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## NCI, American Cancer Society Re-Evaluating Joint Guidelines On Mammography Screening

NCI and the American Cancer Society are re-evaluating their five-year-old consensus guidelines for mammography screening for breast cancer.

At issue is the recommendation that women age 40-49 get a mammogram every one to two years.

A number of key NCI officials are pushing to back away from that recommendation as a result of a controversial Canadian study that cast doubt on the value of screening in that age group, sources said.

(Continued to page 2)

*In Brief*

## Jay Moskowitz Reassigned; Healy To Run For Ohio Republican Nomination To Senate

**JAY MOSKOWITZ**, NIH Deputy Director for Science Policy and Technology Transfer, has been reassigned to the post of Deputy Director of the National Institute on Deafness and Communication Disorders effective Sept. 20. Moskowitz's responsibilities included two of the more controversial NIH programs: technology transfer and unconventional medicine. Following last November's Presidential elections, Moskowitz served as the NIH liaison with transition team of then President-elect Bill Clinton. The transfer will allow **Harold Varmus**, Clinton's choice for NIH Director, to appoint his own candidate for this political hotseat. NIH sources said Varmus has been holding informal meetings on NIH campus. . . . **BERNADINE HEALY**, former NIH Director, has entered her bid for the Republican nomination for the Senate seat of the retiring **Howard Metzenbaum**. In the May 3 Republican primary, Healy will face off with Ohio's Lt. Gov. **Mike DeWine**, who at this time has a strong lead among Republicans in the polls, and state Sen. **Eugene Watts. Joel Hyatt**, Metzenbaum's son-in-law and owner of a chain of legal service offices, is the only announced contender for the Democratic nomination. Healy's campaign is chaired by **Art Modell**, owner of the Cleveland Browns. . . . **GENITOURINARY** Cancer Update conference will be hosted by Roswell Park Cancer Institute Sept. 30-Oct. 2, Buffalo, NY. Contact Gus Mosso, RPCI, Tel. 609/466-1234. . . . **"RESPIRATORY HEALTH** Effects of Passive Smoking: Lung Cancer and Other Disorders," is a new publication by the Environmental Protection Agency. To order, include stock no. 055-000-00407-2 and send $29 per copy to Superintendent of Documents, PO Box 371954, Pittsburgh, PA 15220-7954. . . . **FOX CHASE** Cancer Center has a new affiliate, Riverview Medical Center of Red Bank, NJ.

## NCI, ACS To Seek Consensus On Mammography Screening

(Continued from page 1)

ACS has adhered to the 1988 guidelines, saying evidence still points to a benefit of mammography screening for women in their 40s.

Meanwhile, breast cancer activists caution that backing away from existing guidelines could cause confusion among consumers.

"We may need to temper our statements, but that always results in confusion in the women we have just educated," said Nancy Brinker, founding chairman of the Susan G. Komen Foundation and chairman of the President's Cancer Panel's Special Commission on Breast Cancer.

"My fear is that we may be taking away a useful tool," Brinker said to **The Cancer Letter.** "On a personal level, I have seen too many women who have had cancer detected who were in their 30s and 40s."

In another development that is likely to affect the recommendations physicians give to their patients, NCI's Physician's Data Query computer database has gotten out of the business of issuing cancer screening guidelines. In a change that took place Sept. 1, PDQ's screening section discusses the scientific evidence for various methods of cancer screening, but does not list "guidelines."

### Working Toward Consensus

NCI and ACS could achieve a consensus on mammography screening guidelines within three months, Peter Greenwald, director of NCI's Div. of Cancer Prevention & Control, said to **The Cancer Letter.**

Greenwald met last weekend with the ACS Detection and Treatment Subcommittee on Breast Cancer. The two groups also will try to involve women's groups and other organizations in the process, he said.

"It will take some discussion," Greenwald said to **The Cancer Letter**. "The closer we come to a consensus, the better."

Robert Smith, ACS senior director for detection, said ACS wants to work with NCI to achieve consensus, if that is possible.

"There was strong agreement from the committee that we should do our very best to achieve consensus on the guidelines," Smith said to **The Cancer Letter.** "The obvious benefit is that you have the two major institutions with a similar expression of recommendations, so it is less confusing to the public."

Over the past few months, NCI and ACS appeared to be headed toward a breakup of their 1988 consensus.

A number of NCI officials would like the Institute to back away from the 1988 recommendation for women age 40-49, sources said to **The Cancer Letter**. At an NCI workshop last spring, a panel of experts reviewed the data from screening trials (**The Cancer Letter**, April 2).

"For women 40-49, the panel felt there was no reduction in mortality from breast cancer that could be seen in the trials, and an uncertain mortality past 5-7 years," Greenwald said.

The workshop concluded that for women 50-69 years old, screening reduces mortality by 30 percent, Greenwald said.

At an ACS meeting last spring to review the data on mammography screening, most experts said the guidelines should remain unchanged, or even strengthened to recommend mammography screening every year for women age 40-49.

Though ACS is holding discussions with NCI, the society has not made a decision to alter its guidelines, Smith said.

"A majority of the breast cancer subcommittee members believes the historical evidence still provides sufficient confidence that mammography is effective for women over age 40," he said. "A lot has to do with what kinds of evidence you feel are useful. If you want to go by only the existing trial data, then you are in a different position. The committee must feel there is some room and a desire to work towards a common statement."

Any recommendation by the breast cancer subcommittee to change the guidelines would go to the ACS Detection and Treatment Committee, then to the Medical Affairs Committee, and then to the ACS Board for a vote. It is possible that the process could be completed in time for the ACS Board meeting in November, Smith said.

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Until this week, it appeared NCI was within weeks of publicly announcing its revised guidelines.

Those proposed guidelines are circulating at the Institute, sources said to **The Cancer Letter.** According to a draft, NCI was prepared to encourage women age 40-49, particularly those at higher risk of breast cancer, to consult their physician, but would not recommend routine mammography screening, sources said. It will be up to NCI's Executive Committee to make the final decision on the guidelines.

"We are going through a process," Greenwald said, characterizing NCI's guideline revision as "not imminent."

Greenwald also met this week with HHS Assistant Secretary for Health Philip Lee and other federal agencies.

"Over the next 3 months, we will assimilate all the information and decide on what the best message is," Greenwald said to **The Cancer Letter.**

**PDQ Leaves Guidelines To Others**

As part of NCI's process for developing new guidelines, the Institute's Physician's Data Query computer database no longer refers to "guidelines" in its cancer screening statements. PDQ is used by physicians and other health professionals worldwide for current treatment and screening information.

The PDQ Editorial Board, comprised of Institute staff and outside advisors, approved changes in August that, as of Sept. 1, take PDQ out of the business of issuing screening guidelines. Instead, PDQ refers to "summary of evidence statements." These statements present the scientific evidence for various cancer screening methods.

"The idea was to take the PDQ assessment of science out of the loop," NCI Deputy Director Daniel Ihde said to **The Cancer Letter** this week. "They [PDQ's screening experts] can give their opinions about the scientific data, but they do not write guidelines."

In its "summary of evidence statement" for breast cancer, PDQ has deleted the recommendation for regular mammography screening for women age 40-49.

"There is insufficient evidence to make an informed decision regarding screening in women ages 40-49 years old," the new statement reads.

In effect, PDQ "has made a disconnect between the scientific evaluation of data" and the issuing of guidelines, Ihde said. "The guidelines under consideration now will not be nearly so detailed as what you see in the PDQ system."

"It is the most truthful way to deal with the public," Barnett Kramer, director of DCPC's Early Detection & Community Oncology Program, and a member of the PDQ Screening Board, said to **The Cancer Letter.** "It makes it crystal clear what the facts are, and whenever guidelines change, you can go back into PDQ to look at the evidence statements to see why these guidelines came to pass."

**"Nothing Else As Useful"**

For activist groups working on behalf of women with breast cancer, the possibility of change in the 1988 guidelines is disconcerting.

The Dallas-based Komen Foundation has worked to promote mammography to women over age 40 since its inception. Mammography "is very much an informed decision on the part of a woman," Brinker said to **The Cancer Letter.** "Mammography has been determined to be extremely useful in women over 50. The studies have not been done to show that women under 50 benefit in terms of a mortality reduction."

In younger women whose cancers have been detected through mammography, "we don't know whether those women survive longer, but with everything I know personally, I would recommend to a woman to visit her physician and discuss it on a case-by-case basis," Brinker said.

"There is nothing else we have today that is as useful to detect breast cancer," she said. "It makes me sad that we are not farther along in our knowledge."

**In related developments:**

—The "Journal of the National Cancer Institute" will publish in the next few months the report from the NCI workshop, chaired by Suzanne Fletcher, editor of the "Annals of Internal Medicine."

—Experts in epidemiology and mammography screening are scheduled to meet Sept. 29-Oct. 1 in Geneva, Switzerland, at a meeting sponsored by the International Union Against Cancer (UICC) to review the data from screening trials worldwide and make recommendations for further research.

## PDQ's New Statement: For 40-49, Insufficient Evidence On Screening

Following is the text of PDQ's new statement on breast cancer screening (references and tables have been removed for lack of space; consult PDQ for full text):

**Summary of Evidence**

General: Clinical examination of the breasts and mammography are the basic screening methods. These examinations are complementary and both are necessary to achieve maximum detection rates.

Ages 40-49: There is insufficient evidence to

make an informed decision regarding screening in women ages 40-49 years. In the first 5-7 years of follow-up there is no reduction in breast cancer mortality that can be attributed to screening; there is an uncertain and, if present, marginal reduction in mortality at about 10-12 years; only one study provides information on long-term effects beyond 12 years, and more information is needed.

Ages 50-69: There is strong evidence that, at ages 50-69, screening on a regular basis is effective.

Ages 70 and over: There is insufficient evidence to make an informed decision regarding screening in women at age 70 and older.

**Significance**

In the U.S., breast cancer is the number one cancer in women, with an estimated 180,000 new cases expected in 1992. The incidence has been increasing at an annual rate of 1% over the past 50 years, with only a slight increase in the mortality rate. A woman's lifetime risk is now 1 in 9 of developing breast cancer. In 1992, 46,000 breast cancer deaths were expected. It was the leading cause of death from cancer in women until 1987, when lung cancer took first place. The incidence has been increasing in an interesting way, to be discussed later, but the mortality rate is rather constant, having increased only 1.5% since 1973. Breast cancer in American males constitutes less than 1% of the annual incidence of breast cancer.

The risk of developing breast cancer is increased in women who have already had cancer in one breast or where there is a history of breast cancer in a mother or sister. Risk is also increased in women who have a diagnosis of atypical hyperplasia and possibly in women who have benign breast disease with hyperplasia but without atypia. However, for 85% of women the major risk factor is age. While many older studies have clearly shown a rising incidence with age, recent data from SEER (1987) show a drop-off in incidence rate after age 75. The true incidence of breast cancer may now be confounded by the recent increase in screening rates.

**Evidence of benefit**

In 1973-74, there was a sharp increase in the incidence of breast cancer in the US. This rise in incidence was due to the sudden increase in early detection activity associated with the publicity given the President and Vice President's wives' diagnoses of breast cancer. There was not only an increase in the number of cancers but a shift toward earlier stage and earlier age. This demonstrated the potential of public education to increase early detection rapidly.

In 1980, there began a second acute increase in breast cancer detection, which followed the publication of the American Cancer Society's breast cancer detection guidelines and the initiation of a Breast Cancer Awareness Campaign. NCI and other organizations also joined in the effort. Between 1980 and 1987, there was a 32% increase in breast cancer incidence.

This increase may be due in large part to mammographic detection. The rise in incidence has been associated with an increase in the sale of new mammographic machines and in the number receiving mammograms. The percentage of women over 40 years of age who obtained at least one mammogram rose from 37% in 1987 to 64% in 1990, and the percentage of women who had more than one and who followed the guideline rose from 17% to 31%. The increase has been in smaller cancers and in early stage disease.

The 5-year relative survival rate for breast cancer remained about 74% until 1980, when it increased to 77%. (In situ cancers were excluded from both the incidence and survival rates). The staging system of localized, regional, and distant disease is useful in showing long-term trends.

From 1981-1989, the 5-year relative survival rate for localized disease was 92% for white and 86% for black women, for regional disease it was 72% and 56%, and for distant disease it was 19% and 12%, respectively.

HIP Screening Trial: Randomized clinical trials have shown that early detection of breast cancer results in reduced breast cancer mortality. A study through the Health Insurance Plan of Greater New York to test the efficacy of screening was started in 1963. It involved 62,000 women 40-64 years of age who were randomized into study and control groups. The study group of 31,000 were offered a clinical breast examination and mammography; 67% accepted. After the initial screen, three subsequent annual screens were offered with a 39.4% compliance rate for all four screens.

The control group of 31,000 women received usual medical care, but were followed closely to determine the number of breast cancers and their stage, survival, and the number of ensuing deaths from breast cancer. The HIP trial, was not designed for subgroup analysis by age groups but age has been a focal point of analysis of results. In the first 5 years following entry into the trial, among study group women, 116 breast cancers were detected in the under 50 age group, 145 in the 50-59 age group, and 43 in the 60 and over group. The corresponding numbers in the control group were very similar (114, 133, and 48 for the three age groups, respectively).

The difference in breast cancer deaths between study and control groups was statistically significant

by 5 years after entry. At 10 years from entry, there were almost 30% fewer breast cancer deaths in the study group than in the control group. Differences in mortality due to breast cancer were statistically significant at 5 years from entry in women aged 50 and over, but not in women aged 40-49. However, with time, the number of breast cancer deaths was lower for women aged 40-49 who were diagnosed with breast cancer in the study group compared to those diagnosed in the control group. This evidence of benefit did not emerge until the ninth year of the study.

Improved Mammography and Detection: Using 1960's technology in the HIP trial and despite the fact that only 43% of the breast cancers in the study group were detected through screening (mammography or physical examination) the trial resulted in about a 30% decrease in mortality by the end of 10 years, 23% by the end of 18 years. In women over 50 years of age, shifts occurred from Stage III to Stage II, and from Stage II to Stage I. For women aged 40-49 at the time of screening, there was a shift to smaller sizes of cancers within stage I in the screened group.

From 1973-1982, as a result of the benefits of screening in the HIP Trial, ACS and NCI jointly funded the Breast Cancer Detection Demonstration Project (BCDDP) in 27 widely distributed geographic areas. This project was not a randomized trial, but a demonstration that large numbers of American women (280,000, 35-74 years of age) could be recruited for five yearly clinical and mammographic breast examinations. It was also designed to determine whether breast cancers would be detected earlier than the usual cases seen in community practice. The women in the BCDDP had an incidence rate nearly double that of the Third National Cancer Survey (TNCS) that was conducted from 1969-1971.

The TNCS was a cancer incidence population based survey covering ten cities and two states. The women in the BCDDP were a self-selected volunteer high-risk group. They were characterized by a higher than average income, more white, and more with a personal and family history of breast cancer than was seen in either the HIP Trial or in the general US population. It is noteworthy not only that the incidence rate was double the expected rate as compared to the TNCS, but the incidence of cancer in the age group 45-49 was the same as that in the 55-59 year age group.

Mammography techniques improved in the 1970's. In the HIP Trial, mammography was only able to detect 40% of the cancers in women aged 40-49 and 60% of the cancers in women aged 50-59. In the BCDDP, mammography had improved and detected breast cancer at nearly the same rate: 91% in women aged 40-49 and 92% for women aged 50-59.

Trials in other countries: Many trials have been conducted in other countries as outlined in Table 2. The majority of trials are consistent in showing a decrease in breast cancer mortality.

Benefits In Age 40-49: The segment of the summary of evidence recommending that women aged 40-49 have a mammogram every 1 or 2 years has been controversial. A clear benefit of screening for women aged 40-49 has not been demonstrated in the majority of clinical trials and case-control studies that have included this age group. However, the reasons advanced in support of it are as follows:

1. Twenty-four percent of all deaths from breast cancer occur in women who had the diagnosis made when they were under 50 years of age. Forty-one percent of all years of life lost from breast cancer in women under 80 years of age result from breast cancer diagnosed in women 35 to 49 years of age.

2. In the HIP study, a long term (10-18 years from entry) reduction of 24-25% was observed in breast cancer deaths among women 40-49 years of age with breast cancers diagnosed within 5 years from entry (statistical significance in dispute).

3. Mammography improved greatly between the time of the HIP study and the BCDDP. It improved to the point that breast cancer could be detected nearly as well in younger as in older women. This was also confirmed by in situ, tumor size, and lymph node involvement. Mammography was better in in the 1970's (BCDDP) and was even better in the 1990's. In absence of a control group, comparisons have been made with experiences in SEER programs to assess effectiveness of BCDDP. These show improvement in breast cancer survival and reduced mortality from breast cancer among women aged 40-49 years at entry.

Benefits in Age 75+: There is very little evidence regarding the benefit of mammography with or without clinical breast exam in women 75 and older since no study has data at entry in these older age groups. Nonetheless, it seems prudent to continue screening at regular intervals unless morbid disease is sufficiently severe to limit expected survival or to cause undue short-term discomfort.

Breast Self-Examination: One cohort study found fewer deaths due to breast cancer and improved estimated 5-year survival rates among women who reported performing BSE than among women who reported no BSE. In a nonrandomized breast cancer screening trial in the United Kingdom that included BSE, the preliminary results suggest that following

training in BSE, women found slightly smaller tumors; but no mortality reduction has been reported as yet.

A case-control study in the Seattle area indicated that the frequency of BSE did not differ between advanced-stage breast cancer cases and control subjects: self-described proficiency in BSE was generally low in case and control subjects. Problems, such as self-selection, study design, and recall information associated with studies of the effectiveness of BSE led the Preventive Services Task Force to make no recommendation about the inclusion or exclusion of teaching BSE during the periodic health examination. BSE is considered a supplement to, rather than a substitute for, screening with CBE and mammography.

Palpable Lesions Physicians should be aware that some palpable breast cancers (10%) are not visible on mammograms. Accordingly, all clinically suspicious palpable lesions should be biopsied even though they may not be seen with mammography.

## Memorial Sues Empire Blue Cross Over Reimbursement For Therapies

Memorial Sloan-Kettering Cancer Center has filed a suit seeking a precedent-setting ruling on reimbursement for cutting edge cancer therapy.

In an action against Empire Blue Cross and Blue Shield of New York, filed in the New York Supreme Court (docket No. 93-122816), the cancer center is demanding $2 million in reimbursement for the treatment of 21 patients who received high dose chemotherapy with blood product support as well as for the 37 patients who were treated with Taxol.

In addition, Memorial is seeking $10 million in punitive damages.

### Unusual Suit

The suit is unusual because the plaintiff is a health care provider rather than a patient whose insurance claims had been denied. In a press release, Memorial said it is seeking reimbursement from Empire directly, to avoid taking collection actions against the patients involved.

"This is the only case we are aware of where a health care provider is trying to test the principle of what kind of standard an insurer is applying to decide what kind of care is appropriate," Minna Schrag, an attorney for Memorial, said to **The Cancer Letter**.

"We think that the standards that Empire is trying to apply really need to be challenged," said Schrag, an attorney with the New York firm of Proskauer, Rose, Goetz & Mendelsohn.

Responding to Memorial's announcement of the suit last week, Empire defended its position.

"Empire must be fair to all its customers by using their premiums to cover proven and appropriate medical care and upholding the principle that health insurance was never meant to pay for clinical research," the insurer said in a written statement.

"Covering experimental medicine would force premiums up by hundreds of dollars a year for millions of customers already burdened by high health insurance costs, and would subject many people to hazardous treatments with no proven benefit to their health," Empire's statement read.

Grace Powers Monaco, a patient advocate and attorney who arranges expert review of insurance claims for cutting edge treatments, prased Memorial for filing the suit.

"A cancer center that feels so strongly about the appropriateness of the care it provides to patients that it is willing to shoulder the responsibility of going after the third party payor can certainly be considered a patient advocate," Monaco said to **The Cancer Letter**.

Empire, which serves 8 million people, works differently from most health care plans, which reimburse the patients. Empire, by contrast, contracts directly with the hospitals, including Memorial.

### Actions Costly, Delay Treatment

Most institutions that contract with Empire require patients to guarantee payment prior to treatment, which has led some patients to seek emergency relief against the insurer in court. In most cases, these petitions prevail, but such actions are both costly and likely to delay treatment.

"It is unconscionable that cancer patients must routinely drag, or threaten to drag, Empire into court and suffer uncertainty and delay before they receive treatment that could save their lives," said Roger Parker, Memorial's senior vice president, hospital administration.

"Empire's denial of these claims is unreasonable, inconsistent and arbitrary," Parker said. "Empire has refused to pay for the most effective treatments because it labels them 'experimental.' Empire would, however, pay considerable amounts for less effective 'standard' treatments."

According to court documents, Memorial did not require its patients to guarantee payment.

Empire's refusal to reimburse these claims has therefore undermined the hospital's ability to care for uninsured patients, the suit claims.

"Best treatment must be an option," said George Bosl, head of Memorial's Div. of Solid Tumor Oncology. "Taxol and high dose chemotherapy combined with stem cell support clearly cause tumor shrinkage with the potential for cure in patients with either metastatic disease or a high likelihood of recurrence."

"It is the physician's ethical responsibility to offer the patient the best therapy for his or her condition," said Larry Norton, chief of the Breast and Gynecologic Cancer Medicine.

"It would be a gross abrogation of that responsibility to deny such treatments solely on the basis of an insurance company's ignorance of current data produced by our country's most prestigious research hospitals," Norton said.

**Patients Denied Coverage, Suit Says**

According to the complaint, Empire has refused to pay the total of $1.5 million for high dose chemotherapy with blood product support treatment of 21 patients since 1990. In addition, the insurer declined $600,000 in claims for Taxol treatment involving 37 patients.

According to the complaint, Empire does provide reimbursement for standard treatment, which would require long hospitalization and would be ineffective.

After Taxol first became available, Empire reimbursed all claims for therapy with the drug. Subsequently, the complaint states, "Empire arbitrarily and unreasonably changed its position and stopped paying for Taxol treatments for some patients, while continuing to pay for Taxol treatments for other patients whose history and condition were not significantly different."

Also, Empire paid for some Taxol treatments for some patients, but denied reimbursement for other Taxol treatments for the same patients, the complaints states.

In several cases, Empire made a unilateral decision to recoup its earlier payments for Taxol treatments by reducing payment for Memorial's claims for unrelated services, the suit claims.

Both in the cases of Taxol and HDC with blood product support, Empire rejected Memorial's payment requests without having an oncologist examine the patients' medical histories and without the review of literatire demonstrating the efficacy of Taxol.

According to Memorial, Empire subjects about 40 percent of the cancer center's claims to medical review, which causes months of delay in processing claims. By contrast, other insurance companies subject about 10 percent of Memorial's claims to such review, the complaint states.

The causes of action in Memorial's complaint include breach of contract by Empire, violations of New York insurance and general business laws as well as violations of the state and city human rights laws. The latter claim is based on Empire's denial of reimbursement for HDC with blood product support for breast cancer, which affects women. At the same time, the company reimburses a similar treatment for testicular cancer, which affects men, the suit states.

## Randomized Low-Fat Diet Trial In Early Breast Cancer To Begin

A randomized trial to investigate the possible adjunct effects of a low-fat diet (15% Kcals) on the recurrence and survival rate in women with stage I and II breast cancer has been funded by NCI and will begin this month.

Peri and postmenopausal women receiving standard surgical, tamoxifen, or chemotherapeutic treatment will be enrolled. Its Principal Investigator is Ernst Wynder of the American Health Foundation, and its co-principal investigators are George Blackburn, Cancer Research Institute, New England Deaconess Hospital, and Rowan Chlebowski, Harbor UCLA Medical Center.

Nutritional aspects of the trial are coordinated by The Nutrition Coordinating Center of Minneapolis under the direction of Marilyn Buzzard, and the statistical coordinating eenter is under the direction of Robert Elashoff, at the UCLA Center for Health Sciences.

This outcome trial will involve a total of 2,000 patients. Some 20 cancer centers have already agreed to participate in this trial. Additional principal/affiliated centers are welcome. Funding is per patient accrual.To qualify, centers need to have an active breast cancer service and have access to an experienced research nutritionist.

Inquiries regarding participation in this trial and the detailed protocol can be obtained from the American Health Foundation, 320 E. 43 St., New York NY 10017 (Tel:212-9531900; FAX 212-687-2339). Ask for Wynder or Alice Shapiro, or contact either Blackburn (Tel: 617-632-8543; FAX: 617-6320235) or Chlebowski (Tel:310-222-2217; FAX:310-782-0486).

## Supplements Reduce Deaths In High-Risk Population In China

Nutrient supplements reduced the risk of dying from cancer and other diseases for healthy people and those with esophageal dysplasia in two NCI-sponsored studies in Linxian, China.

Both studies were conducted in a geographic region where the population has chronic nutrient deficiencies and increased rates of certain cancers.

The larger of the two studies, reported in the Sept. 15 issue of the "Journal of the National Cancer Institute," indicates that a specific vitamin/mineral supplement taken daily for 5 years reduced cancer incidence and mortality, as well as overall mortality, among residents of Linxian county in North-Central China. This preliminary, statistically significant finding comes from a trial reported by William Blot, of NCI. The smaller study is reported by Jun-Yao Li, Cancer Institute, Chinese Academy of Medical Sciences, Beijing. Both trials tested for protective effects of vitamin/mineral combinations used to supplement a diet typically low in the intake of several vitamins and minerals.

The potential cancer-prevention benefits of vitamin/mineral supplementation may or may not be applicable in countries such as the United States, where there is much higher dietary consumption of these vitamins and minerals, say editorial writers Steven Bennern and Waun Hong, of M.D. Anderson Cancer Center.

### Diets Low In Fresh Fruit

The typical diet in Linxian County is low in fresh fruit, meat, and other animal products; diet staples include wheat, millet, sweet potatoes, and corn. Rates of esophageal and stomach cancer in this county are among the highest in the world, over 100 times US rates and 10 times those of other areas of China.

In the study described by Blot, 29,584 Linxian residents aged 40 to 69, drawn from the general population, were randomly assigned to receive daily, in the form of an individual oral tablet, one of seven vitamin/mineral supplement combinations (at one to two times the U.S. Recommended Daily Allowance) or a placebo for five and one-fourth years.

Mortality and incidence were monitored for esophageal, gastric cardia (the upper stomach joining the esophagus), the remainder of the stomach, and other cancers.

Among the group receiving a combination of beta carotene, vitamin E, and selenium, mortality from all causes was reduced by 9 percent, cancer deaths dropped by 13 percent, and stomach cancer deaths decreased by 21 percent (all reductions statistically significant). No statistically significant effect was found for any of the other supplements.

The second article by Li descrlbes a smaller study of 3,318 Linxian residents aged 40-69 with esophageal dysplasia, a known precursor of esophageal cancer. Participants were randomly assigned to receive a daily supplement of 14 vitamins and 12 minerals (at two to three times the U.S. RDA) or a placebo for six years.

Using the same methods as in the larger study, cancer lncidence and deaths were monitored. A statistically nonsignificant decrease (8 percent) in esophageal/gastric cardia cancer deaths was observed; however, a more substantial decrease (38 percent) of borderline statistical significance in stroke and other cerebrovascular disease was found.

The researchers speculate that the intervention may have come too late if individuals with dysplasia are less amenable to the potential benefit of nutrient supplementation. Further investigation of the cerebrovascular findings is warranted, they add.

In their editorial on the two studies, Benner and Hong point out that in the multistep process of epithelial cell cancer development (including esophageal and gastric tumors), it is believed genetic abnormalities accumulate over time; response to chemopreventive agents may decrease as genetic damage increases.

This phenomenon may explain why cancer reduction was observed in the larger study of the general Linxian population, but not in those with esophageal dysplasia. Benner and Hong note that more chemoprevention studies are needed to establish dosages, define intermediate markers of efficacy that could shorten the length and cost of trials, and explore the to implications for public health recommendations.

## NCI Contract Awards

Title: Nutrition Intervention Trials in Linxian, China
Contractor: Chinese Academy of Medical Sciences, Beijing, $60,468.

**The Cancer Letter** welcomes Letters to the Editor and other items of interest to cancer professionals. Items may be sent to PO Box 15189, Washington, DC 20003, or via FAX to 202/543-6879.