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In This Issue:	Page

CELL PHONES AND RISK OF BRAIN CANCER

Dr. Peter Inskip

A recent study published in the *New England Journal of Medicine* (2001;344:79-86) by DCEG investigators reported no association between cellular phone use and risk of certain brain tumors. The study was part of a larger DCEG project examining environmental and genetic factors that may influence brain tumor development. "The cell phone component of the study was just one part, actually a relatively small part, of the overall study in terms of total information" but was one of the first components to be published, due to public interest, said lead author Dr. Peter Inskip, of the Radiation Epidemiology Branch.

Dr. Inskip and his colleagues compared 782 brain tumor cases with 799 controls who had been admitted to the same hospitals (in Phoenix, Boston, and Pittsburgh) for other reasons. Each person (or a close relative, if the person had died or could not answer questions) participated in an extensive interview during which he or she was asked about cellular phone use. Interviews were conducted between 1994 and 1998. Cell phone use did not increase the risk of brain tumors, even among people who used one for more than 60 minutes per day or for five years or more. Nor did tumors occur more often on the side of the head where a phone was used. Two other recent case-control studies yielded similar results; neither found an association between cell phone use and brain tumor risk.

"A negative result at this early stage is not definitive," cautioned Inskip. "We don't want our results to be portrayed as proving cell phones don't cause cancer. However, because of the number of people who use cellular phones, it's useful to know even early on whether there is evidence of risk."

Cellular phones were first introduced in the United States in 1984 but did not become widely used until just a few years ago. According to the Cellular Telecommunications Industry Association, nearly 110 million persons in the United States now subscribe to cell phone calling plans. Concerns about brain cancer stem from the close proximity to the head of the phone's antenna, which sends and receives radio-frequency signals. Several years ago, most cell phones operated in the range of 800 to 900 MHz. Since then, the trend has turned toward higher frequencies and digital, rather than analog, phones. The relationship between type of phone or operating frequency and brain cancer risk, if any, is not clear.

"If only very long-term or very heavy use increases cancer risk, it may be too soon to detect any increase," said Inskip. In the DCEG study, only 22 cases (2.8 percent) and 31 controls (3.9 percent) had used a cellular phone for five years or more. "Even if

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Notice of Erratum
The December 2000 *DCEG Linkage* (No. 11) contained a misquote in the article on Breast Implants and Breast Cancer. It should have stated "Cases were diagnosed 'early,' creating a *lower*-than-expected rate of breast cancer during the study's observation period."

long-term use isn't required," Inskip said, "you have to allow time for the tumor to develop." Growth rates are extremely variable among the different types of brain tumor. For example, glioblastomas tend to grow very quickly, but most meningiomas and acoustic neuromas grow slowly. Although some researchers in the field have suggested that nonionizing radiation—such as that emitted by cell phones—may increase the growth rate of an existing but slow-growing tumor, the results from the DCEG study do not support this suggestion.

The brain tumor patients in the DCEG study had recently been diagnosed with glioma, acoustic neuroma, or meningioma. Inskip and his colleagues designed the study to detect a twofold increase in risk for all gliomas combined. "There could be an effect limited to a rare subtype, or only to the tissue closest to the radiotransmitter," he said. "But it's important to bear in mind that if you're talking about a very uncommon subtype, even if use doubles that risk, that's still a very small increase in risk overall."

"Our study may have been done too soon to assess long-term risks," Inskip said, but "there are other studies in the field right now that will be in a better position to do that. These studies are in countries where they've used cell phones longer than we have." One is a study coordinated by the France-based International Agency for Research on Cancer, which is collecting data on 3,000 cases and 3,000 controls. A Danish study involving more than 500,000 cellular phone subscribers is in its final stages, and the United Kingdom recently began a $10 million research program on cell phone use.

Overall, Inskip said, the research into the causes of brain tumors will ideally combine information on possible genetic determinants with information on environmental exposures. "We want to see not only if people with certain genes are at increased risk, but if those genetic differences might be important only if you're exposed to certain chemicals." For now, however, Dr. Inskip thinks cellular phone users should worry less about brain tumors and more about studies that show an increased risk of accidents caused by using phones while driving. He believes the effect of cell phones on brain tumor incidence will be small compared with this risk. ■

Nancy Volkers

INTRAMURAL RESEARCH AWARD WINNERS

DCEG recently announced this year's winners of the Intramural Research Awards (IRAs) program, a competitive funding program for small innovative and interdisciplinary collaborative research projects. The winners are Drs. Philip Castle, Anneclaire DeRoos, Erin Bell, Andrew Flood, Volker Mai, and Mary Lou McMaster, all DCEG fellows.

Dr. Castle, a Cancer Prevention fellow in the Environmental Epidemiology Branch, submitted a proposal to evaluate cytokine profiles in cervical secretions and determine their relationship to human papillomavirus (HPV) persistence and progression to neoplasia. Persistent HPV infections are the central cause of cervical cancer and its precursor lesion, high-grade cervical intraepithelial neoplasia (CIN). Most HPV infections, however, do not progress to high-grade CIN or cancer; instead, they tend to become inapparent within a year. The immune response to HPV infection is the most important known determinant of HPV persistence and, therefore, of cancer risk. Dr. Castle will use recycling immunoaffinity chromatography, an emerging technology for simultaneous ultramicroanalysis of multiple analytes in biologic fluids, to examine cytokines in cervical secretions collected from women participating in a prospective cohort study in Costa Rica. He will evaluate potential associations between baseline cytokine profiles and the risk of HPV progression to high-grade CIN.

Dr. Anneclaire DeRoos and Dr. Erin Bell, of the Occupational Epidemiology Branch, intend to investigate the relationship of immunological biomarkers and the risk of non-Hodgkin's lymphoma (NHL). Populations with profound alterations in the immune system, such as organ transplant recipients and persons with HIV, are prone to NHL. Conditions with milder alterations have also been linked to NHL, but with inconsistent results. Drs. DeRoos and Bell propose a case-control study of NHL nested within a prospective cohort study of Northern California Kaiser Permanente members to assess cytokines, chemokines, and immunoglobulins in prediagnostic sera as risk factors for NHL.

Intramural Research Awards winners (from left to right): Drs. Volker Mai, Anneclaire DeRoos, Mary Lou McMaster, Erin Bell, Philip Castle, and Andrew Flood

In the Nutritional Epidemiology Branch, Dr. Andrew Flood and Dr. Volker Mai will investigate whether dietary patterns associated with high glycemic load play a role in the etiology of colorectal polyps. Using data and blood samples from the Polyp Prevention Trial, they will develop an index of glycemic load on the basis of food frequency questionnaire data; assess the relationship of the index with blood measures of insulin, c-peptide, glucose, and insulin-like growth factor and its binding protein; and evaluate the index and blood measures in relation to polyp recurrence.

Dr. Mary Lou McMaster, of the Genetic Epidemiology Branch, plans to examine familial aspects of Waldenström's macroglobulinemia by combining clinical, epidemiologic, and laboratory approaches. Dr. McMaster plans to assemble a large group of patients with familial Waldenström's macroglobulinemia to determine clinical and laboratory manifestations and to search for associations with candidate genes that may contribute to susceptibility.

In the IRA program, tenure-track investigators and fellows within the Division apply for funds (up to $75,000 per year, renewable for up to three years) for small projects that cross the usual organizational boundaries. Each proposal is reviewed by a member of the NCI Board of Scientific Counselors or another scientist from outside NIH with appropriate expertise, plus a senior scientist within DCEG. The proposals are judged with respect to their potential

for significant scientific or public health impact, innovative aspects of the approach or methodology, interdisciplinary nature of the project (especially in using collaborative links with other research groups), ability to achieve the objectives within the proposed time frame and resources, and programmatic relevance to the mission of our Division. The award can be combined with money from other sources to fund a larger project.

Eligibility for IRAs has changed over time. In 1998, when the IRA program began, tenured and tenure-track principal investigators could receive support for new initiatives through this mechanism. In 1999, pre- and postdoctoral fellows in DCEG also became eligible to apply for IRAs. The most recent change occurred this year; the program was opened to tenure-track investigators and to fellows in DCEG, but not to tenured investigators. We believe that nontenured scientists, who often go on to apply for positions outside of NIH, can benefit the most from documented success in obtaining funding through a competitive mechanism.

More information on the IRA program can be found at this DCEG web site: *http://intranet-dceg.ims.nci.nih.gov/awards/intramural_research.html.* ■

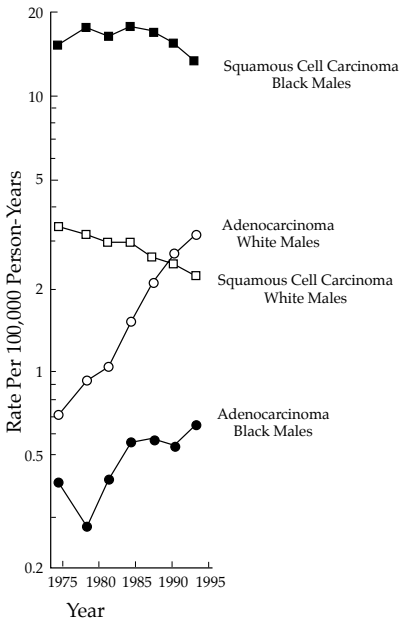
Shelia Hoar Zahm

THE ALARMING INCREASE IN ESOPHAGEAL ADENOCARCINOMAS

One of the great advantages of using the Surveillance, Epidemiology, and End Results (SEER) program to keep close tabs on cancer incidence in the United States is the ability to identify trends early. SEER data have revealed that the incidence of adenocarcinoma of the esophagus has risen more than 350 percent among white men over the past two decades, increasing more rapidly than any other type of cancer. The rate among white men is much higher than that among white women or among black men and women, although incidence is increasing in these groups as well. Dr. Susan Devesa, Chief of the Descriptive Studies Section in the Biostatistics Branch, looked at the incidence patterns of this cancer and observed that from 1974 through 1997, the incidence of esophageal adenocarcinoma increased at a rate of 8.8 percent annually for white men and 8.3 percent annually for white women.

Dr. Devesa pointed out that among white men, the incidence rate for esophageal adenocarcinoma surpassed that for squamous cell carcinoma of the esophagus in 1990. Any rise in the rate of esophageal cancer is alarming because the disease is notoriously difficult to identify early enough and treat effectively. Because the prognosis for esophageal cancer is so poor, it is obviously far better to prevent the disease before it develops.

Unlike squamous cell carcinoma of the esophagus, which is strongly linked to cigarette smoking and alcohol consumption, the risk factors for adenocarcinoma were not known when the marked increase in incidence was first identified. In an effort to identify the causes of these tumors, DCEG Director Dr. Joseph Fraumeni, Occupational Epidemiology Branch member Dr. Wong-Ho Chow, and Dr. William Blot, formerly Chief of the Biostatistics Branch and now with the International Epidemiology Institute, spearheaded a multicenter case-control study to identify causes and preventive approaches that might help quell the increase of this disease. This study was conducted in close collaboration with investigators from the University of Washington, Columbia University, and Yale University.



According to Dr. Fraumeni, "the major risk factor for esophageal adenocarcinoma was shown to be acid reflux, which occasionally initiates a multistage

From left to right: Drs. Susan Devesa, Joseph Fraumeni, and Wong-Ho Chow

process from inflammation, to an intestinal-type metaplasia called Barrett's esophagus, to adenocarcinoma." Acid reflux, or gastroesophageal reflux disease, occurs when the acid contents of the stomach enter the esophagus and produce inflammation, or esophagitis. The incidences of acid reflux disease and Barrett's esophagus, as well as esophageal adenocarcinoma, are all increasing in the general U.S. population, unlike the incidences of peptic ulcer and stomach cancer, which are declining.

"In adenocarcinoma, 95 percent arise in the lower third of the esophagus, where acid reflux is likely to occur," said Dr. Chow. In contrast, "with squamous cell carcinoma, we see the tumors distributed rather evenly along the entire length of the esophagus." Dr. Chow added that cancers of the gastric cardia, the area of the stomach closest to the esophagus, are also occurring more frequently, whereas tumors in other parts of the stomach are steadily declining.

Even though the sequence of reflux disease, Barrett's esophagus, and esophageal adenocarcinoma is well established, the cause of the rise in reflux disease is less clear. One risk factor may be obesity. The multicenter case-control study revealed a strong association of adenocarcinoma with being overweight, an increasingly prevalent condition in the U.S. population. "How obesity increases the risk of this cancer hasn't been fully explored, but it may act by contributing to reflux," said Dr. Fraumeni. "Perhaps the mechanical pressure from abdominal obesity forces the stomach contents to reflux through the lower esophageal sphincter." Dr. Chow noted that the research team is also investigating the role of dietary factors, but analyses have not been completed.

The study also looked for a relationship between risk of adenocarcinoma and medications that relax the esophageal sphincter. Results revealed a possible association with asthma medications, but asthma itself is associated with acid reflux. No correlation was found with drugs used to treat reflux, such as histamine-2 antagonists, but a protective effect from the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was reported by researchers at the University of Washington.

Cigarette smoking was identified as another causal factor of esophageal adenocarcinoma, although the risk was less pronounced than that observed for squamous cell cancer of the esophagus. The risk for developing lung cancer or squamous tumors of the esophagus drops soon after smoking cessation, but the risk for esophageal adenocarcinoma remains high for at least 30 years among ex-smokers. "These findings suggest a long latency period for this tumor, with smoking having an early-stage effect," Dr. Fraumeni said. "If that is the case, the upward trend in incidence may partly reflect the smoking habits of 30 years ago."

Dr. Chow also noted an inverse relation seen with esophageal adenocarcinoma and a virulent strain of *Helicobacter pylori*, the main cause of peptic ulcer and most likely gastric cancer. The frequency of *H. pylori* infection is declining in the population, unlike that of acid reflux or Barrett's esophagus. "How this bacteria might protect against this tumor is not clear," Dr. Fraumeni said. "But the findings are consistent with the hypothesis developed by our collaborator, Dr. Martin Blaser of New York University, who reasoned that the colonization of gastric mucosa by *Helicobacter* organisms may inhibit the production of gastric acid that can reflux into the esophagus, and that eradicating the infection may increase acid secretion and reflux."

Whatever the contributing factors are, the treatment options available once esophageal adenocarcinoma has been diagnosed are not particularly effective. Dr. Fraumeni noted that increasing attention is being paid to developing preventive measures and guidelines of medical practice aimed at Barrett's esophagus, the key precursor lesion. Toward this end, NCI and the National Institute of Diabetes and

Digestive and Kidney Diseases are hosting a series of workshops designed to address the etiology, prevention, clinical management, biologic markers, and other research issues associated with Barrett's esophagus. One focus will be on the use of chemopreventive agents such as NSAIDs known as COX-2 inhibitors, as well as novel diagnostic and therapeutic approaches. ■

Lisa Chiu

DCEG RESEARCH ON HORMONES AND BREAST CANCER

Dr. Catherine Schairer

The continuing high incidence of breast cancer in North America, Western Europe, and other regions ensures that research into this disease's causes maintains a high priority. At DCEG, much of this research has focused on how hormones, including the sex steroids estrogen and androgen, place women at risk. Many events in a woman's personal health history, including her arrivals at menarche and menopause and her decisions about oral contraceptives and estrogen replacement therapy, are "hormonal issues," and each has been the focus of research by DCEG investigators.

A quarter-century ago, Dr. Robert Hoover, Director of the Epidemiology and Biostatistics Program (EBP), became the first investigator to link long-term use of menopausal "replacement" estrogens to increased breast cancer risk in a retrospective cohort study. Over 10 years ago, Dr. Hoover and Dr. Catherine Schairer, in collaboration with Swedish researchers, were the first to report that adding progestins to estrogen replacement therapy might increase risk beyond that imposed by estrogen, results that were subsequently confirmed. Ironically, hormone replacement therapy has also been linked to reduced breast cancer mortality. One explanation is that breast cancers are diagnosed earlier in hormone users because of surveillance, but Dr. Schairer, using data from the Breast Cancer Detection Demonstration Project follow-up study, found this was not the case. Current analyses seek to determine whether replacement therapy is associated with risk of tumors that have more favorable characteristics.

The relationship between oral contraceptives, which contain a fixed amount of estrogen and progestin, and breast cancer has been studied by several DCEG researchers, particularly EEB's Dr. Louise Brinton. An early study among participants in the Breast Cancer Detection Demonstration Project showed no overall association between oral contraceptives and breast cancer, which accords with prevailing opinion today. Research continues in this area, however, and various DCEG initiatives have expanded relevant knowledge. For example, in a study of young women the strongest link with oral contraceptives was found in cancers diagnosed before women had turned age 35. Other research indicates that women who use both oral contraceptives and menopausal hormones may be at particularly high risk and that the oncogene *HER-2/neu* might be linked with oral contraceptives in some important way. Specifically, risk of breast cancer in relation to oral contraceptive use varied with *HER-2/neu* status, with the odds ratios for tumors that overexpress this oncogene being twice that for tumors that did not. Conceivably, *HER-2/neu* is the mechanism by which oral contraceptives affect breast cancer risk, or perhaps it interacts with cofactors in producing the disease.

Diethylstilbestrol (DES), a nonsteroidal estrogen first synthesized in 1938 and once widely used to prevent threatened abortion and premature labor, has been studied extensively in recent decades because of its known carcinogenicity. In 1992, NCI, in collaboration with five clinical centers, began a long-term study on DES (currently led by Dr. Robert Hoover and by Dr. Rebecca Troisi of the EBP), with one primary goal being to measure incidence and mortality of cancer, especially of the breast and reproductive system. In 1998, EBP's Dr. Elizabeth Hatch, who formerly led the project, reported that breast cancer incidence in DES-exposed daughters was not elevated.

A prospective study of women who had donated blood samples for a breast cancer study has provided rich opportunities for research. In one study, Dr. Joanne Dorgan, formerly of EEB, reported that in postmenopausal women higher endogenous levels of estradiol, testosterone, and possibly dehydroepiandrosterone independently increased risk of breast cancer. Elsewhere, EEB's Ms. Roni Falk, using controls from a study of Asian American women, found that blood levels of estrogens and sex hormone-binding globulin did not differ between women born in Asia and those born in the United States, but that women born in the United States had consistently lower androgen levels than those born in Asia (U.S.-born women have a higher breast cancer risk). Ms. Patricia Madigan, also of EEB, found that among postmenopausal women, some reproductive and lifestyle factors may be mediated, in part, through increased endogenous hormone levels.

Some of the current research at DCEG may yield great benefits for researchers elsewhere who are interested in studying breast cancer. For example, EEB's Dr. Xia Xu is developing liquid chromatography/mass spectroscopy methods to measure steroid hormones, hormone metabolites, and phytoestrogens in a single run in urine, blood, and ultimately tissue samples; these methods will require only small sample volumes. In addition, Dr. Ruthann Giusti, of the Clinical Genetics Branch, is exploring methods to measure hormones in breast duct lavage fluid obtained from women carrying mutations in the *BRCA1* and *BRCA2* genes.

In studies currently under way, DCEG researchers are taking a variety of approaches to further our understanding of the link between hormones and breast cancer. For example, a study is under way to understand how hormone levels in umbilical cord blood are associated with characteristics related to cancer risk in offspring; another is assessing the effects of moderate alcohol intake on endogenous hormone levels. Research with a heavy genetic emphasis is also ongoing—case-control studies in the United States and Poland, for example, are investigating polymorphisms in genes involved in the production, metabolism, and bioavailability of sex hormones in relation to breast cancer risk. In cross-sectional studies of premenopausal women, serum sex hormone levels are being examined in relation to polymorphism in these same genes. Another study is designed to determine whether there are genetically identifable subsets of women who are more or less likely to benefit from tamoxifen as a prophylactic measure against breast cancer.

This brief summary illustrates not only the wide range of investigation by DCEG researchers but also the complexity of breast cancer as an etiologic puzzle and the many avenues by which it can be approached. Studies ranging from traditional questionnaires to laboratory investigations incorporating the most current molecular techniques may provide important information useful for prevention, screening, and perhaps treatment as well. ■

Catherine Schairer

FUTURE DIRECTIONS AND EXTENSIONS OF THE GAIL MODEL

The "Gail model," named after Dr. Mitchell Gail, Chief of the Biostatistics Branch, projects the absolute risk of breast cancer over defined age intervals on the basis of age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia on any previous breast biopsy, and number of first-degree relatives (mother, sisters) with a history of breast cancer. The absolute risk is calculated from relative and attributable risks associated with these factors and from composite age-specific incidence rates. The relative risk and attributable risk features of the model were derived from case-control data obtained by Dr. Louise Brinton, Chief of the Environmental Epidemiology Branch, and her colleagues, who studied cases and controls in the Breast Cancer Detection Demonstration Project (BCDDP). Age-specific incidence rates from BCDDP follow-up were also used to compute absolute risk. In adapting the model for the Breast Cancer Prevention Trial (BCPT) of tamoxifen, statisticians Carol Redmond and Stewart Anderson of the University of

Dr. Mitchell Gail

Pittsburgh used Surveillance, Epidemiology, and End Results (SEER) incidence rates instead of BCDDP rates. This modified version is available at NCI's web site *http://cancernet.nci.nih.gov/*. Click on "*Genetics, Causes, Risk Factors, Prevention*," then on "*Breast Cancer*," and finally on "*Estimating Breast Cancer Risk*."

The Gail model is primarily used to counsel women about their risk of breast cancer over various age intervals. The model was developed for this purpose at the request of Dr. John Mulvihill, a former member of NCI's Clinical Epidemiology Branch, who needed this information to advise patients in an NCI clinic who were at high risk of breast cancer. The model has also proven useful for planning clinical trials, such as BCPT, because the power of such studies depends on a reflection of average absolute risk, or the number of breast cancers that develop over the course of the trial. Using this model to identify women at high absolute risk can also inform clinical management. A woman at high absolute risk of breast cancer may benefit more from tamoxifen, other things being equal, than a woman at lower risk of breast cancer, because for the latter the toxicities of tamoxifen can outweigh the benefits. Likewise, a woman in her 40's may be influenced to begin regular mammographic screening if her absolute risk is equivalent to that of a 50-year-old woman.

Although the Gail model has been validated for white women, it needs to be validated and, if necessary, modified for African American women, Hispanic women, and other subgroups. Indeed, some evidence suggests that the model underestimates risk in African American women, for whom BCDDP data on attributable risk are sparse. Investigators conducting population-based case-control studies and cohort studies in minority populations can contribute data to test and improve the model. Incorporating stronger predictors can also improve the Gail model, although it predicts risk accurately on average. Members of the Biostatistics Branch are currently conducting reliability studies and other analyses to determine whether the percentage of dense tissue on a mammogram can be used to strengthen the model. Other potential predictors include molecular or cytological markers from nipple aspirates and genetic predictors. Models that depend only on features of the medical and family history will probably remain useful, however, and can guide decisions regarding the need for more invasive studies to evaluate risk. ■

DR. BLANCHE ALTER, CANCER EXPERT

Hematologist Blanche Alter, Ph.D., M.P.H., took a couple of unusual turns before landing in the Clinical Genetics Branch (CGB) as a cancer expert this past August. A Harvard-trained pediatric hematologist, Dr. Alter focused on clinical oncology in the 1990's, when she headed the Division of Pediatric Hematology and Oncology for the University of Texas Medical Branch in Galveston, Texas. When changing circumstances threatened to leave her with an enormous clinical oncology load and little time to pursue her research, Dr. Alter chose a path less traveled: after a career that had begun in the late 1960's, she went back to school to earn an M.P.H.

Dr. Blanche Alter

DCEG Linkage caught up with Dr. Alter to talk about her plans now that she has joined CGB as a cancer expert.

Why did you choose to go back to school rather than simply look for another position?

I decided to explore ways in which my clinical and laboratory experiences in hematology and oncology might be used in a different and challenging manner. I started looking online at catalogs for schools of public health and discovered I was very interested in all the courses, particularly biostatistics, cancer, and genetic epidemiology. Many of the clinical reviews I had done of rare hematologic syndromes were really epidemiologic in their focus.

How did you decide to take your course work at Johns Hopkins University School of Public Health?

I have a history with Johns Hopkins. Although I did my undergraduate and specialty work in Boston at Radcliffe College and later at Harvard Medical School, I received my medical degree and my pediatric training at Johns Hopkins University. Most of the people I respected told me to go to Johns Hopkins University School of Public Health. One of the faculty there shared my interest in cancer progression in patients with genetic hematologic diseases. Unfortunately, he left shortly after I arrived!

Did you have to change your plans and find a new advisor?

No. that person had several graduate students and came back to Hopkins to meet with them.

I'm here at NCI because of a collaboration with Dr. Mark Greene, Chief of CGB. For my project at Johns Hopkins, I studied patients with Fanconi's anemia. Because medicine has improved our management of their usual problem, aplastic anemia, we've discovered that these patients are living long enough to get specific types of cancer at unusually early ages. But my interest goes beyond patients with Fanconi's anemia. Patients with a number of different "benign" hematologic diseases are at an increased risk for cancer as they get older. We're seeing that we can predict the types of cancer they're likely to get. Here at NCI, I plan to explore this propensity for cancer in patients thought to have these so-called benign diseases.

Do you mean these patients are likely to get other blood-related cancers as they get older?

They get leukemia, but they are likely to get solid tumors as well. For example, Fanconi's anemia arises from a defect in DNA repair. Patients who have Fanconi's anemia are at risk of getting aplastic anemia, acute myeloid leukemia, oropharyngeal and esophageal cancers, and gynecologic cancers like cervical and vulvar cancer.

But it's not quite that simple. Sometimes the bone marrow disease in these patients is cured because they've undergone bone marrow transplantation. We have to look at what roles immunosuppression and graft-versus-host disease may play in the development of these cancers. In addition, we plan to look at the rest of the families to establish the cancer risk among heterozygotes.

Are these patients more susceptible to human papillomavirus infection?

That's one possibility. We are definitely going to look at viruses and whether they are present in these tumor biopsies. But these cancers can also arise without human papillomavirus infection. Whatever turns out to be true, we are going to learn something about cancer pathways.

I'm also looking at patients who have Diamond-Blackfan anemia, a pure red cell aplasia. At least half a dozen of these patients have developed osteogenic sarcoma as well as leukemias and other cancers. Patients with dyskeratosis congenita, an X-linked disorder, often develop oropharyngeal and gastrointestinal cancers similar to patients with Fanconi's anemia. Patients with Shwachman-Diamond syndrome often go on to develop aplastic anemia and leukemia.

How far along is your project?

I'm still trying to get all the collaborators on board. Our patients suffer from multisystem diseases. When we bring patients in, many different specialists will need to meet with them. We also want to perform extensive laboratory evaluations to understand carcinogenesis in these disorders. Eventually, we will bring in one new family a week to the Clinical Center for the study. We also plan a larger study of patients that will not come to the Clinical Center, but who will provide epidemiologic information and laboratory and tumor biopsy materials. I am still at the review stage, which will be followed by full protocol development. ■

Lisa Chiu

KIYOHIKO MABUCHI, CANCER EXPERT


Dr. Kiyohiko Mabuchi

Dr. Kiyohiko Mabuchi came to DCEG for a sabbatical and eventually joined the Radiation Epidemiology Branch (REB) as an expert scientist last April. This veteran of cancer and radiation epidemiology has explored the risks of cancer associated with smoking and arsenic exposure and has directed studies of A-bomb survivors in Hiroshima. *DCEG Linkage* caught up with Dr. Mabuchi to find out what's next on his agenda.

What sparked your interest in epidemiology?

I became interested in epidemiology while I was studying medicine at the Osaka University Medical School. I was rather disappointed with clinical medicine and became more interested in public health. Epidemiology seemed to be a very rational way of deciphering how disease occurred.

What areas of epidemiology did you initially study?

I became involved in cancer epidemiology when I was working at the Sloan-Kettering Institute for Cancer Research, where I worked on smoking and lung cancer. Then, I decided to go to Johns Hopkins University School of Hygiene and Public Health for both master's and doctoral degrees in public health and epidemiology. At Johns Hopkins, I did occupational epidemiology studies on a cohort of people who were exposed to arsenic powder in pesticide production. Arsenic exposure had been linked to skin cancer and lung cancer—which is what I worked on. More recently, it's been discovered that arsenic exposure can also cause bladder cancer.

After graduation I moved to the University of Maryland School of Medicine as an assistant professor in epidemiology and preventive medicine. Besides teaching, I continued to work on epidemiological studies of cancer while I was there.

How did you get involved with studies of the A-bomb survivors?

I got the opportunity to spend some time in Hiroshima, and that's when I became interested in radiation epidemiology. As a result of the studies on these A-bomb survivors—probably the largest cohort with radiation exposure with the longest follow-up—we know a lot more about the cancer risks from radiation exposure. The study of the A-bomb cohorts was initiated in the 1950's. This was a fascinating and epidemiologically robust population to study, and the experience gave me a sense of responsibility because of its societal impact. It opened my eyes to science in a way I hadn't known before.

What were the advantages of working on this cohort?

One of the biggest advantages is that you can get a good estimate of the exposure because of tremendous dosimetry work done over the years. These data have been used to set up worldwide safety standards for radiation exposure. One could say that atomic bomb data has set the standard in radiation health research.

Our understanding of radiation effects has evolved over the years. Before we knew of the link with cancer, we thought that radiation accelerated the aging process. Then, it became clear that radiation caused cancer as well as leukemia, possibly through chromosomal and DNA damage. This suggested to us a mechanism for how radiation increased the risk of cancer. We still don't know exactly how radiation causes cancer, but new molecular biological approaches will help us better understand the mechanisms.

Now, what's become evident is that after 40 or 50 years, there is an increase in diseases other than cancer—primarily cardiovascular disease—as the cohort ages. Many theories exist for how this happens, but we are only starting to investigate them. It really just shows the importance of how long this study has gone on and how much we can learn from it. The effect of radiation is really quite long-lasting, and we don't really have biological models for it.

Why did you decide to leave Hiroshima?

Well, I was interested in learning what NCI was doing and thinking about what should be done with the A-bomb studies. It's always good to get fresh ideas, to get a different perspective. I also like the multidisciplinary environment here. I took a sabbatical leave to come here. Last April, I joined the staff.

Are you continuing your work with A-bomb survivors?

Yes, I plan to. But right now I'm also working with other people in REB on a cohort of 140,000 radiation technologists—mostly women—who've been studied for many years by the Branch. This cohort differs from the A-bomb survivors in that they've received low-level doses over many years. We can address the question of whether health risks from chronic doses are different than those from acute doses of radiation, as biological data suggest.

I'd also like to start new studies here on other forms of radiation, such as ultraviolet exposure and electromagnetic field radiation. These forms affect the tissues and cells differently than ionizing radiation does. Working with experts outside REB would provide an exciting opportunity to learn the biological background of how radiation, together with other factors, leads to cancer, and to help develop more effective methods for disease prevention. ■

Lisa Chiu

NEWSLETTER ANNOUNCEMENTS

Family Research Matters

The Clinical Genetics Branch (CGB), headed by **Dr. Mark Greene,** has published a newsletter entitled "Family Research Matters" for family members involved in the NCI Familial Breast-Ovarian Cancer Study. The newsletter is being distributed to approximately 3,500 family members from the hereditary breast/ovarian kindreds that the Genetic Epidemiology Branch (GEB) has been studying over the past several decades. The intent of the newsletter is to:

- Alert study participants to the organizational transfer of responsibility for ongoing follow-up and new research projects that have been shifted from GEB to CGB;
- Update family members on new research developments;
- Begin providing interested study participants with access to clinical genetic testing; and
- Set the stage for the new studies CGB has planned.

CGB Newsletter

Dr. Ruthann Giusti, Ms. Jennifer Loud, Ms. June Peters, and **Ms. Nancy Weismann** developed the newsletter. The newsletter should facilitate enrollment in a CGB pilot study of magnetic resonance imaging and positron emission tomography imaging of the breast in premenopausal women from mutation-positive families. This study is about to open for accrual.

Beckwith-Wiedemann Syndrome Pamphlet

BWS Brochure

Ms. Nancy Weissman, a clinical social worker in GEB, has published a brochure on Beckwith-Wiedemann Syndrome (BWS). The brochure provides an overview of BWS, clinical care, cancer screening, and available resources. BWS is an overgrowth syndrome associated with cancer in infants and children. About 10 percent of the children with BWS will develop cancer in the first 10 years of life, and the vast majority of those cancers will occur before age 4. The most common cancers are Wilms tumor and hepatoblastoma. Cancers that occur more rarely include adrenal cortical carcinoma, neuroblastoma, and rhabdomyosarcoma. Interestingly, although BWS is a lifelong condition, most children appear to outgrow most visible characteristics of the syndrome by adulthood. Screening by abdominal ultrasound and blood tests should be done every three months until the age of seven or eight, beyond which the risk for cancer decreases. ■

2000 COMBINED FEDERAL CAMPAIGN

The 2000 Combined Federal Campaign came to a very successful close in early February. Both NIH and NCI enjoyed a high level of success. NIH raised a total of $1,453,096, of which NCI raised $244,240, which was 108 percent of its dollar goal. NCI also achieved 49 percent participation.

Ms. Elyse Wiszneauckas and Mr. Mike Stump

Once again, DCEG staff members demonstrated extraordinary generosity and spirit and raised a total of $31,764, which was 154 percent of the Division's dollar goal. The participation rate was 114 percent; contributions came not only from full-time DCEG employees, but also from postdoctoral fellows on training stipends. DCEG had the opportunity to coordinate the campaign for all of NCI. **Mr. Mike Stump** and **Ms. Elyse Wiszneauckas** in the Office of Division Operations and Analysis served as the NCI Program Coordinator and the Deputy NCI Program Coordinator, respectively. Ms. Wiszneauckas also served as the CFC Coordinator for DCEG.

Deserving special recognition and thanks are DCEG's dedicated Branch keyworkers, who selflessly gave their time to ensure the success of the campaign. This year's team consisted of:

Dr. Dalsu Baris, Occupational Epidemiology Branch
Ms. Jennifer Connor, Environmental Epidemiology Branch
Ms. Sandra Coopersmith, Radiation Epidemiology Branch
Mr. Derrick Culbertson, Administrative Resource Center, DCEG
Ms. Annette Cunningham, Biostatistics Branch
Ms. Kit Fox, Office of the Director and the Office of Division Operations and Analysis
Ms. Mary Ann Fuss, Laboratory of Population Genetics and Building 41/ATC
Mr. Romeo Gipson, Nutritional Epidemiology Branch
Ms. Sadie Holmes, Genetic Epidemiology Branch
Ms. Sandy Rothschild, Epidemiology and Biostatistics Program and the Clinical Genetics Branch
Ms. Julie Russell, Viral Epidemiology Branch

Congratulations and a hearty thanks to all who participated in this year's campaign. ■

DCEG WELCOMES THE NEW DEAN FOR THE OFFICE OF EDUCATION

Dr. Demetrius Albanes

Dr. Demetrius Albanes recently joined the DCEG Office of Education to serve as the academic dean for the division. Dr. Albanes will direct the DCEG education and training programs and guide the development of new fellowship opportunities and career development policies for the Division. He will divide his time between his education and training duties and his research interests as a senior investigator in the Nutrition Epidemiology Branch. Dr. Albanes earned his medical degree from the Medical College of Wisconsin. Following his internship at the University of California, Irvine, he served as an Epidemic Intelligence Service Officer for the U.S. Public Health Service, then completed a residency in general preventive medicine with the Centers for Disease Control and Prevention. Dr. Albanes came to NCI as a staff fellow in 1984, and most recently he has worked as a senior research investigator in the Cancer Prevention Studies Branch in the Division of Clinical Sciences. His research interests center on the preventive potential of micronutrients, notably beta-carotene and vitamin E. Vitamin E has exhibited a substantial beneficial impact on prostate cancer incidence and mortality. Dr. Albanes is located in EPS Room 7016 and can be reached at 301-594-2869. The next issue of *DCEG Linkage* will feature a profile on Dr. Albanes. ■

LABORATORY OF POPULATION GENETICS NEWS

The Laboratory of Population Genetics (LPG), headed by Dr. Kenneth Buetow, now has its full complement of five principal investigators.

Dr. Jin Jen, the most recent addition, came to LPG from Johns Hopkins University. She and her team study the biology and genetics of non-small cell lung cancer. Current projects include cDNA expression microarray analyses, *in situ* hybridization to identify differentially expressed genes, gene mutation analyses, and construction of tissue microarrays to study lung cancers.

Dr. Jin Jen

Dr. Maxwell Lee, formerly of Johns Hopkins University and IBM, is currently engaged in both "wet" and "dry" laboratory research. The focus of the wet lab is the positional cloning of tumor suppressor genes on chromosome 13q12, which may play a role in esophageal squamous cell cancer, and on chromosome 4q25, which is important in hepatocellular carcinoma. Dr. Lee's group is also searching for novel imprinted genes and determining the extent of imprinting in the genome to assess the role of such epigenetic changes in cancer. The dry lab is using comparative sequence analyses to look for regulatory elements and is mining gene and protein expression data to identify genetic pathways.

Dr. Maxwell Lee

Dr. Kent Hunter

Dr. Kent Hunter, previously of Fox Chase Cancer Center, is using a mouse model to identify genes involved in cancer progression, specifically metastasis. He and his team have identified a number of inbred mouse strains that significantly alter the kinetics of transgene-induced mammary cancer. The genes responsible for this altered metastasis have been mapped to four chromosomal regions. Currently, the team uses high-resolution genetic mapping, positional cloning, and candidate gene cloning strategies to identify and characterize metastasis susceptibility genes.

Dr. Jeffery Struewing

Dr. Jeffery Struewing transferred to LPG from the Genetic Epidemiology Branch. He and his group primarily study the genetics of *BRCA1/2*-associated cancer sites, such as breast, ovary, and prostate, and they focus their population-based studies on potential environmental and genetic modifiers of cancer risk among *BRCA1/2* mutation carriers. Recent efforts include using epidemiological association studies and biochemical assays to examine DNA damage repair genes, particularly *RAD51*, as potential modifiers of cancer risk.

Dr. Kenneth Buetow and his staff are investigating factors that modulate the risk for developing primary hepatocellular carcinoma (HCC) among populations exposed to aflatoxin B1. They have "tagged" individual family members with new or published polymorphisms that lie in or near known genes of interest and have examined the role of these genes in HCC risk in a nested case-control population. Several genes, *GSTM1*, *GSTP*, *GSTT1*, and *EPHX1*, showed significant association with HCC risk and are candidates for more detailed functional and genetic analysis. The group is also using RT-PCR to monitor the expression of genes involved in cell cycle control, cell signaling, and oncogenesis, and they are using expression arrays to identify novel genes that may modulate HCC risk. ■

Dr. Kenneth Buetow

RECENT SCIENTIFIC HIGHLIGHTS

Brain Cancer

See page 1 for article on brain cancer and cell phone use. ■

Breast Cancer

Tumor Variants in Breast Cancer Patients

This study examined breast cancer records from NCI's SEER database for 19,541 white women with node-negative breast cancer to determine tumor cell characteristics and breast cancer-specific survival in relation to estrogen receptor (ER) or progesterone receptor (PR) status. Age frequency density plots with respect to hormone receptor expression showed two overlapping breast cancer populations with early-onset and/or late-onset etiologies. Independent ER^+ and PR^+ expression was associated with smaller tumor size, better grade, and better cancer-specific survival than was independent ER^- or PR^- expression. Joint ERPR expression exhibited negative biologic gradients for tumor size, grade, and cancer-specific survival: $ER^+PR^+ \rightarrow ER^+PR^- \rightarrow ER^-PR^+ \rightarrow ER^-PR^-$. ER^-PR^- exhibited the worst phenotypes. (Anderson WF, Chu KC, Chatterjee N, Brawley O, Brinton LA. Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the Surveillance, Epidemiology, and End Results database. *J Clin Oncol* 2001;19:18-27)

Breast Reduction and Breast Cancer Risk

In a nested case-control study of 161 breast cancer patients and 483 controls from a Swedish cohort of 31,910 women who had had breast reduction surgery, researchers collected information on the amount of breast tissue removed and other factors that influence breast cancer risk. Compared with subjects that had had at least 1,600 grams of tissue removed from both breasts, subjects with less than 800 grams removed had an odds ratio of 0.24. This ratio persisted within each subgroup examined after data were adjusted for other breast cancer risk factors. This result should be reassuring to women undergoing either cosmetic breast reduction or prophylactic mastectomy. (Brinton LA, Persson I, Boice JD Jr, McLaughlin JK, Fraumeni JF Jr. Breast cancer risk in relation to amount of tissue removed during breast reduction operations in Sweden. *Cancer* 2001;91:478-483) ■

Cervical Cancer

Smoking and Cervical Cancer

In this multicenter case-control study of 124 adenocarcinoma cervical cancer cases, 139 squamous carcinoma cases, and 307 community controls, 18 percent of adenocarcinoma cases, 43 percent of squamous carcinoma cases, and 22 percent of controls were current smokers. After the study was controlled for human papillomavirus and other questionnaire data, adenocarcinomas were consistently inversely associated with smoking (odds ratio [OR] = 0.6, 95 percent CI = 0.3–1.1 for current smokers; OR = 0.7, 95 percent CI = 0.4–1.3 for those who smoked one pack or more per day). Squamous carcinomas were positively associated with smoking (OR = 1.6, 95 percent CI = 0.9–2.9 for current smokers; OR = 1.8, 95 percent CI = 1.0–3.3 for those who smoked one pack or more per day). Although both cervical cancer histologic types are caused by human papillomavirus, etiologic cofactors for these tumors may differ. (Lacey JV, Frisch M, Brinton LA, Abbas FM, Barnes WA, Gravitt PE, Greenberg MD, Greene SM, Hadjimichael OC, McGowan L, Mortel R, Schwartz PE, Zaino RJ, Hildesheim A. Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States). *Cancer Causes Control* 2001;12:153-161)

Human Papillomavirus and Risk of Cervical Cancer

A prevalent case-control study within a population-based cohort of 10,000 women in Costa Rica was used to examine the association between human papillomavirus (HPV) type 16 variants and cervical cancer. Host genotyping was performed on a subset of 140 cases—16 cancers; 55 high-grade squamous intraepithelial lesions; and 69 low-grade squamous intraepithelial lesions, equivocal lesions, or normal cytology. The European-derived HPV16 prototype virus (EP[g]) was detected in 36 subjects. Women with high-grade squamous intraepithelial lesions or cancer who tested positive for non-European-like (NE) variants had a risk ratio of 2.7 (95 percent CI =

0.75–9.9) and 11 (95 percent CI = 2.5–50), respectively. No statistically significant association was observed for persons positive for European-like (EL) variants. (Hildesheim A, Schiffman M, Bromley C, Wacholder S, Herrero R, Rodriguez AC, Bratti MC, Sherman ME, Scarpidis U, Lin QQ, Terai M, Bromley RL, Buetow KH, Apple RJ, Burk RD. Human papillomavirus type 16 variants and risk of cervical cancer. *J Natl Cancer Inst* 2001;93:315-318)

ASCUS/LSIL Triage Study

The ASCUS/LSIL (atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion) Triage Study, a multicenter, randomized trial, compared the sensitivity and specificity of management strategies to detect cervical intraepithelial neoplasia grade 3 (CIN3). Among participants with ASCUS, the underlying prevalence of histologically confirmed CIN3 was 5.1 percent. Sensitivity to detect CIN3 or above by testing for cancer-associated human papillomavirus DNA was 96.3 percent, and 56.1 percent of women were referred to colposcopy. Sensitivity of a single repeat cytology specimen with a triage threshold of high-grade squamous intraepithelial lesions or above was 44.1 percent, with 6.9 percent referred, and sensitivity of a lower cytology triage threshold of ASCUS or above was 85.3 percent, with 58.6 percent referred. Testing for cancer-associated human papillomavirus DNA among women with ASCUS is a more sensitive and more specific detector for CIN3 or above, compared with a single additional cytologic test indicating ASCUS or above. (Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93:293-299)

Self-collected Samples in Human Papillomavirus Testing

The technical feasibility of self-collection of cervicovaginal cells using a Dacron swab for human papillomavirus (HPV) DNA detection was evaluated. A self-collected swab sample was compared with two clinician-administered swab samples from 111 cases and 157 controls in a case-control study of adenocarcinoma and squamous cell carcinomas of the cervix. The overall agreement between the clinician-administered and self-collected swabs was 88.1 percent (correlation = 0.73). The correlation was highest between the two clinician-administered swabs (0.81). However, the correlation was 0.75 between the self-collected swab and the clinical swab from the ectocervix and 0.67 between those from the endocervix. The type-specific agreement between samples was higher for high-risk, cancer-associated HPV genotypes than for low-risk, noncancer-associated HPV genotypes. The agreement did not vary significantly by age, menopausal status, case status, or clinic center. (Gravitt PE, Lacey JV Jr, Brinton LA, Barnes WA, Kornegay JR, Greenberg MD, Greene SM, Hadjimichael OC, McGowan L, Mortel R, Schwartz PE, Zaino R, Hildesheim A. Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction. *Cancer Epidemiol Biomark Prev* 2001;10:95-100)

Clinical Trial for Human Papillomavirus 16 L1 Virus-like Particle Vaccine

A double-blind, placebo-controlled dose-escalation trial was performed to evaluate the safety and immunogenicity of a human papillomavirus type 16 (HPV16) L1 vaccine, VLP, in healthy adults. The prevaccination geometric mean ELISA titer for six seropositive individuals was 202 (range, 40–640). Doses of 10 μg or 50 μg were given intramuscularly. Serum antibody responses at one month after the third injection were dose dependent in patients who received vaccine without adjuvant or with MF59 as the adjuvant. When alum was used as the adjuvant, serum antibody responses were similar at both doses. With the higher dose, the geometric means of serum ELISA antibody titers to purified VLP were 10,240 (95 percent CI = 1,499–69,938) without adjuvant, 10,240 (95 percent CI = 1,114–94,145) with MF59 as the adjuvant, and 2,190 (95 percent CI = 838–5,723) with alum as the adjuvant one month after the third injection. Responses of subjects within each group were similar. Neutralizing and ELISA antibody titers were highly correlated (Spearman correlation = 0.85), which confirmed that ELISA titers are valid proxies for neutralizing antibodies. The HPV16 L1 VLP vaccine was well tolerated and highly immunogenic even without adjuvant, and the majority of the

recipients achieved serum antibody titers approximately 40-fold higher than what is observed in natural infection. (Harro CD, Pang YYS, Roden RBS, Hildesheim A, Wang ZH, Reynolds MJ, Mast TC, Robinson R, Murphy BR, Karron RA, Dillner J, Schiller JT, Lowy DR. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. *J Natl Cancer Inst* 2001;93:284-292) ■

Chordoma

Chordoma in the United States

Chordoma, a rare tumor arising from notochordal remnants, has been described to date only by single-institution case series or small population-based surveys. This study examined data for 400 cases from the Surveillance, Epidemiology, and End Results (SEER) program, 1973–1995, to measure incidence and survival patterns for chordoma in the United States. The overall age-adjusted chordoma incidence rate (IR) per 100,000 was 0.08. Chordoma was more common in males (IR = 0.10) than in females (IR = 0.06) and rare among blacks and patients aged less than 40 years. Within the axial skeleton, 32 percent of cases were cranial, 32.8 percent were spinal, and 29.2 percent were sacral. Cranial presentation was more likely in younger patients (less than 26 years; $p = 0.0001$) and in women ($p = 0.037$). There was no overall increased risk for second primary cancers after chordoma. Median survival was 6.29 years; 5- and 10-year relative survival rates were 67.6 percent and 39.9 percent, respectively. Comparison with other bone sarcomas revealed racial disparities in incidence for the two developmental tumors, chordoma and Ewing's sarcoma. (McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973–1995. *Cancer Causes Control* 2001;12:1-11) ■

Esophageal and Gastric Cancers

Relationship between Selenium Levels and Subsequent Cancer

Selenium levels in pretrial sera from participants in a randomized nutritional intervention trial in Linxian, China, were used to evaluate the subsequent risk of developing cancer. Serum selenium levels were measured in 590 subjects with esophageal cancer, 402 with gastric cardia cancer, and 87 with gastric noncardia cancer as well as in 1,062 control subjects. Highly significant inverse associations were found with the incidence of esophageal and gastric cardia cancers. The relative risk for comparison of highest with lowest quartile of serum selenium was 0.56 for esophageal cancer and 0.47 for gastric cardia cancer. In the study population, the proportion of these cancers attributable to low selenium levels was 26.4 percent. No evidence was found for a gradient of serum selenium associated with incidence of gastric noncardia cancer. (Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF, Blot WJ, Dong ZW, Taylor PR. Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J Natl Cancer Inst* 2000;92:1753-1763)

Risk Factors for Squamous Cell Esophageal Cancer

In a population-based case-control study of squamous cell esophageal cancer among 347 male cases (119 white, 228 black) and 1,354 male controls (743 white, 611 black), odds ratios of 4.3 (95 percent CI = 2.1–8.7) for whites and 8.0 (95 percent CI = 4.3–15.0) for blacks were observed for subjects with annual incomes less than $10,000 compared with those with incomes of $25,000 or more. The combination of all four major risk factors—low income, moderate to heavy alcohol intake, tobacco use, and infrequent consumption of raw fruits and vegetables—accounted for almost all of the squamous cell esophageal cancers (98 percent for whites and 99 percent for blacks) and for 99 percent of the excess incidence among black men. (Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, Schoenberg J, Greenberg R, Liff J, Schwartz A, Dosemeci M, Pottern L, Fraumeni JF Jr. Excess incidence of squamous cell esophageal cancer among U.S. black men: role of social class and other risk factors. *Am J Epidemiol* 2001;153:114-122) ■

Genetics

Cancer in Nordic Ataxia-telangiectasia Patients and Their Families

This study in the Nordic countries followed 1,218 blood relatives of 56 patients with ataxia-telangiectasia (A-T), a recessive genetic neurologic disorder caused by

mutation of the *ATM* gene. Among the patients with A-T, six cancers (four leukemias and two non-Hodgkin's lymphomas) were observed compared with 0.16 expected, yielding a standardized incidence ratio (SIR) of 37.5. Among the 1,218 relatives, 150 cancers were recorded, with 126 expected (SIR = 1.1). Invasive breast cancer occurred in 21 female relatives of A-T patients (SIR = 1.5), including 5 of the 50 mothers (all of whom are obligate *ATM* mutation carriers; SIR = 7.1). Relatives who were less likely to be carriers of a mutant *ATM* allele had no significant increase in the risk of breast cancer. (Olsen JH, Hahnemann JM, Børresen-Dale A-L, Brøndum-Nielsen K, Hammarström L, Kleinerman R, Kääriäinen H, Lönnqvist T, Sankila R, Seersholm N, Tretli S, Yuen J, Boice JD Jr, Tucker M. Jørgen H. Cancer in patients with ataxia-telangiectasia and in their relatives in the Nordic countries. *J Natl Cancer Inst* 2001;93:121-127)

Hereditary Retinoblastoma and Lung Cancer Risk

Survivors of hereditary retinoblastoma are at high risk of dying from a sarcoma, melanoma, or brain tumor attributed to germline mutations in the *RB1* gene. Whether these patients are at increased risk of dying from the common adult epithelial cancers, such as lung cancer, is unknown. This study evaluated mortality, from 1925 through 1997, for 1,604 1-year survivors of retinoblastoma diagnosed in 1914–1984. Mortality was calculated from the appropriate U.S. death rates. Risk of death from other cancers was higher for 964 hereditary retinoblastoma patients (standard mortality ratio [SMR] = 47.0) than for 640 nonhereditary patients (SMR = 3.8). Five lung cancer deaths occurred among the hereditary patients compared with 0.33 expected (SMR = 15.2). Lung cancer was diagnosed by age 40 in the three patients who smoked most heavily. Smoking rates were not abnormally high in retinoblastoma survivors; this excess of early-onset lung cancers suggests that carriers of RB1 mutations may be highly susceptible to smoking-induced lung cancers. No lung cancer deaths occurred among the nonhereditary patients. Hereditary retinoblastoma patients should be specially targeted for smoking cessation. (Kleinerman RA, Tarone RE, Abramson DH, Seddon JM, Li FP, Tucker MA. Hereditary retinoblastoma and risk of lung cancer. *J Natl Cancer Inst* 2000;92:2037-2039)

New System to Characterize Single-nucleotide Polymorphisms

A system for the rapid identification, assay development, and characterization of gene-based single-nucleotide polymorphisms (SNPs) was reported. This system identifies candidate SNPs from public "expressed sequence tag" resources and automatically designs assay reagents for detection by a chip-based, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry platform. This system was validated by a genomewide collection of reagents for 9,115 gene-based SNP genetic markers. (Buetow KH, Edmonson M, MacDonald R, Clifford R, Yip P, Kelley J, Little DP, Strausberg R, Koester H, Cantor CR, Braun A. High-throughput development and characterization of a genomewide collection of gene-based single nucleotide polymorphism markers by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Proc Natl Acad Sci* 2001;98:581-584)

p53 Mutations and Early-onset Cancers

This study examined cancer occurrences among a series of 45 families, plus 140 other affected cases and kindreds reported in the literature, to clarify the tumor spectrum associated with inherited p53 mutations. The analyses included all cancers in patients with a germline p53 mutation and in first-degree relatives, who were almost 50 percent more likely to be carriers. Among 738 evaluable cancers, 569 (77 percent) were the six tumor types (breast and adrenocortical carcinomas, sarcomas of the bone and soft tissues, brain tumors, and leukemias) associated with Li-Fraumeni syndrome. The remaining 169 (23 percent) cancers included diverse carcinomas of the lung and gastrointestinal tract, lymphomas, and other neoplasms that occurred at much earlier ages than expected in the general population. Unusually early ages at diagnosis are characteristic of hereditary cancers and suggest that carriers of germline p53 mutations confer increased risk for a wide range of neoplasms. (Nichols KE, Malkin D, Garber JE, Fraumeni JF, Li FP. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. *Cancer Epidemiol Biomarkers Prev* 2001;10:83-87) ■

Kidney Cancer

Relationship of Obesity and Hypertension to Kidney Cancer

A nested case-control study of physical examination data for 759 men with renal cell cancer and 136 men with renal pelvis cancer was conducted among a cohort of Swedish men. The physical examination data studied were taken prior to the ones leading to a cancer diagnosis. Compared with men in the lowest range for body mass index, men in the middle range had a 30 to 60 percent greater risk of renal cell cancer, and men in the highest range had nearly double the risk. Blood pressure and renal cell cancer risk were directly associated, even after data from the first five years of follow-up were excluded to reduce possible effects of preclinical disease. At the sixth year of follow-up, the risk rose or fell with the change in blood pressure, after data were adjusted for baseline measurements. Current or former smokers had a greater risk than nonsmokers of both renal cell cancer and renal pelvis cancer. No relationship was found between body mass index or blood pressure and the risk of renal pelvis cancer. (Chow WH, Gridley G, Fraumeni JF, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000;343: 1305-1311) ■

Multiple Myeloma

Diet and Nutrition as Risk Factors for Multiple Myeloma

Data from a food frequency questionnaire were analyzed for 346 white and 193 black multiple myeloma patients and for 1,086 white and 903 black controls. Reduced risks were related to frequent intake of cruciferous vegetables (odds ratio [OR] = 0.7, 95 percent CI = 0.6–0.99) and fish (OR = 0.7, 95 percent CI = 0.5–0.9) in both races combined, and to vitamin C supplements in whites (OR = 0.6, 95 percent CI = 0.5–0.9) and in blacks (OR = 0.8, 95 percent CI = 0.5–1.4). The frequency of vitamin supplement use was greater among white controls than black controls. Elevated risks were associated with obese versus normal weight (OR = 1.9, 95 percent CI = 1.2–3.1 for whites and OR = 1.5, 95 percent CI = 0.9–2.4 for blacks), and the frequency of obesity was greater among black controls than among white controls. The greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may explain part of the high incidence of multiple myeloma among blacks, compared with whites, in the United States. (Brown LM, Gridley G, Pottern LM, Baris D, Swanson CA, Silverman DT, Hayes RB, Greenberg RS, Swanson GM, Schoenberg JB, Schwartz AG, Fraumeni JF. Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. *Cancer Causes Control* 2001;12:117-125) ■

Nutrition

Anorexia Nervosa and Cancer Risk

Patients with anorexia nervosa (2,151 women and 186 men) from 1970 through 1993 were identified in the population-based Danish Psychiatric Case Register and the National Registry of Patients and linked to the Danish Cancer Registry to determine whether energy restriction reduces the incidence of malignant tumors. Compared with the general population, the overall cancer incidence among women with anorexia nervosa was reduced by a factor of 0.80 (95 percent CI = 0.52–1.18) on the basis of 25 observed and 31.4 expected cases. Among men, 2 cases of cancer were observed, both in the brain, but 0.2 cases were expected. (Mellemkjaer L, Emborg C, Gridley G, Munk-Jorgensen P, Johansen C, Tjonneland A, Kjaer SK, Olsen JH. Anorexia nervosa and cancer risk. *Cancer Causes Control* 2001;12:173-177)

Obesity and Cancer Risk

In a population-based cohort of 28,129 hospital patients with any discharge diagnosis of obesity from 1965 through 1993, cancer incidence was monitored by record linkage to the nationwide Swedish Cancer Registry. Overall, a 33 percent excess incidence of cancer was seen in obese persons (25 percent in men and 37 percent in women). Significant risk elevations were observed for cancers of the small intestine (standard incidence ratio [SIR] = 2.8; 95 percent CI = 1.6–4.5), colon (SIR = 1.3; 95 percent CI = 1.1–1.5), gallbladder (SIR = 1.6; 95 percent CI = 1.1–2.3), pancreas (SIR = 1.5; 95 percent CI = 1.1–1.9), larynx (SIR = 2.1; 95 percent CI = 1.1–3.5), renal parenchyma (SIR = 2.3; 95 percent CI = 1.8–2.8), bladder (SIR = 1.2; 95 percent CI = 1.0–1.6), cervix uteri (SIR = 1.4;

95 percent CI = 1.1–1.9), endometrium (SIR = 2.9; 95 percent CI = 2.5–3.4), ovary (SIR = 1.2; 95 percent CI = 1.1–1.5), brain (SIR = 1.5; 95 percent CI = 1.2–1.9), and connective tissue (SIR = 1.9; 95 percent CI = 1.1–3.0), as well as for lymphomas (SIR = 1.4; 95 percent CI = 1.0–1.7). Higher risk was observed for Hodgkin's disease only in men (SIR = 3.3; 95 percent CI = 1.4–6.5) and for non-Hodgkin's lymphoma only in women (SIR = 1.6; 95 percent CI = 1.2–2.1). The association of obesity with risk of breast, prostate, and pancreas cancers was modified by age. (Wolk A, Gridley G, Svensson M, Nyren O, McLaughlin JK, Fraumeni JF, Adami HO. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001;12: 13-21) ■

Ovarian Cancer

Certain Ovarian Cysts Are Not Ovarian Cancer Precursors

Transvaginal ultrasonographic findings from the examinations of 20,000 postmenopausal women were compared with data on the established risk factors for ovarian cancer obtained from self-administered questionnaires. High parity, a strong ovarian cancer protective factor, was negatively associated with complex cysts (odds ratio for at least five births versus no births = 0.72). Neither long-term oral contraceptive use, another strong protective factor, nor family history of ovarian cancer or multiple breast cancers, both strong risk factors, was associated with complex cysts. Other identified abnormalities, including simple cysts, bilateral cysts, or all abnormalities combined, also did not share established risk factors for ovarian malignancy. A very small proportion of clinically silent ovarian abnormalities found on ultrasonography are determined to be ovarian cancers; the remaining complex cysts and other clinically suspicious abnormalities do not appear to be immediate precursors of ovarian cancer. (Hartge P, Hayes R, Reding D, Sherman ME, Prorok P, Schiffman M, Buys S. Complex ovarian cysts in postmenopausal women are not associated with ovarian cancer risk factors: preliminary data from the prostate, lung, colon, and ovarian cancer screening trial. *Am J Obstet Gynecol* 2000;183:1232-1237) ■

Prostate Cancer

Body Size and Prostate Cancer: A Population-based Case-control Study in China

A population-based case-control study was conducted in Shanghai to investigate whether body size plays a role in prostate cancer etiology and to explain the rapid increase in the prostate cancer incidence rate in China. On the basis of 238 newly diagnosed cases and 471 controls, a high waist-to-hip ratio, an indicator of abdominal adiposity, was related to excess risk, and men in the highest quartile had an almost threefold risk (odds ratio = 2.71; *p* for trend = 0.0001) compared with men in the lowest quartile. In contrast, men in the highest quartile of hip circumference had a reduced risk (odds ratio = 0.46; *p* for trend = 0.0002) relative to men in the lowest quartile. No association was found for height, usual adult weight, or preadult and usual adult body mass index. These results suggest that even in a very lean population (average body mass index = 21.9 mg/k^2), abdominal adiposity may be associated with an increased risk of clinical prostate cancer, pointing to a role of hormones in prostate cancer etiology. (Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, Xie T, Gao YT. Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2000;9:1335-1341) ■

Radiation

Bone and Liver Cancer in Mayak Plutonium Plant Workers

Bone and liver cancer mortality were evaluated among 11,000 "Russian Mayak" Production Association workers who were exposed to internally deposited plutonium and external gamma radiation. After data were adjusted for cumulative external radiation dose, relative risks (RR) of 17.0 for liver cancer and of 7.9 for bone cancer were observed among workers with plutonium body burdens estimated to exceed 7.4 kBq, and RRs of 2.8 for liver cancer and 4.1 for bone cancer were found among workers in the plutonium plant who were not routinely monitored for plutonium on the basis of urine measurements. In addition, analyses that treated the estimated plutonium body burden as a continuous variable indicated increasing risk of each

cancer with increasing burden ($p < 0.001$). RRs tended to be higher for females than for males, probably because of the lower baseline risk and the higher levels of plutonium measured in females. (Koshurnikova NA, Gilbert ES, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, Romanov SA, Shilnikova NS, Suslova KG, Vostrotin VV. Bone cancers in Mayak workers. *Radiat Res* 2000;154:237-245 and Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, Romanov SA, Shilnikova NS, Suslova KG, Vostrotin VV. Liver cancers in Mayak workers. *Radiat Res* 2000;154:246-252) ■

Statistics

Analyzing Exposure-time-response Relationships with a Spline Weight Function

A procedure was designed to estimate a weight function within a generalized linear model, and ultimately to examine the time-dependent effects of exposure histories on disease. The shape of the weight function, which is modeled as a cubic B-spline, gives information about the impact of exposure increments on disease risk at different times. The method was evaluated in a simulation study and applied to data on smoking histories and lung cancer from a recent case-control study in Germany. (Hauptmann M, Wellmann J, Lubin JH, Rosenberg PS, Kreienbrock L. Analysis of exposure-time-response relationships using a spline weight function. *Biometrics* 2000;56:1105-1108) ■

Viruses

Transmission of HIV-1 by Pregnant Women

In a collaboration among seven European and U.S. prospective studies, 44 cases of vertical HIV-1 transmission were identified among 1,202 pregnant women with RNA virus loads of less than 1,000 copies/mL at delivery or at the measurement closest to delivery. For mothers receiving antiretroviral treatment during pregnancy or at the time of delivery (or both), the transmission rate was 1.0 percent (8 of 834), compared with 9.8 percent (36 of 368) for untreated mothers. In multivariate analysis adjusting for study, transmission was significantly lower with antiretroviral treatment (odds ratio [OR] = 0.10), cesarean section (OR = 0.30), greater birth weight (OR = 0.92), and higher CD4 cell count (OR = 0.86). (Ioannidis JPA, Abrams EJ, Ammann A, Bulterys M, Goedert JJ, Gray L, Korber BT, Mayaux MJ, Mofenson LM, Newell ML, Shapiro DE, Teglas JP, Wilfert CM. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads < 1000 copies/mL. *J Infect Dis* 2001;183:539-545) ■

DCEG PEOPLE IN THE NEWS

Dr. Erin Bell, a fellow in the Occupational Epidemiology Branch, received the Sidney Kark Distinguished Teaching Assistant Award from the University of North Carolina's School of Public Health, Epidemiology Department.

Dr. Mitchell Gail, Chief of the Biostatistics Branch, delivered three invited talks in the last few months. In September, he delivered the Presidential Invited Address to the International Society for Clinical Biostatistics in Trento, Italy, on the topic, "A comparison of cohort, case-control, and family-based designs." In November, he addressed the Second Seattle Symposium in Biostatistics. In January, he spoke at the Inaugural Meeting of the East Mediterranean Region of the International Biometric Society, where he compared designs for estimating gene penetrance.

Dr. Lynn Goldin

Dr. Lynn Goldin, of the Genetic Epidemiology Branch, served as President of the International Genetic Epidemiology Society during 2000. At the annual meeting in October in San Antonio, Dr. Goldin delivered the presidential address entitled, "Genetic epidemiology: 2001 and beyond." Other Branch staff members at the meeting were **Dr. Alisa Goldstein,** who presented a poster entitled "Comparison of case-control designs using unrelated or related controls for detecting gene-environment (GxE) interaction," and **Dr. Christina Bromley,** who presented a poster entitled "Westernization and family history as determinants of breast cancer risk in Asian American women."


Dr. Mark Greene

Dr. Mark Greene, Chief of the Clinical Genetics Branch, has been named a member of American Society of Clincal Oncology's (ASCO's) Cancer Genetics Task Force and will be one of the faculty members for the pre-ASCO Annual Meeting Cancer Genetics Course.


Ms. Neely Kazerouni

Ms. Neely Kazerouni, a member of the Clinical Genetics Branch, has been appointed to the NIH Pre-IRTA Committee, which serves as a resource and liaison between the NIH administration and the NIH pre-IRTA community. The committee serves the needs of prebaccalaureate, postbaccalaureate, and technical fellows, which number about 600 at any one time. Members also coordinate a variety of professional and social events. Ms. Kazerouni replaces outgoing member Ms. Tammy Shields, of the Environmental Epidemiology Branch.


Dr. Qing Lan

Dr. Qing Lan, an Occupational Epidemiology Branch member, received an AACR-AFLAC, Inc. Scholar in Training Award of $1,000 for the abstract "Analysis of lymphocyte subsets among workers exposed to benzene in China," which was co-authored by **Drs. Mustafa Dosemeci, Richard Hayes, Nat Rothman,** and **Martha Linet.** Dr. Lan will use this award to defray her travel and registration expenses when she attends the AACR Annual Meeting. Dr. Lan has also been accepted into the NCI Cancer Prevention Fellowship Program. She will spend a year at Johns Hopkins University, beginning in July, working on a master's degree in epidemiology.

In September, **Dr. Mary Lou McMaster,** of the Genetic Epidemiology Branch, was an invited speaker and participant at a workshop on Waldenström's macroglobulinemia, sponsored by Dr. Bruce Cheson of the NCI Cancer Therapy Evaluation Program. The workshop convened preeminent researchers in this area to reach a consensus about disease definition and to establish international research priorities and criteria. Dr. McMaster's presentation was entitled "Family studies in Waldenström's macroglobulinemia." ■

COMINGS … GOINGS


Dr. Andrea Baccarelli

Dr. Andrea Baccarelli has joined the Genetic Epidemiology Branch as a visiting postdoctoral fellow. Dr. Baccarelli received his M.D. from Perugia University, Italy, and completed a fellowship in endocrinology and metabolic diseases at the University of Milan. He also holds an M.P.H. in epidemiology from the Italian Epidemiology Association. Until recently Dr. Baccarelli served as a medical endocrinologist and epidemiologist at the University of Milan. His research interests include endocrine disrupters in cancer etiology and melanoma. He will be working with Dr. Maria Teresa Landi. Dr. Baccarelli is located in EPS 7115 and can be reached at 301-496-5786.


Dr. Peter Chang

Dr. Peter Chang, Professor at the Institute of Environmental Health Sciences, National Yang Ming University, Taiwan, has joined the Radiation Epidemiology Branch as an Exchange Scientist for five months. Dr. Chang will collaborate with Branch scientists in a study of cancer in persons exposed to gamma radiation in contaminated buildings in Taipei, Taiwan. Dr. Chang has published widely on the dosimetry for measuring building contamination, and during his stay in the Branch, he will work closely with statisticians and epidemiologists to estimate cancer risk from radiation. Dr. Chang has an M.D., an M.P.H. in occupational health from Harvard University, and an Sc.D. in radiobiology from Harvard. His previous research interests include thyroid abnormalities associated with chronic radiation exposure, biomedical effects of chronic extremely-low-dose gamma irradiation and, most

recently, exposure to chronic low-dose gamma radiation from cobalt 60-contaminated construction steel in Taiwan. Dr. Chang is located in EPS 7090 and can be reached at 301-496-6600.


Mr. Larry Chloupek

Mr. Larry Chloupek has joined the Administrative Resource Center as the Deputy ARC Manager. He received his B.A. in business administration from The American University. Mr. Chloupek worked for the U.S. Department of Agriculture and the Office of Personnel Managment before joining NCI in 1991. Most recently, he served as the Deputy ARC Manager for the ARC10B in the Clinical Center. He is located in EPS 8088 and can be reached at 301-594-3992.


Dr. Graca Dores

Dr. Graca Dores recently joined the Radiation Epidemiology Branch through the NCI Cancer Prevention Fellowship Program. Dr. Dores received her M.D. from Brown University, where she completed a residency in internal medicine and a fellowship in hematology and oncology, and she went on to work there as a medical oncologist and assistant professor of medicine. She holds an M.P.H. in epidemiology from the University of Alabama as part of the fellowship program. Dr. Dores' research interests include multiple primary cancers and hematologic malignancies, and she is currently working with Dr. Lois Travis. Dr. Dores is located in EPS 7051 and can be reached at 301-594-3262.


Dr. Sam Mbulaiteye

Dr. Sam Mbulaiteye has joined the Viral Epidemiology Branch as a research fellow. Dr. Mbulaiteye is a medical oncologist from the Uganda Cancer Institute in Kampala. He received his M.D. from Makerere Medical School, where he completed postgraduate training in internal medicine. Dr. Mbulaiteye received a master's degree in epidemiology from Cambridge University, U.K. His primary interests are pediatric and adult lymphomas, Kaposi's sarcoma, and other malignancies that are or may be related to HIV and human herpesvirus 8 infections. For the past two years, he has been project leader for a prospective cohort study examining HIV infection and its determinants in 10,000 people in Uganda. He also is interested in surveillance, diagnosis, and risk factors for adult and pediatric solid tumors in developing countries. In the Viral Epidemiology Branch, Dr. Mbulaiteye will be working primarily with Drs. Robert Biggar and James Goedert on viral cancer studies. He is located in EPS and can be reached at 301-594-7825.

Dr. Catherine Metayer, formerly of the Radiation Epidemiology Branch, has relocated to Northern California.


Dr. Dominique Michaud

Dr. Dominique Michaud joined the Nutritional Epidemiology Branch in December as a tenure-track investigator. She obtained an Sc.D. in epidemiology and nutritional epidemiology at the Harvard School of Public Health, where she then completed two years of training as a research fellow. Her experience at Harvard included coordinating the collection of over 17,000 buccal cell kits. Before her graduate studies, Dr. Michaud gained experience in molecular biology and human genetics by working on the Human Genome Project at the Children's Hospital of Philadelphia. Her current research focuses on dietary factors and their correlation to the incidence of bladder and pancreatic cancers. She is located in EPS 7026 and can be reached at 301-594-6545.

The Division of Cancer Epidemiology and Genetics had the pleasure of working with **Dr. Ruggero Montesano,** who joined the Viral Epidemiology Branch (VEB) as a visiting scientist in December. Dr. Montesano is a molecular pathologist whose main interests are in environmental carcinogenesis and molecular epidemiology. He presently focuses on esophageal and liver cancers. From 1980 through 1999, he was Chief of the Unit of Mechanisms of Carcinogenesis at the International Agency for Research on Cancer (IARC) in Lyon, France.

During his three months at DCEG, Dr. Montesano split his time between VEB and the Laboratory of Human Carcinogenesis in the Division of Basic Sciences. In collaboration with Dr. Greg Kirk of VEB, Dr. Montesano will continue to work on analyses of the Gambia Liver Cancer Study and on detection of molecular markers of liver cancer in serum and plasma. Dr. Montesano returned to IARC at the end of February.

Dr. Barbara Mulach, an NIH Presidential Management Intern, worked with Ms. Betsy Duane in DCEG through February. Prior to coming to NIH, Dr. Mulach received her Ph.D. in biochemistry from the University of Alabama at Birmingham. Since she began the internship program in 1999, she worked in several offices at NIH, including NIAID's Office of Policy Analysis; NLM's Office of Communications and Public Liaison; and NCCAM's Office of Communications, Science Policy and Public Liaison. As an intern, she also spent four months at the National Science Foundation, working with the Division of Graduate Education. At DCEG, Dr. Mulach participated in communications-related activities and projects.

Dr. Stephanie Weinstein, a fellow in the Nutritional Epidemiology Branch, has accepted a position at the Center for Nutrition Policy and Promotion, U.S. Department of Agriculture, in Washington, D.C.

Dr. Mingdong Zhang

In December, **Dr. Mingdong Zhang** joined the Viral Epidemiology Branch as a research fellow. Dr. Zhang received his M.D. and his M.S. in epidemiology from Shanghai Medical University, where he conducted epidemiological research on aflatoxin and primary liver cancer in Chinese patients as well as epidemiological research in other areas. After an additional year of training in epidemiology at the University of Iowa, Dr. Zhang studied molecular virology at the Baylor College of Medicine. He received his Ph.D. from Baylor in 1998; under Dr. Mary K. Estes' supervision, he studied rotoviruses. While at Baylor, he received several graduate student awards for his work. At the Viral Epidemiology Branch, Dr. Zhang will focus on hepatitis viruses, hepatocellular carcinoma, and host genetics under the supervision of Dr. Thomas O'Brien. Dr. Zhang is located in EPS 8011 and can be reached at 301-594-8385. ■

MOLECULAR EPIDEMIOLOGY LEARNING SERIES

Dr. Alice Sigurdson

Because of the explosion of information about genes, pathways, and epigenetic events involved in carcinogenesis, **Dr. Alice Sigurdson** of the Radiation Epidemiology Branch (REB) has developed a Molecular Epidemiology Learning Series (MELS) to inform REB staff members about the latest developments in molecular biology, genetics, and epidemiology, with a particular emphasis on radiation carcinogenesis. Series speakers include molecular epidemiology experts from DCEG and other institutions. MELS is informal and has generated many earnest discussions. ■

WORKSHOP ON NEUROFIBROMATOSIS 2 (NF2)

Dr. Dilys Parry

Dr. Dilys Parry, of the Genetic Epidemiology Branch, was one of three American investigators invited to Chester, England, in late July 2000 to participate in a two-day workshop on "Future Directions in NF2 [neurofibromatosis 2] and Vestibular Schwannoma Research." NF2 is a rare autosomal dominant disorder characterized by the development of bilateral vestibular schwannomas (VS), schwannomas of other cranial and spinal nerves, intracranial and spinal meningiomas, and early-onset cataracts. The disorder results from a germline mutation in *NF2*, a tumor suppressor gene located on chromosome 22q. Several groups have demonstrated that germline mutations that may truncate the NF2

protein generally lead to severe disease (onset before age 20 years, multiple central nervous system tumors in addition to VS, and rapid clinical progression), that splice-site mutations result in variable phenotypes, and that missense mutations and large gene deletions lead to mild manifestations (onset after age 20, few central nervous system tumors other than VS, and slow clinical course). Management usually involves surgical removal of symptomatic tumors, which often results in permanent neurologic damage. Radiosurgery is sometimes performed for VS, but this procedure may increase the risk of malignant transformation.

The workshop began with a series of presentations outlining the current status of NF2 research and management as well as a description of research goals in various areas, including genetics, imaging, electronic implants, cell biology, mouse models, and new therapies. Participants then divided into five groups to discuss assigned themes: auditory brainstem and cochlear implants, quality of life issues, nonsurgical treatment of VS, surgical management of NF2, and genetics. Rapporteurs presented each group's conclusions and priorities for future research to all workshop attendees. Workshop leaders plan to publish the proceedings and to use the research and management priorities developed at the meeting to create an integrated system for managing NF2 patients and for coordinating research efforts. ■

CHORNOBYL RESEARCH PROGRAM MEETINGS

The Chornobyl Research Unit (CRU), Radiation Epidemiology Branch, recently sponsored three events—a tri-national meeting and two workshops—to bring collaborators together to discuss important issues related to recent studies, to foster collaboration between scientists from Belarus and Ukraine, and to standardize study procedures in the two countries. In November 2000, CRU sponsored the second Tri-National Meeting on Collaborative Chornobyl Thyroid Research Projects, which included collaborators from Belarus, Ukraine, and the United States. The project directors, Dr. Valentin Stezhko from Belarus and Dr. Mykola Tronko from Ukraine, reviewed developments since the previous Tri-National meeting, and participants met in several breakout sessions to discuss issues in epidemiology, dosimetry, laboratory, ultrasound, clinical aspects, and project administration. Because of the progress of the studies over the previous year and the impending completion of the first screening cycle, the discussions focused on planning for the second screening cycle, which is expected to begin in early spring 2001. Johns Hopkins University researcher Dr. Genevieve Matanoski, Chair of the Advisory Committee for Energy-Related Epidemiologic Research (ACERER) Subcommittee that was responsible for the congressionally mandated scientific and management review of the Chornobyl Program, summarized the final report with recommendations for improvement. Dr. Shelia Zahm, Deputy Director of DCEG, presented NCI's response to the ACERER recommendations and noted several activities that had already been initiated in response to a previous ACERER report, including the establishment of the Thyroid Advisory Group (TAG) to provide ongoing peer review of the thyroid projects. TAG had its first official meeting concurrent with the second Tri-National Meeting. Following the three-day Tri-National meeting, CRU also sponsored two workshops: the "Iodine Nutrition Assessment in the Post-Chornobyl Thyroid Cancer Study Workshop" and a "Working Session on Operations Manuals and Data Collection Forms for Screening Cycle Two." ■

Chornobyl Thyroid Advisory Group Members (from left to right). Bottom: Dr. Genevieve Roessler, Dr. Shirley Fry, Mr. Bruce Napier, Dr. Maria Demkowicz, and Dr. Evelyn Bromet. Top row: Drs. Ihor Masynk, Gerard Burrow, Joseph Fraumeni, David Becker, and Shelia Zahm. (Missing members: Drs. Christina Durbak, Fred Mettler, and Roy Shore.)

Kathleen Stine