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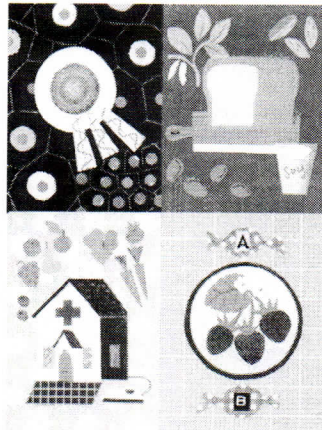
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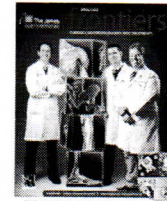
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The Power of Prevention

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Spring 2012 Issue



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THE POWER OF PREVENTION

The adage that "an ounce of prevention equals a pound of cure" carries substantial weight in the realm of cancer control.

BY BOB HECKER
ARTWORK BY
RICHARD LILLASH

"You are the answer to cancer," says Electra Paskett, PhD, MSPH, a cancer prevention and control expert at The Ohio State University. A newly released federal report on cancer status in the United States supports her contention.

When Paskett was president of the American Society of Preventive Oncology (ASPO), she gave a talk focusing on the many ways one person can help end cancer globally, from conducting scientific research, to avoiding environmental risks, to changing lifestyle behaviors.

The *Annual Report to the Nation on the Status of Cancer, 1975-2008*, released in March 2012 by the National Cancer Institute (NCI), builds on the lifestyle aspect of Paskett's talk by highlighting the effects of excess weight and physical inactivity on cancer risk. The report states that several cancers – including esophageal, colorectal, kidney, pancreatic, endometrial, and breast cancer among postmenopausal women – are associated with being overweight or obese, and that some of these cancers also are linked with insufficient physical activity. In addition, the report says there is some evidence that excess weight is associated with thyroid, gallbladder and hematopoietic (e.g., leukemia, myeloma) cancers.

"For more than 30 years, excess weight, insufficient physical activity and an unhealthy diet have been second only to tobacco use as preventable causes of disease and death in the United States," the report states. However, it points out that since the 1960s tobacco use has declined by a third while obesity rates have doubled, "significantly impacting the relative contributions of these factors to the disease burden."

Noting that obesity and inactivity are avoidable causes of cancer, the report contends that, for people who do not smoke, maintaining a healthy weight and getting enough exercise may be among the most important ways that individuals can help prevent this disease. Paskett, associate director for population science at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), concurs. She lists the "obesity epidemic" as one of several high-priority areas for cancer prevention. She also leads a five-state initiative to help people of Appalachia reduce cancer risk by combating obesity (see page 21).

But despite growing knowledge of preventable cancer risk factors, progress in cancer prevention has been seemingly slow and "somewhat disappointing," according to Peter Shields, MD, deputy director of the OSUCCC – James and current president of ASPO.

Shields says epidemiology studies have made only incremental advances, inherent in this type of science, and subsequent intervention studies too often do not validate expected outcomes. This leaves early detection as "the best, and often the only, option for reducing the cancer burden. While there is a lot of promise in early detection, early detection is a backup. We need to fight cancer when those young cancer cells look happy and normal, or at least just a little sick."

For real progress in cancer prevention, he says, continued research is critical. "We need a deeper understanding of cancer's causes, then we must use that understanding to focus behavioral change and develop clinically useful markers of cancer risk and evidence-based reasons for choosing interventions."

This story and sidebar offer examples of innovative cancerprevention research led by scientists at the OSUCCC – James who, both individually and as collaborators, are serving as "the answer to cancer."

Promising Patch

Investigators at the OSUCCC – James hope to begin clinical applications in 2013 with a mucoadhesive medicated patch that releases a chemopreventive drug directly into precancerous oral lesions over an extended time without systemic toxicity. The study (grant CA129609) is led by principal investigator (PI) Susan Mallery, DDS, PhD, and co-PIs Peter Larsen, DDS, and Gary Stoner, PhD, emeritus professor in Medical Oncology at Ohio State and former member of the OSUCCC – James.

The team has tested the patch in simulated saliva and laboratory models with the drug fenretinide, a synthetic derivative of vitamin A that has promising anticancer properties. In both scenarios, therapeutic doses comparable to levels needed in humans were achieved with none of the drug escaping into the system or into surrounding healthy tissue.

Before that study, scientists had failed to achieve a therapeutic systemic dose of fenretinide because of drug toxicity and rapid loss from the body. Mallery says the medicated patch, with its good adherence and Tegaderm backing, "is so secure that no systemic levels of fenretinide are achieved...ergo no systemic toxicity."

The patch – designed in the lab of Steven Schwendeman, PhD, a pharmaceutical chemist at the University of Michigan and a collaborator with Mallery and Larsen's team – has three layers: a disk saturated with fenretinide and polymers to make the drug more soluble in saliva; an adhesive ring to hold the disk in place; and a backing to hold in the medication.

Mallery says the next steps will depend on how the U.S. Food and Drug Administration (FDA) views the team's Investigational New Drug application, which must be approved prior to human clinical uses. "As fenretinide is already an FDA-approved drug, we hope our application will be considered under the 'device' category, since the delivery method is the new component," she explains.

If the FDA approves metabolic studies to determine the amount of drug that penetrates the human oral mucosa and the time of patch application necessary to achieve therapeutic levels, and if it also authorizes a phase IIb pilot study on patients with oral precancerous lesions, "We will move directly into this area," Mallery says, adding that researchers would enroll some 20 patients.

"We would then evaluate tissues before and after treatment for light-microscopic diagnosis, size and clinical appearance of the lesion, and for molecular indicators associated with progression of precancerous oral lesions, such as loss of heterozygosity and methylation of promoter sites," she says, noting that this work "has the potential to change the treatment paradigm for these lesions."

Baking Better Bread

Data analysis continues in an OSUCCC – James study comparing the ability of two functional foods developed at Ohio State to prevent or slow recurrence of prostate cancer among men treated for this disease.

The study, which involved 32 patients, is testing whether consuming soy-almond bread will improve preventive and treatment benefits over consuming soy bread alone. Both breads were created by a team led by Yael Vodovotz, PhD, a physical chemistry researcher and food scientist. Vodovotz is PI for the study (grant CA125909). Steven Clinton, MD, PhD, a medical oncologist and researcher who specializes in treating and preventing prostate cancer, directed the clinical trial, which was closed in spring 2011 so researchers could start analyzing blood and urine samples from participants who consumed the breads.

The study is based on the belief that isoflavones in soy can inhibit hormone-dependent cancers such as prostate cancer. Since soy is not commonly consumed in the Western diet, the researchers tried to better incorporate it by placing it in bread. They later added almonds to improve the taste and boost the health benefits of soy isoflavones.

"Almonds are a rich source of the beta-glucosidase enzyme, which converts the isoflavones to a chemical form that is theoretically better absorbed in the body," Vodovotz says. "We added almonds to produce a bread with a chemical composition that was better absorbed than our original bread."

For eight weeks, half of the participants daily ate three slices of soy bread and half ate three slices of soy-almond bread. Then, after a two-week period of consuming no soy, the groups switched bread types and repeated the pattern for another eight weeks.

"Analysis of samples is not complete, and we hesitate to make any major preliminary conclusions at this time," Clinton says. However, the team reports that study compliance was outstanding and the bread was easily incorporated into the diet "with very good taste characteristics."

They also observe that participants show several different patterns in their metabolism of soy

components. "Our analysis suggests that the metabolic profile of soy metabolites and their potential to impact cancer risk is influenced by other foods you consume and by your genetics," Clinton says.

"It is likely that the genes impacting how we respond to anticancer drugs also impact the metabolism of many dietary components," Vodovotz adds. "All of these issues could affect how soy may work to reduce cancer risk."

When sample analysis is complete, the researchers will publish their findings. They also are working to commercialize their breads for wider consumption.

Faith-Based Obesity Battle

A transdisciplinary health disparities research team is partnering with churches in a five-state region to refine and test a previously piloted faith-based intervention program to promote health and reduce cancer risk by addressing obesity.

Electra Paskett is PI for the project, which is the research component of the larger *Appalachian Community Cancer Network (ACCN)*, funded at \$6.13 million over five years by the NCI. The research component, "Faith-Based Initiative to Promote Health in Appalachia," is funded at \$2.7 million (grant CA153604).

The intervention will employ community-based participatory research strategies aimed at two behavioral causes of obesity: sedentary lifestyle and unhealthy diet. The target region is mainly rural and contains medically underserved populations characterized by low income, education deficits, poor health, increased rates of obesity and high cancer incidence.

"An obesogenic environment promotes obesity by encouraging physical inactivity and limiting healthy food choices," Paskett says.

"The goal of this project is to test a faith-based intervention in 10 churches compared to a comparison program in 10 additional churches where participants will receive information and cancer-screening tests."

Participants in the intervention churches will receive help in increasing physical activity and consuming healthier foods, including more fruits and vegetables daily.

Paskett says part of the intervention involves an e-health computer program that tracks the number of steps per day by participants and provides them with tailored messages and information about increasing physical activity and changing their diets. "We will also explore the willingness of participants to provide biomarkers and biospecimens to further understand the effects of the intervention on markers of obesity and to establish a biospecimen bank within Appalachia," she adds, noting that the two-year e-health program was supported by a \$100,000 "idea" grant from Pelotonia, an annual grassroots bicycle tour that raises money for cancer research at the OSUCCC – James.

"That money helped us secure NCI funding to do the whole research study in 20 churches throughout the ACCN region," Paskett explains. "The project has started and we are recruiting participants. We hope to be in all 20 churches by this time next year."

"We believe this project will have an immediate impact among members of the participating churches," she says, "and the successful strategies could be used to improve the health of residents in other states throughout Appalachia in the future."

Studying Strawberry Strengths

OSUCCC – James investigators have nearly finished a clinical study examining the inhibitory activity of whole foods in the earliest stages of oral cancer in humans. The team is applying a strawberry-based confection to the high-risk oral cavity of current smokers, believing that anticancer compounds in the berries will cause cigarette smoke-altered genes to resemble the genes of never-smokers, thus favoring cancer prevention.

"Compounds such as ellagic acid, quercetin, ferulic acid and beta-carotene found in various berries have been shown to possess cancer-preventive mechanisms: reducing oxidative damage to genetic material; inhibiting cell proliferation and oncogenic expression; promoting expression of tumor-suppressor genes; inducing death of precancer and cancer cells; and preventing formation of blood vessels that sustain tumor cells," says PI Christopher Weghorst, PhD. "With this in mind, we're applying a food-based approach that emphasizes the potential for complex mixtures of preventive agents to inhibit multiple processes of carcinogenesis."

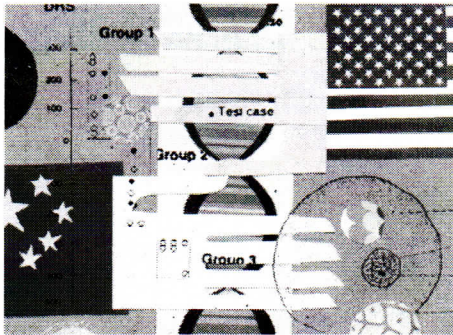
The two-year study, also funded by a \$100,000 Pelotonia "idea" grant, enrolled 20 healthy individuals, half of whom are smokers. Participants received either a strawberry-based or placebo confection for seven days. Then, after 14 days of no treatment, the groups were reversed to receive either a strawberry-based or placebo confection. Blood, urine and mouth-scrape samples were collected before and after each treatment for analysis.

Weghorst says the team – which includes co-PIs Steven Clinton, MD, PhD; Yael Vodovotz, PhD; and Steven Schwartz, PhD – is determining the expression of 41 cigarette smoke-altered genes that were previously identified as being differentially expressed in the oral cavities of 40 smokers as compared with 40 never smokers. That study was conducted and reported by research groups from Memorial Sloan Kettering Cancer Center and Cornell University.

"We are also preparing a Program Project Grant application to the NCI for an integrated and multiproject research program at Ohio State that will focus on black raspberries and the reduction of oral cancer risk," Weghorst says, noting that Ohio State studies with animal models have found strawberries and black raspberries to be equally effective in inhibiting oral cancer.

"If awarded, the NCI grant will enable us to fill any knowledge gaps we need to address before initiating a large-scale national cooperative phase III trial for preventing oral cancer with whole foods," he adds. "This approach may ultimately prove to be an effective, safe and natural method of cancer prevention."

GRANT SUPPORT U.S.- CHINA COLLABORATIVE CANCER STUDY



"Although the supplement grant is not a huge amount, it is very competitive and meaningful. We hope it will open doors for other collaborations with China."

Researchers in China and at the OSUCCC – James are studying biomarkers of precancerous lesions of the esophagus that could lead to chemopreventive strategies for esophageal cancer.

The study is funded by an international collaborative research grant from the National Institutes of Health (NIH) and the National Natural Science Foundation of China. Principal investigator Tong Chen, MD, PhD, a researcher at the OSUCCC – James, says the \$79,109 grant supplements a previously awarded parent grant from the NIH titled "Combinatorial Approaches to the Chemoprevention of Esophageal Cancer" (grant CA131073).

Chen says esophageal squamous cell carcinoma (SCC) is among the most common malignant neoplasms. In the United States, this disease has an overall five-year survival rate of only 13 percent, which is close to the observed survival rates in high-risk countries such as China and other global regions.

Chen believes an association between esophageal dysplasia (precancerous lesions) and SCC risk suggests that a shift in dysplasia grade can help evaluate potential chemopreventive agents. "Because symptoms of esophageal SCC typically remain absent until tumors are advanced, there is an urgent need to investigate molecular alterations in dysplastic lesions and to identify preventive agents that target those changes," she says.

The researchers will study the roles of mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) in animal models (at Ohio State) and in humans (in China) while also examining functions of oxidative stress pathways in esophageal dysplasia in animals (at Ohio State) and in humans (in China).

"A successful outcome will provide important information and rationale to target MAPK, NF- κ B and oxidative stress pathways in chemoprevention strategies for esophageal cancer," Chen says.

"Although the supplement grant is not a huge amount, it is very competitive and meaningful. We hope it will open doors for other collaborations with China."

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