

DEFEAT Cancer

EXERCISE & NUTRITION during/after CANCER

**CURRENT PEER-REVIEWED MEDICAL LITERATURE
and EXPERT COMMENTARY from RELIABLE MEDIA SOURCES and DR. BLEYER**

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Blackberries and grapefruit made E&N news at year's end
Welcome a New Year !

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Exercise and Nutrition

Weight gain hurts breast cancer survival

By Marilynn Marchione

Associated Press

Breast cancer patients might have a powerful incentive to avoid gaining weight: better odds of surviving the disease.

New research suggests that for every 11 pounds a woman gains after being diagnosed with breast cancer, the chances of it proving fatal go up 14 percent.

The study is by no means definitive, but gives the strongest evidence yet that controlling weight — a good idea anytime in life — may be especially important after breast cancer.

"There was a significant trend between increasing levels of weight gain and higher mortality," said Hazel Nichols, a doctoral student at Johns Hopkins Bloomberg School of Public Health. "Lifestyle factors, the things you incorporate after a breast cancer diagnosis such as diet and exercise, do show potential to influence survival."

Nichols led the study and reported results Friday at an American Association for Cancer Research conference in Philadelphia.

Researchers started with 4,021 women in Wisconsin, Massachusetts and New Hampshire who had been diagnosed with breast cancer from 1988 to 2001. They gave information on their height, weight, family history and breast cancer risk factors during telephone interviews.

From 1998 to 2001, all survivors were mailed surveys asking for updated information on these factors and lifestyle habits like exercise and diet.

After an average of six years of follow-up since their diagnoses, 121 breast cancer deaths and 428 non-breast cancer deaths had occurred. **For every 11 pounds of weight gain after diagnosis, the risk of death from breast cancer or other causes increased by 14 percent.**

The link remained even after researchers took into account differences in age, menopausal status, smoking and the stage of disease when the women were diagnosed.

For women classified as obese by body mass index — a measure of weight and height — the death risk was more than twice that of women with a normal body weight.

The study was paid for by the Susan G. Komen for the Cure Breast Cancer Foundation.

"It's a large study, it was a very well-conducted study at several centers in the United States" by well-known researchers on this topic, said Joanne Dorgan, a breast cancer scientist at Fox Chase Cancer Center in Philadelphia.

Doctors have long known that women who are overweight when they are diagnosed with breast cancer have poorer prospects.

"They're more likely to relapse and to die of their cancer than women who are thinner," Dorgan said.

Previous research found that women who exercised after being diagnosed with breast cancer cut their chance of dying by as much as one-half, depending on how much exercise they did.

However, it is very common for women to gain weight after being diagnosed with breast cancer. One reason may be that chemotherapy can leave them tired and ill so they don't feel like exercising, Dorgan said.

The new work shows how important it is to get back on track and keep from gaining pounds over the long term.

"It still matters what your weight gain is after diagnosis," said **Dr. Craig Thompson**, director of the Abramson Cancer Center at the University of Pennsylvania.

Dr. Bleyer:

Dr. Thompson and I were on the faculty together at the University of Washington. He is a wise man.

Look for this report to appear in an important peer-review journal during 2008

Weight gain after breast cancer diagnosis reduces survival

Lisa M. Cockrell

Sixth Annual International Conference on Frontiers in Cancer Prevention Research: Abstract B95.

Presented December 7, 2007.

Medscape Medical News

December 10, 2007 (Philadelphia, Pennsylvania) — Gaining weight after a breast cancer diagnosis increases the risk for mortality, according to a study presented at the American Association for Cancer Research 6th Annual International Conference on Frontiers in Cancer Prevention Research.

Dr. Craig Thompson, MD, director of the Abramson Cancer Center at the University of Pennsylvania, in Philadelphia, who was not involved in the study, said that this work emphasized a "growing appreciation of the problem we have with obesity and metabolic diseases in this country over the past 25 to 30 years," and "an increased understanding of the impact these diseases have on the progression of cancer."

More than 2 million women in the United States have a diagnosis of breast cancer, and more than 30% of US women are obese. This study, designed to investigate the relationship between mortality and weight gained after a breast cancer diagnosis, was presented by Hazel Nichols, from the **Johns Hopkins Bloomberg School of Public Health**, in Baltimore, Maryland.

The 4021 women enrolled in the study received a diagnosis of invasive breast cancer between the ages of 20 to 79 years from 1988 to 2001. These individuals had previously participated in a parent study, and therefore information on their body weight and height had been obtained during a previous telephone interview. After an average of 5.8 years post-diagnosis, further details were gained from a questionnaire sent to breast cancer survivors. This questionnaire was designed to obtain information on treatment, diet, physical activity, and weight after their breast cancer diagnosis. Body-mass index (BMI) was used to

classify the participants as underweight (< 18.5 kg/m²), normal (18.5 – 24.9 kg/m²), overweight (25.0 – 29.9 kg/m²), or obese (> 30 kg/m²).

Using statistics from the National Death Index through 2005, the investigators determined that 121 women had died from a breast-cancer-related mortality, and 421 had died as a result of any cause. According to Ms. Nichols, the finding that an increase in BMI and weight gain was associated with an increased risk for death from both breast cancer and all causes was "not surprising." A significant trend occurred between increasing weight gain after diagnosis and higher mortality risk. For every 5 kg (approximately 11 lbs) of weight gained, the risk for death increased approximately 14%. This was true for both breast-cancer-related and all-cause mortality.

In women who reported gaining more than 10 kg (approximately 22 lbs) after their breast cancer diagnosis, an 83% increased breast-cancer-related mortality risk was shown. Women who were classified as obese after their diagnosis had more than twice the risk for breast-cancer-related death than women with a normal BMI (hazard ratio, 2.39). The risk for death from any cause for obese women also increased, although not as dramatically (hazard ratio, 1.46, compared with women with a normal BMI). Obesity was associated with increased mortality even after other factors, such as age, menopausal status, and smoking, were accounted for.

Additional analysis of the patients in this data set are planned for the future, according to Ms. Nichols. The role of physical activity will be addressed to see whether the relationship between weight gain and breast cancer mortality differs in groups that are more or less physically active. Also, cardiovascular-disease-related mortality will be investigated.

According to Ms. Nichols, 1 of the limitations of this study was the scarcity of information on other age-related medical diseases, and she hopes future studies from other groups will include a complete medical history.

Previously, several epidemiologic studies have shown a correlation between increased weight at the time of diagnosis and decreased breast cancer survival. "What our study is able to contribute that has not as often been looked at is changes in body weight after diagnosis," stated Ms. Nichols.

"These results generally support the recognized health benefits and potential in mortality reduction that is associated with avoiding weight gain." They also add to a "growing body of evidence that postdiagnosis lifestyle factors, the things that you incorporate after a breast cancer diagnosis, such as diet and exercise, do have a potential to improve survival."

Dr. Thompson echoed this, stating that what is clear from this study is that "it still matters what your weight gain is after your diagnosis, and that's something patients can help contribute to and control." Future studies might help to confirm whether weight loss after diagnosis can lead to increased breast cancer survival.

Dr. Bleyer:

More reaction to the report cited above from an objective reporter

Diet and exercise are key factors in determining lung cancer risk [Prevention]

Lisa M. Cockrell

Sixth Annual International Conference on Frontiers in Cancer Prevention Research: Abstract B143.

Presented December 7, 2007.

Medscape Medical News

December 10, 2007 (Philadelphia, Pennsylvania) — Smoking is not the only factor to be considered in the determination of a person's risk of developing lung cancer, according to a recent study presented at the American Association for Cancer Research (AACR) 6th Annual International Conference on Frontiers in Cancer Prevention Research. This study, highlighted at an AACR press conference on the effects of lifestyle on cancer prevention, suggested that, in addition to smoking, diet and physical activity are key in determining a person's overall risk of developing lung cancer. This is important, especially when considering that although smoking is the leading cause of lung cancer, approximately 15% of all lung cancers are diagnosed in people who have never smoked.

"The way we live our lives does influence our risk of getting cancer," said Tim Byers, MD, professor of preventative medicine at the University of Colorado, in Aurora, who was not involved in the study. "Choices we make in tobacco use, sun exposure, food, and physical activity all seem to add up to explain half or more of cancer risk in the population."

Recently, a model to predict lung cancer development in never, former, and current smokers was developed. Although this Spitz model showed clear associations with lung cancer development and smoking history, family history of respiratory disease, and exposure to second-hand smoke or dust, the model did not take into account the relative contributions of several other factors. In the current study, presented by Michele Forman, PhD, from the University of Texas MD Anderson Cancer Center, in Houston, fruit and vegetable intake, as well as physical activity, were examined as potential risk factors. According to Dr. Forman, this study was the first risk-prediction model for lung cancer that took into account, in addition to smoking, both diet and physical activity.

Data were obtained from the same people used in the generation of the Spitz model. Participants included lung cancer patients enrolled from the University of Texas MD Anderson Cancer Center and healthy matched controls recruited from a local private-physician clinic group. The controls were matched on age, sex, and smoking status. All study participants were categorized as either never, former, or current smokers.

A 135-point questionnaire modified from the National Cancer Institute was used to gather dietary data for all participants. For lung cancer patients, dietary data were gathered for the 1 year prior to diagnosis; for the healthy controls, data were gathered for the 1 year prior to recruitment. The questionnaire responses were standardized by converting to 2006 USDA food-pyramid guidelines. In addition, level of physical activity was established for the study participants.

Interestingly, the participants who ate fewer than 3 salads per week (or vegetables that were associated with salads, such as carrots) had more than twice the risk of developing lung cancer than those who consumed more than 4 salads per week. Importantly, this was shown to be true regardless of smoking status, although the effect was more dramatic in former and current smokers.

Impact of Salad Consumption on Developing Lung Cancer			
Odds Ratio (95% Confidence Interval)			
	Never Smokers	Former Smokers	Current Smokers
≥ 4/wk	1.00	1.00	1.00
3/wk	2.09 (1.03 – 4.21)	2.16 (1.39 – 3.37)	1.62 (1.02 – 2.59)
< 3/wk	2.15 (1.17 – 3.95)	2.52 (1.69 – 3.77)	2.72 (1.77 – 4.18)

However, fruit consumption was not found to affect the risk for lung cancer. In addition, Dr. Forman emphasized that "all of the vegetables that we did find [that were associated with a decreased risk] were in the raw form, and this is very important because the raw form of vegetables may have higher levels of nutrients than the processed form."

Dr. Forman stated that another factor, physical activity, also reduced the risk for lung cancer across all smoking groups. For this study, the physical activity assessed was gardening, because current smokers rarely engaged in any other type of exercise. Participants who gardened on a weekly basis experienced a 33% to 46% decreased risk for lung cancer development, with those who never smoked showing the most dramatic decrease.

When the newer risk-prediction model, which incorporated both diet and exercise, was compared with the original Spitz prediction model, Dr. Forman said it was found to have "a significant increased improvement." However, she cautioned that this study was preliminary in that it did not take into account the effects of many other food groups, alcohol, or vitamin use. In addition, she suggested that 1 possible explanation for the decreased risk associated with salad consumption and gardening is that these individuals inherently have a preventive lifestyle overall. Future analyses to look closely at other preventive and lifestyle factors might add to this prediction model.

This study was funded by grants awarded from the Flight Attendant Medical Research Institute, the Public Health Service, and the National Cancer Institute and National Institutes of Health.

Dr. Bleyer:

- I included this *prevention* report since it shows how E&N are powerful enough to be detectable in a cancer for which smoking is an overwhelmingly potent factor
- And the E&N were minimally evaluated: gardening for exercise and salad for nutrition. Had a broader analysis of E&N been undertaken the benefit of E&N may well have been more apparent.

Exercise

No peer-reviewed reports on exercise alone this month

Nutrition

Moderators of interventions designed to enhance physical and psychological functioning among younger women with early-stage breast cancer

Michael F. Scheier, Vicki S. Helgeson, Richard Schulz, Suzanne Colvin, Sarah L. Berga, Judy Knapp, Kristina Gerszten

Journal of Clinical Oncology, Vol 25, No 36 (December 20), 2007: pp. 5710-5714

From Carnegie Mellon University; University of Pittsburgh, Pittsburgh, PA; and Emory University, Atlanta, GA

Purpose: To identify factors that condition or moderate the impact of a previously described set of interventions on psychological and physical adjustment after diagnosis and treatment for early-stage breast cancer.

Patients and Methods: Younger women (age < 51 years, N = 252) with early-stage breast cancer within 2 months of having completed active non-hormonal adjuvant therapy were **randomly assigned to a three-arm clinical trial, consisting of a control arm, an education arm, and a nutrition arm**. Primary end points, assessed before random assignment and 4 and 13 months later, included mental functioning, physical functioning, and depressive symptoms. Four types of moderator variables were identified, including two sets reflecting psychosocial resources, specifically personality factors and factors related to the person's social environment, a set reflecting demographic variables, and a set reflecting treatment and disease variables (including co-morbidities).

Results: Psychosocial factors were more likely to moderate treatment effects than were demographic and disease-related factors, but the **moderating effects of these psychosocial factors were limited to patients receiving the nutrition intervention**. Patients with lower psychosocial resources benefited from the nutrition intervention, whereas patients with a greater amount of psychosocial resources did not.

Conclusion: Future trials of this type should stratify by or select for the moderating variables identified here (ie, dispositional pessimism, unmitigated communion, and negative social interaction) to establish more firmly their role in responses to psychosocial interventions. Effort should also be made to collect data to inform the delivery of interventions to those who might benefit the most.

Dr. Bleyer:

- This is a remarkable study for DEFEAT *per se* since the participants in the two intervention regimens met for two hours once monthly for 4 months (like DEFEAT) and either received information on cancer and how to cope with it (the education group) or they received information on how to adapt to and adhere to a high-fruit, high-vegetable, and low-fat diet (the nutrition group)
- The nutrition group clearly did the best in alleviating depressive symptoms and in physical and mental functioning, especially those with limited psychosocial resources,
- Moreover, the benefit lasted for at least 14 months after just 4 months of one-monthly sessions. I imagine that the results would have been even more striking and applicable to those with excellent psychosocial resources if exercise had been included
- These results suggest that improving nutrition is more powerful than the learning specific coping skills

Mediterranean diet also beneficial in U.S. populations [Prevention]

Medscape Medical News

News Author: Lisa Naingolan; CME Author: Charles Vega, MD

December 18, 2007 - The largest study to evaluate the Mediterranean diet and mortality in a US population has found that adherence to such a diet reduces deaths [1]. Dr Panagiota N Mitrou (now of **University of Cambridge**, UK) and colleagues from the **US National Cancer Institute** report their findings in the December 10/24, 2007 issue of the Archives of Internal Medicine.*

This is the latest in a line of studies to show the benefits of a Mediterranean diet, say the researchers, with all of them having reported reverse associations between this diet pattern and mortality. "Individuals who include more of the Mediterranean diet key components in their diet compared with those who include less have a reduced risk of dying of any cause, including cancer and cardiovascular disease (CVD)," Mitrou told Heartwire.

This is also the **first study of mortality that examines the effect of the Mediterranean diet among smokers and those of differing body mass indexes (BMIs)**, Mitrou said. The researchers found that the diet appears to be particularly beneficial among smokers but that it was not really helpful among obese subjects who had never smoked.

20% reduction in death for those conforming to Mediterranean diet

Mitrou et al followed 214,284 men and 166,012 women in the National Institutes of Health (NIH) AARP (formerly American Association of Retired Persons) Diet and Health Study. During follow-up for all-cause mortality (1995-2005), 27,799 deaths were documented. In the first five years of follow-up, there were 5985 cancer deaths and 3451 CVD deaths.

The researchers modified the traditional Mediterranean 9-point diet score slightly to compose an alternative Mediterranean diet score, thought to better reflect the dietary habits of a US population. One point each is given for intake at or above the sex-specific median intake for components considered to be healthy — **vegetables** (excluding potatoes), **fruits, nuts, legumes, grains, fish**, and monounsaturated-fat/saturated-fat ratio — and one point is given for intake less than the median for those **components considered unhealthy (red and processed meat)**. In addition, one point is given for alcohol intake within a specified range (5-25 g/day).

They looked at conformity with the Mediterranean dietary pattern among participants and calculated hazard ratios (HRs) using age- and multivariate-adjusted Cox models. They found, on average, a 20% reduction in deaths in those conforming highly to the diet (scoring 6 to 9 points) compared with those who had low diet scores (0 to 3 points).

Multivariate adjusted HRs for mortality among men and women scoring 6-9 points on the Mediterranean diet score compared with those scoring 0-3 points

Mortality outcome	Men	P for trend	Women	P for trend
All-cause	0.79	< 0.001	0.80	< 0.001
CVD	0.78	< 0.001	0.81	0.01
Cancer	0.83	< 0.001	0.88	0.04

Mitrou explained to Heartwire that although their primary analysis was based on an alternative Mediterranean diet score, they also ran models using the traditional score and found similar outcomes. All prior research in this field has shown a benefit of the Mediterranean diet, with reductions in mortality ranging from 8% to 31%, she added.

"These findings confirm results from previous studies and suggest that the Mediterranean dietary score is a useful tool for evaluating diet and mortality in a non-Mediterranean US population," she and her colleagues observe.

And although the alternative Mediterranean diet score they used is not exactly the same as the traditional Mediterranean diet, "it does include the key features of this diet and, as we have shown, may have a substantial beneficial impact on mortality in the United States."

Adhering to Mediterranean diet cuts smokers' death risk by up to 45%

Mitrou et al also found the effects of the diet were even more pronounced in smokers and especially in lean smokers. Among smokers with normal BMI (18.0-25.0), the multivariate HR comparing high vs low

levels of adherence to the Mediterranean diet was 0.54 in men and 0.59 in women. This could be due to the diet's antioxidant properties, they suggest.

"It seems from this finding that conformity with the Mediterranean diet may play a particularly important role among smokers, who are characterized by high levels of oxidative stress and an adverse blood lipid profile," says Mitrou.

And they found **an inverse association between adherence to the diet and all-cause mortality in most BMI subgroups, with the exception of never-smokers with a BMI of 30.0 or higher** (HR 0.92 for men scoring 6 to 9 points compared with those scoring 0 to 3 points; p=0.51 and HR 0.89; p=0.12 for women). They suggest that the increased risk of death due to obesity might mask the inverse association of the Mediterranean diet with all-cause mortality.

Mitrou told Heartwire that one previous European study found that risk of death among smokers was lower in those who had the highest adherence to the Mediterranean diet. However, this study did not look at smoking and BMI together, she noted.

As this is the first study to look at the effect of the Mediterranean diet within both smoking and BMI strata, "additional studies are needed to further investigate this finding," she says.

This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. The study authors have disclosed no relevant financial relationships.

*Source: Mitrou PN, Kipnis V, Thiébaud ACM, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population. Results from the NIH-AARP Diet and Health Study. Arch Intern Med. 2007; 167:2461-2468

Dr. Bleyer:

- Although we generally limit these reviews to studies in cancer patients, this prevention article has significant implications for DEFEAT's premise regarding exercise and prevention
- That the diet did not help prevent cancer in obese patients (BMI ≥ 30), but did in those with a lower BMI; assuming that those with a BMI < 30 were more physically active, this is indirect evidence that exercise and diet work together in preventing cancer

Implications of phytoestrogen intake for breast cancer

Christine Duffy, MD, Kimberly Perez, MD and Ann Partridge, MD, MPH
CA Cancer J Clin 2007; 57:260-277

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Dr. Partridge is Assistant Professor of Medicine, Harvard Medical School, Boston, MA.

Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol. Interest in phytoestrogens has been fueled by epidemiologic data that suggest a decreased risk of breast cancer in women from countries with high phytoestrogen consumption. **Women with a history of breast cancer may seek out these "natural" hormones in the belief that they are safe or perhaps even protective against recurrence.** Interpretation of research studies regarding phytoestrogen intake and breast cancer risk is hampered by differences in dietary measurement, lack of standardization of supplemental sources, differences in metabolism amongst individuals, and the retrospective nature of much of the research in this area. Data regarding the role of phytoestrogens in breast cancer prevention is conflicting, but suggest early exposure in childhood or early adolescence may be protective. In several placebo-controlled randomized trials among breast cancer survivors, soy has not been found to decrease menopausal symptoms. There is **very little human data on the role of phytoestrogens in preventing breast cancer recurrence**, but the few studies conducted do not support a protective role. There is in vivo animal data suggesting the phytoestrogen genistein may interfere with the inhibitive effects of tamoxifen on breast cancer cell growth.

Dr. Bleyer:

- The most commonly regarded phytoestrogen today is soy
- The evidence to date does not support a beneficial effect of soy alone on breast cancer recurrence
- And if phytoestrogens as a group are beneficial, it appears that they have to be part of the diet since childhood, or at least adolescence

☑ The bottom line is that no single dietary component is potent enough (even grapefruit, see next report) to affect the overall risk of cancer recurrence, and more important per DEFEAT, diet alone is not sufficient: nutrition and exercise are key

Study links grapefruit to postmenopausal breast cancer [Prevention]

CA Cancer J Clin 2007; 57:321-322

Eating as little as one-quarter grapefruit a day may raise a postmenopausal woman's risk of breast cancer, a recent study suggests.

Could eating grapefruit daily raise a woman's risk of breast cancer? Possibly, researchers from the **University of Southern California** report in the **British Journal of Cancer** (2007;97:440–445). The mechanism appears to be **grapefruit's inhibition of CYP3A4, an isoenzyme that metabolizes estrogen** [and some classes of drugs (Bleyer)]. Although preliminary, the finding is one that warrants further investigation, they say.

"It's an interesting hypothesis, there's biological plausibility, and we want other researchers to look at it," says lead study author Kristine R. Monroe, PhD, Research Associate in the Department of Preventive Medicine at the University's Keck School of Medicine.

Monroe's findings come from data on 46,080 naturally postmenopausal women taking part in the Hawaii-Los Angeles Multiethnic Cohort Study, a prospective study of people from 5 ethnic/racial groups in Los Angeles and Hawaii. Participants reported grapefruit or pomelo consumption as part of a comprehensive food frequency questionnaire. **Only intake of whole grapefruit was examined in this analysis because grapefruit juice was combined with orange juice in the questionnaire.**

Women in the highest intake category—60 grams or more per day, equal to slightly more than one-quarter grapefruit per day or half a grapefruit every other day—had a relative risk (RR) of breast cancer 30% higher than women who ate no grapefruit (RR = 1.30). The trend of **increasing risk with increasing consumption was significant (P = 0.015) after adjusting for weight, exercise**, use of postmenopausal hormone therapy, family history of breast cancer, and other factors that could impact risk.

The same association was evident for women who had never used postmenopausal hormone therapy (RR = 1.44; P = 0.038) and for those with a body mass index below 25, the cutoff for overweight (RR = 1.32; P = 0.011). Although risk also increased for women who were current or past users of hormone therapy (either estrogen-only or estrogen-progestin combination therapy) and for **those with a higher body mass index, the differences were not statistically significant.** This finding suggests grapefruit's effect on estrogen is greatest in women whose baseline levels are lower to begin with, Monroe says.

The results are consistent with a biological effect of grapefruit on estrogen metabolism. At least 2 previous studies have found higher estrogen levels in women consuming grapefruit or grapefruit juice, the authors note, and grapefruit is known to elevate serum concentrations of many drugs, including hormone replacement therapies. The **US Food and Drug Administration requires hormone replacement products to carry warning labels stating that grapefruit juice may increase plasma concentrations of estrogen.**

Monroe stresses, however, that there's not yet enough evidence to recommend women stop eating grapefruit as a means of lowering their breast cancer risk. And because premenopausal women and breast cancer survivors were not part of her cohort, it's not possible to know whether grapefruit would have similar effects on them.

"This needs to be confirmed in other studies," she says. "I would use caution until further studies are done and a scientific conclusion can be reached."

Other experts agree.

"Results from a single epidemiological study are insufficient as a basis for recommendations," says Michael Thun, MD, American Cancer Society (ACS) Vice President of Epidemiology and Surveillance Research. "In this case, however, other studies have established that even modest consumption of grapefruit affects the action of many drugs. Women who have had estrogen receptor-positive breast cancer or are concerned for other reasons could consider substituting other fruit until this issue is clarified."

Additional research is needed to determine whether grapefruit has any effect on the risk of recurrence or progression in breast cancer survivors and how that association might be influenced by the tumor's estrogen-receptor status, the patient's menopausal status, and her current or past treatment.

Until more is known, women would be well-advised to follow ACS nutrition guidelines for cancer prevention, says Marji McCullough, ScD, RD, ACS Strategic Director of Nutritional Epidemiology. **The guidelines emphasize eating at least 5 daily servings of a wide variety of fruits and vegetables of different colors. A varied diet not only maximizes intake of beneficial plant nutrients, but could also limit the amount of potentially harmful substances from any single food. Further, eating fruits and vegetables helps to prevent excess weight gain in adulthood, a factor known to increase the risk of breast cancer.** The full nutrition guidelines are available free online at <http://CAonline.AmCancerSoc.org/cgi/content/full/56/5/310>.

Monroe says future studies of grapefruit should not only seek to confirm her team's findings, but also to quantify grapefruit's effects by measuring estrogen levels before the fruit is eaten and afterward. Studies should also explore how long grapefruit's effect on estrogen lasts in the body, she says, as previous research has shown **elevated levels of some drugs as many as 72 hours after drinking a single glass of grapefruit juice**

Dr. Bleyer:

- ☑ Again, a primary prevention study worth including in our monthly review of the peer-reviewed reports of relevance for *tertiary prevention of cancer recurrence*.
- ☑ For breast cancer patients with estrogen-positive (ER+) tumors, in whom lowering estrogen helps prevent recurrence (with hormonal therapy like tamoxifen, raloxifene or the aromatase inhibitors like anastrozole, etc), grapefruit may have enough inhibitors of estrogen metabolism (elimination) to raise body estrogen and increase risk of recurrence.
- ☑ That it took more than 46,000 women to find an effect of grapefruit suggests that the effect is weak, despite quantification of the risk at approximately 30% higher than no grapefruit consumption.
- ☑ That consumption of grapefruit juice was not included in the analysis weakens the authors conclusions because of the (likely) possibility that women select either grapefruit fruit or juice and not both, and if so, the control group also ingested grapefruit (as a juice)
- ☑ Nonetheless, if the grapefruit effect occurs after a diagnosis of breast cancer, exercise should reduce the risk by decreasing estrogen levels
- ☑ That the grapefruit-associated increased risk of breast cancer was observed only in women with lower BMIs suggests that exercise may be even more important for non-obese women.
- ☑ DEFEAT's focus on fruits and vegetables, and the recommendations to vary the fruits (e.g. by color as stated above) makes even more sense with the grapefruit concern, not only for the breast cancer risk but also because of the potential of grapefruit to increase the levels of some drugs patients may be taking.

Black raspberries may inhibit progression to esophageal cancer

Lisa M. Cockrell

Sixth Annual International Conference on Frontiers in Cancer Prevention Research: Abstract B34.

Presented December 7, 2007.

December 10, 2007 (Philadelphia, Pennsylvania) — Dried black raspberries significantly reduce markers of oxidative stress in patients with Barrett's esophagus, according to a study reported at the American Association for Cancer Research 6th Annual International Conference on Frontiers in Cancer Prevention Research. This pilot study, presented by **Laura Kresty, PhD**, assistant professor at **Ohio State University**, in Columbus, was highlighted at an AACR press conference on diet and cancer prevention. Barrett's esophagus, a complication resulting from chronic gastroesophageal reflux disease (GERD), is a premalignant condition associated with a 30- to 40-fold increased risk for the development of esophageal adenocarcinoma. This is a particularly deadly malignancy, with a 5-year survival rate of 15%. Patients with Barrett's esophagus experience chronic injury insults to the esophagus, resulting in the generation of reactive oxygen species and oxidative stress responses in the tissue. This can lead to key changes in the lipids, proteins, and genes within these tissues, causing tumor progression. Dr. Kresty commented that patients with Barrett's esophagus could particularly benefit from targeted chemopreventive interventions, especially those that would lower oxidative stress.

Dr. Kresty stated that black raspberries were chosen for this dietary chemoprevention study for a number of reasons. First, several epidemiologic studies have suggested that black raspberries are protective against a number of cancers, including esophageal cancer. Second, black raspberries in particular are known to have high levels of several compounds with potential anticancer properties, including antioxidants, vitamins, minerals, fiber, and anthocyanins, the pigments responsible for the characteristic dark coloring of the fruit. Finally, black raspberries are among the most extensively studied fruits in preclinical animal-based studies. In particular, animal models of esophageal cancer have suggested that black raspberries can decrease markers of oxidative stress and DNA damage.

In this phase 2a trial, 20 patients (mean age, 58.9 years) diagnosed with Barrett's esophagus were administered either 32 or 45 g (for females or males, respectively) daily of freeze-dried black raspberries over the course of 6 months. Forty-five grams corresponds to approximately **2 cups of whole black raspberries**, but the fruit was **dried into a powder to obtain a more concentrated sample, allowing patients to mix it into drinking water. Biopsies and urine and blood samples were taken at baseline and at 26 weeks, with an additional set of urine and blood samples at 12 weeks.**

Changes in 2 urinary markers of global oxidative stress, a measure of the total body's oxidative stress, were assessed after administration of the freeze-dried berries. Most important, 8-epi prostaglandin F2 α (8-isoprostane) declined significantly after berry consumption ($P < .05$), with dramatic individual level declines occurring in 58% of the study patients. A second urinary marker, 8-hydroxy-2'-deoxyguanosine (8-OHdG), did not decrease significantly, but all of the patients who showed a decrease in 8-OHdG levels also had decreased 8-isoprostane levels, showing some level of correlation.

Levels of Urinary Biomarker 8-Isoprostane of Oxidative Stress		
(mg/mL of Urine)		
Baseline	Week 12	Week 26
1.59×10^{-10}	1.38×10^{-10}	1.30×10^{-10}

Immunostaining of GST π , a protein important in tissue detoxification, revealed increased expression in the Barrett's tissue of 37% of the patients. This is a particularly promising result, said Dr. Kresty, given the increased oxidative stress these patients experience in this tissue. "If we can increase a molecule that helps to detoxify, we're moving things in the right direction."

The freeze-dried black raspberries did not induce any changes in the rates of cell proliferation within the esophageal tissue. Dr. Kresty commented that the investigators are still analyzing the data to determine whether any changes occurred in NF κ B expression, a protein that plays roles in both inflammatory and growth signaling pathways. An average 3.9-lb weight gain occurred among the study participants, but Dr. Kresty noted that this was not unexpected when weight changes in the general population were considered. However, the investigators did not rule out a possible connection between the weight gain and berry consumption, which added approximately 200 calories to the patient's diet. According to Dr. Kresty, this study supports a broader message in the nutrition community to increase both fruit and vegetable consumption. "Patients can really do something to modify key pathways in cancer," she said. Dr. William Nelson, MD, PhD, from the Sidney Kimmel Comprehensive Cancer Center at **Johns Hopkins**, in Baltimore, Maryland, who was not involved in the study, agreed. "Diet is one of the great modifiable risk factors for the propensity to develop cancer. It's not surprising that there might be things that you can encounter in the diet . . . things that might be helpful and protective." Dr. Kresty believes that these positive results pave the way for a randomized placebo-controlled phase 2b trial, which would include a larger study population and a longer duration of intervention.

Dr. Bleyer:

- Since Barrett's esophagus is an increasingly frequent premalignant condition, in part related to the obesity epidemic, that itself reaching nearly epidemic proportion in the U.S.
- I consider this study to address *secondary* prevention and have thus not labeled it as a *prevention* report
- The findings are chemical (subclinical) in nature and thus not yet clinically significant, and a control group that did not take the blackberry powder is missing.

- ☑ Nonetheless, if something as simple as black raspberries can slow the epidemic, screening for Barrett's esophagus in high risk patients would be more applicable
- ☑ And if the raspberries worked despite the weight gain that occurred in the

Black-raspberry gel may prevent progression of oral precancerous lesions

Sixth Annual International Conference on Frontiers in Cancer Prevention Research: Abstract B35.
Presented December 7, 2007.

Lisa M. Cockrell

December 10, 2007 (Philadelphia, Pennsylvania) — A topical black-raspberry gel showed promise in preventing progression of oral precancerous lesions to oral cancer in a clinical trial presented by **Susan R. Mallery, DDS, PhD**, from the Oral and Maxillofacial Surgery and Pathology Colleges of Dentistry and Medicine and Public Health, at **Ohio State University**, in Columbus, at the American Association for Cancer Research (AACR) 6th Annual International Conference on Frontiers in Cancer Prevention Research. The results of this phase 1/2 trial were noted at an AACR press conference on chemopreventive agents.

Nearly 36% of oral intraepithelial neoplasia lesions progress to squamous-cell carcinoma when left untreated. Dr. Mallery stated that a major problem in the field is that it is currently very difficult to predict which lesions will undergo a malignant transformation, so an effective chemopreventive agent that would limit their progression could be very beneficial to these patients. Black raspberries might offer such an advantage. "Chemoprevention using natural or plant-derived medicines is a very active area of prevention," according to session moderator **Dr. Scott M. Lippman, MD**, from the **University of Texas MD Anderson Cancer Center**, in Houston. "For example, black-raspberry-based extracts turn out to have a very potent preventive activity in certain systems."

In this trial, an oral topical black-raspberry gel was formulated. "The benefit of a local delivery is that you can get a high concentration at the site," said Dr. Mallery. The gel was formulated with a polymer combination so that it would "stick" to the oral mucosa.

This study, funded by the National Cancer Institute, enrolled 20 patients diagnosed with an oral premalignant lesion. An additional group of 10 control patients were included to determine whether the black-raspberry gel caused mucositis or any other oral inflammation. None of the participants reported any adverse effects.

At the beginning of the trial, each experimental patient had one-half of their oral lesion removed to obtain baseline levels of biochemical and molecular markers. After 1 week, the participants initiated the black-raspberry intervention, applying the gel, 0.5 g, to the remaining lesion 4 times a day. This dosing continued for 6 weeks. After the 6-week trial period, the remaining half of the lesion was excised. The effect of the black-raspberry gel was assessed by comparing pre- and posttreatment biopsies.

Histopathologic analysis revealed a dramatic variability among the patients. Approximately 35% of patients experienced a decrease in grade, corresponding to an improvement in lesion appearance; 20% showed an increase in lesion grade; and 45% exhibited stable disease. In addition, examination of the microvascular density within and surrounding the lesion showed that it generally decreased with the topical application of the black-raspberry gel, a strong suggestion that the angiogenic "switch," which occurs during malignant progression, was hampered.

The study investigators measured loss of heterozygosity (LOH) to monitor the effects of the berry gel at the molecular level. LOH, the loss of 1 of the 2 gene alleles responsible for coding a protein, is an important and common occurrence in lesion progression and cancer. LOH analysis revealed a statistically highly significant decrease in LOH ($P < .0005$). Dr. Mallery suggested that this indicated "a return to a state of normal gene pairing" after black-raspberry treatment. Dr. Mallery further explained that cell-based studies suggest that the decrease in LOH induced by the berry treatment in the oral lesions was due to an increase in the death of the molecularly altered cells, limiting the ability of these cells to proliferate and spread.

Importantly, microarray analysis and quantitative real-time polymerase chain reaction (QRT-PCR) revealed that the gel caused a marked increase in the expression of genes known to be involved in keratinocyte differentiation, as well as tumor suppression, in some patients. Further,

immunohistochemistry showed that 2 proinflammatory proteins important in premalignant progression, COX-2 ($P < .001$) and iNOS ($P < .005$), were significantly lower than they were at baseline. The authors discovered that the responses to the black-raspberry gel varied widely among the patients. Patients with only mild dysplasia, or a low lesion grade, at the initial biopsy experienced the most dramatic responses to the black-raspberry gel, and Dr. Mallery hypothesized that this could be due to the fewer biochemical and molecular perturbations in the lesions of these patients. Dr. Mallery speculated that anthocyanins, a type of antioxidant present in the berries, might be largely responsible for the decrease in tumor promotion, but she noted that many other compounds present in the berries could also be important. In the future, Dr. Mallery hopes that this gel will be tested in a larger multicentered randomized placebo-controlled trial, with a longer duration of treatment.

Dr. Bleyer:

- I consider this study to address *secondary* prevention and have thus not labeled it as a *prevention* report
- A different study of raspberries conducted by a different investigator supports the report above

Related Articles

Bariatric surgery, weight reduction and decreased cancer incidence

N Engl J Med 357;25 - December 20, 2007

To the Editor: Sjöström et al. (Aug. 23 issue)¹ report that bariatric surgery was associated with decreased long-term overall mortality, but because of statistical limitations, they were not able to determine definitively whether this finding could be explained by weight loss or by other beneficial effects of the surgery. **In view of the marked reduction in cancer-related deaths in the surgery group as compared with the control group (29 vs. 47 deaths)**, a further specification of the types of cancer that occurred would be interesting. If the decrease in cancer-related deaths could mainly be attributed to a reduced incidence of cancers for which obesity is known to be a risk factor, such as endometrial carcinoma,^{2,3} this would provide indirect evidence of the mortality-reducing effect of weight loss rather than surgery-related factors.

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¹Sjöström L, Narbro K, Sjöström D, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741-52.

²Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007;132:2208-25.

³Modesitt SC, van Nagell JR Jr. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. Obstet Gynecol Surv 2005;60:683-92.

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Dr. Sjöström and colleagues reply: As van der Woude correctly points out, there seemed to be a substantial reduction in cancer-related mortality in the surgery group in our study. However, the study did not have sufficient power to prove that cancer-related mortality was, in fact, significantly reduced in the surgery group. Our study had even less power to look at mortality reduction with respect to specific cancers, but **the qualitative impression we had was that deaths from obesity-related cancers as well as deaths from cancers unrelated to obesity were less common in the surgery group**. Because of long-lasting effects of surgery, a beneficial effect on obesity-related cancers in the surgery group as compared with the control group would not necessarily have supported weight loss over surgery as the cause of the benefit.

Dr. Bleyer:

I included this article because it may be the first direct evidence that weight reduction decreases the risk of cancer. Virtually all prior evidence has been limited to an increase due to weight gain or obesity *per se*. Being able to reduce weight for a long enough interval to demonstrate a reduction in cancer incidence has gone wanting.
