

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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Exercise

Action speaks of health louder than weight

By Nanci Hellmich, USA TODAY- April 15, 2008

Exercise can shrink your waistline and reduce the belly fat shown in recent studies to be so toxic, even if you don't lose much weight, and thereby reduce cancer risk and recurrence

"You can lose a lot of waist without losing a lot of weight," says Timothy Church, director of preventive medicine research at the Pennington Biomedical Research Center in Baton Rouge and former medical director of the Cooper Institute in Dallas. That is the conclusion reached by exercise expert Church and colleagues in a new book, *Move Yourself: The Cooper Clinic Medical Director's Guide to All the Healing Benefits of Exercise (Even a Little)*.

That's important because belly fat, also called visceral or intra-abdominal fat, is considered particularly dangerous, he says. Research has indicated that people with too much fat in their midsection are at greater risk of developing dementia, including Alzheimer's disease.

Walking the weight off

Church and his co-authors — Tedd Mitchell, medical director at the Cooper Clinic, and health writer Martin Zucker — reviewed research conducted at the Cooper Institute. The institute focuses on research into physical activity and health, and the clinic offers consultation and treatment.

In one study, 464 postmenopausal women were directed to do different amounts of exercise, most of it walking. The four subgroups were sedentary or exercised about 73, 135 or 193 minutes a week. The women who were active lost 1 to 2 inches around their middles, even if they didn't lose much weight. They noticed that their pants fit better, Church says.

Other research has yielded similar findings. Scientists at the **Fred Hutchinson Cancer Research Center in Seattle** found that men and women who adhere to an exercise program for a year — about 45 to 60 minutes a day of walking, five to six days a week — had significant decreases in total body fat and belly fat.

The exercisers who did the most — 60 minutes, six days a week — decreased their intra-abdominal fat by 10%, says Anne McTiernan, an internist and director of the Prevention Center at Fred Hutchinson. Regular exercisers should realize that even "if they don't see big changes on the scales or in their measurements, they are still getting big health benefits," McTiernan says. "We saw **a decrease in hormones and other factors that contribute to cancer.**"

Fat cells in the abdomen secrete chemicals that play a role in a number of diseases, Church says. "This deep visceral fat in the belly produces six times more bad chemicals than subcutaneous fat, the stuff you can pinch right under your skin.

"Plus, the plumbing of visceral fat drains directly to the liver, where these chemicals interfere with the liver's ability to metabolize blood sugar and cholesterol."

Danger at 35 or 40 inches

Men have too much fat around their middle if their waist is 40 inches or more. For women, it's 35 inches or more, Church says.

Besides reducing belly fat, physical activity lowers blood pressure, cholesterol and the risk of diabetes and cancer. It reduces depression and anxiety, and it improves bone and joint health, sex drive, sleep and memory, he says.

But Church notes that fewer than 25% of Americans meet the minimum guidelines of being moderately active for 30 minutes five or more days a week, estimates show.

"The average American doesn't understand that other than not smoking, exercise is the most important thing you can do for your health," Church says. "They think exercising is a health suggestion on par with leaving mayonnaise off their sandwich."

He highly recommends wearing a step counter and keeping a physical activity log, especially at the beginning of an exercise program, because these tools help quantify current exercise levels and identify opportunities for activity throughout the day.

Church is always looking for ways to do more. He used to train for Ironman triathlons, but now that he has children, 3 and 5 years old, he jogs for 30 to 35 minutes two to three days during the week. On weekends, he and his wife put their kids in a jogger and go out for fast walk/jog for an hour or more. And they plan active weekends, such as walking around the zoo for an afternoon.

"The bottom line is that most people do not appreciate that exercising, even a little, is the quick fix that they are looking for to improve their health and quality of life."

Dr. Bleyer:

- I think that exercise is not on a par with leaving mayonnaise off the sandwich. It's more like leaving out *all* the detrimental foods.
- The described change on the ability to exercise after getting married and having to take care of a family with children is appropriate. It is also key in that sharing an exercise schedule with someone else, including one's own children, as a source of motivation can actually make it easier.
- The statement about reducing depression and anxiety and improving sex drive, sleep and memory should be appreciated; DEFEAT Cancer advocates exercise and nutrition (E&N) for its effect on quality of life, and less for its effect on prolongation of life.

Exercise and reduced breast cancer risk: A multinational study [Prevention]

Luke Ratnasinghe, Michael Seddon, Rama Modali, Teresa Lehman. Genomic Nanosystems, Beltsville, MD, BioServe Biotechnologies, Ltd., Beltsville, MD

Exercising 15 minutes a day for less than 3 times a week helps prevents breast cancer in persons of all races and ethnicities

Exercise and physical activity are modifiable risk factors for cancer. There is little data evaluating the relationship between exercise and breast cancer risk comparing different ethnic groups. We evaluated the association between exercise and breast cancer risk among 1468 breast cancer cases and 4865 non-cancer controls in the Global Epidemiology Study (GES). The GES is a multinational study to assess disease risk factors with subjects recruited from countries including the United States, Tunisia and Poland. The GES is linked to the Global Repository® that houses biomaterial including blood, serum, DNA, RNA, frozen tissue, formalin-fixed paraffin embedded tissues, and pathology slides. For breast cancer, newly diagnosed subjects provided informed consent and were asked about exercise activity during in-person interviews. The same survey instrument was used for all subjects in this study, following translation to the local language. For all subjects combined, the multivariate-adjusted odds ratio (OR) was 0.5 (95% confidence interval (95% CI): 0.4-0.7) for women who exercised once per week or more after adjusting for age, race, BMI and packyears of smoking. **All ethnic groups in the study population, Caucasian-Americans, African-Americans, Hispanic-Americans, Tunisian-Arabs, and Polish-Caucasians, were at 50% or greater reduced risk for breast cancer if they exercised once or more per week. Women who exercised 4 times per week or more did not gain any additional reduced breast cancer risk.** The amount of time spent exercising per session was also significantly associated with reduced breast cancer risk. **Women who exercised 15 minutes per session or more were at 40% or greater reduced risk for breast cancer** (OR 15-30 mins: 0.5 (95% CI: 0.4-0.7, OR greater than 30 Mins: 0.6 (95% CI 0.5-0.7) in the multivariate model compared to women who exercised less than 15 minutes. Results from our study shows that regular exercise has the potential to reduce breast cancer risk among all women regardless of race.

Dr. Bleyer:

- We really don't need any more evidence that physical activity substantially reduces the risk of cancer
- We need to learn how much exercise is necessary and how it works, biochemically and cellularly, in order to improve the benefit
- It is helpful to know that exercising less than 15 minutes at a time is not protective, and on the other hand, exercising more that four times a week does not provide additional benefit.

Effects of voluntary wheel running on prostate cancer growth and progression in LAPC-4 xenografts

Michael Potter, Stephen J. Freedland, Susan Poulton, Mark Dewhirst, Lee W. Jones, **Duke University**
2008 American Association for Cancer Research Annual Meeting, April 12-16, 2008, San Diego, CA

In mice, voluntary exercise (having a running wheel in the cage) was associated with an increase in the rate of growth of prostate cancer cells injected into the mice

Background: Preliminary evidence suggests that exercise training may be an effective supportive intervention to enhance quality of life and to reduce treatment related symptoms in prostate cancer patients. No study to date has examined the effects of exercise on prostate cancer tumorigenesis using in vivo models. The purpose of this study is to evaluate whether exercise training can modulate tumor growth in vivo using an LAPC-4 xenograft model. **Methods:** Fifty ahythmic male mice consuming an ad libitum Western diet (40% fat, 44% carbs, and 16% protein) were subcutaneously implanted with LAPC-4 prostate cancer (106 cells per mouse) and randomly assigned to voluntary wheel running (n=25) or a non-intervention control group (n=25). Voluntary wheel running was recorded continuously for the entire duration of the study. Tumors were measured twice weekly and mice were sacrificed when tumor volumes reached 1000 mm³. **Results:** The primary endpoint will be tumor growth delay, calculated as the number of days for each tumor reach 1000 mm³. Tumor growth survival growth curves will be compared between groups using Cox model for pairwise comparisons. Serum and tumor samples will be collected at the time of sacrifice and analyzed for postulated biologic mechanisms underlying the association between exercise and prostate tumorigenesis. We anticipate data collection will be completed by February 2007, and final results will be presented at the time of the meeting. **Conclusions:** This study is essential to understand the efficacy of exercise as a potential intervention to inhibit prostate cancer growth and the biologic mechanisms underlying this relationship.

Dr. Bleyer:

- Extrapolations from mice to men (and women) are fraught with all kinds of difficulties
- Of 1000s of chemicals that are effective in treating mice with cancer work in people; the same can be expected of factors that promote cancer growth in mice.
- In this study, the mice were not treated for their cancer (which we try to avoid in people) and the cancer did not arise in them (it was injected), making the extrapolation to people all the more tenuous
- Also, no study of exercise in people with cancer has shown increased cancer growth; they either have demonstrated no benefit or, more frequently, a reduction in cancer occurrence (e.g., above article) or cancer recurrence
- Please read the next study, which was presented at the same meeting and shows that mice allowed to exercise in the same can also have less cancer growth after pancreas tumor cells are injected with or without additional therapy of the cancer

Exercise, alone and in combination with an anti-CEA vaccine, reduces pancreatic tumor cell growth and enhances survival in mice

Connie J. Rogers, Kenneth W. Hance, David A. Zaharoff, Susan N. Perkins, Stephen D. Hursting, Jeffrey Schlom, John W. Greiner. National Cancer Inst., Bethesda, MD, University of Texas, Austin, TX, Univ, of Texas, Dept. Carcinogenesis UT-MD Anderson Cancer Center, Austin, TX

In mice, voluntary exercise (having a running wheel in the cage) was associated with a decrease in the rate of growth of pancreas cancer cells injected into the mice, and the benefit of exercise was further improved with a simultaneous cancer treatment

Regular exercise is strongly associated with reduced risk of colon, breast, and endometrial cancer, and possibly pancreatic and lung cancer. Furthermore, regular exercise is associated with a reduced risk of recurrence and death from colorectal and breast cancer. One mechanism that may mediate the protective effect of exercise on tumor incidence and/or recurrence is an enhancement of anti-tumor immunity. We have previously demonstrated that **exercise significantly enhances NK cell function and vaccine responses** in normal mice. Our laboratory has also demonstrated in both preclinical and clinical studies that therapeutic cancer vaccines targeted against the tumor antigen, carcinoembryonic antigen (CEA),

enhance anti-tumor immunity and increase survival. The goal of this study was to explore the effects of exercise, alone and combined with a therapeutic cancer vaccine, on in vivo tumor growth and survival. The murine Panc02.CEA pancreatic tumor cell line was chosen because it shares many characteristics with human pancreatic tumors and because in vivo anti-tumor immunity against the parental cell line is mediated by NK and CD8+ T cells. CEA.Tg mice were randomized to 1 of 4 treatment groups (n=16/group): vehicle (HBSS), vaccine (V), exercise (EX), or vaccine + exercise (V+EX). Mice in the EX and V+EX groups had access to voluntary running wheels for 8 weeks prior to tumor implantation (10^6 cells) and throughout the vaccination protocol (17 wks) and ran 3.5 ± 0.4 and 3.0 ± 0.3 mi/day, respectively. Mice in the V and V + EX groups received a primary vaccination with 10^8 pfu recombinant vaccinia (rV)-CEA/TRICOM + 10^7 pfu recombinant fowlpox (rF)-GMCSF when mean tumor volume reached 30 mm³, followed by booster vaccinations with 10^8 pfu rF-CEA/TRICOM + 10^7 pfu rF-GMCSF at 2-wk intervals for 15 wks. At day 41 post tumor implantation, the mean tumor volumes in the HBSS, V, EX and V+EX groups were significantly different, 655 ± 138 , 381 ± 105 , 156 ± 61 , 100 ± 46 , respectively ($P < 0.001$), and all treatment groups had enhanced survival ($P < 0.001$). Furthermore, the V+EX group had significantly greater survival than the V group ($P < 0.05$). These results demonstrate that **exercise alone (in a prevention model, 8 wks prior to tumor implantation) is highly effective in reducing the growth of an immunogenic tumor and significantly increases survival**, suggesting that **exercise may augment in vivo immunosurveillance mechanisms**. Furthermore, these results demonstrate that exercise is a viable intervention that may yield significant clinical benefit when used in combination with therapeutic cancer vaccines.

Dr. Bleyer:

- Typical of the mice experiments, opposite results can be demonstrated.
- With the ability to do 1000s of experiments in mice in comparison to what can be done in people, there should be little surprise to have experiments reported in mice with paradoxical results
- One feature of this study that is better than the above report is that the mice were also treated for their cancer (as people would be treated) and the two together (exercise and cancer treatment) were more effective than either alone
- Remarkably, this study showed a greater reduction in the cancer with exercise alone than with the cancer treatment (a vaccine) alone
- Mice are one of men's best friends, but just like human friends, they can teach us different lessons

Nutrition

Anemia Is a significant prognostic factor in local relapse-free survival of premenopausal primary breast cancer patients receiving adjuvant cyclophosphamide/methotrexate/5-fluorouracil chemotherapy

Dubsky P, Sevela P, Jakesz R, et al, for the Austrian Breast and Colorectal Cancer Study Group
Clinical Cancer Research 14, 2082-2087, April 1, 2008.

Anemia during breast cancer chemotherapy is associated with increased local (in the breast or adjacent tissue) recurrence of the cancer

Purpose: To determine the effects of anemia on local relapse-free, relapse-free, and overall survival (LRFS, RFS, and OS, respectively) in premenopausal, primary breast cancer patients receiving adjuvant polychemotherapy, and to determine which conventional prognostic factors affected these outcomes.

Experimental Design: Four hundred twenty-four premenopausal patients with early-stage primary breast cancer and hormone receptor-expressing tumors were treated with i.v. cyclophosphamide/methotrexate/5-fluorouracil (CMF) polychemotherapy as part of an adjuvant phase III trial (Austrian Breast and Colorectal Cancer Study Group Trial 5). The influence of anemia (hemoglobin < 12 g/dL) on LRFS, RFS, and OS was evaluated in a retrospective analysis.

Results: Of 424 patients, 77 (18.2%) developed anemia on CMF chemotherapy. After a median follow-up time of 5 years, 8.9% of nonanemic patients had local relapse compared with 19.6% of anemic patients ($P = 0.0006$). Although mastectomy was associated with anemia (26% versus 13.7% in breast conserving surgery; $P = 0.002$), multivariate analysis did not show mastectomy per se to be a significant risk factor

for LRFS. Age, lymph node status, and hemoglobin had an independent significant influence on LRFS ($P < 0.005$). Anemic patients had a relative risk of 2.96 (95% confidence interval, 1.41-6.23) for developing local relapse in comparison with nonanemic patients.

Conclusion: Premenopausal breast cancer patients who developed anemia during the CMF regimen had significantly worse LRFS. In Austrian Breast and Colorectal Cancer Study Group Trial 5, anemia may have contributed to an almost doubled incidence of local recurrence in the chemotherapy arm. Molecular targets associated with tumor hypoxia and distinct from erythropoiesis should receive further attention in experimental and clinical settings.

Dr. Bleyer:

- ☑ The correlation between cancer progression/recurrence and anemia may be age- or cancer-specific. In children with acute lymphoblastic leukemia (the childhood leukemia), anemia is a favorable prognostic factor; the lower the hemoglobin the more likely the child will survive.
- ☑ An alternative explanation in breast cancer patients is that those who developed anemia had more nutritional deficiencies (e.g. folate or vitamin B12 deficit) and an associated chemotherapy-induced anemia that was worse because of the nutritional status [see next article and commentary]

Anemia increases risk of breast cancer recurrence

NEW YORK (Reuters Health) - Tue Apr 1, 2008

Review, analysis and commentary on the prior report

Women with breast cancer who developed anemia during chemotherapy had nearly three times the risk of local recurrence as those who did not develop anemia, according to a study published this week.

"We speculate that there may be an interaction between chemotherapy/radiotherapy and anemia," study chief **Dr. Peter Dubsy, from the Medical University of Vienna, Austria**, said in a statement.

"Both treatment modalities have been shown to be less effective in anemia patients. Since we do not see the effect in terms of relapse-free survival, the interaction with local adjuvant treatment may play a more important role," Dubsy added.

The results are based on a study of 424 premenopausal women with early-stage disease who were treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) after surgery, as part of the Austrian Breast and Colorectal Cancer Study Group Trial 5. All of the women who had breast-conserving surgery received radiation, whereas radiation was optional in women who had radical mastectomy.

The findings, appearing in the April 1st issue of the journal *Clinical Cancer Research*, indicate that 19.6 percent of women who developed anemia experienced a relapse during 5 years of follow-up compared with just 8.9 percent of women without anemia. This translates into nearly a three-fold increased risk of relapse in anemic patients.

Women without anemia experienced a significantly longer local relapse-free survival than women with anemia, according to the study.

Overall relapse-free survival, however, was not significantly affected by anemia status. "The effect was limited to local recurrences. Any explanation of the limit is pure speculation," Dubsy said.

No difference in overall survival was noted either, although Dubsy believes this may simply be a function of relatively small patient numbers and length of follow-up.

SOURCE: *Clinical Cancer Research*, April 1, 2008.

Dr. Bleyer:

- ☑ Not considered—or at least not discussed—by the authors is the possibility that poor nutrition, associated with a greater likelihood of anemia during chemotherapy, was the underlying cause of earlier cancer progression

Fasting before chemotherapy may protect cancer patients, study suggests

By Denise Gellene

Los Angeles Times - April 5, 2008

Mice that go without food before chemotherapy had fewer side effects and a higher survival rate than mice allowed to need ad lib. A human trial is planned.

Starving mice for a few days before chemotherapy treatments protected their healthy cells from damaging side effects, offering a possible way to shield cancer patients from the debilitating hair loss, nausea and anemia that now plagues the treatments, researchers reported Tuesday.

The study, published in **Proceedings of the National Academy of Sciences**, could also allow the use of more potent chemotherapy doses without endangering patients.

Valter Longo of USC, who led the research, said healthy cells deprived of nourishment stop dividing and become more resistant to stress. That makes them less vulnerable to chemotherapy, which targets cells that are dividing.

Because cancer cells do not respond to their environment in a normal way, starvation does not protect them from the drugs, said Longo, who conducted the research with scientists at **USC and Giannina Gaslini Institute in Genoa, Italy**.

The experiment looked at how healthy and cancerous cells reacted when they were exposed to toxins after being denied glucose, a simple sugar. Healthy yeast cells, for example, were 1,000 times as resistant to chemotherapy damage as yeast cells containing a tumor gene.

An experiment in mice confirmed the protective effects of fasting. Of the 28 mice that received only water for 48 to 60 hours before chemotherapy, one died. By contrast, 20 of the 37 mice that did not fast died from treatment. All mice were given an amount of the cancer drug etoposide equivalent to three times the maximum human dose.

Fasting mice that survived treatment had no visible side effects, researchers said, compared with the second group of mice, which became sluggish and developed ruffled hair because of the drug.

Longo said colleagues at USC/Norris Comprehensive Cancer Center are planning a clinical trial to study the benefits of fasting in cancer patients taking chemotherapy drugs. The trial is expected to begin this year, he said.

People with cancer should not fast before treatment without consulting their doctor because forgoing food could be harmful to some patients, Longo warned.

Dr. Bleyer:

I have a quite different explanation based on research I participated in while at the University of Washington

Foods eaten shortly before chemotherapy are avoided thereafter—a typical Pavlovian reaction—as shown in rats and humans (Bernstein IL. Learned food aversions in the progression of cancer and its treatment. *Ann N Y Acad Sci.* 1985;443:365-80).

It's quite possible that the mice who were allowed to eat their chow stopped eating after chemotherapy because they extinguished their taste for the food and died of malnutrition due to taste aversion.

See two study reports in the Exercise section above for comments on the value of experiments in mice

Fasting found to reduce chemo side-effects

WASHINGTON (Reuters) - Tue Apr 1, 2008

By Maggie Fox, Health and Science Editor

Comment from oncologists on study described in above news report

A few days of fasting might help protect patients from some of the unpleasant and dangerous side-effects of cancer chemotherapy, researchers reported on Tuesday.

They said mice given a high dose of chemotherapy after fasting thrived while half of a group of well-fed mice died, they reported in the *Proceedings of the National Academy of Sciences*.

The researchers stressed that people should not try this on their own yet but said the findings might lead to a way to use chemotherapy to more effectively kill tumors while sparing healthy cells.

"The clinicians tell me that if it works everybody will do it," said Valter Longo of the University of Southern California, who led the study.

People say "they are miserable after they get the chemo and they lose weight because they don't want to eat after they get the chemo."

His lab is preparing to test the idea in humans.

Longo and colleagues first tested yeast cells, then human cells in lab dishes. They found healthy cells starved of nutrients survived the ravages of chemotherapy -- but not cancer cells.

"In theory, it opens up new treatment approaches that will allow higher doses of chemotherapy. It's a direction that's worth pursuing in clinical trials in humans," cancer researcher **Pinchas Cohen of the University of California, Los Angeles**, who was not involved in the study, said in a statement.

Longo and colleagues said animals fed a low-calorie diet live longer, in part because their cells can resist stress better. They also noticed that starved cells go into a kind of hibernation mode, while cancer cells form tumors because they lack an "off" position, growing uncontrollably.

Longo wondered if the starvation response might be a way to differentiate healthy cells from cancer cells. One reason chemotherapy causes side-effects is that it affects all active and growing cells -- tumors, but also hair follicles, the lining of the intestines and other cells.

"We administered an unusually high dose of etoposide (80 mg/kg) to ... mice that had been starved for 48 hours. In humans, one-third of this concentration of etoposide is considered to be a high dose and therefore in the maximum allowable range," they wrote.

The high dose killed 43 percent of the mice that were fed normally but just one starved mouse. The starved mice regained their lost weight within four days.

"**They can start eating and being well right away**," Longo said in a telephone interview.

They found the effect with four different chemotherapy drugs, he said.

An even higher dose killed all of the well-fed mice from a different genetic strain but none of the starved mice, and again the mice that fasted regained their weight.

Other cancer experts said a few days of fasting would not harm most cancer patients.

"This could have applicability in maybe a majority of patients," said **Dr. David Quinn of the University of Southern California**.

"We have passed the stage where patients arrive at the clinic in an emaciated state. Not eating for two days is not the end of the world," agreed **Felipe Sierra, director of the Biology of Aging Program at the National Institute on Aging**.

Dr. Bleyer:

None of the invited experts comment on the food aversion theory I cite in comments on prior article

"They [the mice] start eating and being well right away" could also apply to humans, who we have observed avoid favorite foods on day they start emetogenic chemotherapy

Related Articles

Taking the scary out of breast cancer stats

By Carol Tavriss and Avrum Bluming

Los Angeles Times - April 17, 2008

Headline-grabbing reports citing alarming risk factors are often meaningless

American women fear breast cancer more than heart disease, according to most studies, even though heart disease is responsible for 10 times as many female deaths every year -- and heart disease deaths exceed breast cancer deaths in every decade of a woman's life.

Of women who are diagnosed early with breast cancer, more than 90% will survive, and most will not need disfiguring mastectomies or even chemotherapy. But the media understand how deeply women fear breast cancer, and the result is that every study that seems to find a link between some new risk factor and the disease makes headlines everywhere, captures public attention and stimulates the blogosphere into overdrive.

Grapefruit is the most recent culprit. According to a study in the Journal of the American Medical Assn., eating a quarter of a grapefruit a day increases the risk of breast cancer by 30%. For many women, grapefruit immediately was toast.

To assess these studies for their real-life implications, let alone for making decisions about our own behavior, the public needs to **understand the difference between absolute risk and relative risk**. If we

tell you that the relative risk of breast cancer is increased by 300% in women who eat a bagel every morning -- Relax! It's not! -- that sounds alarming, but it is not informative. You would need to know the absolute numbers of bagel-eating breast cancer patients. If the number shifted from one in 1,000 women to three in 1,000 women, that is a 300% increase, but it's meaningless. If the risk had jumped from 100 women to 300, we might reasonably be concerned.

In the large epidemiological studies that generally include tens of thousands of people, it is very easy to find a small relationship that may be considered "significant" by statistical convention but that, in practical terms, means little or nothing. For example, in July 2002, the **Women's Health Initiative reported a 26% increase in breast cancer risk for women on hormone replacement therapy**, which sounded worrisome. Even if that number were statistically significant -- and it was not, by the way -- this is what it translates into: The risk of breast cancer would **increase within the studied population from five in 100 women to six in 100 women.**

We now have a fat file folder of all the studies we could find that have reported an association between some purported risk factor and breast cancer. Of these, the ones that got the most attention were three Women's Health Initiative reports. In 2002, investigators found an increased relative risk of 26% from using combined estrogen and progesterone; in 2003, it was 24%; and in 2004, the relative risk from using estrogen alone was minus 23% (suggesting it was protective against breast cancer).

To put those findings in perspective, consider these published studies showing the increased **relative** risk of breast cancer from:

- * eating fish: 14%
- * eating a quarter of a grapefruit a day: 30%
- * gaining more than 33 pounds in pregnancy: 61%
- * being a Finnish flight attendant: 87%
- * being a Dutch survivor of childhood famine: 201%
- * using antibiotics: 207%
- * having a diagnostic chest X-ray: 219%
- * being an Icelandic flight attendant: 410%
- * using an electric blanket: 630%

(but only if you are a black woman who used it for more than 10 years but less than six months in a given year).

Why was there no call for Icelandic flight attendants to quit (or transfer to Lufthansa), for black women to use electric blankets for more than six months a year but only for nine years, for labeling antibiotics as carcinogens? Because these findings, which were improbable to begin with, were never replicated. In contrast, the increased relative risk of lung cancer from smoking is consistently between 2,000% and 3,000%. That's a finding that means something.

Unfortunately, good news doesn't travel as fast as fear does. In 2006, the Women's Health Initiative investigators reanalyzed their data and found that the risk of breast cancer among women who had been randomly assigned to take hormone replacement therapy was no longer significant. Women assigned to take a placebo but who had used hormone replacement therapy in the past actually had a lower rate of breast cancer than women who had never taken hormones.

This reassuring but non-scary news did not make headlines. Neither did the real findings from the March 2008 Women's Health Initiative report, which followed women in the sample who had stopped taking hormones for the previous three years. The researchers reported that the risk of cardiovascular events, malignancies, breast cancers and deaths from all causes was higher in the hormone-replacement-therapy group than in the placebo group even three years after stopping the therapy -- pretty alarming. But when we read the article closely, we saw that not one of the associations between hormone replacement therapy and breast cancer, or between the therapy and mortality rates from any cause, was statistically significant. Unfortunately, this did not stop the investigators from highlighting their negative findings as meaningful and troubling, and that is what most of the media picked up.

No wonder the public, assaulted by numbers and frightening headlines, alternates between panic and cynicism. Physicist **Richard Feynman** once said, "**If something is true, really so, if you continue**

observations and improve the effectiveness of the observations, the effects stand out more obviously, not less obviously."

The association between hormone replacement therapy and breast cancer becomes less obvious with every study. We all want to understand the risk factors in breast cancer that are "really so," but to do that, we have to give up entrenched beliefs when the data do not support them, and look elsewhere. In the meantime, enjoy your grapefruit.

Carol Tavris, a social psychologist, is a coauthor of "Mistakes Were Made (but Not By Me)." Avrum Bluming is a clinical professor of medicine at USC and a medical oncologist.

Dr. Bleyer:

- ☑ The concept of relative risk (vs. absolute risk) is inherently difficult to understand; the authors make it easier.
 - ☑ I'm a fan of Feynman (as is Dr. Comerford). He's right to impugn results that don't get stronger with time and more observations
 - ☑ As you have been reading in these monthly summaries, the evidence for the benefit of exercise and nutrition on cancer prevention and recurrence is getting stronger and stronger
 - ☑ DEFEAT Cancer expect that the combination of exercise and nutrition (**E&N**) will be strengthened even more as studies are done of both, in comparison to the rate of increasing strength of the evidence for either alone
-