American Association for Cancer Research

Frontiers in Cancer Prevention Research

October 30- November 2, 2005, Baltimore, MD

PRESS CONFERENCE SCHEDULE

Monday, October 31, 2005

9:00 a.m., EST, Novel Preventatives in Diet

3442 Daily Intake of Sulforaphane-Rich Broccoli Sprouts Improves Gastritis in H. pylori-Infected Human Subjects

2597 Sulforaphane-Containing Broccoli Sprout Extracts Protect against UV-Light-Induced Skin Carcinogenesis in SKH-1 High-Risk Mice

3697 Joint Association of High Cabbage/Sauerkraut Intake at 12-13 Years of Age and Adulthood with Reduced Breast Cancer Risk in Polish Migrant Women: Results from the US Component of the Polish Women's Health Study (PWHS)

3654 Ginkgo Biloba and Ginkgolides as Potential Agents for Ovarian Cancer Prevention

2543 Diallyl Sulfide Antagonizes PhIP Induced Alterations in the Expression of Phase I and Phase II Metabolizing Enzymes in Human Breast Epithelial Cells

10:30 a.m., EST, Cancer Vaccines

2625 Investigational Prophylactic Human Papillomavirus (HPV) Vaccines

2327 Prophylactic Vaccination Against Human Papillomavirus

2462 Therapeutic Human Papillomavirus Vaccines

1:00 p.m., EST, Oils, Fat, and Cancer

3472 A 13-year Prospective Study of Blood N-6 Fatty Acid Levels and Risk of Prostate Cancer: The Physicians' Health Study.

3664 Effect of COMT and CYP1B1 Genotype on Changes in 2- and 16a-Hydroxyestrone Metabolism after Flaxseed Consumption

3716 Fish Oil Diet Increases Polyunsaturated Fatty Acids (PUFA) in Colonic Phospholipids detected by Computational Lipidomics and Reduces Growth of Colonic Polyps in the Min Mouse

2640 Dietary Patterns and Breast Cancer Risk in Women Participating in the Black Women's Health Study EP5

3513 Updated Evidence on the Proportion of Cancer Due to Obesity

Tuesday, November 1, 2005

9:00 a.m., EST, Genetics and Biomarkers

3701 C-Reactive Protein and Risk of Incident Endometrial Cancer in Three US Cohorts
3670 Reproducibility and Expression of Skin Biomarkers in Sun-Damaged Skin
3456 A Randomized Phase II Biomarker Trial of Low Dose Tamoxifen in HRT Users

10:30 a.m., EST, Latest Evidence about Lowering Risk

2115 Hypothyroidism and the Risk of Colorectal Cancer
3733 NSAIDs and Breast Cancer Incidence in the VITAL Cohort: A Preliminary Report
3503 A Peptide that Prevents Breast Cancer is Fully Active after Oral Administration: AFPep
2315 Prevention of Prostate Cancer Progression with Vitamin D Compounds in the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) Model

1:00 p.m., EST, Chemoprevention

2497 Potent Protection against Aflatoxin-Induced Tumorigenesis through Induction of Nrf2-Regulated Pathways by the Synthetic Triterpenoid, CDDO-Imidazole
3711 Use of Thiazolidinediones and Lung Cancer Survival in Type 2 Diabetes Patients
3480 NSAIDs and COXIBs: The Burden of Proof

Wednesday, November 2, 2005

8:30 a.m., EST, Tobacco and Nicotine

3477 Carcinogen Exposure across Oral Tobacco and Medicinal Nicotine Products
2684 Smokeless Tobacco as a Substitute for Cigarettes: An Appraisal of the Evidence
2565 Nicotine Vaccine: A Promising Treatment for Nicotine Addiction
3474 Chemoprevention of Lung Cancer: What's Next?

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FOR IMMEDIATE RELEASE
October 25, 2005

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LEADING EXPERTS TO PRESENT THE LATEST IN CANCER PREVENTION RESEARCH

Novel Preventatives in Diet, Chemoprevention and Genetic Biomarkers

Baltimore, Md. – Leading cancer researchers will convene at the 4th Annual *Frontiers in Cancer Prevention Research* meeting of the American Association for Cancer Research (AACR), the premier gathering of its kind in the world, which features the latest developments in cancer prevention research.

The meeting will take place October 30 – November 2, 2005 in Baltimore, Maryland, and will focus on innovative research in the field of cancer prevention. Studies highlight diet, early intervention through new screening methods and lifestyle.

"Although there have been great strides in cancer treatment, the prevention of cancer is our goal in turning this life-threatening disease into a chronic illness," said William G. Nelson, V, M.D., Ph.D., of Johns Hopkins University and Program Chair of the meeting. "The integration of new technologies and medicines are improving our understanding of the preventive value of certain agents against cancers throughout the body."

To address prevention strategies and techniques, the meeting will highlight research that focuses on new developments such as targeted therapies, inflammation and cancer with a focus on COX-2 inhibitors, screening technologies, obesity and risk of cancer, and novel preventatives in the diet.

The meeting offers attendees a variety of sessions, including educational programs, talks on specific organ sites, a forum on the challenges of chemoprevention and the pharmaceutical industry, special events for young investigators, three poster sessions, and the Fourth Annual

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AACR-Cancer Research and Prevention Foundation Award Lecture for Excellence in Cancer Prevention Research.

"These studies give us hope for the future of cancer prevention. Our goal with this meeting is to educate the community about a broad range of the promising agents and strategies that are working in the fight against cancer," said Nelson.

Researchers will present exciting cancer prevention research to members of the media during a series of press briefings:

- **Monday, October 31**
  - Novel Preventatives in Diet: 9:00 a.m. - 9:45 a.m.

  * **SPECIAL SESSION: New Cancer Vaccines: 10:30 a.m. - 11:15 a.m.**
    In this special press session, leading experts will share pioneering research offering evidence that cancer vaccines may be powerful preventatives against the onset of a number of cancers. Highlights will include updated findings about a new cervical cancer vaccine and successful data on a vaccine against HPV.

  - Oils, Fat, and Cancer: 1:00 p.m. - 1:45 p.m.

- **Tuesday, November 1**
  - Genetics and Biomarkers: 9:00 a.m. - 9:45 a.m.
  - Latest Evidence about Lowering Risk: 10:30 a.m. - 11:15 a.m.
  - Chemoprevention: 1:00 p.m. – 1:45 p.m.

- **Wednesday, November 2**
  - Tobacco and Nicotine: 8:30 a.m. - 9:15 a.m.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

American Association for Cancer Research

Frontiers in Cancer Prevention Research
October 30- November 2, 2005, Baltimore, MD

Embargoed for Release at:
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Broccoli Sprouts, Cabbage, Ginkgo Biloba and Garlic:

A Grocery List for Cancer Prevention

Baltimore, Md. -- In the high-tech 21st century, the most rudimentary natural products continue to reveal exciting ant-cancer properties to scientists, offering people relatively simple ways to help protect themselves from the disease.

Five studies presented today during the American Association for Cancer Research's 4th annual Frontiers in Cancer Prevention Research meeting in Baltimore, Md., add to the arsenal of research that shows adding certain vegetables and herbs to the diet can prevent or, in some cases, halt the growth of cancer.

Moreover, it is not just a matter of mechanical prevention, such as adding fiber to the diet to maintain digestive health. This research deals with the chemical interactions between compounds found in foods and the body's cells and DNA, and it shows that the addition of these foods to the diet can reap benefits at any stage of life.

Broccoli Sprouts Relieve Gastritis in *H. pylori* Patients; May Help Prevent Gastric Cancer (Abstract #3442)

Broccoli sprouts may not be a culinary favorite for some, but their chemical properties are becoming increasingly popular among those interested in preventing cancer.

In the latest series of studies, a team from Japan has found that a diet rich in broccoli sprouts significantly reduced *Helicobacteri pylori (H. pylori)* infection among a group of 20 individuals. *H. pylori* is known to cause gastritis and is believed to be a major factor in peptic ulcer and stomach cancer.

"Even though we were unable to eradicate *H.* pylori, to be able suppress it and relieve the accompanying gastritis by means as simple as eating more broccoli sprouts is good news for the many people who are infected," said Akinori Yanaka from the University of Tsukuba, Japan, lead investigator of the study.

Scientists are focusing on the anti-cancer properties of a chemical derived from broccoli sprouts called sulforaphane. Among other things, this chemical has the ability to help cells defend against oxidants, the highly reactive and toxic molecules that damage DNA and kill cells, leading potentially to cancer.

Previously, researchers working with *H.* pylori discovered that sulforaphane acts against the bacterium *in vitro,* alleviating gastritis in *H. pylori*-infected mice through its antioxidant activity.

None of these findings had been tested in people, however, until the Yanaka-led team added broccoli sprouts (the plant at its youngest and most sulforaphane-rich, just two or three days old) to the diet of 20 individuals infected with *H. pylori*. Another group of 20 infected with the bacterium received alfalfa spouts instead of broccoli sprouts. Each received 100 grams of fresh sprouts daily for two months.

"We wanted to test alfalfa spouts together with broccoli sprouts," Yanaka explained, "because the chemical constituents of the two plants are almost identical."

However, the way in which they differ is significant. Broccoli sprouts contain 250 milligrams of sulforaphane glucosinolate per 100 grams per serving, whereas alfalfa sprouts contain neither sulforaphane nor sulforaphane glucosinolate.

Glucosinolates occur in cruciferous vegetables, like broccoli and cabbage, and are broken down enzymatically into sulforaphane and a variety of other, biologically active compounds when damage occurs to the plant—that is, by cutting or chewing it.

The presence of *H. pylori* was assessed by performing urea breath tests and evaluating *H. pylori*-specific stool antigen. The degree of gastritis was evaluated by measuring the level of pepsinogen in the blood. Pepsinogen is also an indicator of gastric atrophy. These tests were performed just before adding broccoli and alfalfa sprouts to the diet, and at one and two months after starting the dietary regimen. Following two months' consumption of 100 grams of broccoli sprouts per day, patients showed significantly less *H. pylori* and markedly decreased pepsinogen. Alfalfa sprouts had no effect, and the broccoli failed to eliminate *H. pylori* completely. Two months after eliminating broccoli sprouts from the diet, *H. pylori* and pepsinogen returned to pre-test levels in the subjects.

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"The data suggest strongly that a diet rich in sulforaphane glucosinolate may help protect against gastric cancer, presumably by activating gastric mucosal anti-oxidant enzymes that can protect the cells from *H. pylori*-induced DNA damage," Yanaka concluded.

Broccoli Sprout-extract Protects Against Skin Cancer from UV Light in High-risk Mice (Abstract #2597)

Eat it or wear it? That is the question.

If you ask Albena T. Dinkova-Kostova, Ph.D., of Johns Hopkins University in Baltimore, she will likely answer "both."

In the laboratory of Paul Talalay, M.D., who first reported the indirect antioxidant properties of sulforaphane, the compound derived from cruciferous vegetables like broccoli, Dinkova-Kostova and her colleagues applied broccoli sprout extract to the skin of hairless mice, and found it counteracted the carcinogenic response to ultraviolet light exposure.

Mice from a strain characterized by post-weaning hair loss were exposed to a dose of UV light comparable to what a person would get sunbathing at the beach on a clear day, twice a week for 20 weeks. After irradiation, broccoli sprout extracts containing either a low or high dose of sulforaphane were applied to the backs of the mice, five days a week for 11 weeks. Acetone (known commonly as the ingredient in nail polish remover) was used as the vehicle for delivering the sulforaphane, and it alone was applied on the control group. At the conclusion of the study period, 100 percent of the control mice had developed cancerous skin tumors.

The incidence and number of tumors was reduced by half, however, in the mice receiving the high dose of broccoli sprout extract. The rate of tumor reduction was less among the low-dose recipients, but even in their case, some benefit was observed.

"We weren't looking for a sunscreen effect," Dinkova-Kostova is quick to point out. "The sulforaphane-containing extract was applied after the period of regular exposure to ultra-violet light. That's more relevant, since most people receive some sun damage to their skin in childhood, particularly adults who grew up before effective sunscreen lotions were developed."

Previous research has shown that sulforaphane boosts protective and detoxifying reactions in cells, inactivating carcinogens and reactive oxygen intermediates that contribute to the disease by damaging DNA. As in other studies involving the anti-cancer potential of sulforaphane, Dinkova-Kostova's group notes that broccoli sprouts contain much more of the compound than adult broccoli.

"Our findings suggest a promising strategy for skin cancer prevention after exposure to UV light," Dinkova-Kostova said.

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Change in Diet at Any Age May Help Protect Against Breast Cancer (Abstract #3697)

Many find it to be the perfect companion to hot dogs and sausage, but new studies suggest that sauerkraut may have another beneficial side effect—it may protect women from breast cancer.

Results from the U.S. component of the Polish Women's Health Study are showing an association between cabbage and sauerkraut consumption, and a constituent called glucosinolate, and a lower risk of breast cancer. The influence seemed to be highest among women who consumed high amounts beginning in adolescence and throughout adulthood.

"The observed pattern of risk reduction indicates that the breakdown products of glucosinolates in cabbage may affect both the initiation phase of carcinogenesis—by decreasing the amount of DNA damage and cell mutation—and the promotion phase—by blocking the processes that inhibit programmed cell death and stimulate unregulated cell growth," said Dorothy Rybaczyk-Pathak, Ph.D., from the University of New Mexico.

Pathak, along with colleagues from Michigan State University and the National Food and Nutrition Institute of Warsaw, Poland, evaluated the diet of Polish immigrants to the United States, living in Chicago and surrounding Cook County, Ill., and the Detroit, Mich., metropolitan area. Women with higher rates of raw- or short-cooked cabbage and sauerkraut consumption, three or more servings per week, compared to those who consumed less than one serving a week, had a significantly reduced breast cancer risk.

Like broccoli, cabbage is a cruciferous vegetable—its flowers are in the shape of a cross—and a member of the Brassica family, which includes broccoli, Brussels sprouts, kale, collard greens and cauliflower. These plants contain glucosinolates and the enzyme myrosinase which, when broken down by chewing or cutting, release several biologically active products which previous studies have shown to possess anti-carcinogenic properties.

Pathak began the study by wondering why the breast cancer risk of Polish women rose three-fold after they immigrated to the United States. She hypothesized that dietary changes were among the environmental factors contributing to this rapid increase in risk. In Poland, where abundance of food is a recent phenomenon, women traditionally eat an average of 30 pounds of cabbage and sauerkraut per year, as opposed to just 10 pounds per year among American women. Moreover, Polish women traditionally eat more raw cabbage and sauerkraut, in salads, or short-cooked, as a side dish.

She observed the lowest rate of breast cancer among women who consumed high amounts of raw- or short-cooked cabbage during adolescence, but found that high consumption during adulthood provided a significant protective effect for women who had eaten smaller quantities of this vegetable during adolescence. Cabbage cooked a long time, such as in hunter's stew, cabbage rolls and pierogi, had no bearing on breast cancer risk.

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Possible Chemoprevention of Ovarian Cancer by the Herbal, Ginkgo Biloba (Abstract #3654)

Researchers in Boston, led by Drs. Bin Ye and Daniel Cramer of Brigham and Women's Hospital, have developed new laboratory and epidemiological evidence that demonstrates, for the first time, that ginkgo biloba appears to lower the risk of developing ovarian cancer.

In a population-based study which involved more than 600 ovarian cancer cases and 640 healthy, matched controls, women who took ginkgo supplements for six months or longer were shown to have a 60 percent lower risk for ovarian cancer.

Ye and his colleagues found that ginkgo, echinacea, St. John's Wort, ginseng, and chondroitin were the most commonly used herbals among study participants. A further analysis of the data showed that ginkgo was the only herb linked to ovarian cancer prevention. The preventive effect was more pronounced in women with non-muncious ovarian cancers, with data showing that ginkgo may reduce the risk of this type of ovarian cancer by 65-70 percent.

"Among the mixture of ginkgo chemicals," said Ye, "we found laboratory evidence that ginkgolide A and B—terpene compounds—are the most active components contributing to this protective effect."

Ye's team, which included scientists from Dana-Farber Cancer Institute at Harvard Medical School, Boston University and Linden Bioscience, next took the evidence demonstrated by their population studies to the laboratory. *In vitro* experiments showed that a low dosage of ginkgolide caused ovarian cancer cells to stop growing. They observed significant cell cycle blockage in non-mucinous ovarian cancer cells. Ginkgolides appeared to be less effective against the mucinous type of ovarian cancer cells.

"While the detailed mechanism of ginkgo action on ovarian cancer cells is not yet well understood," Ye explained, "from the existing literature it most likely that ginkgo and ginkgolides are involved in anti-inflammation and anti-angiogenesis processes via many extra- and intra-cellular signal pathways. In the future, these findings could potentially offer a new strategy for ovarian cancer prevention and therapy, using the active forms of ginkgolides."

Ovarian cancer is the most deadly of all gynecological cancers. It is called a "silent killer" because most cases are discovered only in very advanced stages.

Changing Genes: Garlic Shown to Inhibit DNA Damaging Chemical in Breast Cancer (Abstract #2543)

Legend suggests that garlic may ward off evil spirits, such as vampires. Now scientists are finding that garlic, or a flavor component of pungent herb, may help ward off carcinogens produced by meat cooked at high temperatures.

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Cooking protein-rich foods like meats and eggs at high temperatures releases a chemical called PhIP, a suspected carcinogen. Epidemiological studies have shown that the incidence of breast cancer is higher among women who eat large quantities of meat, although fat and caloric intake and hormone exposure may contribute to this increased risk.

Diallyl sulfide (DAS), a flavor component of garlic, has been shown to inhibit the effects of PhIP that, when biologically active, can cause DNA damage or transform substances in the body into carcinogens.

Ronald D. Thomas, Ph.D., and a team of researchers at Florida A&M University in Tallahassee hypothesized that PhIP enhances the metabolism of the enzymes linked to carcinogenesis. They further suggested that the diallyl sulfide derived from garlic might counter this activity.

“We treated human breast epithelial cells with equal amounts of PhIP and DAS separately, and the two together, for periods ranging from three to 24 hours,” said Thomas. “PhIP induced expression of the cancer-causing enzyme at every stage, up to 40-fold, while DAS completely inhibited the PhIP enzyme from becoming carcinogenic.”

The finding demonstrates for the first time that DAS triggers a gene alteration in PhIP that may play a significant role in preventing cancer, notably breast cancer, induced by PhIP in well-done meats.

Thomas noted that no studies have shown a link between cooking vegetables and fruits and PhIP, regardless of the method used.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: *Cancer Research; Clinical Cancer Research*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research;* and *Cancer Epidemiology, Biomarkers & Prevention.* AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Daily Intake of Sulforaphane-Rich Broccoli Sprouts Improves Gastritis in H.pylori-Infected Human Subjects
Abstract # 3442, Akinori Yanaka, University of Tsukuba, Japan.
Poster Session C. 7:30 a.m., Wednesday, November 2, 2005.

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Sulforaphane-Containing Broccoli Sprout Extracts Protect against UV-Light-Induced Skin Carcinogenesis in SKH-1 High-Risk Mice
Abstract # 2597, Albena Dinkova-Kostova, Johns Hopkins University, Baltimore, Md.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

Joint Association of High Cabbage/Sauerkraut Intake at 12-13 Years of Age and Adulthood with Reduced Breast Cancer Risk in Polish Migrant Women: Results from the US Component of the Polish Women's Health Study (PWHS)
Abstract # 3697, Dorothy Rybaczyk-Pathak, University of New Mexico, Albuquerque.
Poster Session C. 7:30 a.m., Wednesday, November 2, 2005.

Ginkgo Biloba and Ginkgolides as Potential Agents for Ovarian Cancer Prevention
Abstract # 3654, Bin Ye, Brigham and Women's Hospital, Boston, Mass.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

Diallyl Sulfide Antagonizes PhIP Induced Alterations in the Expression of Phase I and Phase II Metabolizing Enzymes in Human Breast Epithelial Cells
Abstract # 2543, Ronald Thomas, Florida A&M University, Tallahassee.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

Abstract 3442

Daily Intake of Sulforaphane-Rich Broccoli Sprouts Improves Gastritis in *H. pylori*-Infected Human Subjects

Authors: Akinori Yanaka,1 Songhua Zhang,1 Masayuki Yamamoto,2 Jed W. Fahey.3 Department of Gastroenterology, University of Tsukuba,1 Tsukuba, Ibaraki, Japan, Center for Tsukuba Advanced Research Alliance,2 Tsukuba, 305-8575, Japan, Department of Pharmacology & Molecular Sciences, Johns Hopkins University, School of Medicine,3 Baltimore, Maryland.

Background and Aim: Sulforaphane protects cells from oxidative injury by activating NF-E2 p45-related factor2 (nrf2) mediated antioxidant enzymes (PNAS, 94:10367, 1997) and possess bactericidal activity against *H. pylori in vitro* (PNAS 99:7610, 2002). Broccoli sprouts are a rich source of sulforaphane glucosinolate (glucoraphanin) which is enzymatically converted to sulforaphane upon ingestion of fresh sprouts. We have previously shown that sulforaphane mitigates high salt diet-induced gastritis in *H. pylori*-infected mice via activation of nrf2 dependent anti-oxidant enzyme activities (Gastroenterology 124:A5, 2003). However, effects of sulforaphane on *H. pylori*-infected human gastric mucosa have not previously been reported. The aim of this study is to determine if daily intake of sulforaphane-rich broccoli sprout inhibits *H. pylori* colonization and mitigates gastritis in *H. pylori*-infected human subjects. Methods: Forty *H. pylori*-infected subjects agreed to participate in this study with a written informed consent, were randomly assigned to eat 100 grams daily, for 2 months, of either fresh Broccoli Sprouts (BS; n=20) or Alfalfa Sprouts (AS; n=20). The compositions of BS and AS are almost identical except for their phytochemicals: notably, BS contains 250 mg sulforaphane glucosinolate/100g serving, whereas AS contains no sulforaphane or sulforaphane glucosinolate. *H. pylori* colonization was evaluated by performing urea breath test (UBT) and by measurement of *H. pylori*-specific stool antigen (HpSA). Degree of gastritis was evaluated by measuring serum level of pepsinogen (PG) I, II, and I/II ratio. All the measurements were performed just before the intervention, at 1 and 2 months after the intervention, and at 2 months after cessation of the intervention. Results: 1. Two months intervention with BS, but not with AS, significantly decreased the values of UBT and HpSA, but failed to achieve complete eradication of *H. pylori*.

These values recovered to the initial levels at 2 months after cessation of the intervention with BS. 2. Two months intervention with BS, but not with AS, significantly decreased levels of PGI and PG II, and increased the PG I/II ratio, which returned to the initial values at 2 months after cessation of the intervention with BS. Conclusion: The present results show that daily intake of sulforaphane-rich BS suppresses *H. pylori* colonization and improves gastritis in *H. pylori*-infected human subjects. Our data further suggest that a diet rich in sulforaphane glucosinolate may be useful in chemoprevention against gastric cancer.

NOVEL PREVENTATIVES IN DIET

Abstract 2597

Sulforaphane-Containing Broccoli Sprout Extracts Protect against UV-Light-Induced Skin Carcinogenesis in SKH-1 High-Risk Mice

Authors: Albena T. Dinkova-Kostova,1 Stephanie N. Jenkins,1 Jed W. Fahey,1 Lingxiang Ye,1 Scott L. Wehage,1 Karen T. Liby,2 Katherine K. Stephenson,1 Kristina L. Wade,1 Paul Talalay.1 Johns Hopkins University,1 Baltimore, MD, Dartmouth Medical School,2 Hanover, New Hampshire.

UV radiation, genetic susceptibility, and immune status are important contributors to skin cancer development. UV radiation causes direct DNA damage, generates reactive oxygen intermediates, and causes inflammation thus increasing the risk for carcinogenesis. Induction of phase 2 enzymes via the ARE/Nrf2 pathway is an effective strategy for counteracting oxidative and inflammatory stress and the isothiocyanate sulforaphane, isolated from broccoli, is a powerful inducer of these protective enzymes. Treatment of murine and human keratinocytes with sulforaphane elevated phase 2 enzymes and glutathione and protected against oxidant toxicity. In macrophages, sulforaphane inhibited cytokine-stimulated induction of the inflammatory marker iNOS. Topical application of sulforaphane-containing broccoli sprout extracts induced the phase 2 response in mouse skin in vivo and inhibited skin tumor formation in high risk mice. SKH1 hairless mice were exposed to UV light (30 mJ/cm2 twice weekly for 20 weeks). After completing the irradiation schedule, extracts containing either 0.3 mmol [low dose] or 1.0 mmol [high dose] sulforaphane were applied to the backs of these mice 5 days a week, for 11 weeks. At this time 100% of the control mice had developed tumors. Tumor incidence and multiplicity were reduced by 50% in the animals that received the high dose but not the low dose of protector. However, tumor burden was reduced at both doses, suggesting heterogeneity in tumor susceptibility to the protective agent. Thus, topical application of sulforaphane-containing broccoli sprout extracts is a promising strategy for protecting against skin tumor formation after exposure to UV radiation.

NOVEL PREVENTATIVES IN DIET

Abstract 3697

Joint Association of High Cabbage/Sauerkraut Intake at 12-13 Years of Age and Adulthood with Reduced Breast Cancer Risk in Polish Migrant Women: Results from the US Component of the Polish Women's Health Study (PWHS)

Authors: Dorothy R. Pathak,1 Jianping He,2 Jadwiga Charzewska.3 University of New Mexico,1 Albuquerque, NM, Michigan State University,2 E. Lansing, MI, National Food and Nutrition Institute,3 Warsaw, Poland.

Cabbage is a member of Brassica vegetables which contain glucosinolates (GLS). The break-down products of GLS include indole-3-carbinol and its digestive derivative, 3,3'-diindolylmethane and isothiocyanates, all of which have been shown to have anti-carcinogenic properties both in vitro and *in vivo* studies. Consumption of cabbage and sauerkraut is high in Poland (30 lbs/year) relative to US (10lb/year). Polish migrant women to the US experience a tripling in breast cancer (BC) mortality, reaching in their lifetime the high rates observed for US-born women. We hypothesized that reduced consumption of cabbage/sauerkraut that follows acculturation could contribute to the increased risk of BC in Polish migrant women. Methods: The PWHS is a case-control study of BC in Poland and Polish-born immigrants to the US**. Using a 143-item food frequency questionnaire, we ascertained food consumption for ages 12-13 years and during 1985-89, a period immediately prior to introduction of the market economy in Poland. Specifically we assessed consumption of cabbage foods that can be categorized as: raw salads (sauerkraut and fresh cabbage), short-cooked (sauerkraut as side dish and steamed cabbage), and long-cooked (hunter's stew, cabbage rolls, and pierogi). Results: There was no association between case status and consumption of long-cooked cabbage foods. Results are based on analyses of raw and short-cooked cabbage foods, thus accounting for bioavailability of active compounds. Consumption for both time periods was categorized as: low (L) ≤1.5, medium (M) =1.5-3, high (H) >3 servings/week. Conditional logistic regression was used with age/site (Chicago, Detroit) categories as strata. The odds ratios (ORs) are adjusted for energy intake, physical activity, reproductive history and hormone use. The OR for the joint effect of (adolescence, adulthood) of (H, H) consumption relative to the reference of (L, L) was OR=0.28, $p<0.5$. Similar effect was observed for the (H, M) and (H, L) consumption subgroups. For the medium consumers in adolescence a dose response was observed for the effect of adult consumption with (M, H) category, OR=0.27, $p<0.05$. For low consumers in adolescence a non-significant reduction in risk was observed for the (L, H) group, OR=0.37, $p=0.15$. Discussion: Results from the US component of the PWHS provide epidemiological evidence for a significant decrease in BC risk with high intake of raw/short-cooked cabbage/sauerkraut during adolescence. The protective effect was present irrespective of the level of cabbage/sauerkraut consumption during adulthood. High consumption during adulthood continues to provide significant protective effect for women with medium or low consumption during adolescence. This pattern of risk reduction indicates that breakdown products of glucosinolates in cabbage foods may affect both the initiation phase of carcinogenesis, by decreasing the number of initiated cells, and the promotion phase, by blocking the processes that inhibit apoptosis and stimulate cell growth. Therefore, increased consumption of cabbage/sauerkraut foods in adolescence and adulthood may be an important primary prevention for breast cancer. **CA69670

NOVEL PREVENTATIVES IN DIET

Abstract 3654

Ginkgo Biloba and Ginkgolides as Potential Agents for Ovarian Cancer Prevention

Authors: Bin Ye,1 Margarita Aponte,1 Yan Dai,2 Lily Li,3 Ming-Chih D. Ho,3 Allison Vitonis,1 Dale Edwards,1 Tai-Nang Huang,3 Daniel W. Cramer.1 Brigham Women Hospital,1 Boston, MA, Boston University,2 Boston, MA, Linden Bioscience,3 Woburn, MA.

Herbal supplements have been of great interest as alternative therapies for the prevention or treatment of cancer, but often little scientific evidence supports their use. In this study, we examined potential protective effects of various herbal supplements using epidemiological data from 668 cases with ovarian cancer and 721 controls. Overall 10% of cases had used an herbal supplement at least weekly for six months or longer (prior to their disease) compared to 11.1% of controls (no significant). Among the herbal therapies, 4.2% of controls compared to 1.6% of cases had regular used *gingko biloba* for an estimated relative risk (ad 95% confidence limits) of 0.41 (0.20-0.84) (p=0.01) and the effect was most apparent in women with non-mucinous types of ovarian cancer, RR= 0.33 (0.15-0.74) (p=0.007). We then sought to investigate how and what specific components of *Ginkgo biloba* might potentially affect the incidence of ovarian cancer through a series of *in vitro* cell line studies. Data from these experiments showed that among the tested flavonoids and terpenoids constituents of *Ginkgo biloba*, the compounds of ginkgolide A and B showed significant and subtype-specific inhibition on non-mucinous ovarian cancer cell regression. Following 100 μM ginkgolide treatment for 72 hours, proliferation rate of serous type of ovarian cancer cells (OVCA433) was inhibited up to 80%, but not effect was present on the mucinous (RMUG-L) cells. The cellular inhibitory effect was found to be associated with the cell cycle blockage at phase G to phase S. Combined both epidemiological and biological evidence, we conclude that Ginkgo biloba, and specifically its ginkgolide components, may have value in the prevention of ovarian cancer.

NOVEL PREVENTATIVES IN DIET

Abstract 2543

Diallyl Sulfide Antagonizes PhIP Induced Alterations in the Expression of Phase I and Phase II Metabolizing Enzymes in Human Breast Epithelial Cells

Authors: Chantell L. Wilson, Ayoola A. Aboyade-Cole, Selina Darling-Reed, Ronald D. Thomas. Florida A&M University, Tallahassee, FL.

The heterocyclic amine PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine), is rapidly absorbed, metabolized and bioactivated to DNA damaging species. Metabolism of PhIP has been shown to lead to mammary carcinomas in female rats, thus metabolic activation is the speculated mechanism by which PhIP causes cancer in humans. Diallyl Sulfide (DAS) is a naturally occurring organosulfur compound found in garlic which has been shown to prevent cancer in several animal models via metabolic modulation. We hypothesize that PhIP increases the expression of Phase I enzymes (CYP1A1, CYP1A2 and CYP1B1) which enhances its metabolism. We further propose that DAS will down regulate the expression of these Phase I enzymes resulting in decreased PhIP metabolism. We also propose that DAS has the ability to increase the gene expression of glutathione-S-transferase (GST) and superoxide dismutase (SOD) which may inhibit PhIP induced toxicity. To test this hypothesis MCF-10A cells were treated with 100μM PhIP, 100μM DAS and 100μM PhIP/DAS for 3, 6, 9, and 24 hours. Total RNA was isolated, reverse transcribed, and gene expression was analyzed by Real-Time PCR. PhIP induced the expression of CYP1A1 at all time points by 7.5, 12, 30 and 40 fold, respectively. DAS completely inhibited the PhIP induced enzyme induction. Similar results were seen with CYP1A2 and CYP1B1. PhIP did not alter the expression of SOD or GST at any time. DAS increased the expression of SOD by 2 fold at 3 hours and 13 fold at 6 hours. However, this induction reverted to that of the control at 9 and 24 hours. Combination treatments of PhIP and DAS caused a time dependent increase of SOD 3, 25, 29, and 39 fold, respectively. Similar results were seen with GST expression. We have demonstrated that DAS has the ability to attenuate the PhIP induced expression of cytochrome P450s in such a way as to inhibit the formation of reactive metabolites. Furthermore, DAS can induce detoxifying enzymes alone and in the presence of PhIP. This gene alteration may play a significant role in the prevention of PhIP induced cancer. Supported by NIH/RCMI Grant #RR3020.

SPECIAL SESSION
NEW CANCER VACCINES

MONDAY, OCTOBER 31
10:30 A.M.- 11:15 A.M.

Session Moderator:

***H. Kim Lyerly**, Duke University, Duhram, N.C.*

Panelists:

Eliav Barr, Merck Research Laboratories, West Point, Pa.
Investigational Prophylactic Human Papillomavirus (HPV) Vaccines
Abstract # 2625 Oral Presentation

Richard Roden, Johns Hopkins University, Baltimore, Md.
Prophylactic Vaccination Against Human Papillomavirus (HPV)
Abstract # 2327 Oral Presentation

Tzyy-Choou Wu, Johns Hopkins University, Baltimore, Md.
Therapeutic Human Papillomavirus (HPV) Vaccines
Abstract # 2462 Oral Presentation

American Association for Cancer Research

Frontiers in Cancer Prevention Research
October 30- November 2, 2005, Baltimore, MD

Embargoed for Release at:
10:30 a.m., EST, Monday, October 31, 2005

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UPDATED DATA ON NOVEL HPV VACCINE CONFIRMS EFFICACY IN LARGE POPULATION

Research To be Presented at AACR's *Frontiers in Cancer Prevention Research*

Baltimore, MD – (October 31, 2005) Updated data from a study on a promising new vaccine against a pre-cancerous cervical virus shows superior efficacy in preventing cervical pre-cancers and non-invasive cervical cancer, according to a study presented today during the American Association for Cancer Research's 4th Annual *Frontiers in Cancer Prevention Research* meeting in Baltimore.

Final results of the phase III study, originally published in early October, confirmed the vaccine's efficacy from available combined phase II and phase III data sets, incorporating an additional 7,000 patient records as compared to the interim results. The researchers concluded from these analyses that the administration of this vaccine, known as GARDASIL, is highly effective in preventing high-grade pre-cancerous illnesses and non-invasive cervical cancers.

Of the 8,487 women who received the vaccine, none were diagnosed with high-grade cervical pre-cancers (CIN 2/3+, cervical intraepithelial neoplasia) or non-invasive cervical cancers associated with human papillomavirus (HPV) types 16 and 18. Of the 8,460 women who did not receive the vaccine, 53 such cases were diagnosed.

In the larger population analysis, which included women who may have become infected with HPV during the vaccination period or who may have violated the protocol (e.g. by missing visits, etc.), the vaccine prevented 99 percent of HPV 16 or 18-related high-grade cervical pre-cancers (1 of 9,342 pts versus 81 of 9,400 in the placebo group) with an average follow up of 25 months.

The vaccine was generally well tolerated, and the most common adverse event reported in the trial was local discomfort at the injection site.

The study is part of an ongoing phase III program involving more than 25,000 people in 33 countries. For the FUTURE II study, a prospective, randomized, double-blind, placebo-controlled study, women aged 16 to 26 years were randomized to receive a three-dose regimen

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of either the vaccine or placebo at Day 1, Month 2, and Month 6. The analyses evaluated the incidence of cervical pre-cancers through follow up for an average of 20 months after completion of the regimen.

HPV, particularly types 16 and 18, is the primary cause of cervical cancers and other related illnesses, infecting more than 20 million Americans. Globally, cervical cancer is among the leading cancers in women, with an estimated 470,000 new cases every year, disproportionately within the developing world, and the availability of a vaccine to prevent the disease

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Investigational Prophylactic Human Papillomavirus (HPV) Vaccines
Abstract # 2625 Eliav Barr, Merck Research Laboratories, West Point, Pa.
Oral Presentation, 7:00 am, Tuesday, November 1, 2005

CANCER VACCINES

Abstract 2625

Investigational Prophylactic Human Papillomavirus (HPV) Vaccines

Author: Eliav Barr. Merck Research Laboratories, West Point, Pennsylvania.

Introduction: HPV is the essential cause of cervical cancer, an important cause of cancer-related death in women, particularly young women, with approximately 250,000 deaths worldwide annually. Of the approximately 40 HPV types known to infect the anogenital epithelium only a small number cause the majority of disease. Notably HPV16 and 18 cause approximately 70% of cervical cancers, HPV6 and 11 cause approximately 90% of genital warts and types HPV 6/11/16/18 together cause a significant proportion of cervical intraepithelial neoplasia (CIN) leading to abnormal PAP smears. HPV is transmitted by genital contact and the majority (an estimated 70%) of sexually active individuals will contract HPV in their lifetime. Thus an efficacious quadrivalent vaccine targeting HPV types 6/11/16/18 should substantially reduce the burden of HPV diseases. Clinical Program: Merck & Co. has developed GARDASIL™, a quadrivalent HPV (Types 6/11/16/18) L1 virus-like-particle (VLP) vaccine expressed in yeast and formulated on aluminum adjuvant. Both the yeast production system and the adjuvant have extensive safety records through their use in other vaccines. Initial studies of the monovalent HPV11, 16 or 18 L1 VLP components showed them to be well-tolerated and immunogenic. A randomized, placebo-controlled study of a prototype HPV16 L1 VLP vaccine included 2,391 women. After a median follow-up of 40 months post-completion of the vaccination regimen, the overall vaccine efficacy in women who were HPV16-naïve at baseline was 94% for preventing persistent HPV16 infection (primary endpoint) and 100% for preventing HPV16-related CIN. A high efficacy against clinical disease was also observed in the Phase II results for GARDASIL™. A 3-year, placebo-controlled trial of GARDASIL™ showed that vaccination reduced the combined incidence of persistent HPV6, 11, 16 or 18 infection or related genital disease by 90%, compared to placebo, in young women who were HPV6, 11, 16 or 18-naïve at baseline. In this study no genital disease (CIN or genital warts) related to vaccine types was observed in the women who received GARDASIL™. Vaccine-induced antibody responses one month following completion of the vaccination series were up to 145-fold higher than those observed following natural infection. In a study performed in male and female adolescents aged 10-15 years, GARDASIL™ was generally well-tolerated, and produced ~2-fold higher anti-HPV responses in adolescents compared with young women 16-23 years who are the reference groups for GARDASIL™ efficacy studies. These results support vaccination strategies in pre-adolescents prior to peak of exposure. Phase III efficacy and safety studies of GARDASIL™ are underway in >25,000 subjects worldwide. These studies will provide definitive evaluation of the impact of GARDASIL™ on HPV-related clinical disease and in particular CIN 2/3 and genital warts in adolescents and in young adult women. Discussion: If proven safe and effective, a vaccine that prevents cervical cancer, cervical lesions and genital warts due to HPV6, 11, 16, and 18 will be a major public health advance. First efficacy and safety results from phase III studies are expected soon.

CANCER VACCINES

Abstract 2462

Therapeutic Human Papillomavirus Vaccines

Author: T.-C. Wu, Johns Hopkins University, Baltimore, MD

More than 99% of cervical cancers have been associated with human papillomaviruses (HPVs), particularly HPV type 16. Two HPV oncogenic proteins, E6 and E7, are consistently co-expressed in HPV-expressing cervical cancers and are important in the induction and maintenance of cellular transformation. Therefore, immunotherapy that targets E6 and/or E7 proteins may provide an opportunity to prevent and treat HPV-associated cervical malignancies. It has been established that T cell-mediated immunity is one of the most crucial components to defend against HPV infections and HPV-associated lesions. Therefore, effective therapeutic HPV vaccines should generate strong E6/E7-specific T cell-mediated immune responses.

DNA vaccines have emerged as an attractive approach for antigen-specific T cell-mediated immunotherapy to combat infectious diseases and cancers. Intradermal administration of DNA vaccines via gene gun can efficiently deliver genes of interest into professional antigen presenting cells (APCs) in vivo. The skin contains numerous bone marrow-derived APCs (called Langerhans cells) that are able to move through the lymphatic system from the site of injection to draining lymph nodes, where they can prime antigen-specific T cells. Gene gun immunization therefore provides the opportunity to test vaccine strategies that require direct delivery of DNA to APCs. We previously used this approach to test several intracellular targeting strategies, including Mycobacterium tuberculosis heat shock protein 70 (HSP70), calreticulin (CRT), or the sorting signal of the lysosome-associated membrane protein 1 (LAMP-1), that are able to route HPV-16 E7 to desired subcellular compartments, and enhance antigen processing and presentation to CD4+ and/or CD8 + T cells. Therefore, direct delivery of DNA vaccines into DCs via gene gun provides an opportunity to modify the quality and quantity of DNA-transfected DCs and influence vaccine potency.

Recently we found that a variety of anti-apoptotic factors can enhance DC survival and E7-specific CD8+ T cell immune responses when co-administered with E7 DNA. Because intracellular targeting and anti-apoptotic strategies modify DCs via different mechanisms, we have combined anti-apoptotic strategies for prolonging DC life with intracellular targeting strategies to improve DNA vaccine potency. Such approaches resulted in a significant antigen-specific CD8+ T-cell mediated immune response and anti-tumor effect against an E7-expressing murine tumor model. The impressive pre-clinical data generated from our studies have led to several HPV DNA vaccine clinical trials scheduled to begin in 2005.

CANCER VACCINES

Abstract 2327

Prophylactic Vaccination against Human Papillomavirus

Author: Richard Roden, Johns Hopkins University, Baltimore, MD.

Persistent infection by "high risk" human papillomavirus (HPV) genotypes is a necessary cause of cervical cancer. Thus, cervical cancer and other HPV-associated malignancies might be prevented or treated by the induction of the appropriate viral antigen-specific immune responses. Conceptually, two different types of HPV vaccines can be designed: prophylactic vaccines that prevent HPV infection, and therapeutic vaccines that cure established HPV infections and their sequelae. Since the capsid proteins are not detectably expressed by infected basal keratinocytes or in HPV-transformed cells, therapeutic vaccines generally target the non-structural early viral antigens. This presentation will summarize prophylactic vaccines that prevent HPV transmission by targeting the capsid proteins rather than early protein-dependent elimination of an established HPV infection.

The papillomavirus major capsid protein is L1. L1 spontaneously forms pentameric L1 capsomers that further self-assemble into empty capsids, or VLPs, when over-expressed in mammalian, insect, yeast or bacterial cells. Parenteral vaccination with VLPs, or even capsomers, induces both high serum neutralizing antibody titers and provides protection from experimental infection with animal papillomaviruses in several laboratory animal models. Koutsky et al provided the first demonstration that a monovalent HPV-16 L1 VLP vaccine effectively prevents persistent HPV-16 infections. Notably HPV 16-associated pre-malignant lesions were only seen in the placebo arm. A quadrivalent HPV VLP vaccine (types 6, 11, 16, and 18) was well tolerated, and protected against infection by all four HPV types as well as extragenital and premalignant lesions associated with these HPV types. Importantly HPV VLP vaccines are likely to prevent not only cervical cancer, but also the many other HPV-associated malignancies including a significant proportion of head and neck cancers, vulvar cancers, penile cancers, and other HPV-related anogenital conditions. However the cost of VLP manufacture and need for needles, a cold chain and multiple immunizations are likely to prove significant barriers to its widespread use in developing countries in which ~80% of cervical cancer cases occur. Research into second generation HPV vaccines that are applicable worldwide should focus upon cost, needleless administration, and product stability at ambient temperature is critical.

Eventual eradication of cervical cancer and cessation of PAP screening programs requires comprehensive protection against more than 15 oncogenic HPV genotypes. Clinical studies suggest that L1 VLP-dependent protection is largely type specific. Thus, broad protection against all of the oncogenic types would require a highly multivalent L1 VLP-based vaccine that would be complex to formulate. A better alternative for comprehensive protection is to define a single broadly protective antigen. In this regard, vaccination with the minor capsid protein L2 shows promise. Although L2 is less immunogenic than VLPs, vaccination with recombinant L2 protein alone elicits neutralizing antibody and effectively protects animals from experimental viral challenge. Importantly, L2 antisera broadly cross-neutralizes multiple divergent HPV types. Indeed we have recently demonstrated that ability of L2 vaccination to induce cross type protection in rabbits. L2 peptide-specific immunity in rabbits is mediated by neutralizing antibody, not cellular immunity. Vaccination with an L2 fusion protein without adjuvant was well tolerated by patients and generated low levels of cross-neutralizing antibodies. However, a potent adjuvant may be required for long lasting L2-specific immunity since the humoral responses of patients to L2 without adjuvant are much weaker than those observed for L1 VLP vaccines. Thus, if the immune responses to L2 can be enhanced with appropriate adjuvants or epitope display, L2-based vaccines show great promise as an approach to prevent infection by all oncogenic HPV types and HPV-related disease.

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How Good Fats, Bad Fats and Other Dietary Patterns May Influence Risk for Cancer

Baltimore, Md. -- Though scientists have long suspected that diet and obesity play a significant role in cancer risk, the latest results are suggesting the problem may be more serious than previously thought.

Updated population studies suggest that the projected burden of cancer resulting from overweight and obesity may thwart other efforts to reduce cancer incidence over the next couple of decades, including curtailment of smoking.

Poor eating patterns, generally referred to as the "Western diet," may contribute to increased incidence of breast cancer among African-American women, according to a large study presented at this meeting.

On the other hand, consumption of fatty oils from other sources, including fish, flaxseed, corn and vegetable oils, may prove to be beneficial for some – perhaps depending on an individual's genetic makeup.

Results from these studies, summarized below, will be presented this week during the AACR *International Conference on Frontiers in Cancer Prevention Research*.

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Updated evidence on the proportion of cancer due to obesity (Abstract # 3513)

Growing evidence suggests that overall cancer incidence and mortality resulting from overweight and obesity is increasing, potentially thwarting other prevention and treatment efforts aimed at reducing these dire statistics.

"Given the trends in obesity and the increasing evidence of a broad range of cancers caused by excess energy balance, the projected burden of cancer over the coming years is worrisome," according to Graham Colditz, professor of epidemiology with the Harvard School of Public Health.

The latest projections represent a departure from an earlier report prepared in 2002 by the International Agency for Research on Cancer Committee on Weight Control and Physical Activity (IARC), based on European estimates for cancer prevalence (see table below).

That report concluded that overweight and obesity are related to cancers of the colon, endometrium, kidney and esophagus, as well as postmenopausal breast cancer. The study was based on estimates that 50 percent of all men, and 35 percent of all women were overweight, with 13 percent of men and 19 percent of women classified as obese.

The new projections stem from a review of published studies, updates to the IARC report from 2002, and data from the Nurses' Health Study II, which includes 116,686 women.

"Given the trend to increasing prevalence of obesity, these estimates are conservative," Colditz said.

Furthermore, he said that scientists now recognize a broader range of cancers associated with cancer mortality. These include myeloma, lymphoma and pancreatic cancers. Other sites are under review.

"The epidemic of obesity will run counter to the improving trends, such as a decrease in current smoking, that may suggest the incidence of cancer can be reduced," said Colditz.

Cancer	**EU**	**USA**
Colon	11%	14%
Breast (postmen)	9	11
Endometrium	39	49
Kidney	25	31
Esophagus	37	39
Pancreas		27
Lymphoma		20
Myeloma		17

"Western" diet increases breast cancer risk among African-American women (Abstract 2640)

African-American women who eat more foods from what many refer to as a typical "Western" diet appeared more than twice as likely to get breast cancer in their lifetimes than others who consume far less, according to a study of individuals participating in the Black Women's Health Study.

As described by the study, the "Western" diet is characterized by higher intakes of refined grains, red meat, processed meat, high fat dairy, eggs, fries, sweets, soda and snacks.

By contrast, those who consume far more foods from a so-called "prudent" diet appeared to have a decreased risk of developing breast cancer. The "prudent" diet features higher intakes of cruciferous vegetables, other vegetables, fruits, whole grain, cereals, fish, poultry and beans.

The study involved a self-reported questionnaire of dietary patterns and other potential risk factors for breast cancer among 57,877 women. Between 1995 and 2003, some 816 women in the study group were diagnosed with breast cancer.

As such, it represents the largest yet to study the relationship between diet and breast cancer among African-American women.

"Epidemiological studies have been inconsistent in supporting a role of dietary patterns in breast cancer risk," said Tanya Agurs-Collins, Ph.D., R.D., program director with the Health Promotion Research Branch of the National Cancer Institute, and the study's lead investigator. "Our results suggest that an overall healthy diet can decrease one's risk from breast cancer. Should these results be confirmed, the public health implications are that women can decrease their risk from breast cancer by consuming a healthy diet that is high in fruits and vegetables, low in fat, and by avoiding obesity."

After adjusting for breast cancer risk factors -- such as age, smoking, education, alcohol, family history, age of first birth, body mass index, exercise, and energy intake – the scientists concluded that those individuals in the highest tertile of the "prudent" diet – those who ate the highest amount of foods from this diet – appeared to have a decreased risk for developing breast cancer.

Interestingly, when stratified on body mass index, women who consumed the most foods from the "prudent diet" and were not obese had the greatest protection from breast cancer.

Fish oil slows growth of colon polyps in laboratory mice (Abstract 3716)

The protective effect of fish oils, called marine n-3 or omega-3 fatty acids, may be extended to colon cancer, according to animal studies conducted by researchers at the Vanderbilt-Ingram Cancer Center in Nashville, Tenn.

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Their results showed that colon polyps were generally smaller among laboratory mice fed a diet rich in fish oil compared to other mice on a high-fat diet. Specifically, the scientists found that half the mice on the high fat diet had polyps greater than 2 millimeters in size, compared to only 18 percent of mice on the fish oil diet.

Upon closer inspection, the scientists found that the fish oil diet resulted in a four-fold increase in polyunsaturated fats (PUFA) and a decrease in other lipids in the intestinal tracts of these specially bred animals called *Min* (for multiple intestinal neoplasia) mice, used to study early-stage colon tumor progression.

"Our hypothesis is that a PUFA, or a pattern of PUFAs, contributes to slowing the growth of polyps that sporadically arise in this mouse model of colon cancer," said J. Oliver McIntyre, a research professor at Vanderbilt. "This needs to be tested by further experiments.

For their experiment, the scientists employed a relatively new analytical approach called "computational lipidomics," which compares hundreds of lipids from two different populations, such as polyps and normal tissue, using mass spectrometry and computer algorithms.

Future work will focus on the molecular mechanisms that are triggering, in animals on a diet rich in fish oil, the reduced growth of colonic polyps seen in these series of experiments.

"At this stage, our work is basic science, though we expect that our kind of approach will be useful in identifying targets for prevention, whether through lifestyle factors of chemoprevention and that it will have some relevance in the future for people interested in reducing their risk from colon cancer," said McIntyre.

Consumption of omega-6 fatty acids may lower risk of prostate cancer (Abstract 3472)

In the largest study of its kind to date, a team led by scientists at the Harvard School of Public Health has found that omega-6 fatty acids typically found in salad dressings, corn and other non-hydrogenated vegetable oils may actually offer some protection against prostate cancer.

The 13-year prospective study, involving U.S. physicians from The Physician's Health Study, found that men with the highest blood levels of linoleic acid – the major omega-6 fatty acid in non-hydrogenated vegetable oils – were 40 percent less likely to get prostate cancer as those with the lowest level of this fatty acid in their blood.

The study results confirm the findings of some smaller European studies, but also differ from others that have suggested the opposite conclusion.

"This study is the largest one conducted to date exploring the association between biomarkers of fatty acid intake and risk of prostate cancer," said Jorge E. Chavarro, a doctoral candidate in the departments of Nutrition and Epidemiology at the Harvard School of Public Health, and the study's lead investigator.

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"If the findings are confirmed, the implications are that intake of linoleic acid is not harmful to the prostate and may actually be beneficial to help lower the risk of prostate cancer," he added.

To conduct the study, the scientists analyzed blood collected and frozen in 1982 as part of the Physician's Health Study, which involved 14,916 U.S. physicians. Omega-6 fatty acid levels as a percentage of all fatty acids were determined for 479 individuals from this group diagnosed with prostate cancer through 1995, along with 491 matched controls.

While higher blood levels of linolic acid were associated with reduced risk from prostate cancer, several other fatty acids including gamma linolenic acid (GLA) and dihomo gamma linolenic acid, (DHGLA) along with arachidonic acid (AA), were linked to an increased risk.

"Blood levels of linoleic acids are a good biomarker of linoleic acid intake, mostly intake of salad dressings and non-hydrogenated vegetable oils," said Chavarro. "Thus our results suggest that intake of linoleic acid may reduce the risk of prostate cancer.

"On the other hand, blood levels of GLA, DHGLA and AA are not good biomarkers of intake of these fatty acids. The blood levels of these fatty acids most likely represent the activity of the enzymes that metabolize these fatty acids, not diet."

Future research will focus on clarifying the role of omega-6 fatty acids in prostate cancer, and to determine if some other dietary or behavioral factor may also be contributing to the results seen in this study.

Potential Cancer Preventative Benefits of Flaxseed Depends on Genetic Makeup of the Individual (Abstract 3664)

Dietary flaxseed and its components have been shown to reduce the levels of sex hormones associated with breast cancer in animal studies and among postmenopausal women. But studies now suggest that flaxseed might be more beneficial to women with a particular genetic makeup.

In this case, the scientists focused on variations in two key genes responsible for the conversion of estrogen to specific metabolites. "This is likely a partial explanation for why not everyone who is exposed to something, such as diet, may have a good or bad result from it," said Susan McCann, with Cancer Prevention and Population Studies at the Roswell Park Cancer Institute, Buffalo, N.Y.

In their study, the scientists examined how variants in the two genes – COMT and CPP1B1 – affected estrogen metabolism from flaxseed consumption among 132 healthy, postmenopausal women aged 46 to 75 years. Participants consumed 10 grams of ground flaxseed daily for seven days, with no other dietary changes. Flaxseed is an excellent dietary source for substances called lignans, classified as phytoestrogens (plant estrogens) because they seem to mimic the action of estrogen in animals.

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In previous studies, flaxseed consumption was shown to result in higher conversion of estrogen to a metabolite called 2-hydroxyestrone, which has been linked to lower breast cancer risk in animal and human studies. The new results successfully replicated these findings, in addition to showing that flaxseed consumption results in a higher ratio of 2-hydroxyestrone to another estrogen metabolite called 16-hydroxyestrone.

However, the findings also revealed that women with specific variants in these two genes converted more estrogen to the relevant metabolites than those women with two common genes. In the study group, about 28 percent of the women had two variants for COMT, while 16 percent had variants for CYP1B1.

“One should keep in mind that we only examined two genes,” said McCann. “The body has a number of complementary pathways, so that if one pathway doesn’t work well, another one can take its place.

“What we would eventually like to do is to be able to target specific interventions to those people most likely to benefit.”

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Updated Evidence on the Proportion of Cancer Due to Obesity
Abstract # 3513, Graham Colditz, Harvard School of Public Health, Boston, Mass.
Oral Presentation. 7:00 a.m., Tuesday, November 1, 2005.

Dietary Patterns and Breast Cancer Risk in Women Participating in the Black Women’s Health Study EP5
Abstract # 2640, Tanya Agurs-Collins, National Cancer Institute, Bethesda, Md.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

Fish Oil Diet Increases Polyunsaturated Fatty Acids (PUFA) in Colonic Phospholipids detected by Computational Lipidomics and Reduces Growth of Colonic Polyps in the Min Mouse
Abstract # 3716, J. Oliver McIntyre, Vanderbilt-Ingram Cancer Center in Nashville, Tenn.
Poster Session C. 7:30 a.m., November 2, 2005.

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A 13-year Prospective Study of Blood N-6 Fatty Acid Levels and Risk of Prostate Cancer: The Physicians' Health Study
Abstract # 3472, Jorge Chavarro, Harvard School of Public Health, Boston, Mass.
Poster Session C. 7:30 a.m., November 2, 2005.

Effect of COMT and CYP1B1 Genotype on Changes in 2- and 16a-Hydroxyestrone Metabolism after Flaxseed Consumption
Abstract # 3664, Susan McCann, Roswell Park Cancer Institute, Buffalo, N.Y.
Poster Session B. 5:15 p.m., Tuesday, November 1, 2005.

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High Dietary Calcium Intake May Increase Prostate Cancer Risk

Baltimore, MD – (November 1, 2005) Men with a high intake of dietary calcium are at greater risk of developing prostate cancer, according to a study presented today during the American Association for Cancer Research's 4th annual Frontiers in Cancer Prevention Research meeting in Baltimore.

Researchers from the Division of Cancer Epidemiology and Genetics of the National Cancer Institute (NCI) reviewed data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study to evaluate the relation between calcium, vitamin D, phosphorus as well as dairy products and occurrence of prostate cancer. The current research was based on 17 years of follow-up and 1269 incident cases of prostate cancer.

Results showed that higher intakes of dietary calcium were associated with a significant increase in prostate cancer risk – men who consumed more than 2000 mg of calcium per day nearly doubled their risk of developing prostate cancer. While dairy product intake increased the risk of prostate cancer, no association remained after controlling for calcium. With the exception of cream which showed a significant trend toward an increased prostate cancer risk across intake levels, other individual dairy products showed no association. Moreover, there was no evidence of a link for intake of vitamin D or phosphorous.

"The results of our study suggest that high intakes of dietary calcium are related to an increased risk of prostate cancer," according to Panagiota Mitrou, of the NCI and lead author of the study. "These results might explain the positive association seen with dairy products in our and previous studies. Further research should focus on how dietary calcium could affect prostate cancer."

The ATBC Study was a large prospective cancer prevention trial conducted by the U.S. National Cancer Institute (NCI) and the National Public Health Institute of Finland from 1985 to 1993. The purpose of the study was to determine whether certain vitamin supplements would prevent

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cancer in a group of 29,133 male (aged 50 to 69) smokers in Finland. The trial ended in 1993, but ongoing follow-up of the participants enables continued research into the causes and prevention of multiple diseases, including cancer.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Intakes of Calcium, Dairy Products, and Prostate Cancer Risk in the ATBC Study
Abstract # 3688, Panagiota Mitrou, National Cancer Institute, Bethesda, Md.'
Poster Session B. 5:15 p.m., Tuesday, November 1, 2005

OILS, FAT AND CANCER

Abstract 3472

A 13-year Prospective Study of Blood N-6 Fatty Acid Levels and Risk of Prostate Cancer: The Physicians' Health Study

Authors: Jorge E. Chavarro,1 Meir J. Stampfer,2 Haojie Li,3 Hannia Campos,1 Tobias Kurth,4 Jing Ma.3 Department of Nutrition, Harvard School of Public Health,1 Boston, MA, Department of Epidemiology, Harvard School of Public Health,2 Boston, MA, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School,3 Boston, MA, Divisions of Aging and Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School,4 Boston, MA.

Purpose: To evaluate the association between whole blood n-6 fatty acid levels and risk of prostate cancer. Methods: We conducted a nested case-control study among 14,916 U.S. physicians who provided a blood sample in 1982. Blood samples were frozen at baseline and kept at -82° C until laboratory analyses were performed. Incident prostate cancer cases accrued through 1995 were matched to controls by age, smoking status at baseline and length of follow-up. N-6 fatty acid levels as percentage of total fatty acids were determined for 479 cases and their 491 matched controls using gas chromatography. Cases and controls were divided into groups according to quintiles of fatty acid levels among the controls. Conditional logistic regression models were used to estimate the relative risk (RR) of prostate cancer in a given quintile of fatty acid level in relation to the lowest quintile. Results: There was an inverse association between blood levels of linoleic acid (LA) and prostate cancer risk. The RR of prostate cancer for men in the highest quintile of LA levels was 0.60 (95% confidence interval [CI] = 0.40–0.91), compared to men in the lowest quintile (Ptrend = 0.02). Conversely, γ-linolenic acid (GLA) and dihomo- γ-linolenic acid (DHGLA) were associated with an increased risk of prostate cancer. For GLA, the RR (95% CI; Ptrend) comparing the highest and lowest quintile was 1.47 (0.98–2.21; 0.03) and for DHGLA the corresponding RR (95% CI; Ptrend) was 1.58 (1.06–2.36; 0.01). Arachidonic acid (AA) levels were not associated with overall prostate cancer risk. When results were divided according to tumor stage at diagnosis, LA and GLA were more strongly related to localized tumors (stage A or B); the RRs (95% CI; Ptrend) comparing extreme quintiles were 0.54 (0.32–0.92; 0.03) for LA and 1.84 (1.06–3.17; <0.01) for GLA. On the other hand, DHGLA and AA were more strongly associated with advanced tumors (stage C or D); the corresponding RRs (95% CI; Ptrend) were 2.38 (0.98–5.80; 0.01) for DHGLA and 2.66 (1.12–6.31; 0.05) for AA. Further adjustment for potential confounders did not substantially change these results. Conclusions: Our prospective data suggest that whole blood levels of linoleic acid, the major fatty acid in non-hydrogenated vegetable oils, are associated with a reduced risk of prostate cancer. The concentration of fatty acids resulting from the elongation and de-saturation of linoleic acid are associated with an increased risk of prostate cancer. Further, different fatty acids may be involved in different stages of prostate carcinogenesis.

OILS, FAT AND CANCER

Abstract 3664

Effect of COMT and CYP1B1 Genotype on Changes in 2- and 16α-Hydroxyestrone Metabolism after Flaxseed Consumption

Authors: Susan E. McCann,1 Jean Wactawski-Wende,2 James Olson,2 Bladmir Ovando,2 Susan Nowell,3 Peter G. Shields,4 Jo L. Freudenheim.2 Roswell Park Cancer Institute,1 Buffalo, NY, Univ. at Buffalo,2 Buffalo, NY, University of Arkansas for Medical Sciences,3 Little Rock, AR, Lombardi Cancer Center,4 Washington, DC.

Lignans are a class of phytoestrogens found widely in whole grains, vegetables, and fruits commonly consumed in Western diets. Although consumed in relatively small amounts, flaxseed is a particularly rich source of lignans. Dietary interventions with flaxseed have been shown to increase the estrogen etabolite 2-hydroxyestrone (2OHE1). An increased ratio of 2OHE1 to 16α-hydroxyestrone (2:16OHE1) has been associated with lower breast cancer risks in epidemiologic studies. Genetic variation in a number of estrogen metabolizing genes have also been associated with breast cancer risk. CYP1B1 is important in the conversion of estrone to 2OHE1 and COMT further metabolizes 2OHE1 to 2-methoxyestrone for elimination. Because of the structural similarity of lignans to estrogen, and evidence that lignans may inhibit steroid-related genes, we investigated the relationship between COMT and CYP1B1 genotypes and the effect of flaxseed on these hydroxyestrone metabolites in a brief dietary intervention among 132 healthy, postmenopausal women, ages 46 to 75 years. Participants were volunteers who consumed 10 g ground flaxseed daily for seven days. No other changes were made in diet or in other activities. Blood and urine samples were collected at baseline and immediately post-intervention. COMT val158met and CYP1B1 leu432val genotypes were determined using PCR-RFLP methods; both were in Hardy-Weinberg equilibrium. Urinary 2OHE1 and 16αOHE1 were quantified with a competitive-inhibition ELISA assay (ImmunaCare Corporation). Pre- and post-intervention 2OHE1, 16αOHE1, and 2:16OHE1 levels were compared with the Wilcoxon signed rank test, and the effect of genotype on intervention-related changes in the metabolites and their ratio was assessed with the Kruskal-Wallis (K-W) test. Mean changes in 2:16OHE1 were calculated with generalized linear models adjusting for age, with each gene mutually adjusted for the other gene. As expected, after seven days of flaxseed consumption, urinary 2OHE1 (ng/mg creatinine) was significantly higher than baseline [mean (SD) 16.1 (10.6) vs. 9.3 (6.9), respectively; $p<0.01$], resulting in a significantly higher than baseline 2:16OHE1 ratios [mean (SD) 2.73 (1.47) vs. 1.54 (0.75), respectively; $p<0.01$]. The intervention-related change in 2:16OHE1 increased with increasing numbers of variant alleles for both COMT (mean change: val/val 0.90, val/met 1.15, met/met 1.50; K-W $p=0.17$) and CYP1B1 (leu/leu 0.89, leu/val 1.32, val/val 1.51; K-W $p=0.04$). Our findings suggest that variation in hormone-related genes may modify the effect of dietary phytoestrogen exposures on estrogen metabolism.

OILS, FAT AND CANCER

Abstract 3716

Fish Oil Diet Increases Polyunsaturated Fatty Acids (PUFA) in Colonic Phospholipids detected by Computational Lipidomics and Reduces Growth of Colonic Polyps in the *Min* Mouse

Authors: J. Oliver McIntyre,1 Mark Byrne,2 Xiangjian Zheng,2 Kathy J. Carter,1 Pavlina T. Ivanova,2 Stephen B. Milne,2 Jeffrey S. Forrester,2 Sedef Everest,1 Lynn M. Matrisian,1 H. Alex Brown.2 Department of Cancer Biology, Vanderbilt University Medical Center,1 Nashville, TN, Department of Pharmacology and the Vanderbilt Institute of Chemical Biology, Vanderbilt University Medical Center,2 Nashville, TN.

Computational lipidomics is an analytical approach that couples mass spectrometry with statistical algorithms to facilitate the comprehensive analysis of large numbers of molecular species of lipids from cell or tissue extracts. Electrospray ionization mass spectrometry (ESI-MS) was applied to lipid extracts from colon polyp biopsy samples from Multiple Intestinal Neoplasia (*Min*) mice maintained on either an 11% fat (HF) or a 20% fish oil (FO) diet. The *Min* mouse is a model for studying early-stage colon tumor progression as a result of its similarity in genotype and phenotype to human familial adenomatous polyposis (FAP) syndrome that predisposes to colon cancer. Comparison of *Min* colonic polyps versus control biopsies, extracted and analyzed by ESI-MS, revealed numerous lipid species either elevated or depressed in polyps. The FO diet significantly altered multiple classes of lipids in the major organs including the intestinal tract and across all mice, e.g., an ~4-fold increase in the relative total peak height of phosphatidylinositols (PI) 38:5, 38:6, 40:5 and 40:6, containing 20:5, 22:5, and 22:6 polyunsaturated fatty acids (PUFA), and an ~25% decrease in PI 38:4 (identified as 18:0, 20:4), the major arachidonoyl(ARA)-PI in colonic lipids. The growth of colonic polyps was reduced in *Min* mice on the FO diet [22 of 44 mice (50%) on HF diet with one or more polyps >2 mm versus 3 of 17 mice (18%) on the FO diet] but had no significant effect on the number of polyps (4.1 vs. 4.5 polyps/colon for HF vs. FO). These results indicate that: 1) direct injection ESI-MS is a viable technique for the identification of numerous molecular species of glycerophospholipids in lipid extracts from tissue biopsies; 2) a subset of lipid markers appear to be associated with colonic polyps from *Min* mice; 3) the FO diet modifies the phospholipid composition of major organs, increasing the PUFA/ARA ratio; and 4) the FO diet attenuates growth of colonic polyps. Ongoing work seeks to identify specific species and/or pattern changes that can be used as biomarkers and prognostic indicators and to identify lipid signaling pathways that may influence the development of colonic polyps. (Supported in part by R01 CA60867 to LMM; GM58516 and the Alliance for Cell Signaling to HAB, and the VICC CCSG P30 CA68485).

OILS, FAT AND CANCER

Abstract 2640

Dietary Patterns and Breast Cancer Risk in Women Participating in the Black Women's Health Study

Authors: Tanya Agurs-Collins,1 Kepher Makambi,2 Julie R. Palmer,3 Lynn Rosenberg,3 Lucile L. Adams-Campbell.2 National Cancer Institute,1 Bethesda, Maryland, Howard University Cancer Center,2 Washington, DC, Slone Epidemiology Center, Boston University,3 Boston, MA.

Epidemiological studies have been inconsistent in supporting a role of dietary patterns in breast cancer risk. We prospectively examined the association between dietary eating patterns and breast cancer risk in the Black Women's Health Study (BWHS). Among 59,000 black women aged 21 to 69 years at baseline, 57,877 with baseline self-reported information on dietary intakes and other risk factors for breast cancer were included in the analyses. Between 1995 and 2003, a follow-up of 385,850 person-years, 816 women were diagnosed with breast cancer. Dietary intake was assessed by a baseline 68-item validated food-frequency questionnaire. Through factor analysis, two dietary patterns "Western" and "Prudent" were identified. The Western diet was characterized by higher intakes of refined grains, red meat, processed meat, high fat dairy, eggs, fries, sweets, soda, and snacks. The Prudent diet was characterized by higher intakes of cruciferous vegetables, other vegetables, fruits, whole grain, cereals, fish, poultry, and beans. Time dependent Cox regression models were used to obtain incident rate ratios (IRR). We compared the highest with the lowest tertile for the Prudent and Western diet. After adjusting for other breast cancer risk factors (age, smoking, education, alcohol, family history, age at first live birth, parity, BMI , exercise, and energy intake), the highest tertile of the Prudent diet was associated with a reduced breast cancer risk, IRR=0.58 (95% CI= 0.35- 0.95; p for trend = 0.03). We then stratified by body mass index (BMI). The Prudent dietary pattern was associated with a lower risk of breast cancer among women with a BMI of < 30 kg/m2: the IRR for the highest versus lowest tertile was 0.37 (95% CI=0.19- 0.70; p for trend=0.002), whereas the comparable IRR among women with a BMI >30 was 1.26 (95% CI=0.53- 2.99; p for trend = 0.60). Moreover, the Western dietary pattern was associated with a higher risk for breast cancer. The IRR for the highest versus lowest tertile was 2.18 (95% CI=1.06- 4.48; p for trend=0.03). Our data offer support for an association between dietary patterns and breast cancer risk among African-American women.

OILS, FAT AND CANCER

Abstract 3513

Updated Evidence on the Proportion of Cancer Due to Obesity

Author: Graham Colditz. Harvard Medical School, Boston, MA.

In 2002 The International Agency for Research on Cancer Committee on Weight Control and Physical Activity concluded that overweight and obesity are related to cancers of the colon, endometrium, kidney and esophagus as well as postmenopausal breast cancer. Using the Bergstrom estimates for the prevalence of Europe, they reported that the population attributable risk for these cancers due to overweight were:

Colon cancer 11%
Postmenopausal breast caner 9%
Endometrial cancer 39%
Kidney cancer 25%
Esophageal cancer 37%

Of note, the European prevalence of overweight and obesity used as a basis for these PAR estimates are that 50% of men and 35% of women were overweight and 13% of men and 19% of women are obese. Given the trend to increasing prevalence of obesity, these PAR estimates are conservative. Furthermore, Calle et al., analyzing the ACS CPSII cohort, reported increased mortality associated with obesity for a broader range of cancers than those noted above.

Since that report, continuing epidemiologic investigation has focused on the range of cancers suggested by the ACS mortality report to be related to cancer risk. Growing evidence that obesity is related to increased incidence of myeloma, lymphoma, pancreatic cancer, and cancer at other sites will be reviewed.

Given the trends in obesity and the increasing evidence of a broad range of cancers caused by excess energy balance, the projected burden of cancer over the coming years is worrisome. Projections for the burden of cancer diagnosis in the US based on age specific incidence rates from 1995 to 1999, show that the aging of the population will increase the number of incident cancers from 1.3M per year in 2000 to over 2M per year soon after 2020. The epidemic of obesity will run counter to the trends (such as current smoking) that may suggest the incidence of cancer can be reduced.

OILS FATS AND CANCER

Abstract 3688

Intakes of Calcium, Dairy Products, and Prostate Cancer Risk in the ATBC Study

Authors: Panagiota N. Mitrou,1 Demetrius Albanes,1 Stephanie Weinstein,1 Pirjo Pietinen,2 Phil Taylor,1 Jarmo Virtamo,2 Michael F. Leitzmann.1 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health,1 Bethesda, MD, Department of Epidemiology and Health Promotion, National Public Health Institute,2 Helsinki, Finland.

Intakes of calcium and dairy products have been hypothesized to enhance prostate cancer risk. The putative mechanism involves a calcium-induced suppression of the production of 1,25 dihydroxy vitamin D leading to an increased proliferation of normal and malignant prostate cells. However, prospective data regarding these associations are sparse. In 2000, Chan and colleagues suggested that men with lower calcium and higher phosphorus intake were at increased risk of prostate cancer in the Alpha-Tocopherol-Beta-carotene Cancer Prevention Study (ATBC Study), a cohort of 29,133 male smokers aged 50-69 years. That report was based on follow-up from 1985 through 1993 and 184 incident cases of prostate cancer. We now report findings based on 17 years (336,503 person-years) of follow-up and 1270 incident cases of prostate cancer. We, therefore, further evaluated the relation between these nutrients as well as dairy products and occurrence of prostate cancer in the ATBC Study. Dietary intake was assessed at baseline using a validated 276 food and beverage item questionnaire. We used the residual method to adjust all foods and nutrients for total energy intake. Cox proportional hazards regression was used to adjust for known or suspected risk factors for prostate cancer. Higher intakes of dietary and total calcium were associated with a marked increase in prostate cancer risk (relative risks (RRs) for top vs. bottom quartiles of intake were 1.95 (95% confidence interval (CI), 1.42 to 2.69; P trend <0.0001) and 1.54 (95% CI, 1.13 to 2.09; P trend =0.007), respectively). The results for advanced prostate cancer cases also showed increased relative risks for both dietary and total calcium intake but did not reach statistical significance. Dairy product intake increased risk of prostate cancer (RR for top vs. bottom quintiles of intake was 1.32 (95%CI, 1.09 to 1.58; P-trend=0.02) but no association remained after controlling for calcium, vitamin D and phosphorus (RR, 1.16, 95%CI, 0.88 to 1.53; P-trend=0.51). When dairy food was divided into subgroups, the results were null overall with the exception of cream, which showed a statistically significant trend toward an increased risk across intake levels (P-trend=0.02) after adjusting for total calcium, vitamin D and phosphorus. There was no evidence for an association between higher intakes of vitamin D (dietary or total) or phosphorus. The results from this large prospective study suggest that intake of calcium (dietary) is related to increased risk of prostate cancer and this might explain the positive association seen with dairy products.

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Genetics, Molecular Biomarkers Form Molecular Basis for Cancer Prevention Risk-Limiting Strategies and Therapeutic Tactics

One of the goals for cancer prevention is to identify, as early as possible, molecular changes in the body that signal the onset of disease. Such "biomarkers" may be isolated from subtle biological changes in an individual's cells, proteins or genetic makeup.

Useful biomarkers to help prevent, diagnose and monitor treatment for cancer must share two essential characteristics: they must be consistently reliable, and they must display significant difference in expression between normal tissue and the various stages of cancer progression.

Three studies presented at the 2005 American Association for Cancer Research Frontiers in Cancer Prevention Research meeting in Baltimore discuss molecules that scientists have identified as markers for skin, endometrial or breast cancer. The results suggest how these biomarkers may help monitor early onset malignancies that can be prevented from advancing to life-threatening conditions.

Blood levels of C-reactive proteins indicative of increased risk for endometrial, colorectal cancers (Abstract # 3701)

People with elevated concentrations of a protein associated with chronic low-grade inflammation are at higher risk for developing endometrial cancer, according to a new study.

C-reactive protein is a highly sensitive indicator of inflammation, and is associated with diabetes, metabolic syndrome and hyperandrogenic states. The protein is made by liver cells in response to several pro-inflammation signaling molecules known as cytokines.

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In a three-part study including more than 35,000 women, C-reactive protein levels were higher in the circulation of women who developed endometrial cancer compared to blood levels of women who remained free from endometrial cancer. The risk for women who averaged 2.44 mg C-reactive protein per liter of blood was twice that of women whose blood contained an average of 1.8 mg per liter of the inflammation related biomarker.

“This is the first prospective study to report on the association between C-reactive protein, a non-specific marker for chronic inflammation, and endometrial cancer,” said Dana K.Christo, MPH, from the Johns Hopkins University School of Public Health and the study’s lead author. Also participating in the study were scientists from the Fox Chase Cancer Center and the National Cancer Institute.

“This finding gives us a clue that inflammation is associated with progression to endometrial cancer, but it should be confirmed in other studies,” said Christo. “However, our results suggest that other known risk factors, such as obesity, may lead to cancer through inflammation, which should be amenable to prevention strategies.”

P53, Polyamine Levels Rise in Sun-Damaged Skin of Individuals Harboring AK (Abstract # 3670)

People with actinic keratosis (AK) due to exposure to the sun had increased levels of two biomarkers associated with AK lesions of the skin, according to studies conducted by researchers from the University of Arizona Cancer Center.

“Actinic keratosis is a very common lesion in aging, sun-exposed populations,” said Janine Einspahr, Ph.D., research assistant professor at the University of Arizona and lead author of the study. “AK is much more common than the malignant condition of squamous cell carcinomas (SCC).”

SCC account for about 20 percent of skin cancers, and are non-melanoma malignancies stemming from a type of skin cells called keratinocytes.

“Since AK are precursor lesions of SCC they represent a good model of early progression in UVB-induced skin cancer, and a good model for the dissection of the molecular alterations that take place in this SCC progression,” Einspahr said.

Examining biopsies from the forearms of 789 people with sun damage, 33 people with AK, and 32 people who had previously had SCCs surgically removed, the Arizona researchers determined that individuals with AK had increased p53 levels, putricine and spermadine compared to those with sun-damaged skin.

The University of Arizona studies show that p53 expression and polyamine content in skin forearm biopsies are reliable measures over time in sun-damaged skin.

"Specific genetic alterations, such as mutation or overexpression of p53, and phenotypic, biochemical characteristics of AKs, cell proliferation/PCNA/polyamines, can be used to demonstrate the effect of chemopreventive agents. Identification of these biomarkers in even earlier stages of progression would allow targeting of populations at an even lower risk for preventive strategies," said Einspahr.

By identifying biomarkers that consistently and accurately predict progression of skin conditions toward malignant states, Einspahr and her colleagues have established assays that can be effective in detecting precancerous conditions.

"Clinical trials to assess cancer incidence require large sample-sizes, long follow-up, and are very costly," Einspahr said. "Useful biomarkers could circumvent this with smaller sample sizes and studies of shorter duration."

The Arizona cancer researchers examined biomarkers that include specific genetic alterations (mutation or overexpression of p53) and phenotypic and biochemical characteristics of AKs, (cell proliferation, PCNA, and polyamines).

PCNA is a cell cycle related protein expressed in the nucleus of cells that are in the proliferative growth phase. Polyamines are ubiquitous polycations that are essential for normal cellular proliferation and differentiation. Putrescine is the first polyamine in the pathway, spermidine the second and spermine the last. PCNA and polyamines are required for normal epidermal homeostasis but, when dysregulated, represent tissues undergoing increased cell growth and division such as in neoplasm or early cancer progression.

Italian Research Suggests Enhanced Safety in Low Doses of Tamoxifen with HRT Use (Abstract # 3456)

Early indications from the HOT Trial suggest that women can safely take a combination of hormone replacement therapy (HRT) and tamoxifen at reduced dosages. Analysis of the Italian Tamoxifen Chemoprevention Trial showed a reduction of breast cancer among women who were under continuous HRT and tamoxifen in contrast to those who received HRT and a placebo.

"Tamoxifen at reduced dosages retained its antiproliferative effect," said Bernardo Bonanni, M.D., Condirettore, Divisione di Farmacoprevenzione, Istituto Europeo di Oncologia.

"The combination was particularly effective when the HRT was administered transdermally, either with a patch or gel, and the dose of tamoxifen was reduced to 5 mg/day." Bonanni noted that the reduced tamoxifen level was just a quarter of the dose administered in the WHI studies.

"The differences we are seeing in the HOT study may be due to the very different subject characteristics, different route of taking the medication, as well as the reduced dosage regiment administered in this more recent study," Bonanni said

The HOT Trial is an ongoing Phase III trial that examines a series of biomarkers in women on HRT and tamoxifen. Among the markers of interest are changes in plasma levels of the growth factor IGF-I, as well as the growth factor's binding protein, IGFBP-3, lipids, C-reactive protein, homocysteine and other biomarkers.

The study includes 210 HRT users who receive either 1 or 5 mg/day, or 10 mg/week doses of tamoxfen. The control arm of the study includes HRT users who also take a placebo. Low doses of tamoxifen in combination with the HRT result in significantly modulated levels of biomarkers of breast carcinogenesis and cardiovascular risk among women taking HRT.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

C-Reactive Protein and Risk of Incident Endometrial Cancer in Three US Cohorts
Abstract # 3701, Dana Christo and Kathy Helzlsouer, Johns Hopkins University, Baltimore, Md.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

Reproducibility and Expression of Skin Biomarkers in Sun-Damaged Skin
Abstract # 3670, Janine Einspahr, Arizona Cancer Center, Tuscon.
Poster Session B. 5:15 p.m., Tuesday, November 1, 2005.

A Randomized Phase II Biomarker Trial of Low-Dose Tamoxifen in HRT Users
Abstract # 3456, Aliana Guerrieri-Gonzaga, European Institute of Oncology, Milan, Italy
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

GENETICS AND BIOMARKERS

Abstract 3701

C-Reactive Protein and Risk of Incident Endometrial Cancer in Three US Cohorts

Authors: Dana K. Christo,1 Joanne F. Dorgan,2 Louise A. Brinton,3 Sandy C. Hoffman,1 George W. Comstock,1 Kathy J. Helzlsouer.1 Johns Hopkins School of Public Health,1 Baltimore, MD, Fox Chase Cancer Center,2 Philadelphia, PA, Division of Cancer Epidemiology and Genetics, National Cancer Institute,3 Bethesda, Maryland.

Background: Low grade chronic systemic inflammation has been hypothesized to increase cancer risk. Elevated C-reactive protein (CRP) concentration, a biomarker of chronic systemic inflammation, has been associated with an increased risk of colorectal and ovarian cancers. Higher levels of circulating CRP are associated with diabetes, metabolic syndrome, and hyperandrogenic states, also known risk factors for endometrial cancer. The aim of this study was to evaluate the hypothesis that pre-diagnostic, circulating levels of CRP are associated with subsequent risk of developing endometrial cancer. Methods: This case control study was nested in three prospective, population-based cohorts. Clue I enrolled 20,305 Washington County, Maryland residents (14,134 women) in 1974. Clue II enrolled 25,081 residents of the same county (14,625 women) in 1989. The Columbia, Missouri cohort enrolled 6,720 women between 1977-87. Participants in all cohorts were cancer free when they donated a blood sample and completed a brief questionnaire, ascertaining demographic and clinical data, at baseline. During up to 30 years follow-up, a total of 226 cases of incident endometrial cancer were identified through linkage to cancer registries and National Death Index (NDI). One control per case was matched on race (100% Caucasian), age (+/-2 years), menopausal status or cycle day for premenopausal women, date and hour of blood donation, and study cohort. Cases and controls using oral contraceptives or hormone therapy at blood collection were excluded from this analysis. Circulating CRP levels were measured using a high sensitivity ELISA assay (ALPCO Diagnostics, Windham, NH). Intra-pair coefficient of variation was 3.7% based on blinded quality control samples. Conditional logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals (95% CI). All models were adjusted for smoking history (never, former, current). Results: Among control participants, CRP was positively correlated with age, body mass index (BMI), systolic and diastolic blood pressure. Circulating CRP levels were higher among endometrial cancer cases compared to controls (median CRP, 2.43 vs. 1.84 mg/L; p=0.04). Women in the highest fourth of
CRP had a two-fold increased risk of developing endometrial cancer compared to women in the lowest fourth (OR, 2.19; 95% CI, 1.24-3.84; p-trend=0.01). Adjustment for BMI, a factor postulated to be part of the causal chain, attenuated the risk estimate but did not eliminate the positive association between CRP and endometrial cancer. Risk of endometrial cancer was stronger for women older than 50 at the time of blood collection compared to younger women. Associations were attenuated with longer time to diagnosis. Conclusions: Higher prediagnostic concentrations of CRP are associated with an increased risk of endometrial cancer. Because associations were strongest among those diagnosed within 5 years of blood sample, this may be a marker of late stage progression to cancer.

GENETICS AND BIOMARKERS

Abstract 3670

Reproducibility and Expression of Skin Biomarkers in Sun-Damaged Skin

Authors: Janine G. Einspahr, James Ranger-Moore, James Warneke, Kathylynn Sabota, Paul Bozzo, Min-Jian Xu, Laura Duckett, Rayna Goldman, Po Lin, Julie Buckmeier, David S. Alberts. Arizona Cancer Center, Tucson, AZ.

Useful tissue biomarkers must be reliable and differ in expression with neoplastic progression. To explore the utility of p53 and PCNA expression and polyamine content as biomarkers, we performed a study to determine their reproducibility over 3 months in sun-damaged skin and AK. Forearm biopsies (BX) were collected from 78 subjects with sun-damage, 33 with AK on forearms, and 32 with a previously resected SCC. An AK was also removed in subjects with AK. In addition, participants with sun-damage were randomized either to sunscreen use or no sunscreen to evaluate its effect. There were no significant differences in p53 expression or in polyamine content over time or in the sunscreen group compared to no sunscreen. In contrast, PCNA in the sun-damaged group alone changed significantly over time ($p=0.005$). p53 (± SE) was significantly increased in the forearms of subjects harboring AK compared to sun-damaged skin (11.5% ± 1.2 vs. 20.9 ± 2.3, $p=0.001$). p53 expression in AK was 25.4% ± 2.6 ($p=<0.001$ vs sun-damage). PCNA expression in sun-damaged forearms was 9.9% ± 0.7 versus 12.1% ± 1.6 in forearm BX from subjects with AKs ($p=0.29$). PCNA expression in the AK lesion was 16.1% ± 2.2 ($p=0.01$ vs sun-damaged BX). Putrecine showed a significant increase from 65.5 ± 1.9 mmol/g in sun-damaged skin to 81.7 ± 3.9 in forearms of subjects harboring AK ($p < 0.00001$). Spermidine levels were also significantly increased from 187.7 ± 3.3 in sun-damaged skin to 209.4 ± 8.2 in forearms of subjects with AK ($p=0.006$). We show that p53 expression and polyamine content in skin BX are reliable measures over time in sun-damaged skin and furthermore that both of these markers are significantly elevated in sun-damaged skin of individuals harboring AK and in the AK lesion itself relative to sun-damaged skin of individuals without AK.

GENETICS AND BIOMARKERS

Abstract 3456

A Randomized Phase II Biomarker Trial of Low-DoseTamoxifen in HRT Users

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Background: the combination of hormone replacement therapy (HRT) and a SERM such as tamoxifen may retain the benefits while reducing the risks of either agent. A *post hoc* analysis of the Italian Tamoxifen Chemoprevention Trial showed a reduction of breast cancer among women who were on continuous HRT and tamoxifen as compared with those on continuous HRT and placebo. Our recent studies have shown that the standard dose of tamoxifen may be reduced to one quarter without loss of its antiproliferative effect and, possibly, with a reduction of endometrial cancer risk. Finally, the prolonged half-life of tamoxifen and its main metabolites (1-2 weeks) provides the rationale for a weekly drug administration. Study design and endpoints: Current or de novo HRT users for menopausal symptoms were assigned on a double-dummy fashion to one of the following 4 arms: tamoxifen 5mg/day+placebo/week, tamoxifen mg/day+placebo/week, placebo/day+tamoxifen 10mg/week, or placebo/day+placebo/week. Subjects were stratified by center, route of HRT, current versus de novo HRT use. The primary endpoint was the change of plasma IGF-I. Secondary endpoints were changes of plasma IGFBP-3, IGF-I/IGFBP3 ratio, lipid profile, fibrinogen, antithrombin III, osteocalcin, homocysteine, C-reactive protein, C-telopeptide. Additional endpoints included mammographic %density, ultrasound evaluation of endometrial thickness and endometrial proliferation (ki67) in 3 compartments (superficial gland, deep gland, stroma) in samples obtained at 12 months by Pipelle curettage. Results: 210 HRT users were assigned to tamoxifen 5 mg/day (n=53) or 1 mg/day (n=52) or 10 mg/week (n=52) or placebo (n=53) for 12 months; 175 fully completed the study while 37 dropped-out: 25 refusals, 10 adverse events (2 SAEs) and 2 lost to follow-up. Mean age at randomization and mean age at menopause were 54±3, 50±3, and mean BMI (kg/m2) was 24.2±3.6. Compared to placebo, there was a significant decline of IGF-I on tamoxifen without significant dose-response relationship; 12-month levels were 103.1 ng/ml for 5 mg/day, 118.6 for 1 mg/day, 113.9 ng/ml for tamoxifen 10 mg/week, 123.1 ng/ml for placebo. Likewise, tamoxifen increased IGFBP-3 and lowered IGF-I/IGFBP-3, antithrombin-III and CRP, without differences among doses. There was no change of lipids, homocysteine and C-telopeptide. Tamoxifen significantly increased ultrasound endometrial thickness, while endometrial proliferation was not significantly augmented. Indeed, there was a trend to a lower proliferation of the 5 mg/day arm in all 3 compartments compared with placebo. Tamoxifen induced a borderline significant reduction of mammographic %density. Pre-specified menopausal symptoms showed a slight worsening on tamoxifen. Conclusions: Tamoxifen at low doses ranging from 1-5 mg/day or 10 mg/week significantly modulates biomarkers of breast carcinogenesis and cardiovascular risk in HRT users without increasing endometrial proliferation. Menopausal symptoms were only slightly increased on tamoxifen. A phase III trial of tamoxifen 5 mg/day in HRT users is underway to assess efficacy and safety of this regimen. Supported by the S. Komen Breast Cancer Foundation.

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Research Advances New Cancer Preventive Strategies from Myriad Sources

Baltimore, Md. — Promising new ways to prevent cancer emerge regularly from the laboratories of research institutions around the world. With every deposit to the scientific bank of knowledge about the human body and disease processes comes an opportunity to posit and test fresh theories. The results often suggest simple measures people can take to improve their chances of cheating cancer.

Among the studies presented this morning are two dealing with some of life's more common phenomena: Having babies and taking aspirin.

Two others show the possible anti-cancer benefit of compounds long- and widely used to treat other conditions.

Synthetic Peptide Shows Promise in Conveying Pregnancy-induced Protection Against Breast Cancer to All Women (Abstract #3503)

It's a benefit of childbirth generally not considered when the new arrival appears on the scene: Pregnancy seems to protect women from the onset of breast cancer later in life. The question before scientists is how.

A team of researchers at the Albany Medical College, led by Thomas T. Andersen, Ph.D., created a peptide with the same chemical characteristics as alpha-fetoprotein, a pregnancy-associated molecule they believe is among those responsible for reducing the risk of breast cancer among mothers. The synthetic peptide AFPep (cyclic 9-amino acid), administered by

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mouth, stopped the growth of human breast cancer cells implanted in one group of mice, and decreased the incidence and number of breast cancer tumors in a second cohort of mice that had been injected with a carcinogenic chemical.

When combined with the chemotherapy drug tamoxifen, AFPep reduced the number of tumor-bearing rats by 77 percent. AFPep alone yielded a 23 percent decrease in the cancer rate.

"We are heartened by our results, which found that oral administration of AFPep is safe and effective for the treatment and prevention of breast cancer in these animal models," said Andersen. "We believe we are making strides to help protect all women from developing breast cancer, and hopefully extend and save the lives of those who do."

Naturally occurring alpha-fetoprotein (AFP) is produced by the fetus and is apparent in the mother's blood at around the 12th week of gestation. AFP levels in women decrease soon after they give birth.

In the Albany study, the female mice with chemically induced carcinogenesis were given a one-time dose of either AFPep or tamoxifen—some orally and some by injection. The animals were palpated weekly for 100 days to assess the number of mice with tumors, and the number and size of tumors within each mouse. Mice with human breast cancer tissue were used to test the therapeutic value of AFPep, with 30 days considered the end point.

Even at very high doses, AFPep showed no signs of toxicity.

NSAIDS and Breast Cancer: Risk Varies Between Baby Aspirin, Regular-strength Aspirin and Ibuprofen (Abstract #3733)

It has been many years since baby aspirin supplanted the apple as the recommended daily dose for doctor avoidance. Millions of people take this most common of the non-steroidal anti-inflammatory drugs (NSAIDs) to help prevent heart attack and stroke. Now, studies suggest women who do so may also be minimizing their breast cancer risk.

Scientists at the Fred Hutchinson Cancer Research Center in Seattle compared the incidence of invasive breast cancer with the amount and frequency of NSAID use among participants in its Vitamins and Lifestyle Study (VITAL). They found that women who took an average of four or more baby aspirins a week over the previous ten years experienced a 34 percent decreased risk of breast cancer compared to those who did not use NSAIDs.

Conversely, study participants who reported the same cumulative dose of regular or extra strength aspirin were at an increased risk for the disease. Regular-strength aspirin contains 325 milligrams of the active ingredient acetylsalicylic acid, versus 81 milligrams in low-dose or baby aspirin.

Ibuprofen and other, non-aspirin NSAIDs showed no association with breast cancer, at any dose.

"Based on the preliminary results of our study and previous studies, there is a suggestion that breast cancer risk may vary depending on NSAID type and/or dose," said Ann Ready, N.D., who was lead investigator on the Hutchinson study. She added, "However, due to the inconsistency of the evidence at this point, it would be premature to recommend NSAIDs for the prevention of breast cancer until further studies have been conducted."

The VITAL Study is a prospective cohort study of the associations between lifestyle factors and supplement use with cancer risk in Washington. A total of 77,738 men and women in the western part of the state, aged 50–76 years, entered the study between 2000 and 2002 by completing a detailed questionnaire on supplement use, diet and other cancer risk factors. Seventy percent also provided DNA self-collected DNA samples.

For the investigation of a relationship between NSAID use and breast cancer, the Hutchinson researchers reviewed data for 35,368 women enrolled in the VITAL Study. Participants completed a baseline questionnaire assessing their breast cancer risk factors, lifestyle factors and NSAID use. Breast cancer incidence among these women was monitored through the Western Washington Surveillance Epidemiology and End Results (SEER) cancer registry. The amount of NSAIDs used by the women was determined from their reports of the average number of days per week they had taken one of the drugs during the preceding ten years.

Vitamin D Compounds Show Promise for Prostate Cancer Prevention (Abstract #2315)

Researchers from Roswell Park Cancer Institute in Buffalo, N.Y., found that the active metabolite of vitamin D, calcitriol, and the vitamin D analogs, QW-1624-F2-2 and paricalcitol, are promising chemopreventive agents against prostate cancer.

Calcitriol is used clinically to treat a variety of disorders, including recently, in clinical trials for established cancer. A major obstacle to the clinical use of calcitriol is dose-limiting hypercalcemia, a condition characterized by abnormally high concentration of calcium in the blood. QW, developed at Johns Hopkins University, and paricalcitol (Zemplar) have been shown to reduce the levels of the hormones which regulate the metabolism of calcium and phosphorus in the body.

In vitro, researchers demonstrated that the three drugs inhibit cell growth, inhibit DNA synthesis, and promote cell cycle arrest. Additionally, the vitamin D compounds regulated several proteins that affect tumor growth.

The researchers then studied the effects of calcitriol and QW on the prevention of androgen-dependent prostate cancer in the transgenic adenocarcinoma of mouse prostate (TRAMP) model, which develops prostate cancer as the mice age. Both calcitriol and QW slowed the progression

of prostate cancer in intact TRAMP mice after 14 weeks of treatment as indicated by decreased reproductive tract and prostate weight. In addition, chronic treatment of mice with calcitriol markedly reduced tumor burden, although side effects were seen in some mice.

The effect of calcitriol and QW on hormone refractory prostate cancer was also investigated, using castrated TRAMP mice. Results showed that vitamin D had no effect on disease progression in castrated mice as measured by reproductive tract and prostate weight.

"Our pre-clinical data using the TRAMP mouse model, which mimics human prostate cancer, suggests that calcitriol and QW-1624-F2-2 are promising for prevention of androgen-dependent prostate cancer progression. Further studies are under way in our laboratory to better understand how these agents prevent prostate cancer," said Adebusola Alagbala of Roswell Park Cancer Institute and lead author of the study. The studies, funded by the National Institutes of Health, were conducted in the laboratory of Dr. Barbara A. Foster at Roswell Park Cancer Institute.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Hypothyroidism and the Risk of Colorectal Cancer
Abstract # 2115, Gad Rennert, Carmel Medical Center, Haifa, Israel.
Poster Session B. 5:15 p.m., Tuesday, November 1, 2005.

NSAIDs and Breast Cancer Incidence in the VITAL Cohort: A Preliminary Report
Abstract # 3733, Ann Ready, Fred Hutchinson Cancer Research Center, Seattle, Wash.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

A Peptide that Prevents Breast Cancer is Fully Active after Oral Administration: AFPep
Abstract # 3503, Thomas Andersen, Albany Medical College, N.Y.
Poster Session B. 5:15 p.m., Tuesday, November 1, 2005.

Prevention of Prostate Cancer Progression with Vitamin D Compounds in the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) Model
Abstract # 2315, Adebusola Alagbala, Roswell Park Cancer Institute, Buffalo, N.Y.
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STUDY SHOWS THYROID DRUG REDUCES RISK OF COLECTORAL CANCER

Baltimore, Md. -- Long term use of L-thyroxin, the principal hormone secreted by the thyroid gland, reduces the risk of colorectal cancer by 50 percent, according to a study presented today at the American Association for Cancer Research's 4th annual *Frontiers in Cancer Prevention Research* meeting in Baltimore.

Use of L-thyroxin, which is commonly used to treat hypothyroidism, for five or more years was associated with a significantly reduced risk of colorectal cancer (CRC) across study participants of all genders, ages, origins and religions, but reached statistical significance in Jewish females, participants aged 65 and older, and European-American born participants, which were the largest study sub-populations.

Researchers from the Carmel Medical Center, the B. Rappaport Faculty of Medicine, Technion and Clalit Health Services National Cancer Control Center in Haifa, Israel and the University of Michigan Departments of Medicine and Medical Genetics researched the association of long-term use of L-thyroxin as a surrogate measure of hypothyroidism and colorectal cancer using the Molecular Epidemiology of Colorectal Cancer Study (MECC), a population-based case–control study of patients who received a diagnosis of colorectal cancer in northern Israel between 1998 and 2004 and controls matched according to age, sex, clinic, and ethnic group.

Protection against CRC was seen with the use of L-thyroxin in both the right and left colon as well as the rectum. Use of L-thyroxin remained protective after adjusting for patients' use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), statin use, first-degree family history of CRC, level of sports activity and degree of vegetable consumption.

"We are pleased that our study showed the effective use of L-thyroxin in patients at most risk for colorectal cancer," according to Dr. Gad Rennert, Carmel Medical Center, Technion and Clalit Health Services National Cancer Control Center, and lead author of the study. "While more

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research is needed, we believe that knowledge about the role of L-thyroxin could lead to development of a potential preventive treatment against this deadly disease."

"Studies have shown that right-sided colon cancer is associated with an increased risk of thyroid cancer, and a predisposition to thyroid cancer is a well described feature of Familial Adenomatous Polyposis, a disease that is marked by the formation, especially in the colon and rectum, of numerous benign polyps which typically become cancerous if left untreated," said Dr. Stephen Gruber from the University of Michigan. Hypothyroidism is known to impair colonic motility and transit time, suggesting its relation to colon cancer.

The use of L-Thyroxin was recorded through structured, in-person interviews with participants as was all other medication use, for five years or more. Use of L-thyroxin was verified through computerized prescription records. Researchers based the results on 2,102 matched pairs of participants.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Hypothyroidism and the Risk of Colorectal Cancer
Abstract # 2115 Gad Rennert, Carmel Medical Center, Technion and Clalit Health Services National Cancer Control Center, Israel
Poster Presentation, 5:15 pm, Tuesday, November 1, 2005

LATEST EVIDENCE ABOUT LOWERING RISK

Abstract 2115

Hypothyroidism and the Risk of Colorectal Cancer

Authors: Gad Rennert,1 Ronit Almog,1 Joseph D. Bonner,2 Hedy S. Rennert,1 Mila Pinchev,1 Marcelo Low,1 Stephen B. Gruber.3 Department of Community Medicine and Epidemiology, Carmel Medical Center and B. Rappaport Faculty of Medicine, Technion, and Clalit Health Services National Cancer Control Center,1 Haifa, Israel, Department of Internal Medicine, University of Michigan,2 Ann Arbor, Michigan, Departments of Epidemiology, Internal Medicine, Human Genetics, University of Michigan,3 Ann Arbor, MI.

Background: Increased incidence of thyroid disease has been reported in breast cancer patients. Right-sided colon cancer has been associated with increased risk of thyroid cancer and a predisposition to thyroid cancers is a well described feature of Familial Adenomatous Polyposis. No studies have as yet been reported regarding the association of hypothyroidism with reduced risk of colorectal cancer or a possible role of L-thyroxin in reducing risk of colorectal cancer (CRC). However, laboratory evidence suggests that thyroid hormone (T3) suppresses the beta catenin activation of the cyclin D1 promoter, which is of major importance in the Wnt-signaling pathway in colon cancer formation. In addition, hypothyroidism is known to impair colonic motility and transit time, suggested to be related to the risk of colon cancer. We investigated the association between long-term use of L-thyroxin as a surrogate measure of hypothyroidism and CRC in a population-based case-control study. Methods: The Molecular Epidemiology of Colorectal Cancer Study (MECC) is a study of incident CRC diagnosed in northern Israel between 1998 and 2004, and population-based controls matched for age, gender, clinic, and religion. Use of L-thyroxin was measured by a structured, in-person interview, where all medications used for 5+ years were recorded. Self-reported L-thyroxin use was verified from computerized prescription records of CHS in 95.5% of the participants reporting use. Results: Based on the results of 2,102 matched pairs, use of L-Thyroxin for five years or greater was associated with a significantly reduced risk of CRC (odds ratio, OR 0.49, 95% CI 0.35 – 0.68). This association was evident in all gender, religion, origin and age groups, but reached statistical significance only for Jewish females, for participants older than 65, and for European-American born participants. The protective association was seen in the right and left colon as well as in the rectum. Use of L-Thyroxin remained significantly protective (OR 0.54, 95% CI 0.38 – 0.77) after adjustment for aspirin or NSAID use, statin use, first-degree family history of CRC, sports activity, and vegetable consumption. Conclusions: Long-term L-Thyroxin use, most commonly used for the treatment of hypothyroidism, is associated with a 50% reduction in the risk of colorectal cancer after adjustment for other known risk factors for CRC.

LATEST EVIDENCE ABOUT LOWERING RISK

Abstract 3733

NSAIDs and Breast Cancer Incidence in the VITAL Cohort: A Preliminary Report

Authors: Ann Ready, Emily White. Fred Hutchinson Cancer Research Center, Seattle, WA.

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are being widely investigated as chemopreventive agents in many human cancers, including breast cancer. Several prospective studies have suggested protective effects of aspirin and ibuprofen, including the Women's Health Initiative (Cancer Res 2003;63 6096-101), but reports are inconsistent. At least two large prospective studies found an increased risk of breast cancer associated with 5+ years of regular use of ibuprofen. Evaluation of these medications individually and collectively as chemopreventive agents is needed. Methods: We examined the association between NSAIDs and the incidence of invasive breast cancer in the Vitamins and Lifestyle Study (VITAL), a large prospective cohort recruited from 2000-2002. Women were eligible if they were age 50-76 years and lived in Western Washington State. After exclusions, the cohort included 35,368 women. NSAID usage and other breast cancer risk factors were determined from a detailed self-administered baseline questionnaire. NSAID use was modeled as average days/week of use over the previous 10 years (years of use in past 10 years/10 multiplied by days per week of use). Women were followed prospectively for breast cancer incidence through linkage to the Western Washington SEER cancer registry. As of December, 2003, 363 cases of invasive breast cancer were documented. Breast cancer risk was modeled by the Cox proportional hazard regression with age as the timeline. All hazard ratios (HR) are therefore age-adjusted; no other confounders were found to change the hazard ratios by more than 10%. Results: Baby aspirin use of >= 4 days/week over the past 10 years was associated with a borderline significant 34% decrease risk of breast cancer versus no use of any NSAID (HR = 0.66, 95% CI 0.42, 1.03). However, regular strength aspirin use at this cumulative dose was associated with an increased risk (HR= 1.50, CI 1.06, 2.12). Non-aspirin NSAID use at a cumulative dose of 4+ days/week was not associated with breast cancer (HR= 1.24, CI 0.85, 1.82), nor was ibuprofen use (HR= 1.09, CI 0.66, 1.79). Conclusion: Based on this study and previous studies, breast cancer risk appears to vary depending on NSAID type and/or dose. Continued follow-up of this cohort may help clarify these associations.

LATEST EVIDENCE ABOUT LOWERING RISK

Abstract 3503

A Peptide that Prevents Breast Cancer is Fully Active after Oral Administration: AFPep

Authors: Thomas T. Andersen, Justin Georgekutty, Ikenna Anaka, Rahul Parikh, Neil Gildener-Leapman, Herbert I. Jacobson, James A. Bennett. Albany Medical College, Albany, NY.

Background: We have postulated that alpha-fetoprotein is one of the pregnancy-associated molecules responsible for the reduction in risk of breast cancer for parous women. We have synthesized a cyclic nonapeptide (AFPep) that is an active site mimic of alpha-fetoprotein, and have explored its potential for the prevention or treatment of breast cancer, using animal models. Here we report on the efficacy and safety of AFPep for the prevention or treatment of breast cancer, after subcutaneous or oral administration of the peptide, either alone or in combination with tamoxifen. Methods: For prevention studies, virgin female Sprague-Dawley rats were administered carcinogen (N-nitroso-N-methyl urea) at 50 days of age. AFPep or tamoxifen was administered, via oral gavage or by subcutaneous injection, to groups of animals. Animals were palpated weekly for 100 days, and the number of animals with tumors (incidence), number of tumors per animal (multiplicity), time to tumor generation (latency) and tumor volume were noted as endpoints. For therapy studies, a human breast cancer xenograft model in mice was used, with tumor growth after 30 days being reported as an endpoint. Toxicity studies evaluated body weights and organ weights in mice and rats receiving AFPep. Results: Orally administered AFPep stopped the growth of human tumor xenografts in mice and decreased the incidence and multiplicity of breast cancers in carcinogen-exposed rats, producing effects similar to those obtained for AFPep administered by either *i.p* or *s.c.* routes. AFPep (100 µg) or tamoxifen (0.05 µg) reduced by 23% the number of tumor-bearing rats when compared to MNU-exposed animals, whereas in combination at these same doses, AFPep and tamoxifen yielded a 77% reduction because these agents inhibit growth by different mechanisms. In rodents, no evidence of toxicity was seen for the peptide, even at very high doses. Conclusion: Chronic oral administration of AFPep is safe and effective for the treatment or prevention of breast cancer in animal models.

LATEST EVIDENCE ABOUT LOWERING RISK

Abstract 2315

Prevention of Prostate Cancer Progression with Vitamin D Compounds in the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) Model

Authors: Adebusola A. Alagbala,1 Michael T. Moser,1 Candace S. Johnson,1 Donald L. Trump,1 Gary H. Posner,2 Barbara A. Foster.1 Roswell Park Cancer Institute,1 Buffalo, NY, Johns Hopkins University,2 Baltimore, MD.

The active metabolite of vitamin D3, 1α,25-dihydroxyvitamin D3 (calcitriol), which has potent anti-tumor activities, is being developed for prostate cancer (CaP) prevention and treatment. However, dose-limiting hypercalcemia has limited its therapeutic utility, prompting the development of less calcemic analogs such as QW-1624-F2-2 (QW) and paricalcitol (D2). We hypothesize that vitamin D compounds can be used as chemopreventive agents to slow/prevent CaP. *In vitro,* we examined the molecular response to vitamin D analogs using vitamin D sensitive murine squamous cell carcinoma (SCC) cells. We have demonstrated that calcitriol, QW and D2 inhibit cell growth using MTT assay, inhibit DNA synthesis using BrdU incorporation assay, promote G0/G1 cell cycle arrest using propidium iodide staining and induce apoptosis as measured by annexin V staining. In addition, western blot analysis indicated that vitamin D compounds regulated expression of the following proteins in SCC cells: increased expression of the vitamin D receptor and p27; decreased p21, cdk2, Akt, phospho-Akt, phospho-MEK1/2 and phospho-Erk1/2 levels; and promoted caspase 3 cleavage. These compounds also inhibited p21 and cdk2 mRNA levels in SCC cells. *In vivo,* we tested the effects of calcitriol and QW on prevention of CaP in the transgenic adenocarcinoma of mouse prostate (TRAMP) model. To study prevention of androgen-dependent CaP, 20μg/kg calcitriol, 50μg/kg QW or vehicle was given to 4 week-old hormone-intact TRAMP mice i.p. 3x week for 14 weeks. Calcitriol and QW slowed progression of CaP in intact TRAMP mice as indicated by decreased reproductive tract and prostate weight. Western blot analysis was performed on prostatic tissues from mice treated with vehicle, calcitriol or QW. Calcitriol and QW decreased phospho-Erk1/2 expression and increased p53 and p27 levels. In addition, SV40 T antigen was expressed in all tumor samples, indicating that vitamin D treatment did not interfere with the transgene. To study the effect of long-term vitamin D treatment on CaP progression, 20μg/kg calcitriol or vehicle was chronically administered to 4 week-old hormone-intact TRAMP mice i.p. 3x week for up to 30 weeks. Calcitriol markedly reduced tumor burden over time, although toxicity was observed in some animals. We also examined the effect of calcitriol and QW on androgen-independent CaP. Twelve week-old castrated TRAMP mice were treated with 20μg/kg calcitriol, 50μg/kg QW or vehicle for 12 weeks. Vitamin D treatment had no effect on disease progression in castrated mice as measured by reproductive tract and prostate weight. Prostatic tissues are currently being graded to determine the role of differentiation in the antiproliferative effects of vitamin D in androgen-dependent CaP. Our data indicates that calcitriol and QW inhibit androgen-dependent CaP progression in TRAMP mice and are promising chemopreventive agents for CaP.

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New Strides Being Made in Cancer Chemoprevention

Baltimore, Md. -- There are a number of things people are told to do to prevent cancer – eat well, exercise, don't smoke. However, despite these obvious preventive measures, many individuals will develop the disease.

Researchers have been trying to develop methods to identify why certain individuals are more susceptible to cancer and from these insights, determine the molecular causes of the disease. Based on these results, scientists are now seeking to pinpoint compounds that can reduce the incidence or recurrence of cancer, a field of study known as chemoprevention. Several studies presented today at the American Association for Cancer Research's 4th annual *Frontiers in Cancer Prevention Research* meeting in Baltimore are focusing on new directions in this promising new field.

"We have made great strides in recent years in identifying the risk factors for pre-cancer as well as cancer by studying large groups of individuals who have and do not have cancer," according to David S. Alberts, M.D., Regents' Professor of medicine, pharmacology, nutritional science, and public health at the University of Arizona College of Medicine and director of the Arizona Cancer Center. "Chemoprevention is a promising field that may help us develop new drugs to combat this deadly disease before patients begin suffering from its symptoms."

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Use of Thiazolidinediones and Lung Cancer Survival in Type 2 Diabetes Patients (Abstract 3711)

Patients with type-2 diabetes, treated with a class of drugs called thiazolidinediones (TZDs), had a significantly reduced risk of death from lung cancer compared to non-users, according to a retrospective study of patients from the South Central VA Health Care Network, also known as the Integrated Service Network (VISN 16).

Specifically, the study found that patients with both diabetes and lung cancer, treated with TZDs, had a 33 percent reduced risk of mortality compared to non-users. Patients using TZDs to control diabetes versus patients who were not using any medication to control the disease experienced a 23 percent reduced risk of mortality. Diabetics who used insulin to control their disease were at a 70 percent increased risk of mortality from lung cancer compared to lung cancer patients not using insulin to control diabetes.

TZDs are part of a class of drugs called peroxisome proliferators-activated receptor gamma (PPARγ) ligands. Since PPARγ ligands induce cell death, scientists have theorized that they also may suppress growth of lung-cancer tumors.

The study population comprised 128,571 males who were forty years of age or older with a diagnosis of diabetes mellitus, 3,600 of whom were diagnosed with lung cancer. Data on the diagnosis of lung cancer, use of TZDs, other oral anti-diabetic agents, insulin and other variables were also obtained from the VISN database. Survival analysis methods were used to assess the association between TZD use and lung cancer survival. Hazard ratios were adjusted for confounders, including age, race, body mass index, use of insulin, and other oral anti-diabetic agents.

"We were encouraged that the use of TZDs in diabetic patients was associated with a significant reduction in risk of death from lung cancer," said Luke Ratnasinghe, of the National Center for Toxicological Research, FDA and lead author of the study. Also participating in the study were scientists from Central Arkansas Veterans Healthcare System and the University of Arkansas for Medical Sciences.

"Based on these results, more research is needed to see whether the use of this class of drugs may be beneficial in reducing rates of death in lung cancer patients in the clinic," added Dr. Ratnasinghe.

Potent Protection against Aflatoxin-induced Tumorigenesis through Induction of Nrf2-Regulated Pathways by the Synthetic Triterpenoid, CDDO-Imidazole (Abstract 2497)

A synthetic version of oleanolic acid, found in olive leaf extracts, significantly reduced the growth of liver tumors in laboratory animals, according to researchers from Johns Hopkins University and Dartmouth Medical School.

In their study, the use of small amounts of the artificially produced leaf extract, a triterpenoid analog called CDDO-Im, yielded a greater than 85 percent reduction in the volume of liver tumors. Larger doses produced a 99 percent reduction.

"Even at low-doses, CDDO-Im induces cell protecting genes, inhibits DNA damage by aflatoxin and dramatically blocks development of liver tumors," according to Melinda Yates of Johns Hopkins University and lead author of the study.

As described in their study, laboratory rats were given CDDO-Im three days per week for three weeks, with doses ranging from from 1 to 100 μmol/kg body weight. Beginning one week after the start of CDDO-Im, they were given daily doses over a two-week period of aflatoxin B1, a known cancer-causing agent produced by molds in stored agricultural crops.

Aside from the significant reduction in liver tumor formation, the scientists also confirmed that CDDO-Im activated Nrf2, a gene that acts as a master regulator of the majority of antioxidant pathways and detoxifying enzymes for environmental pollutants.

"The unparalleled potency of CDDO-Im in rats highlights the chemopreventive promise of targeting Nrf2 pathways with triterpenoids, and provides a new direction for drug development," said Dr. Yates.

"The triterpenoid CDDO-Im appears to be at least 100-fold more potent in this model than other drugs targeting Nrf2 that are currently in clinical development."

NSAIDs and COXIBs: The Burden of Proof (Abstract 3480)

The effectiveness of non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs), the related cyclooxygenase-2 selective inhibitors (COXIBs), and aspirin against colorectal cancer has been confirmed and established by an enormous body of data. More than 35 epidemiologic studies have consistently associated routine aspirin or NA-NSAID use with a 40 to 50 percent reduced risk of benign colorectal (CR) tumors, CR cancer and CR cancer-related mortality, regardless of age, gender, family history, nationality, health care setting or study design.

Researchers from the National Cancer Institute (NCI) believe that four strategies have evolved that may allow researchers to build upon the chemopreventive benefits of aspirin and NA-NSAIDs and/or reduce their risk: modify the recommended regimen to separate effectiveness from safety concerns; provide gastrointestinal protection through use of proton pump inhibitors; conduct trials with similar drugs that have greater specificity for anti-cancer effects (e.g., COX-2 inhibitors or NA-NSAID derivatives); and identify combinations of chemopreventive agents that will synergize the effectiveness of aspirin or another NA-NSAID.

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Through recent long-term chemoprevention trials with rofecoxib and celecoxib, researchers discovered a previously unrecognized cardiovascular toxicity, of relatively low frequency but significant magnitude, associated with the drugs. These reports have not only diminished interest in the use of NA-NSAIDs and COXIBs in cancer chemoprevention, but have also caused some researchers to question the notion of chemoprevention more broadly.

"The questions raised by recent developments with the use of COXIBs are similar to those faced by prior researchers studying cancer chemoprevention with tamoxifen or fenasteride," according to Ernest Hawk of the NCI and lead author of the study. "Establishing an acceptable balance between risks and benefits is critical in all areas of medicine, but medical oncology has rarely been dissuaded by an initial suboptimal therapeutic index. The risks posed by NA-NSAIDs and COXIBs should be seen as a stimulus for research to improve the balance of benefits versus risks, rather than a mandate to abandon one of the most consistent and powerful classes of chemopreventive agents known."

Indeed, before making any such decisions, researchers need to evaluate the data on the potential chemopreventive benefits of COXIBs in these studies. If studies show remarkable effectiveness in all or a subset of patients, they may yet prove to be useful despite their shortcomings. If COXIBs are not shown to work, researchers need to continue to study why in light of their substantial preliminary promise.

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Founded in 1907, the American Association for Cancer Research is a professional society of more than 24,000 laboratory, translational, and clinical scientists engaged in all areas of cancer research in the United States and in more than 60 other countries. AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication, and advocacy. Its principal activities include the publication of five major peer-reviewed scientific journals: Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; and Cancer Epidemiology, Biomarkers & Prevention. AACR's Annual Meetings attract nearly 16,000 participants who share new and significant discoveries in the cancer field. Specialty meetings, held throughout the year, focus on the latest developments in all areas of cancer research.

Use of Thiazolidinediones and Lung Cancer Survival in Type 2 Diabetes Patients
Abstract # 3711, Luke Ratnasinghe, University of Arkansas for Medical Sciences, Little Rock.
Poster Session C. 7:30 a.m., Wednesday, November 2, 2005

Potent Protection against Aflatoxin-Induced Tumorigenesis through Induction of Nrf2-Regulated Pathways by the Synthetic Triterpenoid, CDDO-Imidazole
Abstract # 2497, Melinda Yates and Thomas Kensler, John Hopkins University, Baltimore, Md.
Poster Session A. 5:30 p.m., Monday, October 31, 2005.

NSAIDs and COXIBs: The Burden of Proof
Abstract # 3480, Ernest Hawk, National Cancer Institute, Bethesda, Md.
Oral Presentation, 2:00 p.m., Monday, October 31, 2005.

CHEMOPREVENTION

Abstract 2497

Potent Protection against Aflatoxin-Induced Tumorigenesis through Induction of Nrf2-Regulated Pathways by the Synthetic Triterpenoid, CDDO-Imidazole

Authors: Melinda S. Yates,1 Mi-Kyoung Kwak,1 Patricia A. Egner,1 John D. Groopman,1 Karen J. Baumgartner,2 B. D. Roebuck,2 Mark M. Yore,2 Tadashi Honda,3 Gordon W. Gribble,3 Michael B. Sporn,2 Thomas W. Kensler.1 Johns Hopkins University,1 Baltimore, Maryland, Dartmouth Medical School,2 Hanover, New Hampshire, Dartmouth College,3 Hanover, New Hampshire.

Synthetic triterpenoid analogues of oleanolic acid are potent inducers of the phase 2 response as well as inhibitors of inflammation. We show that the synthetic triterpenoid, 1-[2-cyano-3-,12-dioxooleana-1,9(11)
-dien-28-oyl]imidazole (CDDO-Im), is a highly potent chemopreventive agent that inhibits aflatoxin-induced tumorigenesis in rat liver. The chemopreventive potency of CDDO-Im was evaluated by measuring inhibition of formation of putative pre-neoplastic lesions (glutathione S-transferase Pi-positive foci) in the liver of rats exposed to aflatoxin B1. Rats were gavaged with CDDO-Im 3 days/week for three weeks with doses ranging from 1 to 100 μmol/kg body weight. Beginning one week after the start of CDDO-Im, rats were gavaged daily with aflatoxin B1 five days/week for two successive weeks. CDDO-Im produces a greater than 85% reduction in the hepatic focal burden (volume percent) of pre-neoplastic lesions at 1 μmol/kg body weight and a greater than 99% reduction at 100 μmol/kg body weight. Protection against aflatoxin-DNA adduct formation is important for inhibition of aflatoxin-induced pre-neoplastic lesions. Rats were given a single dose of CDDO-Im, dosed with aflatoxin B1 48 hours later, and sacrificed 2 hours after aflatoxin treatment. Hepatic levels of aflatoxin-N7-guanine adducts were measured by liquid chromatography-mass spectrometry. CDDO-Im treatment reduces levels of aflatoxin-DNA adducts by approximately 40 to 90% over the range of 1 to 100 μmol/kg body weight. Additionally, changes in mRNA levels of genes involved in aflatoxin metabolism were measured in rat liver following a single dose of CDDO-Im. GSTa2 (3.1-fold), GSTa5 (2.0-fold), AFAR (13.3-fold), and EPHX1 (3.6-fold) are induced 6 hours following a 1 μmol/kg body weight dose of CDDO-Im, while no effect on CYP2c11 expression was seen. The effect of Nrf2 genotype on expression of phase 2 and antioxidant genes in mouse liver was also measured following treatment with CDDO-Im. Wild-type and Nrf2 knockout mice were gavaged with 150 μmol/kg body weight. Microarray analysis confirms that many phase 2 and antioxidant genes are induced in an Nrf2-dependent manner. Thus, low micromole doses of CDDO-Im induce cytoprotective genes, inhibit DNA adduct formation and dramatically block hepatic tumorigenesis. As a point of reference, the potency of oltipraz, an established modulator of aflatoxin metabolism in humans, is 100-fold weaker than that of CDDO-Im in this rat antitumorigenesis model. The unparalleled potency of CDDO-Im *in vivo* highlights the chemopreventive promise of targeting Nrf2 pathways with triterpenoids. Supported by NIH grants T32 GM08763, CA39416, CA94076, CA78814 and Reata Pharmaceuticals.

CHEMOPREVENTION

Abstract 3711

Use of Thiazolidinediones and Lung Cancer Survival in Type 2 Diabetes Patients

Authors: Luke Ratnasinghe, Rang Govindarajan, Debra Simmons, Nicholas Lang. University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Thiazolidinediones (TZDs) are used to treat diabetes mellitus and are Peroxisome Proliferator-Activated Receptor gamma (PPARγ) ligands. PPAR γ ligands induce cell cycle arrest and are postulated to have tumor suppressor activity in lung cancer. To assess the association between TZDs use and lung cancer mortality, we conducted a retrospective study of diabetes mellitus patients (N=128,571) in ten Veteran Affairs medical centers. Methods: The study population consisted of male patients forty years and older with a diagnosis of diabetes mellitus in the ten VA medical centers comprising VISN-16. Data on the diagnosis of lung cancer, use of TZDs, other oral antidiabetic agents, insulin and other co-variates were also obtained from the VISN 16 database. Survival analysis methods were used to assess the association between TZDs use and lung cancer survival. Hazard Ratios (HR) were adjusted for confounders including age, race, body mass index, use of insulin and other oral antidiabetic agents. Results: Among the type 2 diabetes patients in this study 3600 individuals had lung cancer. In the lung cancer patient group we observed a 33% reduction in hazard ratio of death among TZDs users compared to non-users after adjusting for confounders (HR: 0.67; 95% CI: 0.57- 0.80). When the analyses were conducted with the group using no medications to control diabetes as the reference group, users of TZDs were at 23% reduced risk of mortality (HR: 0.77; 95% CI: 0.60- 0.99) and users of insulin were at 70% increased risk of mortality (HR: 1.70; 95% CI: 1.45 - 1.99) from lung cancer. Conclusions: In diabetes patients, TZDs use was associated with a significant reduction in risk of death from lung cancer.

CHEMOPREVENTION

Abstract 3480

NSAIDs and COXIBs: The Burden of Proof

Authors: Ernest Hawk,1 Jaye Viner.2 NCI/OCTR,1 Bethesda, MD, NCI-DCP,2 Bethesda, MD.

An enormous body of data confirms the efficacy of aspirin and non-aspirin nonsteroidal antiinflammatories (NA-NSAIDs) against colorectal neoplasia across a spectrum of progression (e.g., ACF, adenomas, cancer, and cancer-associated mortality). Although incompletely understood, the best-described chemopreventive activity of NSAIDs relates to the inhibition of one or both cyclooxygenase enzymes (i.e., COX-1 and COX-2), although other mechanisms (e.g., stimulation of peroxisome proliferator-activated receptors or inhibition of Akt phosphorylation) have been proposed as well. COX-2, in particular, is commonly over-expressed in human pre-cancers and cancers and a number of studies have correlated its over-expression with poorer survival among cancer patients. Inhibition of one or both COX enzymes with aspirin or NA-NSAIDs has been reported to result in reductions in cellular proliferation and neo-angiogenesis, as well as promotion of apoptosis and immunologic surveillance.

More than 35 epidemiologic studies over the last two decades consistently associate routine aspirin or NA-NSAID use with a 40-50% reduced risk of colorectal adenomas, cancer, and cancer-related mortality, regardless of patient age, gender, family history, nationality, healthcare setting, or study design. More than 15 case series have reported reductions in the adenoma burden of patients with familial adenomatous polyposis (FAP) exposed to sulindac or other NA-NSAIDs for as little as a few months; in some cases, effects were sustained for years. Recently, a re-analysis from the Nurses' Health Study (NHS), which has been collecting survey data on aspirin use and disease outcomes since 1980, showed that women who took 2 or more standard aspirin tablets weekly were 25% less likely to develop adenomas, as compared to those who took it less often; and those at the highest dose level had the lowest risk of adenoma development. Two other trials involving pre-phenotypic FAP patients – one evaluating sulindac and the other evaluating aspirin with or without resistant starch – showed null results with regard to adenoma development.

Three randomized, placebo-controlled trials of aspirin in patients with prior colorectal neoplasia have reported significant preventive effects against colorectal adenomas. Two of these trials demonstrated significant effects in patients taking ASA 300-325 mg/day, and data from the third study showed a significant 19% reduction at the 81 mg/day dose level. Despite these positive findings, safety concerns related to long-term aspirin or NA-NSAID use have tempered enthusiasm for their routine use in colorectal neoplasia prevention.

In an effort to build upon the chemopreventive benefits of these agents and/or reduce their risks, at least four strategies have evolved: 1) modifying the recommended regimen to separate efficacy from safety concerns, 2) providing concomitant GI protection via proton pump inhibitors, 3) applying similar agents with greater specificity for anti-cancer effects (e.g., COX-2 inhibitors or NA-NSAID derivatives), and 4) identifying combinations based on aspirin or one of the NA-NSAIDs. The investigation of COX-2 selective inhibitors (COXIBs) for cancer chemoprevention seemed particularly promising because of their profound efficacy in several different animal models of cancer, and because of their apparent improved therapeutic index - primarily due to a reduced frequency of gastrointestinal ulceration. The first placebo-controlled trial of celecoxib demonstrated significant reductions in the burden of colorectal adenomas after 6 months of exposure. Ancillary translational studies demonstrated cellular and molecular activities of the drug that supported their efficacy in these patients. Thus, COXIBs seemed poised to offer an important new option for patients at increased risk for colorectal cancer; therefore several large, definitive, placebo-controlled trials were initiated.

In late 2004, the situation changed with the APPROVe trial's report of cardiovascular toxicity associated with long-term administration of rofecoxib. A few months later, one of two trials investigating celecoxib (the APC Trial) in adenoma prevention reported a 2-3 fold increased risk of cardiovascular toxicity as well. Observational data suggest that the CV risks of COXIBs may extend to other NA-NSAIDs as well, resulting in recent labeling changes for the class of agents. Thus, evidence of a previously unrecognized cardiovascular toxicity – of relatively low frequency but significant magnitude – has dampened enthusiasm for the use of NA-NSAIDs/COXIBs in cancer chemoprevention and caused some to question the notion of chemoprevention more broadly. Surprisingly, these queries have come despite the fact that efficacy results from the COXIB trials have not yet been reported.

But, cancer chemoprevention has faced these questions before. Data with tamoxifen, finasteride, and beta-carotene were never as uni-directionally beneficial as one would have hoped. Nevertheless, medical oncology has rarely been dissuaded by a suboptimal therapeutic index. The cv risks posed by NA-NSAIDs/COXIBs can just as reasonably be seen as a stimulus for iterative research to improve the balance between benefits and risks, or a call to refine our developmental strategy, rather than a mandate to abandon one of the most consistent and powerful classes of chemopreventive agents known.

In the near-term, the question of what to do with COXIBs in cancer chemoprevention depends wholly on the efficacy side of the equation. If they are remarkably effective, or highly effective in a subset of patients, they may yet prove useful despite their shortcomings. If their efficacy is more limited, we will be challenged to understand why that was the case, given their preliminary promise.

Avenues for further investigation of aspirin, NA-NSAIDs, and COXIBs in cancer prevention are many. Can concomitant proton pump inhibitors tilt the risk:benefit and cost-effectiveness scales of aspirin to favor its use in those at risk for colorectal cancer? Can combinations of NSAIDs with other chemopreventive agents improve their therapeutic index to an acceptable degree? Can we identify the specific patient subsets most likely to benefit - or those most likely to be harmed – prior to drug exposure so we can target our interventions more effectively? Should we be asking more complex questions of chemopreventive agents, which in turn, require more sophisticated models of health risks and potential benefits that transcend current disease categorizations? All of these paths are important, but each must bear the burden of proof before they merit our faith.

American Association for Cancer Research

Frontiers in Cancer Prevention Research
October 30 - November 2, 2005, Baltimore, MD

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Focus on Lung Cancer: How to Prevent and Treat It

Baltimore, Md. -- Since smoking became popular in America in the 1930s, lung cancer rates have continued to climb. Today, it is still the leading cause of cancer-related deaths, with totals more than the other five leading cancers combined.

Armed with these sobering statistics, scientists have launched several innovative projects to find therapies that will effectively treat, and hopefully reduce the overall incidence of lung cancer. Several are being presented today during the American Association for Cancer Research's 4th annual *Frontiers in Cancer Prevention Research* meeting in Baltimore.

"We have begun to develop innovative strategies to target lung cancer with targeted medicines and new vaccines, but we have a long way to go," said William G. Nelson, V, M.D., Ph.D., of Johns Hopkins University and Program Chair of the meeting. "We hope that increased attention to research and treatment options will improve the outlook for the increasingly large patient population."

Nicotine Vaccine: A Promising Treatment for Nicotine Addiction (Abstract 2565)

To combat cigarette smoking, researchers are seeking ways to combat the habit which affects more than 45 million Americans. One new option is a vaccine that targets the nicotine rather than the brain's reaction to it. Researchers from the University of Minnesota, supported by the

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National Institute of Drug Abuse and Nabi Biopharmaceuticals, have tested this new vaccine in humans with positive tolerability and efficacy.

"We are encouraged by the results of this study, which suggest that a nicotine vaccine may be a safe and potentially effective way to reduce tobacco dependence or as a relapse prevention aid," said Dorothy Hatsukami, of the University of Minnesota and lead author of the study.

The nicotine vaccine in question stimulates the immune system to develop antibodies that specifically attach to the nicotine molecules. The resulting antibody-nicotine combination is too large to pass through the blood to the brain, resulting in less nicotine in the brain.

Animal studies have confirmed that the vaccine works by reducing and also slowing the amount of nicotine that enters the brain, reducing nicotine's addictive effect.

Preliminary human studies have been conducted to determine the safety of the nicotine vaccine, as well as the best dosage and optimal dosing schedules. A multi-site clinical trial randomly assigned 68 smokers to receive different doses of vaccine, or placebo, and followed them over 38 weeks. The vaccine was well tolerated among the subjects. Aches and tenderness at injection sites were reported; systemic reactions included headaches, malaise or myalgia or muscle pain, although these latter reactions were similar between the vaccine and placebo. Most symptoms were mild and self-limited, resolving within a few days, and none required medical intervention.

There was no evidence of withdrawal after vaccine injection or evidence that smokers increased smoking intensity to compensate for the reduced nicotine in the brain. Preliminary analysis shows that the highest dose of vaccine in participant smokers, who had not necessarily been interested in quitting, showed significantly higher rates of 30-day abstinence than placebo.

"Two additional human clinical trials with other nicotine vaccines have been conducted which showed similar safety profiles and higher abstinence rates in the highest nicotine vaccine dose or antibody level groups, and we hope to conduct further trials to confirm these results," said Hatsukami.

Chemoprevention of Lung Cancer: What's Next? (Abstract 3474)

Doctors are working diligently to make progress in preventing lung cancer, the deadliest cancer in America today. To do so, researchers are trying to better understand the biology of lung tumor development and design tactics using effective clinical models to interrupt the process without undue side effects. Efficacy and minimal toxicity are critical features of a successful treatment strategy. Doctors are working to identify populations who are at high-risk for the disease outside of tobacco exposure so that prevention strategies can focus on those who are most likely to benefit from them.

Using the documented role of inflammation in cancer development, doctors have identified key enzymes involved in the metabolism of arachidonic acid (AA) as potential targets for the prevention of a variety of epithelial cancers (in cells that line organs). AA, which is involved in inflammatory and other processes that regulate organ function, is generated from lipids and is metabolized by cyclooxygenases (COX-1 and COX-2 enzymes that control the production of prostaglandins and are blocked by aspirin) and lipoxygenases (LOX enzymes involved in diseases like cancer, inflammation, and asthma).

Animal tumor studies have suggested that inhibiting AA interrupts the growth of lung tumors, and have found that glucocorticoids (steroid hormones produced by the adrenal gland) are particularly effective in inhibiting cancer formation in mice. A recent phase IIb study of inhaled budesonide, a corticosteroid, did not show any efficacy in regressing or preventing precursor lesions for squamous cell cancer, but the treatment did reduce peripheral lung nodules, which may be precursors to lung adenocarcinomas. With regard to testing and review mechanisms, the recent availability of improved spiral CT images may now allow for clinical trials that specifically address cancer prevention in the peripheral lung compartment.

Agents that are currently being studied include inhibitors of AA metabolism such as non-steroidal anti-inflammatory agents and the leukotriene inhibitor and anti-asthma drug zileuton. With the promise of COX and LOX inhibitors, researchers are developing dual function COX-LOX inhibitor products to offer an alternative to combination therapies. In addition, PPARg ligands (peroxisome proliferator-activated receptor gamma), which include anti-diabetic drugs, have shown tumor inhibition in a variety of lung cells. Newer molecularly targeted drugs, which are potent anti-cancer drugs in mice, are struggling in lung cancer prevention trials due to concerns with drug-associated side effects.

However, as targeted agents with fewer side effects and preventive efficacy enter clinical trials, researchers will soon be able to evaluate “prevention-relevant” variables during early drug development to evaluate effects on precancerous lesions, providing valuable information for subsequent prevention trials. Such data may help to determine if promising agents that may have some side effects should be investigated further for cancer prevention in people at particularly high risk for lung cancer development.

“A better understanding of the mechanisms leading to the development of lung cancer is crucial to developing targeted therapies for prevention of the disease,” said Eva Szabo, of the National Cancer Institute. “The combination of new clinical trial formats and new chemopreventive treatment options will help provide the answers necessary to reduce the incidence of this devastating disease.”

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Nicotine Vaccine: A Promising Treatment for Nicotine Addiction
Abstract # 2565, Dorothy Hatsukami, University of Minnesota, Minneapolis.
Oral Presentation. 10:30 a.m., Wednesday, November 2, 2005.

Chemoprevention of Lung Cancer: What's Next?
Abstract # 3474, Eva Szabo, National Cancer Institute, Bethesda, Md.
Oral Presentation. 7:00 a.m., Tuesday, November 1, 2005.

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Alternative Tobacco Products: A Better, Safer Option for Smokers?

Baltimore, Md. – According to the U.S. Centers for Disease Control and Prevention, nearly one-fourth of Americans are smokers. That's more than 60 million people who are at increased for lung cancer, the leading cause of cancer-related deaths nationwide.

Despite the risks, many people have trouble kicking this addictive habit. As a result, health officials and doctors are trying to find less harmful alternatives to cigarette smoking. But some products, like smokeless tobacco, may not be effective replacements, according to research presented today during the American Association for Cancer Research's 4th annual *Frontiers in Cancer Prevention Research* meeting in Baltimore.

"While new products are being developed and marketed as less harmful alternatives to cigarettes, they should be evaluated for efficacy in reducing smoking use, as well as actual reduced incidence of related diseases," said William G. Nelson, V, M.D., Ph.D., of Johns Hopkins University and Program Chair of the meeting. "With such a large population at risk for serious health consequences, we need to move quickly on strategies to thwart this dangerous habit."

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Carcinogen Exposure across Oral Tobacco and Medicinal Nicotine Products (Abstract 3477)

Smokeless oral tobacco products including lozenges and moist snuff may be safer than cigarette smoking, but neither represents a good alternative for those wishing to quit smoking, according to studies conducted by scientists at the University of Minnesota.

Instead, the best aid appears to be medicinal nicotine products such as the patch.

“Collectively, these results indicate that most smokeless tobacco products are not necessarily a safe alternative to smoking and are inferior to medicinal nicotine products with respect to carcinogen exposure,” said Stephen Hecht, Ph.D., of the University of Minnesota Cancer Center and lead author of the study.

“Smokeless tobacco products should not be considered an acceptable substitute for cigarette smoking, especially when relatively harmless medicinal nicotine products are available.”

In their study, the Minnesota researchers evaluated carcinogen levels in smokeless tobacco and medicinal nicotine products as well as carcinogen biomarker levels present in the users. The study compared the carcinogen levels of several types of oral tobacco products made in the U.S, which have carcinogen levels at least 100 times that of other consumer products designed for oral use. The lowest levels were found in hard snuff lozenges and only trace amounts were found in medicinal nicotine products. The most prevalent strong carcinogens in smokeless tobacco products are the tobacco-specific nitrosamines (cancer causing chemical agents), of which the strongest carcinogens are in N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

In a separate study, 54 users of popular U.S. smokeless tobacco brands used their usual brand for two weeks and were then randomized to use either Swedish snus (a type of snuff) or a nicotine patch for four weeks. Levels of the strongest carcinogens were measured in the urine at baseline, then two weeks and four weeks after switching to snus or patch. Carcinogen levels were significantly lower in those who previously used smokeless tobacco after the switch to snus or patch. Importantly, among subjects who used the nicotine patch, carcinogen levels were significantly lower than in those who used snus, suggesting that medicinal nicotine is a safer alternative than snus.

The new results conflict with some prior research that suggested that smokeless tobacco, including moist snuff, may be a less harmful alternative to cigarette smoking because many of the carcinogens in cigarette smoke are either reduced or not present in smokeless tobacco.

Smokeless Tobacco as a Substitute for Cigarettes: An Appraisal of the Evidence. (Abstract 2684)

One of the most popular forms of smokeless tobacco (ST) in the U.S. and parts of Europe is moist snuff, which is used by placing the product in the mouth. Because there are fewer side effects and risks associated with its use than with standard cigarette smoking, use of snuff has been proposed as a safer alternative for smokers unable or unwilling to quit using tobacco.

The "Swedish experience" is used as evidence that ST is effective in smoking cessation and harm reduction because there is a reduced use of cigarettes and increased consumption of moist snuff, while the incidence of tobacco-related cancers has decreased. But the correlation appears to be largely related to other factors.

In a study from the University of Florida, researchers conclude that use of smokeless tobacco in Sweden was not associated with smoking cessation. In fact, it's possible that smokeless tobacco may actually encourage some teens to take up smoking.

What's more, recent cohort studies suggest that U.S. males are more likely to switch from smokeless tobacco to cigarettes than the reverse. Use of both smokeless tobacco and cigarettes is a more common pattern in the U.S. than switching from cigarettes to smokeless tobacco.

"Based on this evidence, we feel that the use of smokeless tobacco is rarely a successful strategy for smoking cessation in the U.S., and may actually be a risk factor for starting to smoke," said Scott Tomar, of the University of Florida, and lead author of the study.

"There is insufficient evidence that using smokeless tobacco is effective, feasible or acceptable as a smoking cessation strategy in most populations," he added.

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Carcinogen Exposure across Oral Tobacco and Medicinal Nicotine Products
Abstract # 3477, Stephen Hecht, University of Minnesota Cancer Center, Minneapolis.
Oral Presentation. 10:30 a.m., Wednesday, November 2, 2005.

Smokeless Tobacco as a Substitute for Cigarettes: An Appraisal of the Evidence
Abstract # 2684, Tomar Scott, University of Florida, Gainsville.
Oral Presentation. 10:30 a.m., Wednesday, November 2, 2005.

TOBACO AND NICOTINE

Abstract 3477

Carcinogen Exposure across Oral Tobacco and Medicinal Nicotine Products

Authors: Stephen S. Hecht,1 Irina Stepanov,1 Irene Baumgart,2 Joni Jensen,2 Dorothy Hatsukami.2 Univ. of Minnesota Cancer Ctr.,1 Minneapolis, MN, Univ. of Minnesota Transdisciplinary Tobacco Use Research Ctr.,2 Minneapolis.

Oral tobacco products such as "smokeless tobacco" or "spit tobacco" have been suggested as less harmful alternatives to cigarette smoking because many of the harmful and carcinogenic combustion products which are present in cigarette smoke are either lacking or greatly reduced in smokeless tobacco. Medicinal nicotine products have found widespread acceptance and are effective in smoking cessation strategies. In this study, we evaluated carcinogen levels in some smokeless tobacco and medicinal nicotine products, and also investigated carcinogen biomarker levels in individuals who used these products. The most prevalent strong carcinogens in smokeless tobacco products are the tobacco-specific nitrosamines. The commonly measured tobacco-specific nitrosamines are N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanatabine (NAT), and N'-nitrosoanabasine (NAB). Among these, NNN and NNK are the strongest carcinogens, and are ranked by the International Agency for Research on Cancer (IARC) in Group 1, carcinogenic to humans. We compared levels of tobacco-specific nitrosamines in several types of oral tobacco products. Total tobacco-specific nitrosamines ranged from 1.3-9.2 µg/g tobacco in popular oral snuff products made in the U.S. The corresponding levels were 2.0-3.7 µg/g in Swedish snus. The lowest levels of total tobacco-specific nitrosamines in oral tobacco products- 0.19-0.28 µg/g, were found in hard snuff lozenges. Only trace amounts of these compounds were found in medicinal nicotine products. The amounts of these nitrosamines in popular oral snuff products are at least 100 times higher than those of nitrosamines in other consumer products designed for oral use. In a second study, 54 users of popular U.S. smokeless tobacco brands used their usual brand for 2 weeks and were then randomized to use either Swedish snus or nicotine patch for 4 weeks. Levels of the NNK metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (total NNAL) were measured in urine at baseline, then 2 weeks and 4 weeks after switching to snus or nicotine patch. Total NNAL levels were statistically significantly lower in users of smokeless tobacco after the switch to snus or to nicotine patch than they were before the switch, although the overall mean total NNAL level among subjects who used the nicotine patch was significantly lower than among those who used snus, indicating that medicinal nicotine is a safer alternative than snus. Collectively, these results indicate that most smokeless tobacco products are not a safe alternative to smoking and are inferior to medicinal nicotine products with respect to carcinogen exposure. The contamination of smokeless tobacco products with carcinogenic nitrosamines has been known for 30 years, and there has been relatively little change in their levels in most products marketed in the U.S. There is concordance between cancers attributed to smokeless tobacco products by IARC and target tissues for carcinogenesis of NNK and NNN in rats. Recent epidemiologic data reported by the American Cancer Society also indicate that smokeless tobacco products are a risk factor for coronary heart disease and stroke (S.J. Henley et al, Cancer Causes and Control 16: 347 (2005). In summary, smokeless tobacco products are not an acceptable substitute for cigarette smoking, when relatively harmless medicinal nicotine products are available.

TOBACO AND NICOTINE

Abstract 2684

Smokeless Tobacco as a Substitute for Cigarettes: An Appraisal of the Evidence

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Smokeless tobacco (ST) includes an array of tobacco products that are not burned at the time of use and usually are used by placing the product in the oral cavity. Moist snuff is the most popular form of ST in the USA and parts of Europe. Because moist snuff use conveys lower risks for morbidity or mortality than does cigarette smoking, its use has been proposed as a harm reduction strategy for smokers unable or unwilling to quit using tobacco. Moist snuff manufacturers are aggressively seeking to promote their products as safer alternatives to cigarettes and are seeking policy changes in the US and the European Union to allow expanded marketing and explicit health claims. ST manufacturers and some researchers point to the "Swedish experience" as evidence that ST is effective in smoking cessation and harm reduction; i.e. Sweden has experienced a decline in cigarette consumption and an increase in moist snuff consumption during the past two decades and has lower incidence rates than other Western industrialized countries for many major tobacco-related cancers. However, encouraging smokers to switch to moist snuff may have unintended public health consequences such as delayed smoking cessation, ubiquitous ST advertising reaches young people in addition to inveterate smokers, communicating the risks associated with various tobacco products may be a major challenge, and factors other than moist snuff likely contributed to Sweden's tobacco and disease patterns. This presentation critically reviews new and published epidemiologic evidence from USA and other countries for ST use as a method for quitting smoking. There are no published randomized clinical trials testing the efficacy of ST for smoking cessation. Recent cross-sectional and prospective cohort studies suggest that US adolescent and adult males are more likely to switch from ST to cigarettes than to switch from cigarettes to ST. Dual use of ST and cigarettes is a more common pattern than is complete switching to ST in the USA. Perceived harm of using cigarettes or ST among US high school students suggests young smokers substantially underestimate their risks, so messages regarding relative risks of ST and cigarettes may have little effect in reducing teen smoking. Swedish cohort studies found that daily smokers who used moist snuff were no more likely than non-snuff users to quit smoking, although they were more likely to become non-daily smokers. Birth cohort analysis using Swedish survey data suggests that most of the growth in ST use in Sweden during the past decade has been among males aged 16–24 years in 1989, the birth cohort that also had the lowest decline in prevalence of daily smoking during the 1990s; the greatest decline in daily smoking occurred among birth cohorts that also showed a decline in ST use. Although daily smoking has declined among adolescents and young adults in Sweden, occasional smoking remains prevalent, suggesting ST may serve largely as a complementary source of nicotine dosing. Recent Swedish survey data suggest ST is frequently used by adult males as a smoking cessation strategy, although the net effectiveness appears to be limited. Recent patterns in Norway suggest that snuff use is growing in popularity, but does not seem to be associated with a reduction in cigarette smoking. In summary, the available evidence suggests that ST use plays a very minor role in smoking cessation in the USA and more likely is a risk factor for smoking initiation. In Sweden, available evidence suggests moist snuff has played a small role in smoking cessation and a very minor role in preventing smoking initiation. The available evidence on the effectiveness of moist snuff use as a smoking cessation method is limited and warrants an evidence-based grade of recommendation of "C". The feasibility and acceptability of this smoking cessation strategy in most populations remains unknown.

TOBACO AND NICOTINE

Abstract 2565

Nicotine Vaccine: A Promising Treatment for Nicotine Addiction

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Nicotine immunization is a novel treatment that targets the drug rather than the brain. The nicotine vaccine stimulates the immune system to develop antibodies that binds with the nicotine molecule. The complex that is formed when the antibody attaches to nicotine is too large to pass through the blood brain barrier. Study results have shown that nicotine vaccines do indeed reduce the distribution of nicotine to the brain in rats, in clinically relevant acute and chronic nicotine doses. Animal studies have also shown a slowing of nicotine distribution to the brain and a slowing of nicotine elimination. These effects lead to less reinforcement from smoking. Several animal studies support this reduced reinforcement effect.

Vaccination of rats against nicotine (or passive immunization with nicotine-specific IgG to simulate vaccination) results in reduced: a) nicotine discrimination, b) the development of nicotine dependence, c) the reversal of nicotine abstinence signs by nicotine, d) the reinstatement of nicotine responding, and e) acquisition of nicotine self-administration. Data also suggests that vaccination after acquisition of nicotine self-administration reduces nicotine self-administration in rats without significant compensation. These data provide support for the hypothesis that immunization can impact nicotine drug effects, including those responsible for maintaining nicotine addiction.

In the past several years, preliminary human studies have been conducted to determine the safety of the nicotine vaccine, the dose of nicotine vaccine leading to sufficient antibody titers, and the scheduling of doses that leads to the greatest boost in antibody titers. We have recently completed a multisite clinical trial (N=68, 3 sites) which involved randomly assigning smokers who were not necessarily interested in quitting to receive either 50, 100, or 200 µg of vaccine or alum placebo on days 0, 28, 56, and 182. Subjects were followed over the course of 38 weeks. The results showed that the vaccine was well tolerated. The most frequent injection site reactions were transient ache or tenderness. Injection site reactions did not differ between the treatment groups. Almost all of the patients reported at least one systemic reaction, of which headache, malaise or myalgia was most frequently reported. These event rates were also similar between the treatment groups. Both local and systemic reactions did not increase after subsequent injections. Most events were mild and self-limited, resolving within a few days. None required medical intervention. Vaccine immunogenicity was dose-related ($p < 0.001$), with the highest dose eliciting antibody concentrations within the anticipated range of efficacy. Antibody levels were low after the first dose, but increased after subsequent doses. Levels were maximal at 8-16 weeks and thereafter declined when no further injections were given. There was no evidence of compensatory smoking or precipitation of nicotine withdrawal with the nicotine vaccine. The rate of 30 day abstinence was significantly different across the four doses, with the 200 µg showing the highest rate of abstinence. Two additional human Phase I-II clinical trials have been conducted which showed similar safety profiles and higher abstinence rates in the highest nicotine vaccine dose or antibody level groups. In summary, the nicotine vaccine appears to be a promising medication for tobacco dependence, as a complement to other treatments or as a relapse prevention aid.

TOBACO AND NICOTINE

Abstract 3474

Chemoprevention of Lung Cancer: What's Next?

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Progress in lung cancer prevention is predicated on understanding the biology of lung carcinogenesis, identifying strategies that interrupt this process without undue side effects, and developing clinical trials models that efficiently test these promising strategies and correctly identify the ones that truly work. Maintaining the balance between efficacy and toxicity of interventions is critical to long-term successful application of chemoprevention to high-risk populations. Therefore, identifying the population at the highest risk for subsequent cancer, above and beyond tobacco exposure, remains a priority so that prevention strategies can appropriately focus on those who are most likely to benefit from them. Equally important is the development of phase II preliminary efficacy clinical trials models that are truly predictive of cancer prevention efficacy.

An expanding understanding of the contribution of inflammation to cancer development has identified key enzymes involved in the metabolism of arachidonic acid (AA) as potential targets for the prevention of a variety of epithelial cancers. AA is generated from phospholipids by the phospholipase A2 (PLA2) enzyme family and is ultimately metabolized by cyclooxygenases (the constitutive COX-1 and inducible COX-2 enzymes) and lipoxygenases (various LOX enzymes) to form a variety of bioactive metabolites involved in inflammatory and other homeostatic processes. Animal carcinogenesis studies provide strong evidence that inhibitors of AA metabolism interrupt lung adenocarcinogenesis. Both systemic and inhaled glucocorticoids, which inhibit PLA2, are particularly effective in inhibiting adenoma and adenocarcinoma formation in carcinogen treated mice. However, a recent phase IIb study of inhaled budesonide did not show any efficacy in regressing or preventing bronchial dysplastic lesions, which are precursors to squamous cell carcinoma. Budesonide treatment did, however, result in a small but significant decrease in peripheral nodules identified by spiral CT, raising the possibility of efficacy in adenocarcinoma prevention analogous to that seen in animal models. The availability of spiral CT to examine the peripheral lung (the site of adenocarcinoma development) may allow, for the first time, the design of clinical trials to specifically address cancer prevention in the peripheral lung compartment.

Other agents that are currently being studied include downstream inhibitors of AA metabolism such as the non-steroidal anti-inflammatory agents and the 5-lipoxygenase inhibitor zileuton. Since inhibition of both COX and LOX pathways appears to be promising, new dual function COX-LOX inhibitors offer an intriguing alternative to combination treatment. Ligands of the peroxisome proliferator-activated receptor gamma (PPARg), which include the anti-diabetic thiazolidinedione drugs, induce maturation in lung cancer cell lines and inhibit tumorigenesis in a variety of epithelial cell types. These agents are currently being tested and show promise in the treatment of oral cancer premalignant lesions. The need to maintain the balance between drug-associated side effects and risk of disease has prevented many of the newer molecularly targeted agents such as farnesyltransferase inhibitors and EGFR inhibitors (both of which are also potent inhibitors of tumorigenesis after carcinogen exposure in mice) from entering clinical trials for lung cancer prevention to date.

As targeted agents with more favorable toxicity profiles and potential cancer treatment as well as preventive efficacy are entering clinical trials, an opportunity to assess “prevention-relevant” endpoints early during overall drug developing is arising. This can be achieved by introducing pre- and post-treatment bronchoscopies with targeted biopsies to assess effects on intraepithelial neoplasia into lung cancer treatment clinical trials. This could occur within the context of advanced cancer treatment trials or adjuvant treatment trials and would provide valuable information for subsequent cancer incidence prevention trials. Such a clinical trials model could

provide the necessary data to determine if promising, but somewhat toxic agents such as EGFR inhibitors should be investigated further for true prevention purposes.

A better understanding of the mechanisms of lung carcinogenesis is crucial to the development of targeted therapies for prevention of lung cancer. Equally important is the development of novel clinical trial designs to appropriately test new agents in a timely fashion. Recent progress in both of these areas provides hope for progress in prevention of lung cancer.