Debate Rages Over Breast Cancer Study

A proposal for a massive trial to investigate a possible link between fat consumption and breast cancer has hit some scientific roadblocks

Maureen Henderson. *The preliminary study shows that a full-scale trial is feasible.*

AFTER months of vigorous debate, the National Cancer Institute will soon decide whether to fund a $130-million study to investigate a possible link between breast cancer and fat consumption. The study, which would be the most expensive single experiment ever funded by the institute, has seen its political prospects rise and fall over the past year as various committees have argued over its pros and cons.

At one point, an NCI advisory group voted in favor of proceeding with the trial, but later reversed itself when new data cast doubt on the proposal and the price of the trial ballooned more than tenfold. The fate of the study, which would involve rigorously controlling the diets of some 10,000 women and monitoring them over 10 years, is likely to hang on a report that will be presented to a key NCI advisory group on 7 January. The report, written by a group of outside experts, is expected to recommend that the clinical trial not be conducted at this time.

"The toughest question has been, 'Is this hypothesis sufficiently credible to justify a study of this magnitude?' " says Philip T. Cole, an epidemiologist at the University of Alabama's School of Public Health in Birmingham who is chairing the group of experts. Their report will be presented to the NCI's Board of Scientific Counselors.

Breast cancer is the second leading cause of cancer deaths among women in the United States. In 1987, it accounted for an estimated 41,000 deaths, according to NCI figures. A consumer brochure published by NCI about the role of nutrition in cancer prevention says that a low-fat diet "may reduce the risk" of breast cancer. "The operative word in that sentence is 'may,' " says David Byar, head of NCI's biometry branch and an advocate of the study.

For the past 40 years, evidence from animal and human studies has suggested that dietary fat might be linked to breast cancer. Animal studies in the early 1940s first indicated a possible relationship when rats fed a high-fat diet and exposed to a carcinogen developed more mammary tumors than a control group.

Much of the current interest has been generated by human data collected internationally in the past 15 years, says Ross Prentice, an epidemiologist at the Fred Hutchinson Cancer Research Center in Seattle who has played a key role in designing the proposed study. Prentice has collected information from 21 countries about breast cancer rates for women 45 to 69 years old and national data on fat calories consumed per capita. When the two factors are plotted against each other on a graph, a straight line can be drawn through a scattering of dots representing the data from each country. Prentice found no correlation between breast cancer incidence and intake of nonfat calories, from foods including carbohydrates and protein.

Other studies indicated that women who migrated from countries where low fat diets are the norm to a country with higher fat consumption eventually "adapt" to the second country's higher rate of breast cancer. For example, the incidence of breast cancer among women from Poland rose after they migrated to the United States, Prentice says. Similarly, the rates among women who have migrated from Japan and China to the United States increased also, but more slowly, according to other studies. The biological mechanism underlying a possible relationship between fat and breast cancer is still a mystery to researchers.

The international and migrant information tantalized NCI enough in 1983 to approve in concept a large-scale trial to test the relationship between fat and breast cancer more directly. The project as originally conceived by NCI was itself ambitious in size and design. The randomized trial would include 6000 women who are healthy but have a family history of breast cancer or became pregnant for the first time after age 25. It would test whether an intensive educational campaign could successfully teach the women, ranging in age from 45 to 69, to cut their fat intake, and it would analyze whether the low-fat diet would lead to a drop in breast cancer incidence.

The goal of the trial is to cut the women's total fat consumption from 40% of total calories, which is common among Americans, to 20%. (Total fat includes saturated and unsaturated fats.) Women would have to be highly motivated to enroll because they would have to modify their lifestyles, their approach to grocery shopping, cooking, and eating. They would be taught to change their food habits by attending 2-hour seminars run by nutritionists once a week for 6 weeks. Every 2 years they would keep 4-day food records and have their blood sampled for serum cholesterol levels. The women would be tracked for a total of 10 years.

But before embarking on the massive project, NCI first funded a smaller study to test whether women could be recruited easily enough and also whether participants would actually adhere to the dietary changes over a long period. The 2-year feasibility study subsequently showed that women could be recruited and that they would stick to the food plan, says one of the lead investigators of the project, Maureen Henderson, director of the cancer prevention research unit at the Hutchinson Center. About 1500 women in Seattle, Houston, and Cincinnati have signed up so far. Nearly 200 women have been monitored for 2 years for compliance and the results showed they maintained a low-fat diet compared to the controls, Henderson said.

But as part of the feasibility study, Prentice, who is a highly regarded epidemiologist, reviewed NCI's assumptions in the study design. He found major statistical flaws. As a result, he recommended that the original study size be increased more than five times to 32,000 women, including some 20,000 controls. With that, the price tag of

the trial soared from about $20 million to a staggering $130 million for total costs.

Prentice found that NCI had overestimated the expected reduction in breast cancer rates. The institute had predicted that the low-fat diet would lead to a 35% drop in breast cancer incidence almost immediately. Prentice said in an interview, "We assumed that there would a gradual reduction and that the rate would drop 17% over the length of the trial, 10 years." The sample size then had to be enlarged to detect the smaller reduction.

As the cost of the study increased, doubts about the wisdom of the study began to appear. NCI advisory groups challenged the strength of the hypothesis. They questioned the validity of the animal, international, and migrant data. They debated whether total calories rather than fat could play a role in reducing the cancer rate. They raised the possibility that the trial would target the wrong age group; a low-fat diet might only make a difference when it is followed by younger women.

They questioned the trial's methodology too. They were uncertain whether the small-scale study would adequately predict compliance for the thousands of women to be enrolled.

In the past 6 months, four NCI advisory groups have debated the study protocol. Transcripts from the meetings stack up a foot high. The NCI policy advisory committee, which had initially voted unanimously in July to go ahead with the large-scale trial, recommended 2 months later not to proceed with it. The National Cancer Advisory Board, whose members are a mix of nonscientists and researchers, decided it did not have enough expertise and bounced the issue back to the Board of Scientific Counselors. The scientific board then said it did not have the capability either. On 15 December a special subcommittee of the scientific board met to discuss the issue one more time before writing their recommendations.

Subcommittee chairman Cole remarked in an interview that the hypothesis of the trial "is somewhere between dubious and speculative." He and others challenge the international data, for example. They note that the United States is above the line on the graph comparing breast cancer incidence against fat calories, which raises the possibility that other factors besides fat consumption are important. "That is a real concern," remarked Paul Engstrom, vice president of cancer control at the Fox Chase Cancer Center in Philadelphia and chairman of one of NCI's advisory committees, at a National Cancer Advisory Board meeting in September.

American data cited by Cole muddies the neat international correlation. According to Cole, fat consumption in the United States has risen from roughly 25 to 30% of total calories at the turn of the century to about 40% in 1980. But breast cancer mortality rates have remained fairly steady for about the same time period.

In addition, "The migrant data are much less clear," Cole remarked in an interview. There is no doubt that the daughters of migrant women move toward the breast cancer incidence of the host country, he said, but it is troublesome that some first generation migrant women, such as Asians, do not show the higher cancer rates as quickly. They may have been protected by their low-fat diets when they were young, or, as Prentice argues, some migrant women change their native diets slowly. There is speculation, although not very good evidence, that hormones may play a role in prevention or that the ratio of polyunsaturated fats to saturated fats in the diet influence breast cancer rates.

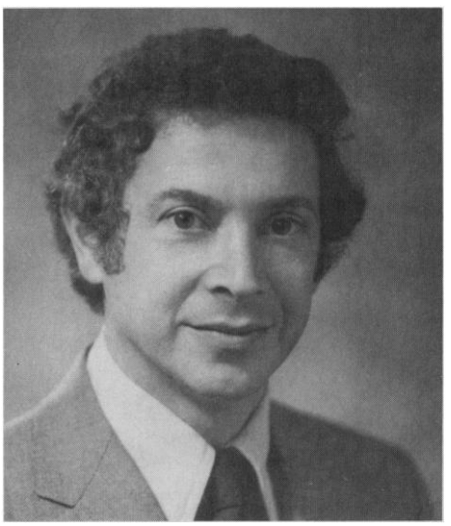
Cole says there have been "many epidemiological studies on breast cancer and diet, but there have been severe limitations in each of the studies. I think it's fair to say that these studies have not supported a link with fat in the diet and breast cancer. The better studies have been the least supportive."

Morever, the animal data "are very difficult to interpret," Cole remarked. "The associations [between fat intake and mammary tumors] are complex and may only apply to certain situations." In some studies, for example, the animals exposed to a carcinogen developed tumors but were "deprived of calories."

The advisory groups spent a lot of time discussing the need for a biochemical marker to verify that the women are complying with the low fat diet. But there is no consensus about what the marker itself should be. In the feasibility study, serum cholesterol was monitored. But findings from a separate study conducted simultaneously cast doubts on the validity of relying on this as a marker and prompted one NCI advisory group to reverse its vote and recommend that the full-scale trial not be conducted.

The study, sponsored jointly by NCI and the U.S. Department of Agriculture (USDA), examined the relationship between two groups of women on precise diets consisting of 40 and 20% fat and their serum cholesterol levels. The 49 women involved were actually fed breakfast and dinner prepared by the USDA and given special box lunches.

The study found that the cholesterol levels of the women on the 20% diet dropped substantially. But the levels among women in the feasibility study did not fall as much.



Peter Greenwald. *"How much evidence do you need to support the hypothesis before doing the trial?"*

This made some NCI advisers skeptical that the women in the feasibility study were reporting accurately what they were eating, perhaps because they had not properly learned how to measure their fat intake. And, given the sheer size of the study, the advisers worried that too many women would not adhere to the low fat diet for 10 years and feared that the study would amount to a waste of effort and money.

"The USDA study was irrelevant," argues Henderson. It "was a short-term study, so it is not appropriate to compare it to the long-term results of the feasibility study. I think the change of heart by the advisory committees comes from the fact that the trial will cost lots of money to study one type of cancer."

Henderson and Prentice also argue that the study design does not exclude the possibility that a low-fat diet among young women may be important in preventing breast cancer. But the proposed study is structured to test how to block the promotion, not the initiation, of cancer, they say.

Peter Greenwald, director of NCI's division of cancer prevention and control, says, "Any study is a bit of a gamble. The question is, 'How much evidence do you need to support the hypothesis before doing the trial?' If we can't convince a group of reasonable scientists, then there's a problem. The main issues have been scientific."

But Henderson says with frustration, "I really think it comes down to money." Prentice acknowledges that the trial is "very expensive. I have sympathy for the reviewers." But at this point, after months of deliberations, "I think everyone is tired of arguing," says Prentice. ■ **MARJORIE SUN**