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In this issue:

Director's Update...1

Building a Molecular Foundation for Cancer Prevention

Mouse Models Offer Promise in the Science of Cancer Prevention...1

Cancer Susceptibility Genes ...3

Epigenetics and Cancer Prevention ...4

Fine Tuning Prevention Drugs...5

Improving Cancer Screening through Technology, Access, and Communication...6

A Conversation with...6

Dr. Stephen J. Chanock

Tobacco and Cancer Prevention...7

Unmasking Diet's Impact on Cells and Cancer Risk...8

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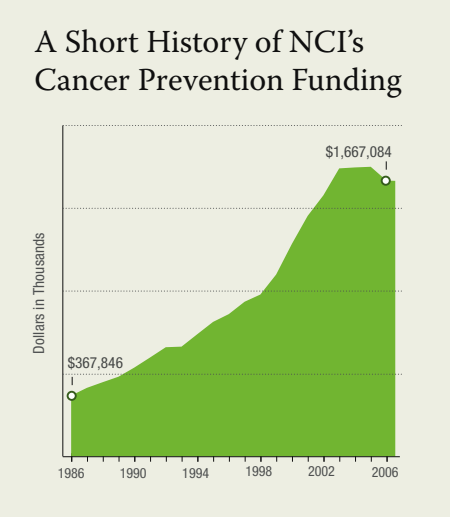
Director's Update

Building a Molecular Foundation for Cancer Prevention

In this issue of the *NCI Cancer Bulletin*, we offer a closer look at cancer prevention research. It's an enormous topic, but I think you'll see as you read that, beyond what we already know about behavior change and cancer prevention, the field is transitioning toward studies that delve into the molecular foundations of health and disease.

Some of the most promising science under way takes advantage of advances in fields such as genomics, transcriptomics, proteomics, and metabolomics—what some call "molecular prevention."



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Mouse Models Offer Promise in the Science of Cancer Prevention

The new generation of genetically-engineered mouse models (GEMs) holds promise for helping cancer prevention researchers refine and speed up testing of potential preventive agents. These mice are programmed to develop specific types of cancer in ways that mimic human cancer. That may make it easier for scientists, using sophisticated imaging technologies, to gauge the effects of cancer preventive substances.

This summer, NCI will convene a "think tank" of 15–18 invited experts from the fields of early intervention, prevention, and prevention screening, as well as from the NCI Mouse Models of Human Cancers Consortium (MMHCC), to develop research plans that fully explore the promise of GEMs.

"The meeting will bring together a cadre of scientists from diverse fields," noted Dr. Cory Abate-Shen, professor with the Center for Advanced Biotechnology and Medicine, UMDNJ-Robert Wood Johnson Medical School. "This will facilitate a dialogue, which is critical. Working together, we can develop ideas for studies that will enable us to assess the value of these newer mouse models for cancer prevention."

In NCI's Division of Cancer Prevention (DCP), the Chemopreventive Agent Development Research Group, as well as many NCI funded investigators, have published more than a hundred studies using GEMs for the

(continued on page 2)

(Director's Update continued from page 1)

In the following pages, for example, you'll see that researchers are investigating the genetic and epigenetic events related to carcinogenesis and their interplay with diet and environmental exposures; they are conducting whole-genome scans using genomic single nucleotide polymorphisms (SNPs) and beginning the use of whole genome sequencing to identify all of the genes predicting risk and involved in the development of cancer; and they are using genetically engineered mouse models that may be able to provide important details about precancerous states and possibly accelerate the development of preventive agents, such as those supported by the Division of Cancer Prevention's RAPID program, which expedites extramural agents through development, proof of concept, and phase I clinical trials.

I see a close relationship between research focused on preventing disease in those known to be at high risk and detecting disease at its very earliest stages based on genetic or protein expression signatures. Research such as this is going on throughout NCI, including the Early Detection Research Network, the Clinical Proteomics Program, and the Cancer Family Registries, with opportunities for the cross-fertilization of ideas that can lead to important advances.

Any discussion of cancer prevention would be incomplete without highlighting the recent approval of the vaccine that protects against human papilloma virus (HPV). The benefits of this vaccine will probably not be seen for years to come, so it is imperative that all women continue regular screening.

Along those lines, during a visit to the Ohio State University Comprehensive Cancer Center last week, I attended a presentation on an innovative study called CARE aimed at addressing the unusually high cervical cancer rates in the Appalachian regions of Ohio by, among other measures, improving Pap smear screening rates.

The program highlights that access to cutting-edge science and care is critical to decreasing the cancer burden. That reality is a driver behind the pilot program to be launched later this year, the NCI Community Cancer Centers Program. And, of course, continuing to support innovative ways to influence behavioral risk factors, including diet, exercise, and tobacco use, remains a key part of cancer prevention.

I hope you enjoy this special issue. It provides only a snapshot of the diverse efforts by NCI and others in the research community to prevent cancer. But I believe it also presents a bright future in which we have a variety of effective tools at our disposal to fight cancer incidence and vastly improve public health in the United States and beyond. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

(Mouse Models continued from page 1)

past decade. These studies in multiple organ systems have identified a variety of agents that have progressed to human clinical trials, including nonsteroidal anti-inflammatory drugs (NSAIDS), nitric-oxide-releasing NSAIDS, glucocorticoids, retinoid X receptor agonists, aromatase inhibitors, tazarotene, and ACAPHA (a mixture of Chinese herbs). However, more recently developed GEM models may be especially well suited to future prevention studies.

The upcoming think tank will address several key questions related to this, explained NCI's Dr. Cheryl Marks, who administers the MMHCC. "The intent of the meeting is to identify the principal challenges facing early intervention and prevention, define the future goals, identify limitations of mouse models and strategies to overcome those limitations, and discuss how to effectively use these newer mouse models for cancer prevention."

Until now, research with GEMs and other mouse models in the MMHCC has focused more on their applicability for safe and effective treatments for cancer rather than on prevention.

Last year in *Toxicologic Pathology*, participants from a previous MMHCC workshop reported on precancer research. "The scientific community suddenly possesses a wealth of precancers available for study in a variety of organ systems," they wrote. "Since most of the GEMs have been constructed to test oncogenes or tumor suppressor genes known to be involved in human cancer, these precancers should become primary targets for understanding, treatment, and prevention and ideal representations of processes occurring in human precancers."

Dr. Abate-Shen noted that human clinical trials for cancer preventive agents can take many years before delivering definitive results, whether positive or negative, about the drug or nutritional supplement. "Our goal would be to test agents in these newer mouse models to understand their mechanism of action and to guide clinical studies," she said. ◆

Cancer Susceptibility Genes

Cancer prevention efforts aim to identify individuals at risk of the disease so that they can benefit from interventions or surveillance. DNA testing can detect mutations in known susceptibility genes such as *BRCA1*, but such genes are relatively rare and account for a small part of the inherited risk of cancer in the population.

To find common genes that confer modest amounts of risk, researchers have begun to survey the human genome for DNA variants such as single nucleotide polymorphisms (SNPs) that are associated with some common cancers. Genome-wide association studies are underway for common diseases, including diabetes. Last year, NIH launched two initiatives to support such efforts.

The NCI-sponsored Cancer Genetic Markers of Susceptibility (CGEMS) project is using high-throughput technology to identify susceptibility genes for breast and prostate cancers. The genotyping data are being made available online so that other investigators can have access to the information.

"The hope is that genome-wide association studies will be a discovery tool for identifying genes that no one knew were involved in cancer," said Dr. Margaret Tucker, director of the Human Genetics Program in the Division of Cancer Epidemiology and Genetics (DCEG). "These genes could point to novel environmental risk factors and biological mechanisms in the disease."

Some research groups have been establishing consortia and pooling resources to assemble the large number of individuals required to detect modest effects of genes on cancer risk and to replicate preliminary findings.

The NCI-sponsored Cohort Consortium is an international collaboration of researchers responsible for about 25 population cohorts involving 2.6 million individuals. The Cohort Consortium provides an integrative framework for studies of specific cancers to systematically evaluate biomarkers of susceptibility and disease.

A recent study by another group, the Breast Cancer Association Consortium, suggests that researchers can confirm or refute associations reported previously in the scientific literature by pooling data. The consortium used data on 33,000 women in 13 countries to confirm that a SNP in the gene *CASP8* may offer modest protection against the disease.

The finding does not have immediate implications for prevention. But it suggests that researchers could use the same approach to identify panels of genetic variants that collectively influence a woman's risk, said Dr. Montserrat Garcia-Closas of DCEG.

Identifying SNPs linked to disease in genome-wide scans is an important first step, but additional work is usually necessary to identify the genes involved. "The data from these scans should be a rich discovery resource for the whole community and should stimulate new areas of research," said Dr. Tucker. ◆

Relevant Resources

For the public

Information on Prevention from NCI —http://www.cancer.gov/cancertopics/prevention-genetics-causes/prevention

Risk Calculators—http://understandingrisk.cancer.gov/!!!start.cfm

NCI's Cancer Information Service—http://www.cancer.gov/help or 1-800-4-CANCER.

From the American Cancer Society—http://www.cancer.org/docroot/PED/ped_1.asp?sitearea=PED

MedlinePlus—http://www.nlm.nih.gov/medlineplus/cancer.html

For the clinical and research communities

"Radiation & Pediatric Computed Tomography: A Guide for Health Care Providers"— http://www.cancer.gov/cancertopics/causes/radiation-risks-pediatric-CT

"Interventional Fluoroscopy: Reducing Radiation Risks for Patients and Staff"—http://www.cancer.gov/cancertopics/interventionalfluoroscopy

Health Information National Trends Survey—http://hints.cancer.gov/hints/

For everyone

NCI-Sponsored Clinical Trials—http://www.cancer.gov/clinicaltrials/search

Other Government and Private-Sponsor Prevention Trials—http://www.clinicaltrials.gov/ ◆

Epigenetics and Cancer Prevention

Some cancers involve the inappropriate silencing or activation of genes through epigenetic changes—chemical modifications to DNA and proteins that control gene activity without causing a change in DNA sequence.

Though the epigenetic silencing of certain genes is critical throughout life, epigenetic information is less stable than the DNA sequence and may change over a lifetime. Some epigenetic changes can be modified by environmental factors, including drugs.

Epigenetic regulation of genes is essential for health, and flaws can lead to cancer and other diseases. But the flaws themselves could potentially be used to detect and even prevent tumors.

For example, the gene *GSTP1* normally protects cells from damage by environmental toxins. But, in some prostate tumors, the gene is silenced by the addition of chemicals called methyl groups to DNA. Researchers at Johns Hopkins University developed an experimental screening test to detect this DNA methylation, the most common epigenetic change.

"Cancer epigenetics is important for prevention because we may be able to use methylation markers to identify people at higher risk of cancer and perhaps detect cancer earlier," said Dr. Mukesh Verma in NCI's Division of Cancer Control and Population Sciences (DCCPS), one of several divisions conducting epigenetics research.

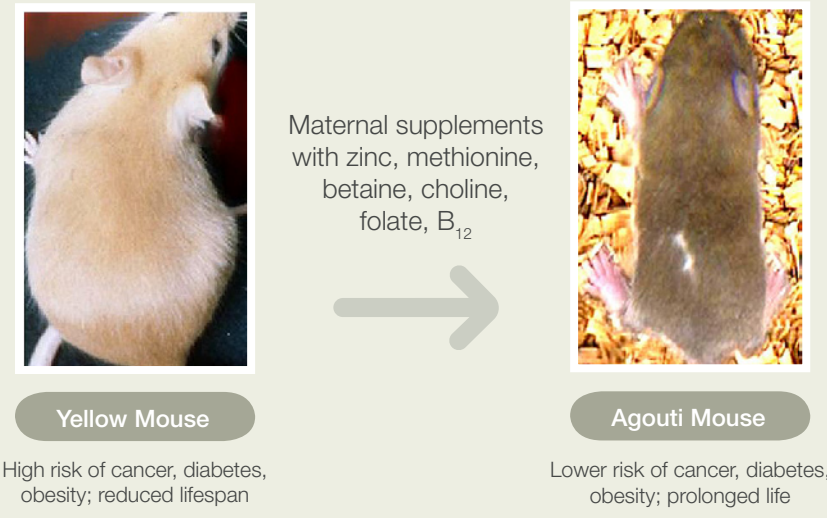
Investigators in DCP's Early Detection Research Network are engaged in analytical validation of *GSTP1* methylation for prostate cancer, as well as other genes linked to breast, kidney, and bladder cancers.

DCP has also led workshops and discussions on potential application of hypermethylation as a biomarker for early cancer detection, diagnosis, and prognosis. A recent workshop sponsored by the DCP Cancer Biomarkers Research Group and the National Institute of Standards and Technology developed guidelines and recommendations for reagents, tools, and protocols for quantitative measurement of methylation in affected organ sites. A summary by Drs. Jacob Kagan and Sudhir Srivastava of DCP will be published soon in *Cancer Research.*

"We cannot reverse genetic mutations, but by using drugs we may be able to reverse changes in methylation," said Dr. Verma. "This approach has promise for prevention."

Diet also may affect methylation. Giving pregnant mice diets rich in methyl donors—including folic acid, choline, methionine, and genistein, an ingredient in soy—can modify the methylation patterns of a certain gene in their offspring. This can cause a change in coat color that may be associated with a reduced cancer risk.

"Epigenetic information presumably can be modified by environmental factors, including diet, and that's intriguing," said Dr. Sharon Ross of DCP. "We're getting closer to understanding how we might modify epigenetic changes associated with disease." ◆



Mouse models are helping researchers understand the genetic and epigenetic changes associated with cancer, as well as factors that can influence this risk.

Fine Tuning Prevention Drugs

When the results of the STAR clinical trial were published last year, they showed that the anti-osteoperosis drug raloxifene was as effective at reducing breast cancer risk in high-risk women as tamoxifen, but with lower toxicity. The results also highlighted the evidence-based path prevention researchers follow to test more effective, less toxic agents.

That approach begins with NCI's chemoprevention agent portfolio. More than 108 agents are currently being tested in NCI-supported preclinical studies. And 100 unique drugs (alone or combined) have been or are now in early clinical trials.

While most of these compounds are in preliminary stages of research, other more established drugs are in large clinical trials. For colorectal cancer prevention, for example, results from two phase III clinical trials published last year demonstrated a significant risk-reduction benefit for people at increased risk of disease taking the COX-2 inhibitor celecoxib. However, the trials also raised significant concerns because of the cardiac toxicities associated with the drug in some participants.

"Once a treatment is proven to be effective, rarely is it abandoned because of toxicity concerns," said Dr. Asad Umar, acting chief of the Gastrointestinal and Other Cancers Research Group in DCP. "Instead, we do additional research to try to better understand the toxicities, hopefully finding ways to minimize them and improving the treatment's effectiveness. We approach prevention the same way."

Celecoxib is already approved by the FDA for risk reduction, along with surgery, in people with familial adenomatous polyposis (FAP), a hereditary disorder that significantly increases colorectal cancer risk. And DCP's Dr. Iqbal Ali is using proteomic technologies to analyze blood from people with FAP to pinpoint molecular clues indicative of celecoxib chemopreventive activity and/or cardiovascular toxicity. "Our pilot study has identified novel celecoxib-modulated proteins of various molecular functions, some of which are highly relevant for carcinogenesis and cardiovascular pathology," Dr. Ali said.

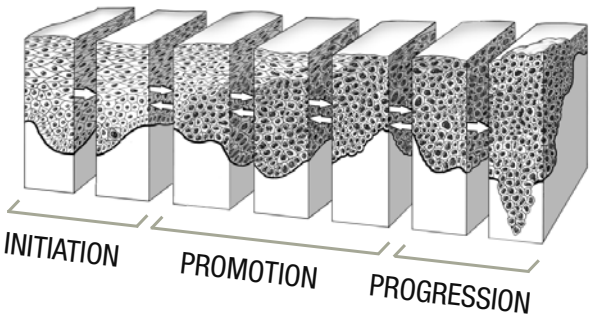
This research, she continued, is focused on identifying systemic changes after celecoxib treatment to identify which individuals at high risk of developing colorectal cancer are most likely to benefit from it.

The same approach is being used to try to refine the benefit-to-risk ratio of the first chemoprevention agent ever approved by the FDA, tamoxifen. Although recently published results have affirmed tamoxifen's preventive benefits and eased concerns about toxicity, prevention researchers are taking steps to further target its use.

Using blood samples from the breast cancer cases that occurred in the first large U.S. clinical trial testing tamoxifen for breast cancer prevention, the Breast Cancer Prevention Trial (BCPT), Dr. Barbara Dunn from DCP and Dr. Mark Greene from DCEG are leading a BCPT substudy, one of several directed by the National Surgical Adjuvant Breast and Bowel Project, that is examining a pre-identified set of genes, SNPs, and repeat sequences primarily in the cell-signal pathways for tamoxifen and estrogen metabolism. Their goal: to determine the impact SNPs have on tamoxifen or estrogen activity in preventing breast cancer.

"This is part of the movement toward individualized prevention," Dr. Dunn said. "Ideally, you would be able to genotype a woman not only to determine whether she is at high risk, but also whether she is likely to benefit from tamoxifen." ◆

A Model for Epithelial Tumors



Years of scientific research have demonstrated that cancer occurs not as single, catastrophic event, but rather as the result of a complex and long-evolving process that can take decades to complete, providing time and opportunity to intervene to stop or reverse its progress before the clinical appearance of cancer.

Improving Cancer Screening through Technology, Access, and Communication

Screening for early-stage disease remains vital to cancer prevention. New technologies are especially needed for cancers such as ovarian and pancreatic cancer, which often do not produce symptoms until they have spread from the tissue of origin. To this end, NCI launched the Early Detection Research Network to fund a diverse consortium of researchers attempting to turn molecular biomarkers of cancer into useful clinical tools.

NCI performs and funds research to improve existing screening technologies, as well. Dr. Philip Castle of DCEG is validating several molecular tests to screen women for clinically relevant types of human papillomavirus (HPV). For years Pap smears have successfully detected precancerous cervical lesions, but molecular tests for cancer-causing types of HPV are more clinically sensitive and are better precancer predictors than Pap smears and other cytologic methods.

"The goal essentially for these kinds of tests is to make the current screening system more efficient," explained Dr. Castle. "HPV testing is a more clinically sensitive test than cytology, so you can go to longer screening intervals among women who test negative for cancer-causing types of HPV because of the greater reassurance. This in turn reduces the overall cost of the cervical cancer prevention program, which is billions of dollars annually, without reducing the effectiveness."

Dr. Castle and colleagues are working on increasing cervical cancer screen-

(continued on page 7)

A Conversation with... Dr. Stephen J. Chanock

Director of the Core Genotyping Facility in NCI's Advanced Technology Center and head of the Genomic Variation Section in CCR's Pediatric Oncology Branch.

External influences are dominant in cancer development, so why is it important to understand the role of genetic variation in this disease?

While the role of the environment is undoubtedly important, it is rarely the sole determinant of cancer risk. Rather, it is the interplay between the environment and our genes or, more specifically, the variations found in our genome, that result in differing responses to the environmental exposures and lifestyle factors that can lead to the onset of cancer. The genomic revolution has given us the tools to examine common genetic variants in a comprehensive manner, allowing us to evaluate the effects of modest or small changes in a gene's function or expression that may contribute to cancer risk. New technological advances make it possible to survey a well-chosen set of common genetic variations and identify markers of disease risk. However, these findings must be further validated in successive replication studies before we can begin to investigate the functional consequences of genetic variation.

Given the genetic and molecular research currently under way, what might cancer prevention look like 5, 10, or 20 years from now?

We cannot fully anticipate the future course of cancer prevention, but we are in a position to make at least a few educated guesses. The value of genetic testing and counseling should continue to increase over time, along with our knowledge base, as we conduct more clinically relevant studies. One can envision a day when individual profiles of genetic risk factors may help to inform lifestyle choices or to accelerate the rate of screening for early detection of specific cancers. Furthermore, the identification of genetic mechanisms and pathways underpinning cancer will provide insights into the development of new diagnostic, preventive, and therapeutic measures. Still, we should be wary of underestimating the complexity of cancer and, for this reason, continue to pursue integrated approaches that bring together observations across many disciplines—including genetics, cancer biology, and epidemiology—to advance cancer prevention research. ◆

(Screening continued from page 6)
ing for disadvantaged women worldwide, where more than 80 percent of cervical cancer is found. DCEG's Mississippi Delta Project has partnered with local organizations to test the effectiveness of HPV testing using self-collected cervicovaginal samples in a population of medically underserved women living in the rural southern United States.

Improving access and compliance is important for all types of cancer screening. "You can have the most effective test available, but if you can't get physicians to recommend it, and you don't address patient barriers to using it, it's not likely to benefit the public health," said Dr. Helen Meissner, chief of the Applied Cancer Screening Research Branch in DCCPS.

NCI has extensive research efforts underway "to understand factors that improve compliance with screening from a health care delivery and systems standpoint," explained Dr. Rachel Ballard-Barbash, associate director of DCCPS's Applied Research Program. "This may involve developing automated systems that prompt physicians to encourage their patients to undergo screening or remind patients to schedule appointments for screening, as well as systems for improving how screening tests, such as mammograms, are interpreted by radiologists. The assumption that all the focus of attention needs to be with the individual person rather than the system of health care delivery may miss major opportunities to make great improvements in health care." ◆

Tobacco and Cancer Prevention

Cigarette smoking remains the leading preventable cause of premature death, accounting for one in every five deaths in the United States, many of these due to cancer. NCI supports research to identify factors that contribute to smoking initiation, cancer development, and successful quitting, as well as tools to help people quit, including those available at http://www.smokefree.gov and through NCI's smoking quitline at 1-877-44U-QUIT.

Efforts to stop people before they start smoking have identified peer smoking, family members who smoke, and tobacco industry marketing and advertising as important influences, and there has been some progress in targeting these factors.

Cancer Incidence from Tobacco

Lung	78%
Esophagus	5%
Pancreas	4%
Mouth	3%
Bladder	3%
Kidney	2%
Larynx	2%
Stomach	2%
Cervix	1%
Leukemia	1%

However, 22 percent of high school students and 21 percent of adults continue to smoke, and as researchers are beginning to realize, this may have something to do with their genes.

"Genetic factors associated with nicotine dependence and addiction might have an influence on who maintains tobacco use," said Dr. Gary Swan, director of the Center for Health Sciences at SRI International in Menlo Park, CA, and an NCI-funded expert whose research focuses on nicotine dependence, genetic and environmental determinants of addiction, and pharmacogenetics.

Genetic research, for example, has identified variants in the *CYP2A6* gene associated with nicotine metabolism. Some people with these variants are able to metabolize nicotine faster with fewer unpleasant side effects, such as nausea and headache, and thus are more likely to become a regular smoker. Conversely, individuals who metabolize nicotine slower are less likely to become regular smokers because the adverse side effects they experience help them resist further use.

Other research is showing that nicotine dependence might be associated with a genetic variant in the dopamine pathway, which regulates feelings of pleasure and reward. People with fewer dopamine receptors are more likely to become regular smokers, presumably because the rewarding effect of nicotine compensates for the lack of dopamine receptors.

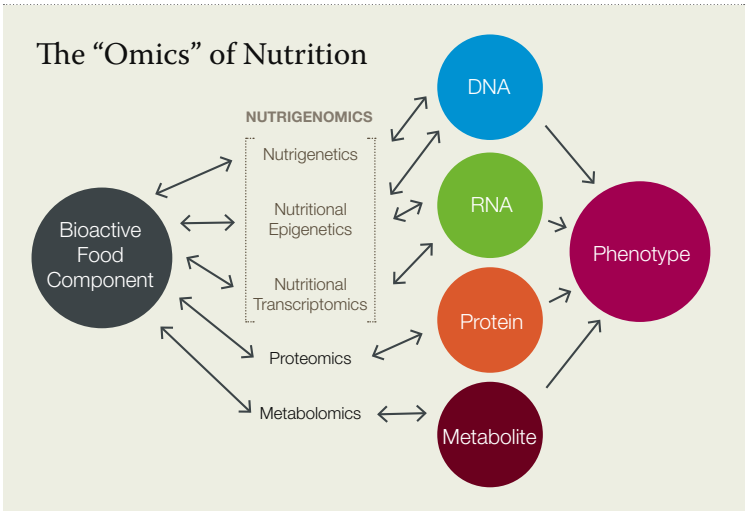
Knowledge of genetic variants such as these may eventually help researchers tailor cessation drug treatments according to an individual's genetic

(continued on page 8)

Unmasking Diet's Impact on Cells and Cancer Risk

By some estimates, 30 to 35 percent of all cancers are related to environmental factors. Of those factors, diet is considered one of the most significant.

And although studies are frequently reported that suggest one type of food may increase or decrease your risk of cancer or other diseases, the truth, said Dr. John Milner, chief of the DCP Nutritional Sciences Research Group, is that those risks are going to vary from person to person.



Dietary components can influence not only the inherent qualities of cells, but also the way cells respond to drugs and other treatment interventions.

"Not all people respond identically to anything, whether it's food or drugs or exercise," Dr. Milner said.

For a long time, researchers have been attempting to help unravel how and why these different responses occur. Some of the research supported by Dr. Milner's group at NCI is focused on better understanding the impact of dietary components—both essential nutrients like calcium or selenium, and nonessential nutrients like flavonoids and n-3 fatty acids—on things like gene expression, often called nutrigenomics. But nutrition, he stressed, also has an impact on proteomics and metabolomics.

Using advanced technologies like microarrays and RNA interference, researchers are identifying the molecular sites of action of certain bioactive food components and teasing out how these nutrients influence processes such as carcinogen metabolism, inflammatory response, and DNA repair.

Dr. Milner pointed to the example of studies demonstrating that omega fatty acids, such as those found in abundance in certain types of fish, may inhibit the HER2 receptor, the same protein targeted by trastuzumab (Herceptin) that is linked to a particularly aggressive form of breast cancer.

But underlying this line of research, he continued, is the need to account for the differences between individuals that influence their response to the more than 25,000 bioactive food components in the diet.

"We have consistently seen a lot of variability in the response to different dietary components, and that's linked to a number of things," said Dr. Milner. "It's the number of interactions with those components and their interactions with the genes of the individual. There's also the influence of the duration and the timing of exposure. What we're trying to do is define the circumstances when dietary interventions can minimize cancer risk and change tumor behaviors." ◆

(Tobacco continued from page 7)

makeup, as well as identify new targets for these drugs.

"These fields are still pretty young," said Dr. Swan. "They've only been in operation for about 8 years, with most of the activity in the last 4 years. Compared to cancer genetics, which began in the 1970s with the declaration of the 'war on cancer,' we have a long way to go." ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov.

Contact the *NCI Cancer Bulletin* staff at ncicancerbulletin@mail.nih.gov.