16%; OR = 0.7; CI = 0.4–1.2). HHV-8 seroprevalence was increased in heavier (at least one drink/day) compared to lighter consumers of alcohol among women (16% vs. 4%; OR = 5.2; CI = 2.3–12), but not among MSM (33% vs. 28%; OR = 1.2; CI = 0.9–1.6) or heterosexual men (13% vs. 13%; OR = 1.1; CI = 0.6–2.0). HHV-8 seropositivity was positively associated with chlamydia infection (OR = 4.3; CI = 1.2–13) and with marital status among women (*p* for heterogeneity = 0.03), and with hepatitis (OR = 1.6; CI = 1.2–2.1), gonorrhea (OR = 1.5; CI = 1.1–1.9), genital warts (OR = 1.5; CI = 1.1–2.0), and nitrate inhalant use (OR = 1.7; CI = 1.3–2.3) among MSM. Smoking and drinking may influence KS risk, at least in part, by altering the natural history of HHV-8 infection. **(Mbulaiteye SM, Atkinson JO, Whitby D, Wohl DA, Gallant JE, Royal S, Goedert JJ, Rabkin CS. Risk factors for human herpesvirus 8 seropositivity in the AIDS Cancer Cohort Study. *J Clin Virol* 2006;35:442–449)**

HHV-8 Transmission

A risk factor for Kaposi sarcoma (KS)–related herpesvirus (KSHV, also known as HHV-8) infection in children is having a KSHV-seropositive mother. *K1* sequences from 6 of 10 mother-child pairs were obtained. In one pair, the subtypes differed between mother and child. The mother and child in two other pairs shared the same subtype, but the sequences differed. The mother and child in two pairs shared KSHV strains with exact (100%) nucleotide homology. The last pair showed evidence of viral strain concordance between mother and child but also showed evidence of evolution of the viral sequence within the child. Findings are consistent with KSHV transmission from maternal and nonmaternal sources in KS-endemic regions. Results also provide evidence for ongoing evolution of the *K1* gene in KSHV-infected children. **(Mbulaiteye S, Marshall V, Bagni RK, Wang CD, Mbisa G, Bakaki PM, Owor AM, Ndugwa CM, Engels EA, Katongole-Mbidde E, Biggar RJ, Whitby D. Molecular evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus in Uganda and *K1* gene evolution within the host. *J Infect Dis* 2006;193:1250–1257)**

DCEG PEOPLE IN THE NEWS

Sonja Berndt, Pharm.D., Occupational and Environmental Epidemiology Branch (OEEB), gave a presentation on "Genetic polymorphisms in DNA repair genes and the risk of colorectal cancer" at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in March.

Parveen Bhatti, Ph.D., Radiation Epidemiology Branch (REB), joined the Branch as a predoctoral fellow from the Department of Environmental and Occupational Health Sciences at the University of Washington. In March, he successfully defended his dissertation entitled "DNA double-strand break repair polymorphisms, ionizing radiation exposure, and breast cancer risk" and received his Ph.D. in environmental health.


Parveen Bhatti

Robert Biggar, M.D., Viral Epidemiology Branch (VEB), gave an invited talk on "Predicting the future risk in persons with AIDS" at the AIDS Malignancy Working Group meeting in February at NIH.

In February, **Aaron Blair, Ph.D.** (OEEB), gave two invited seminars in Norway: "Agricultural exposures" at the National Institute of Occupational Health of Norway and "Confounding and exposure misclassification" at the Norwegian Cancer Registry.


Aaron Blair

Nilanjan Chatterjee, Ph.D., Biostatistics Branch (BB), delivered invited talks on "Powerful strategies for linkage disequilibrium mapping by exploiting gene-gene and gene-environment interactions" before the Department of Biostatistics at the Harvard School of Public Health in February; for the Department of Statistics at the University of Florida, Gainesville in March; and at a session on Recent Advances in Statistical Methods for Genetic Epidemiology at the Eastern North American Region of the International Biometrics Society in Tampa in March.

Mitchell Gail, M.D., Ph.D. (Chief of BB), gave a talk titled "On criteria for evaluating models of absolute risk" for the Department of Biostatistics at the University of Pennsylvania in December.

Barry Graubard, Ph.D. (BB), gave an invited talk on "Using national surveys to compute the number of deaths attributable to a risk factor" in a session on Health Survey Data at the Eastern North American Region of the International Biometric Society meeting in Tampa in March.

In an all-day session devoted to the Chornobyl accident, **Maureen Hatch, Ph.D.** (REB), gave a presentation entitled "The Ukrainian-American studies of thyroid diseases and leukemia following the Chornobyl accident" at the Academy of Medical Sciences of Ukraine in Kiev in March.


Maureen Hatch

In May, **Michie Hisada, M.D., M.P.H., Sc.D.** (VEB), gave an invited talk on "Geographic variations in risk of virus-associated cancers: Challenges in the era of genetic and molecular epidemiology" at the Viruses and Cancer: Recent Lessons and Future Directions Symposium sponsored by the Cancer Epidemiology Program of the Dana-Farber/Harvard Cancer Center and the Department of Epidemiology at the Harvard School of Public Health. The Symposium was held on the occasion of the retirement of Dr. Nancy Mueller, who was Dr. Hisada's doctoral advisor.


Ann Hsing

In March, **Ann Hsing, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), gave an invited talk on "Obesity, metabolic syndrome, and prostate cancer" at the Metabolic Syndrome and the Onset of Cancer Symposium at Harvard University Medical School. She also recently became a member of the Nominating Committee of the American College of Epidemiology.


Peter Inskip

Peter Inskip, Sc.D. (REB), gave an invited presentation on "Secondary breast cancer in the Childhood Cancer Survivor Study" for Adverse Events after Childhood Cancer: Quest for Identification of At-risk Populations at the Children's Oncology Group meeting in Chicago in March.

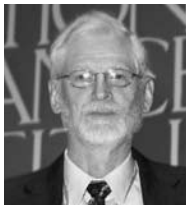

José Jeronimo

José Jeronimo, M.D. (HREB), gave a lecture on "New developments in the diagnosis and treatment of pre-invasive lesions of the uterine cervix" at the Bi-national Symposium on Cervical Cancer held by the American Cancer Society in Tijuana, Mexico in February.

In March, **Daehee Kang, M.D., Ph.D.** (OEEB), gave an invited talk on "Genetic susceptibility to breast cancer in Korea" at the Centers for Disease Control and Prevention's Office of Genomics and Disease Prevention in Atlanta. He was also selected by the American Association for Cancer Research to reside on the editorial board of *Cancer Epidemiology, Biomarkers & Prevention*.


James Lacey

In March, **James Lacey, Ph.D.** (HREB), spoke on "Exogenous hormones and gynecologic cancer risk" at the Hormones and Women's Cancers Symposium at Mount Carmel East Hospital in Columbus and at the Georgetown University Department of Internal Medicine Medical Grand Rounds in Washington, DC.


Charles Land

In December, **Charles Land, Ph.D.** (REB), was the honorary chair for the Annual Gilbert W. Beebe Symposium at the National Academy of Sciences in Washington, DC and presented an invited talk on "The uncertain world of radiation-related risk: Policy implications at low doses." In February, he gave invited talks on the same subject to the Radiation Biology Center at Kyoto University; the Nuclear Radiation Safety Association in Tokyo; and the Radiation Effects Research Foundation in Hiroshima. He also gave invited presentations on "Probability of causation for possibly radiation-related cancers" to the Veterans Affairs Advisory Board on Dose Reconstruction in Los Angeles and the Radiation Effects Research Association in Tokyo in January.


Michael Leitzmann

Michael Leitzmann, M.D., Dr.P.H., Nutritional Epidemiology Branch (NEB), gave talks entitled "Body size and selected outcomes in the Asia Cohort Consortium" and "Instruments for assessing obesity and physical activity in the Asia Cohort Consortium" at the Asia Cohort Consortium Workshop in Washington, DC in March. He has also been selected to serve as chair of the Obesity and Physical Activity Working Group of the Consortium.


Ihor Masnyk

In April, **Ihor J. Masnyk, Ph.D.** (REB), spoke on the U.S.-Ukraine thyroid cancer and leukemia studies at several conferences, including the 20 Years after Chornobyl Catastrophe Conference in Minsk-Gomel, Belarus; 20 Years after Chornobyl Accident: Future Outlook in Kiev, Ukraine; and Chornobyl: The Next Generation at the University of Illinois at Chicago. In June, he participated in the Chornobyl, 20 Years Later: Health, Environment, & the Sociology of a Disaster Zone Symposium at the University of Illinois at Urbana-Champaign. In April, he received a letter of gratitude from the Chair of the Belrusian Red Cross, Dr. L. A. Postoyalko, for his significant contribution in providing aid to the population suffering from the Chornobyl catastrophe.

Rayna Matsuno, M.S. (BB), gave a talk on "Breast cancer incidence and survival: Post-menopausal differences between the U.S. and Japanese populations" at the George Washington University Medical Center's 11th Annual Research Day in March, for which she won the Best Public Health Presentation Award.

In January, **Roxana Moslehi, Ph.D.** (BB), gave an invited presentation titled "Genetic epidemiologic studies of cancer and cancer precursors" at the Department of Epidemiology and Biostatistics of the School of Public Health at the State University of New York at Albany and "Studies of predisposition to cancer and cancer precursors" at Fox Chase Cancer Center. She also used her NIH FARE Award for travel to the AACR Special Conference on Cancer Susceptibility and Cancer Susceptibility Syndromes in Maui, where she gave a poster presentation on "N-acetyltransferases (*NAT1* and *NAT2*) and the risk of advanced colorectal adenoma" in March.


Ruth Pfeiffer

Ruth Pfeiffer, Ph.D. (BB), delivered a talk titled "A model-free approach to combining diagnostic markers" at the Biostatistics Seminar at Yale University in March.

In January, **Elaine Ron, Ph.D.** (REB), spoke on "Thyroid cancer and Chornobyl" at the Scientific Colloquium on Radiation and Health in Paris. In March, she spoke on "Radiation and thyroid cancer" at the American Thyroid Association Spring Symposium on Thyroid and the Environment: Threats and Effects in Washington, DC. In April, she spoke on "Thyroid cancer among exposed populations" at the National Council on Radiation Protection Meeting: Chornobyl in Washington, DC and on "Radiation and cancer" for the Columbia University Course on Radiological Science in the Context of Radiological Terrorism in New York. Lastly, in May, she spoke on "Thyroid cancer and Chornobyl" at


Elaine Ron

the Massachusetts Eye and Ear Infirmary Meeting in Boston on Chornobyl Thyroid Cancer Twenty Years after the Disaster.


Philip Rosenberg

In May, **Philip Rosenberg, Ph.D.** (BB), was elected to the American Society of Hematology in recognition of his research on inherited bone marrow failure syndromes.


Mark Sherman

In March, **Mark Sherman, M.D.** (HREB), spoke at Pathology Grand Rounds at the University of Pennsylvania on "Human papillomaviruses: From first principles to prevention."


Mary Ward

In February, **Mary Ward, Ph.D.** (OEEB), participated in the Global Environment Forum and spoke on "Nitrates and health" as part of the International Lecture Series, an online course coordinated by the University of Iowa in Iowa City.

Tania Mara Welzel, M.D., M.H.Sc. (HREB), gave a talk on "HLA-B Bw4 and Bw6 alleles and risk for HIV-1 transmission in HIV-serodiscordant heterosexual couples" at the 13th Conference on Retroviruses and Opportunistic Infections in Denver in February.


Tania Mara Welzel

COMINGS . . . GOINGS

After 26 years of service in the federal government, including 17 years in the Radiation Epidemiology Branch (REB), **Shirley Boggins** retired in March. She has launched her new career in interior design in Charlotte, North Carolina.


Shirley Boggins received DCEG Special Appreciation Award. *(Photograph Credit: Sadrea Muhammad)*

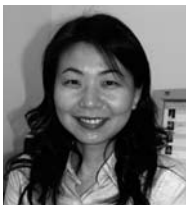
Abhijit Dasgupta, Ph.D., a postdoctoral fellow in the Biostatistics Branch (BB), has joined the faculty of Thomas Jefferson University in Philadelphia as an Assistant Professor in the Department of Biostatistics of the School of Pharmacology and Experimental Therapeutics.


Bryan Dolan

Bryan Dolan has joined the Viral Epidemiology Branch (VEB) as a predoctoral fellow. He graduated from Amherst College, having completed premedical training and obtaining a bachelor's degree in English. He will be editing manuscripts for VEB and analyzing data from hemophilia and Egyptian studies with **James Goedert, M.D.,** and **Sam Mbulaiteye, M.D.,** respectively.

Claudia Giambartolomei has joined the Clinical Genetics Branch (CGB) as a predoctoral fellow. She recently graduated from George Washington University with a B.S. in biology. She is working with CGB investigators on familial cancer susceptibility projects.


Claudia Giambartolomei


Angela Huang

Angela (An-Tsun) Huang, Ph.D., has joined the Occupational and Environmental Epidemiology Branch (OEEB) as a postdoctoral fellow. She will be working on exposure assessment and analysis of risk factors in the New England Bladder Cancer Study and other research projects. She received her Ph.D. from the Department of Environmental Health Sciences at the University of Michigan.


Stella Koutros

Stella Koutros, M.P.H., has joined the Agricultural Health Study research team in OEEB and will be working with **Michael Alavanja, Dr.P.H.** (OEEB), on pesticide-specific cohort analyses and evaluations of lifestyle factors and risk of cancer. She received her M.P.H. from Yale University and is now a doctoral candidate in epidemiology.

In May, **Hongchuan Li, Ph.D.,** completed a four-year postdoctoral fellowship with VEB and joined Dr. Stephen Anderson in the Laboratory of Experimental Immunology at NCI-Frederick, where he will study mechanisms of natural killer cell functions.


Stefan Lönn

Stefan Lönn, Ph.D., joined REB in February. He received his Ph.D. in epidemiology from the Karolinska Institute in 2004. His dissertation was entitled "Mobile phone use and the risk of intracranial tumors." While at REB, Dr. Lönn will continue his research on the

etiology of tumors of the brain and nervous system and broaden his research on the relation between radiation and different types of cancer.


Rayna Matsuno

Rayna Matsuno, M.P.H., joined BB as a predoctoral fellow in January after receiving her M.P.H. from George Washington University. **William Anderson, M.P.H., M.D.** (BB), is acting as her mentor. They are currently working on descriptive studies of breast cancer.

Mahboobeh Safaeian, Ph.D., who recently joined the Hormonal and Reproductive Epidemiology Branch (HREB) as a Sallie Rosen Kaplan Postdoctoral Fellow, received an M.P.H. from the University of Pittsburgh in 1996 and recently completed her Ph.D. in epidemiology from the Johns Hopkins Bloomberg School of Public Health. She trained with Dr. Patti Gravitt and Dr. Ronald Gray at Johns Hopkins University, examining human papillomavirus (HPV) natural history in an HIV-endemic population in Rakai, Uganda. Her thesis was entitled "Utility of self-collected vaginal swabs for studying the epidemiology of HPV infection." She will be working with **Philip Castle, Ph.D., M.P.H.** (HREB), and **Mark Schiffman, M.D., M.P.H.** (HREB), on new diagnostic technologies for HPV and cervical cancer and on the natural history of HPV infection.


Mahboobeh Safaeian


Sharon Savage

Sharon Savage, M.D., has joined the CGB as a tenure-track investigator. She distinguished herself at the University of Vermont Medical School by winning the prestigious Howard Hughes Medical Institute Fellowship, through which she spent two years in the NCI laboratory of Dr. Elise Kohn. She completed her pediatrics training at Children's National Medical Center in Washington, DC and her pediatric hematology/oncology training with the NCI Pediatric Oncology Branch/Johns Hopkins University Fellowship Program. Working with **Stephen Chanock, M.D.,** Director of the Core Genotyping Facility, she developed considerable expertise in the telomere maintenance pathway genes. Her first major project in CGB will target families with dyskeratosis congenita, one of the hereditary bone marrow failure disorders in which germline mutations in telomere pathway genes play a major etiologic role.

Debbie Schoenberg and **Rashida Williams** have joined the DCEG Administrative Resource Center (ARC) as administrative technicians. Ms. Schoenberg arrives in ARC with a wealth of federal travel knowledge, having worked as a contractor for the National Defense University for three years. Ms. Williams joins ARC after working with the Genetic Epidemiology Branch (GEB) as a contractor handling many of their travel requests for the past four years and as an administrative assistant for Edge BioSystems in Gaithersburg, Maryland.


Debbie Schoenberg (left) and Rashida Williams (right)

Roel Vermeulen, Ph.D. (OEEB), has accepted a position as Assistant Professor at the Institute of Risk Analysis Sciences at the University of Utrecht in the Netherlands.

CHANGES IN THE VIRAL EPIDEMIOLOGY BRANCH

Following predoctoral and postdoctoral fellowships in VEB, **Elizabeth Brown, Ph.D.,** has accepted a position as Assistant Professor in the Departments of Epidemiology, Medicine, and Microbiology at the University of Alabama at Birmingham School of Public Health.

In May, **Michie Hisada, M.D., M.P.H., Sc.D.,** a tenure-track investigator in VEB, accepted the position of Medical Director of Pharmacovigilance at TAP Pharmaceutical Products, Inc., located in Lake Forest, Illinois. TAP is a joint venture by Abbott Laboratories and the Takeda Pharmaceutical Company of Japan.

In May, **Shunro Sonoda, M.D., Ph.D.,** Professor Emeritus at Kagoshima University, completed a 12-month sabbatical with VEB. During his sabbatical, Dr. Sonoda conceived and launched an *in vitro* study of the induction of oxidative damage through chronic cellular immune response against human T-cell lymphotropic virus type I. He also provided critical advice on the role of human leukocyte antigen with various diseases.


Shunro Sonoda, Michie Hisada, and Elizabeth Brown.

ROBERT W. MILLER LEAVES AN ENDURING LEGACY

Robert Warwick Miller, M.D., an epidemiologist, pediatrician, and Scientist Emeritus in the Clinical Genetics Branch who played a pivotal role in creating the NCI epidemiology program and in understanding the causes of childhood cancer, died on February 23 at the age of 84.

Dr. Miller was a pioneer in linking forms of childhood cancer to congenital malformation syndromes. In particular, his studies of retinoblastoma, Wilms tumor, and familial cancer occurrences were instrumental in identifying cancer susceptibility genes that opened new avenues of research in molecular and cellular biology.

Dr. Miller arrived at NCI as Chief of the Epidemiology Branch in 1961 and developed a cancer epidemiology unit that achieved worldwide recognition. He recruited many young physicians and scientists, who were drawn to the program's clinical and biological orientation. During his tenure as Branch Chief until 1994, and subsequently as a Scientist Emeritus, he was an active investigator and mentor for many young scientists.

Throughout his career, Dr. Miller called attention to the importance of the alert clinician, whose observations provided the initial clues to the causes of cancer, birth defects, and other conditions. He was asked to organize a Princess Takamatsu international symposium in Tokyo entitled "Unusual Occurrences as Clues to Cancer Etiology" and to edit

Robert Warwick Miller

the proceedings. Dr. Miller was fond of quoting Yogi Berra, who said, "You can observe a lot by watching."

Dr. Miller advised and participated in many high-visibility projects, including studies of Japanese atomic bomb survivors and populations heavily exposed to radioactive fallout, dioxin, and Agent Orange. From 1979 to 1980, he served concurrently at NCI as Director of the Office of International Affairs, where he developed binational agreements and workshops that stimulated collaborative studies with scientists from other countries.

As a fellow of the American Academy of Pediatrics, Dr. Miller served as Chairman of the Committee on Environmental Hazards, where he evaluated the risks from early-life exposures to environmental toxins. He helped establish the annual Practitioner Research Award to honor exemplary office-based research by pediatricians. He received the Outstanding Service Award in 1999.

Dr. Miller was born and raised in New York City. He received his undergraduate (1942) and medical (1946) degrees from the University of Pennsylvania. He then trained in pediatrics at Buffalo Children's Hospital and in radiation medicine at Case Western Reserve and Duke Universities.

From 1955 to 1960, Dr. Miller served as Chief of the Pediatrics Department at the Atomic Bomb Casualty Commission in Hiroshima. He earned a doctorate in public health at the University of Michigan in 1961.

Dr. Miller served as President of the Teratology Society (1970) and as Clinical Professor of Pediatrics at Georgetown University School of Medicine. He received the NIH Director's Award in 1993 and the Distinguished Graduate Award from the University of Pennsylvania School of Medicine in 2002.

Dr. Miller and his wife Haruko (Holly) established the annual NIH Astute Clinician Award Lectureship, which honors a U.S. scientist who has observed an unusual clinical occurrence and, by investigating it, has spurred new research.

A memorial service was held on April 29, where the first NCI Lifetime Achievement Award was presented to Mrs. Miller to honor Dr. Miller for his "visionary leadership and mentorship over a 45-year career at the National Cancer Institute." ■

—Joseph F. Fraumeni, Jr., M.D.

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