

TAMOXIFEN AND BREAST CANCER

HEARING
BEFORE A
SUBCOMMITTEE OF THE
COMMITTEE ON APPROPRIATIONS
UNITED STATES SENATE
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SECOND SESSION

SPECIAL HEARING

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TAMOXIFEN AND BREAST CANCER

TUESDAY, APRIL 21, 1998

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN
SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 1:40 p.m., in room SD-192, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.
Present: Senators Specter and Faircloth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENTS OF:

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RICHARD D. KLAUSNER, DIRECTOR, NATIONAL CANCER INSTITUTE

NONDEPARTMENTAL WITNESSES

STATEMENTS OF:

DR. NORMAN WOLMARK, CHAIRMAN, NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT
HELENE WILSON, PARTICIPANT, NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT, BREAST CANCER PREVENTION TRIAL
CYNTHIA PEARSON, EXECUTIVE DIRECTOR, NATIONAL WOMEN'S HEALTH NETWORK
DR. BERNARD FISHER, CHAIRMAN AND PRINCIPAL INVESTIGATOR, NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT

OPENING REMARKS OF SENATOR SPECTER

Senator SPECTER. The hearing of the Subcommittee on Labor, Health and Human Services, and Education will now proceed.

We very much appreciate this distinguished group coming in today. We have Dr. Harold Varmus, head of NIH, Dr. Richard Klausner, head of the NCI, and our distinguished panelists, Ms. Cindy Pearson, Ms. Helen Wilson, and Dr. Norman Wolmark.

We have convened this hearing in order to examine the progress which has been made on tamoxifen. The very remarkable news was released recently about a single pill a day having very dramatic results for women who are at high risk for cancer. Just yesterday,

the information came out about raloxifene and the tremendous strides which that pill has given with lesser side effects. There is a great concern publicly about what the import of these two pills are, where we are heading on further studies, where we are heading on further announcements.

I know there is to be some official statement made in the near future and we are in the midst, at this moment, of considering the budget for the National Institutes of Health. It is always controversial as to whether we are going to get the kind of funding we are looking for.

It seems to me at this particular time, with the budget very much under consideration and with so much public interest in these two pills, that it would be very useful to have this hearing.

There has been much said about dramatic increases in funding for NIH. But, Congress has not been quite so ready to appropriate the funds.

Last year, we had a sense-of-the-Senate resolution to double NIH funding in 5 years. Then, when last year's budget came down, the health account was \$100 million short.

Senator Harkin and I joined together to offer an amendment to add \$1.1 billion, an across the board cut, which was defeated 63 to 37. This year, again the accounts for this subcommittee were frozen.

Although some may make calculations about an increase in NIH funding, it would have to come out of the other vest pocket, so it is not there. Again, Senator Harkin and I offered an amendment this time to increase NIH funding by \$2 billion, which is still short of doubling in 5 years. It would take about \$2.7 billion to do that.

Again, that amendment was defeated on the Senate floor 2 weeks ago Thursday when we finished up on our budget considerations.

We have been successful in having very significant increases in cancer funding—from fiscal year 1995, \$2.13 billion; 1996, \$2.25 billion; 1997, \$2.39 billion; and 1998, \$2.55 billion. We were successful last year in finding some \$907 million after conference. We had \$952 million in the Senate mark. We are trying to project ahead this year for even more funding.

It is a question as to whether the increases in funding have led us to the remarkable progress on these two pills and whether additional funding would produce even more.

Although many grants are being awarded, the number is 28 percent. There are still many doors which are unopened as to what those research applications would bring.

For those reasons, we are very pleased to be able to proceed at this relatively early moment to have what I consider to be a very important hearing.

I am delighted to yield to my distinguished colleague from North Carolina.

OPENING REMARKS OF SENATOR LAUCH FAIRCLOTH

Senator FAIRCLOTH. Thank you, Chairman Specter. Thank you for holding this hearing.

As you know, we are gathered today to respond to the recent NIH decision to stop one of their research trials 14 months earlier

than planned. This decision has resulted in both celebration and some confusion and concern.

But this announcement offers hope for the first time to women of great risk of developing breast cancer, women who live with the knowledge that every woman in every generation in their family has developed the disease.

For the first time, women will be able to take steps to protect themselves from developing breast cancer by taking a pill every day. This is certainly an exciting and remarkable step forward.

I want to commend the NIH for stopping the trial once the results became known. You cannot argue with a 45-percent reduction in breast cancer.

But I especially want to commend the women, the brave women, who were willing to enter this trial before these results were known. These women fought for this trial to be held and for their right to participate in it. They did so on behalf of their sisters, daughters, nieces, aunts, mothers, and grandmothers. They did it for women all over. We owe them a debt of thanks.

We also owe them our promise that we will exercise responsibility in communicating this remarkable news as quickly and as widely as possible and address any questions about risks and side effects which demand attention.

I thank you, Mr. Chairman, and I look forward to hearing the testimony.

Senator SPECTER. Thank you very much, Senator Faircloth.

We would like to proceed with our customary approach of 5 minutes for opening statements. To the extent that the witnesses can conform to that, it would be appreciated. If you take some extra time, we understand that.

All statements will be made a part of the record.

SUMMARY STATEMENT OF DR. HAROLD VARMUS

We are going to lead off now with Dr. Harold Varmus, who has been Director of the National Institutes of Health since November 1993. While at the University of California at San Francisco, Dr. Varmus earned the Nobel Prize for his work on the causative link between certain genes and cancer. He is a graduate of Amherst College, Harvard University, and the Columbia Medical School.

Again, Dr. Varmus, you are a frequent guest, visitor, lecturer, and witness here. You may proceed.

Dr. VARMUS. Thank you very much, Mr. Chairman. I want to congratulate you for holding this very timely hearing to discuss these extremely important issues.

Senator Faircloth, thanks to you as well.

Before other members of the panel talk about the topic that has brought us here today, namely the tamoxifen trial, I would like to provide a very brief perspective on prevention and the kind of research on which it is based.

At the NIH, indeed medical research in general has a long and deep commitment to various strategies for preventing disease, strategies that block the initiation of disease processes, strategies that slow the appearance of manifestations of disease, and strategies that reduce the complications of disease.

The techniques and methods that underlie these strategies include vaccines against infections. They include healthy behaviors—low fat diet, exercise, smoking cessation, and the avoidance of risks, such as accidents or sexually transmitted infections.

Strategies to prevent disease include early diagnosis, like colonoscopy, blood pressure measurements, various x-ray techniques, including mammography, tests for prostate specific antigen and other indicators of early disease, screening for eye disease by examination.

The last strategy includes the use of medications, the topic of today's discussion, which is used to control diabetes or hypertension, to reduce cholesterol levels or to interfere with transmission of HIV from mother to child. There are many such drug based prevention strategies.

These strategies each incorporate a wide range of risks and benefits for every individual who undertakes them. Let me give you a couple of examples.

Smoking cessation may be difficult for an individual to achieve, but it presents, by itself, no risk and offers major reductions in the incidents of certain common diseases.

Exercise, another example, entails little risk but offers modest reduction in the incidence of some common diseases. Vaccines may be associated with a little more risk in some cases, but often protect nearly completely against diseases, some common and some uncommon diseases.

The use of a variety of drugs to reduce cholesterol levels or to control blood pressure will protect some, but not all, against coronary artery disease or renal disease with small or uncertain long-term risks.

There are many other examples, such as use of aspirin to try to reduce the incidence of coronary artery disease, again associated with a small degree of risk and some modest benefit.

Now in most of these situations, we ask the patient and the patient's doctor to consider all of the available information and then to make an individual decision. This is also true of the situation that applies to the topic here today, the chemoprevention of cancer, as we will discuss in more detail.

Now across this very broad range of prevention activities, we at the NIH are committed to obtaining through research that information that is necessary to make those decisions, and we are committed to transmitting the information that our research develops to the physicians and patients in a way that serves the patients' interests.

Thanks very much.

Senator SPECTER. Thank you very much, Dr. Varmus.

SUMMARY STATEMENT OF DR. NORMAN WOLMARK

Our next witness is the distinguished Dr. Norman Wolmark, president of the National Surgical Breast and Bowel Project, which oversees the National Breast Cancer Prevention Trial.

He is a principal investigator of the study's operation center, located at the Allegheny Campus of the Allegheny University of Health Sciences, a graduate of McGill University Medical School,

professor and chairman of the Allegheny University's Department of Human Oncology of the Health Sciences.

Welcome, Dr. Wolmark. We look forward to your testimony. The floor is yours.

Dr. WOLMARK. Thank you, Senator Specter, Senator Faircloth. I am grateful for the opportunity to review the data from the breast cancer prevention trial which, after all, is the basis of this afternoon's discussion. I would briefly like to summarize the conduct of this study.

Senator FAIRCLOTH. Doctor, if you don't mind, would you pull the microphone up much closer, please.

Dr. WOLMARK. Much closer. Very well.

How's that?

Senator FAIRCLOTH. That's fine. Thank you, and I'm sorry.

Dr. WOLMARK. Between June 1992 and September 1997, 13,388 women 35 years of age or older who were at increased risk for the development of breast cancer were randomized to receive either a placebo or tamoxifen for a period of 5 years. Neither the participant nor her physician was aware of the allocated treatment.

Women were eligible for this study if their breast cancer risk was at least as great as that of a 60-year-old woman.

An independent data monitoring committee not affiliated with the NSABP was established to review the risks and benefits of treatment on an ongoing basis. Following a regularly scheduled meeting of this committee on Tuesday, March 24, 1998, it was concluded that the primary endpoint of the study had been met, namely, that there was a substantial reduction of the incidence of invasive cancer attributable to the use of tamoxifen and that the overall benefits of treatment outweighed the overall risks.

It was only after this conclusion was reached that I or any other member of the NSABP operation center had an opportunity to review the results. The findings were then shared with Dr. Klausner, Director of the National Cancer Institute on Thursday, March 26, 1998, and we agreed to accept the recommendations of the data monitoring committee.

It was concluded that any additional data that could be gained by continuing the study in its double blinded form did not justify withholding this information from the participants. The results were publicly disclosed during a press conference held on Monday, April 6, 1998.

The reduction in the incidence of breast cancer as a result of tamoxifen treatment was highly significant. With a meantime on study of approximately 4 years, there was a 45-percent reduction in the number of invasive breast cancers and the data appear on the plotted graphs to your left, on the poster.

There were 154 invasive breast cancers in the group assigned to the placebo, compared with 85 in women who had received tamoxifen. There was a concomitant reduction in the incidence of noninvasive breast cancer from 59 in the placebo group to 31 for women treated with tamoxifen. These differences were seen across all age groups.

Tamoxifen also reduced the number of hip, wrist, and spine fractures from 71 in the placebo group to 47 in the treated participants.

The use of tamoxifen was also associated with infrequent, but potentially life-threatening, adverse events. Although these adverse events were no greater than had been predicted prior to the initiation of the study, they must be given careful consideration in determining the propriety and utility of tamoxifen.

The risks associated with tamoxifen appear on the bar graph to your right. The risk of tamoxifen associated adverse events was predominant in women older than 49 years of age. In this age group, there were 26 endometrial cancers in the tamoxifen treated group compared with 6 in the placebo group. There was also an excess of vascular events, or thromboembolic phenomena, stroke or transient ischemic attacks, 81 in the tamoxifen group versus 53 in the placebo group. The increased risk of vascular events was similar to that noted in postmenopausal women taking hormonal replacement therapy.

There was no increased incidence of ischemic heart disease, including myocardial infarction.

We can conclude that the benefits of tamoxifen are achieved at the price of an increased incidence of adverse events.

There are, however, well defined patient categories in whom the benefits appear to outweigh the risks. These categories include: (1) Women who are under 50 years of age in whom, to date, there has been no excess of endometrial cancer or thromboembolic phenomena; (2) women older than 49 years of age who have had a hysterectomy. This is not a small group and it actually comprised 37 percent of all women entered into our study. Finally, and in all likelihood, the third group were women with a history of lobular carcinoma in situ or atypical hyperplasia.

Senator Specter, in your introductory remarks you mentioned that another drug is on the horizon which seems to have equivalent efficacy to tamoxifen with perhaps fewer adverse effects. We believe that it is absolutely critical to determine what the true efficacy of raloxifene is compared to tamoxifen using the scientific method, namely that of a large, randomized, prospective clinical trial.

We also view this trial, the breast cancer prevention trial, as only one step in a continuum that will undoubtedly lead to better agents with fewer adverse side effects. And in order to be able to accomplish this vital task, we will require the total support and commitment of you and the other members of this committee.

PREPARED STATEMENT

In conclusion, I would like to echo the remarks made by Senator Faircloth, which is to acknowledge the courage, the conviction, the selflessness, the dedication of the 13,388 women who participated in this trial. Clearly, this is their achievement and the recognition belongs to them.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. NORMAN WOLMARK

Good afternoon, Senator Specter and members of the Subcommittee. I am Norman Wolmark, Chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP).

In April of 1992, the NSABP, with funding from the National Cancer Institute, initiated the Breast Cancer Prevention Trial (BCPT) in order to determine whether the non-steroidal anti-estrogen, tamoxifen, could reduce the incidence of breast cancer in women who were at high risk for the development of the disease. Prior to initiation, the study was approved by an NCI appointed peer review committee, the Food and Drug Administration, the Office for Protection from Research Risks (OPRR) and the Institutional Review Boards of the more than 300 institutions who enrolled participants in the trial. In addition, an Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC) was established and charged with the task of reviewing the toxicity of treatment and adverse side effects, as well as the effectiveness of tamoxifen. ERSMAC members were not affiliated with the NSABP. The data were not available to me or to any other member of the NSABP Operations Center until it had been determined by this committee that the primary endpoint of the trial had been met. ERSMAC functioned in an independent manner and the recommendation to disclose the data was made taking into account the benefits and risks of tamoxifen therapy.

Between June of 1992 and September of 1997, 13,388 women 35 years of age or older who were at increased risk for the development of breast cancer were randomized to receive either a placebo or tamoxifen for a period of 5 years; neither the participant nor her physician was aware of the allocated treatment. Women were eligible for this study if their breast cancer risk was at least as great as that of a woman 60 years of age.

Following a regularly scheduled meeting on Tuesday, March 24, 1998, ERSMAC members concluded that the primary endpoint of the study had been met, namely, that there was a substantial reduction in the incidence of invasive breast cancer attributable to the use of tamoxifen and that the overall benefits of treatment outweighed the overall risks. It was only after this conclusion was reached that I or any other members of the NSABP Operations Center had an opportunity to review the results. The findings were then shared with Richard Klausner, M.D., Director of the National Cancer Institute and other representatives of the National Cancer Institute on Thursday, March 26, 1998 and we agreed to accept the recommendations of ERSMAC. It was concluded that any additional information that could be gained by continuing the study in its double-blinded form did not justify withholding this information from the participants. The results were publicly disclosed during a press conference held on Monday, April 6, 1998.

The reduction in the incidence of breast cancer as a result of tamoxifen treatment was highly significant. With a mean-time on study of approximately 4 years, there was a 45-percent-reduction in the number of invasive breast cancers; there were 154 invasive breast cancers in the group assigned to placebo compared with 85 in women who had received tamoxifen. There was a concomitant reduction in the incidence of non-invasive breast cancer from 59 in the placebo group to 31 for women treated with tamoxifen. The reduction in the incidence of breast cancer was seen across all age groups and the magnitude of this reduction persisted throughout the period of available follow-up. Tamoxifen also reduced the number of hip, wrist and spine fractures from 71 in the placebo group to 47 in treated participants.

The use of tamoxifen was also associated with infrequent but potentially life-threatening adverse events. Although these adverse events were no greater than had been predicted prior to the initiation of the study, they must be given careful consideration in determining the propriety and utility of tamoxifen in reducing breast cancer risk. The risk of tamoxifen-associated adverse events was predominant in women older than 49 years of age. In this age group, there were 26 endometrial cancers (cancer of the uterus) in the tamoxifen treated participants compared with 6 in the placebo group. There was also an excess of "vascular events" (thromboembolic phenomena, stroke and transient ischemic attacks), 81 in the tamoxifen group versus 53 in the placebo group. The increased risk of "vascular events" was similar to that noted in postmenopausal women taking hormonal replacement therapy. There was no increased incidence of ischemic heart disease including myocardial infarction.

The results of this study are the first from a randomized prospective trial to show that tamoxifen can significantly reduce the incidence of breast cancer in women who are at high risk for the development of this disease. When considering the use of tamoxifen in order to decrease the incidence of breast cancer, one must weigh the benefits against the adverse effects. Having said this, there are well defined patient categories in whom the benefits appear to outweigh the risks. These categories include: (1) women who are under 50 years of age in whom, to date, there has been no excess of endometrial cancer and thromboembolic events; (2) women older than 49 years who have had hysterectomies (a group which represented 37 percent of all

women entered into this study); and (3) women with a history of lobular carcinoma in situ or atypical hyperplasia.

Efforts are currently underway to better define the risk benefit ratio associated with tamoxifen. This task must be carried out in a careful, methodic and step-wise manner. The model that was used to predict the risk of breast cancer prior to the initiation of the study must now be refined in light of the actual breast cancer incidence observed. This may enable the revised model to more accurately define the risk benefit ratio of tamoxifen treatment in specific populations. These efforts have been initiated by the NCI and members of the NSABP Biostatistical Center.

It must be emphasized that the results from this study apply only to women who are at increased risk for the development of breast cancer and have characteristics that would have made them eligible for this study. Examples of these high risk characteristics appear in Attachment A. Results of this trial as well as the characteristics that defined high risk, have been disseminated through the April 6, 1998 joint NCI/NSABP press release and related documents including commonly asked questions with answers and copies of tables of the data presented at the press conference of April 6, 1998. This information has been placed on two internet web pages: the NCI Clinical Trials page (<http://cancer.trials.nci.nih.gov>) and the NSABP web page (<http://www.nsabp.pitt.edu>). In addition to the broadcast of the press conference on national television, the results of the trial have been publicized in the press. Responses to a recent survey distributed by the NSABP to individuals at BCPT participating sites and feed-back from our Participant Advisory Board indicate that, on the whole, women have responded in a measured and thoughtful manner to the information.

From a global perspective, it is important not to regard this chemoprevention trial as an isolated study, but rather as part of a continuum of studies that will enhance our understanding of breast cancer. This study is a clear demonstration of proof of principle that the evolution of this disease can be altered. It is our hope that the results from the present study will lead to the rapid implementation of the next chemoprevention trial in which it is anticipated that effective agents with fewer side-effects can be identified. If this effort is to succeed, we will require the continued help and support of this Subcommittee.

Finally, I would like to acknowledge the courage, dedication and perseverance of the 13,388 women who participated in this study. This is their trial and the credit for the findings belongs to them.

TAMOXIFEN AND RALOXIFENE

Senator SPECTER. Dr. Wolmark, before proceeding to Dr. Klausner, let me assure you that you have my support and I am confident the support of the entire subcommittee, full Appropriations Committee and the Congress. We want to be as helpful as we can. With the public news in the last couple of weeks about tamoxifen and the news yesterday about raloxifene, we want to know what we can do further to help.

Dr. Klausner has made the comment publicly and we will hear from him in a moment or two about the fact that there is no easy message to send home at this particular point given the side effects.

What we want to do is to find out what the timeline is. When do you expect to be able to answer some of the questions about tamoxifen, as to the collateral problems which have appeared in the news media. What are the relative benefits of raloxifene? It has less on some forms of cancer, such as cervical cancer, as I read in the media, and when results can be expected and whether additional funding at this time would expedite the processes which you are under.

So those are the issues which we look at here today. We want your guidance as to how we can be helpful to you. This is the place to come, the appropriations subcommittee.

Dr. Klausner, welcome again to the subcommittee. Dr. Richard Klausner is the 11th Director of the National Cancer Institute with

a research specialty in the regulation of genetic networks in human cells. He is a graduate of Yale University and Duke Medical School. He has served in a variety of leadership posts in the medical research community at NIH and has published extensively in the scientific literature.

Thank you for joining us, Dr. Klausner. The floor is yours.

SUMMARY STATEMENT OF DR. RICHARD D. KLAUSNER

Dr. KLAUSNER. Thank you, Mr. Chairman and Senator Faircloth.

Let me make a few points about this study. First, it is a step forward and, to answer your query, it would not have happened without the support of the NIH. It takes us across a threshold into a new area of cancer research and, ultimately, of cancer practice but with new questions and new conundrums. It is the offspring of much previous work and it must be followed by a good deal more for many questions remain.

As Dr. Wolmark said, with this study women at high risk of breast cancer now have, for the first time, a demonstrated option to consider in order to lower their risk. While this study did demonstrate an overall 45 percent risk reduction, we would like to know many things: whether tamoxifen delays the discovery of breast cancer or truly prevents it, perhaps by destroying very early cancers or precancerous lesions. We do not yet know for how long tamoxifen can or should be given. We do not know if it would be possible to predict whether certain women at high risk for breast cancer would benefit more or less than others from tamoxifen.

If chemoprevention of cancer is to work, which I believe it will and which this study demonstrates in principle, we will need even more effective agents and agents with fewer side effects.

We are confident that newer, selective estrogen response modifiers, this whole class of chemicals called SERM's, will be available at least for testing for future clinical trials, for they are the only way in which we will determine whether, indeed, new agents have those desired characteristics.

As we have all emphasized, the decision to consider tamoxifen for preventing breast cancer is a very complex one and one that must be made between a woman and her physician.

It will depend first upon a best attempt to assess the risk that any particular woman has of getting breast cancer. The expected reduction of that risk that this study gives and the clear risks of side effects also demonstrate it.

Weighing the benefit of a reduced risk of one disease as opposed to an increased risk of other problems can in part be calculated but, in the end, will depend very much on how all of these risks are perceived by each woman.

There will be no cut and dry formula for this. What is necessary is the delivery of clear and useful information which the NCI and the NSABP has, we believe, been trying to do. In fact, we are particularly concerned as to how the information that has been released over the last several weeks has served, or whether it has served, the needs of women and their physicians.

Soon after the release of the study, the NCI began monitoring over 300 NSABP sites, all 57 NCI cancer centers, the 19 regional centers of the Cancer Information Service, and directors of 10 advo-

cacy organizations to determine whether physicians and women felt they had adequate information to respond to inquiries and their concerns.

About 3,500 inquiries to date have been analyzed and the majority have felt that the information available was adequate. And we are also using the many questions that we received in this input to update and improve constantly the resources available to people.

The message that we should not rush to judgment, that we cannot oversimplify this message, was clear from all.

In my discussions with physicians and with advocacy groups at multiple recent town meetings that I have had around the country, with our cancer centers, with directors of the American Society of Clinical Oncology and many others, we all agree that the deliberate process of digesting new information, of discussion, and the dissemination of information is how we will all proceed.

I would like to commend the media for what I think has really been a superb job at reporting the excitement, the limitations, the complexity and the caution that attends this study and for communicating well the personal decisionmaking that the emerging availability of preventive interventions for cancer will demand. If there is any one take-home message, it is one of individual risk.

In moving forward, the NCI will work to help communicate tools to physicians to calculate a woman's risk of breast cancer along with her. We are now making available breast cancer risk determination materials to health care providers. They can be obtained through our website, through the Internet, by e-mail, or through the telephone based Cancer Information Service to enable physicians to utilize the risk models that we used in this study.

Importantly, we will soon convene and support the much needed research to continue to improve and refine risk assessment. We will, as I said, support the critical research we need to answer questions about whether other agents are more effective and with less side effects and work to help try to define those for whom taking these drugs poses a risk.

PREPARED STATEMENT

Our colleagues at Pittsburgh and elsewhere, and especially all the women who participated in this trial, are to be congratulated. That we move forward from this point with deliberative wisdom of the community is the prudent, indeed the only, way to best serve women at risk for breast cancer.

We all thank you and the committee for your support of the NIH, support that enables us to conduct important studies, such as these.

Senator SPECTER. Thank you, Dr. Klausner.
[The statement follows:]

PREPARED STATEMENT OF DR. RICHARD D. KLAUSNER

Good afternoon, Senator Specter and members of the subcommittee. I am Richard Klausner, Director of the National Cancer Institute (NCI). I am pleased to testify before you today on a remarkable advance in cancer prevention.

The goal of preventing cancer has long been a hope and a central focus of the National Cancer Program. Prevention can take many forms, from smoking cessation and other behavioral changes to vaccines or antimicrobial agents against cancer-causing infections to a new field in which medicines specifically interfere with the

biologic processes of cancer development. For the past several years, the National Surgical Adjuvant Breast and Bowel Project (NSABP), an NCI-funded national clinical trials organization, has been carrying out a historic trial—called the Breast Cancer Prevention Trial, or BCPT—to determine whether women at increased risk of developing breast cancer can prevent the development of that cancer by taking a well-known medicine, tamoxifen. More than 13,000 women who participated in this study have been our partners in this work.

As with all of our clinical trials, an independent Endpoint Review, Safety Monitoring, and Advisory Committee regularly examines the data generated by the study to monitor whether either unacceptable or unexpected toxicities have arisen or whether the trial has succeeded in answering the questions it has been designed to answer. This committee met most recently on March 24. The committee concluded that the question of whether tamoxifen can significantly reduce the incidence of breast cancer in women at increased risk had been answered; and the answer is an unequivocal yes. Nevertheless, there were, as you have heard, adverse effects of tamoxifen which may make the very personal decision about taking tamoxifen complex. For all of these reasons, the committee recommended that the participants of the study be notified of these important results. It has been our commitment to the participants from the very start to notify them as soon as clear results had been achieved.

On March 26, the NSABP leadership presented these recommendations and the data behind them to the NCI and we—NCI and NSABP—agreed to accept the recommendations of the independent advisory committee. This afternoon, NCI and NSABP will share this information with you, describing the study, its results, and its implications, and very importantly, place this study in the context of the larger march of science and research towards the control of this dread disease.

The results are remarkable. They tell us that breast cancer can be prevented. A forty-five percent decrease in the incidence of this disease represents one of the more dramatic findings we have seen. They represent the power of the Nation's investment in research and the value of carefully conducted clinical trials. The insight that tamoxifen might prevent breast cancer came from another NSABP clinical trial for the treatment of breast cancer. That this drug does prevent breast cancer fits with our deep understanding of the role of estrogen and estrogen receptors in breast cancer and an enormous amount of science about this drug, which has been under study for over 25 years.

While it is tempting to generalize, our conclusions must adhere to the data available. For women whose predicted risks of breast cancer match those of the participants of this study, they have the option to take tamoxifen with confidence that it can lower the risk of developing breast cancer. This study provides the evidence for the magnitude of this reduction, as well as the extent of a variety of risks that women who take this drug could face. Women need to discuss with their physicians their own risks for breast cancer and the benefits and risks of taking tamoxifen. The NCI will provide information about this study to the public and health care providers through the Cancer Information Service (CIS) and through PDQ and the new NCI clinical trials web site. The data from this study will continue to be analyzed and the information will be made available through peer reviewed publications and via the different communication outlets of the NCI.

The NCI is committed to communicating the importance of research findings to women and their physicians in a clear and understandable manner. NCI has solicited feedback about the impact the Breast Cancer Prevention Trial announcement has had on those who counsel women regarding their decision to take tamoxifen for the prevention of breast cancer. The feedback concerning the handling of the announcement and the materials provided to date has been very positive. This feedback is being used to assist NCI and the NSABP to develop tools to help each woman, and her health care provider, when making a decision about whether use of tamoxifen is appropriate for her.

The preliminary findings from a survey of Cancer Center Directors, NCI's Cancer Information Service, Principal Investigators of the NSABP, and the advocacy community indicate that it has been possible for them to respond to most inquiries and counseling requests using information already provided by NCI and NSABP. This information was disseminated through existing NCI and NSABP communication mechanisms before or at the time of the public announcement of the trial's early results. A new mechanism was also used. NCI launched on the day of the announcement a new clinical trials web site, which included information about the benefits and risks of tamoxifen.

For women whose risks of developing breast cancer fall within the range of this study, tamoxifen can provide, for the first time, an option to reduce that risk, much

as new cholesterol-lowering medication can reduce the risk of heart attacks. But that option must be weighed carefully and on an individual basis.

This emphasis on individual risk is important. Our ability to identify individuals at risk for disease and to begin to rationally intervene, based upon our knowledge of the disease process, is what medicine will become.

Great interest has been generated about genetic predisposition to breast cancer, and we know that some breast cancer is linked to certain mutations. It is likely that some of the women in this study, especially those with very strong family histories of breast cancer, carry such a genetic predisposition. While it is reasonable that such women would also experience a decreased risk of breast cancer with tamoxifen, no specific gene testing has been done. As further analyses of the data from this clinical trial are done, we hope to be able to provide more information over the next 6–12 months as to whether women with alterations in BRCA 1 and 2, the two known genes whose alterations predispose to breast cancer, were protected from cancer in this trial. I would like to emphasize, however, that there are many important considerations as to how new knowledge about genetics can and should be made a part of medical decision-making that further complicate this process.

This study is not an end. It is rather a very propitious beginning. But it tells us that it is possible to prevent breast cancer. Tamoxifen is far from ideal. Its efficacy is only partial and it has significant risks. To move forward will require new agents and new clinical trials. Newer selective estrogen receptor modifiers are being developed and will be tested. The NCI hopes to be able to follow this study soon with additional clinical trials to find answers to the many questions that remain.

Thank you, Mr. Chairman, for your continued support for cancer research. I would be pleased to answer any questions the Subcommittee may have.

HIGH RISK CATEGORY

Senator SPECTER. Before moving to Ms. Wilson, let me ask you a question which is on the minds of people who have heard you generally and certainly people who have heard you today. A woman knows she is in the high risk category for breast cancer. She has seen the preliminary studies. She knows that there are possible, adverse side effects. She wants to take tamoxifen. Is it available for her today if her individual doctor prescribes it?

Dr. KLAUSNER. Of course, tamoxifen is an approved drug and so a physician certainly could prescribe it. We want to emphasize that for those women, it is important to sit down with their physician to make sure that perceived risk of breast cancer is accurate and to understand what possible side effects she might experience, how to look for them. And, as Dr. Wolmark said, even with that, one size does not fit all. Women below 50 seem to experience, so far in these 4 years of this study, no significant increased risk associated with tamoxifen. But we need to see how that goes. Women above 50 had significant risks.

We are concerned about the underlying risk factors of women which they might have for clotting events and whether or not a woman has a uterus. It is uterine cancer that was the cancer that is increased from taking tamoxifen.

So the message very much is each woman is different. The message of hope, I think as you will hear from Ms. Wilson, is that there are many women who are at very high risk of breast cancer and this does provide an option.

Senator SPECTER. So the option of tamoxifen is available today with the categories and risks outlined. The specifics ought to be reviewed by her own physician, but help is presently available with tamoxifen.

Dr. KLAUSNER. Of course, this drug is not approved by the FDA for this use. Immediately upon receiving this information, the data from NSABP, from the study, was forwarded to the FDA, as well

as to the company that provided the tamoxifen, Zeneca, and a process will begin, has begun, in an expedited way, to review all of this data by the FDA in order to evaluate it for this indication.

Senator SPECTER. Dr. Klausner, as you say, tamoxifen has been approved by the FDA but it has not been approved for this specific purpose.

Dr. KLAUSNER. That's right.

Senator SPECTER. A physician may prescribe an approved drug for another purpose if the physician feels that it meets the needs and is a remedy for that other purpose.

Dr. KLAUSNER. That's right, sir.

Senator SPECTER. So even though it is not approved for breast cancer, a doctor may prescribe tamoxifen for breast cancer.

Dr. KLAUSNER. It is approved actually for breast cancer in the treatment setting. We are talking about being approved not for breast cancer but for use in healthy women to reduce the risk of breast cancer that the FDA will be looking at.

Dr. VARMUS. I might add, Senator Specter, that Michael Friedman, who is the lead deputy of the FDA, has promised that he will complete the FDA review of this particular use within 6 months.

SUMMARY STATEMENT OF HELENE WILSON

Senator SPECTER. Well, we want to explore why 6 months. We will do that after we hear from Ms. Wilson.

Ms. Wilson, welcome.

Ms. Wilson is a resident of North Wales, PA, a patient in the tamoxifen clinical trial. She is a registered nurse who manages clinical trials for a major pharmaceutical company and also serves as a member of the study's participant advisory board.

She is a nursing graduate of Mercy College.

We welcome you here today, Ms. Wilson, and look forward to your testimony.

Ms. WILSON. Good afternoon and thank you very much for inviting me this afternoon to testify about my experience as a participant in the NSABP breast cancer prevention trial.

As you just mentioned, I am a resident of North Wales, PA, a registered nurse and a divorced mother of two children. I have a daughter, age 30, a son, age 26, and I have a granddaughter, age 1.

I am currently employed by Merck & Co., where I am a senior manager in clinical research and manage clinical trials using our Merck products.

This career has provided me with experience and an understanding of the conduct and efficacy issues surrounding clinical trials.

I became a participant in the breast cancer prevention trial, the BCPT, in October 1992, and finished taking my 5 years of study drug therapy which actually turned out to be tamoxifen therapy in October 1997.

When I discovered that I was eligible to participate in the BCPT, I felt as though I had won the lottery. I was elated at being offered a chance to take a proactive step toward preventing breast cancer.

My maternal grandmother, my mother, my mother's sister, and my father's sister all died of breast cancer. And as if this were not enough devastation for one family to endure, early signs of this

dreadful disease began affecting me. I have had approximately seven biopsies, most of which turned out to be benign.

However, the last few biopsies showed signs of atypical hyperplasia and microcalcifications, both thought to be strong indications of impending breast cancer. In my doctor's words, I was a "walking time bomb."

People have asked why I joined the trial. Because of my strong family history and what was beginning to be a personal history, I felt that enough is enough. I needed to do something other than just wait for the cancer to occur. Before hearing about the BCPT, I was seriously considering undergoing a procedure called prophylactic mastectomy. That is a procedure where both breasts and the surrounding tissue are removed. This would have been an attempt to escape the onset of breast cancer.

Since even this drastic step did not offer complete confidence that I would not develop breast cancer, I decided to forego the mastectomies until I heard more about the BCPT.

I met with individuals at our local hospital, the Montgomery Cancer Center, who extensively explained the study, the consent form, and the risks and benefits of tamoxifen and participating in a clinical trial. I completed a risk assessment form used to evaluate my relative risk for developing breast cancer, underwent blood tests, a physical, a gynecologic exam, a mammogram, and was finally accepted into the trial as a participant.

Being a participant in the BCPT has been a very positive experience. I feel that I am doing something proactive in my own care, which is very important to me. I do not want to sit back and just wait for breast cancer to strike. Participating in this clinical trial has allowed me to become more aware of my own health and at the same time I am taking a step forward for future generations.

I was informed throughout the trial of all information. Shortly after the trial started, the NSABP committed to informing participants of any new information before the media and before the general public. The NSABP appointed a participant advisory board, the PAB, of which I am a member. This board consists of a group of 16 participants, whose purpose is to offer a voice for all participants and to assist in communicating the concerns and thoughts of the women in the trial.

The NSABP also implemented other tactics to strengthen the commitment they had promised to the participants of the trial. They developed a newsletter to update participants between office visits and there was always a phone number available where questions could be answered or concerns addressed.

Additionally, women in the trial were reconsented when any new information about tamoxifen emerged. During my reconsenting process, additional risks were identified and explained to me and I was given the option to withdraw my consent or to continue to participate in the trial.

The NSABP has truly kept its promise and it made a great effort to keep participants informed every step of the way in this trial.

Throughout the conduct of the trial, I felt that I was given all new information with full explanations and in a timely manner.

As a participant advisory board member, I was told of the initial results during a conference call with all PAB members. It is my un-

derstanding that other participants received a call from their study coordinator or they received a letter that explained that the initial results of the BCPT were available. The letter that came to me as a participant in the trial contained instructions for me to contact my study doctor to learn which arm of therapy I had been assigned. The letter also explained that these results were initial and that more information would be forthcoming at a later date once the data was more fully analyzed.

Although there are no concrete prevention guidelines, I feel that this information adequately explained the initial findings of the BCPT to the participants who actually made the study possible. As a participant, the type of data that I was most interested in is the decreased rate of breast cancer. It lets us know that there is hope.

Personally, as a participant, I was very happy to hear the results first. I know that if the information were not statistically significant, the NSABP would not have released the information. Additionally, I strongly believe that the participants needed to know. It would be unethical to keep a participant on placebo, an inactive agent, for up to 5 years when the comparative arm, tamoxifen therapy, did show a benefit.

Also, the process for obtaining an indication from the FDA for tamoxifen for the prevention of breast cancer could not start until the trial was completed and the data fully analyzed.

Although the manner used to release this information was unorthodox, I believe it was handled in an appropriate way. By that I mean in other clinical trials the results are presented at a scientific meeting or published in a peer review journal first, a process that has not been followed for this trial. But in a sense the entire trial has been unorthodox because it is evaluating a prevention for rather than a treatment of breast cancer.

The use of a participant advisory board is also new and unconventional in clinical trials. All of these elements are different from the norm, but they work. It demonstrates that different does not always have to be wrong.

I am an African-American and I have been asked on a number of occasions about the concern that the results may not apply to African-Americans because of the low minority representation in the BCPT. I am not concerned that we may not know if the results will apply to women of color. We do have a small minority representation in the BCPT and I am sure that, as the analysis of the data continues, researchers will look at the data from the women of color to see if there was any difference in this subgroup.

The thing that does concern me was how difficult it was to recruit women of color to a clinical trial. I believe that there are cultural reasons why people of color do not participate in clinical trials. But I am concerned more that women of color do not get exposed to medical care at the level that most of the general population does nor do they have the same opportunities to participate in clinical trials.

The NSABP attempted to change this by developing programs specifically intended for increasing minority representation in the BCPT. Nancy Wilson became a national spokesperson and similar efforts were attempted at the local level.

I personally spoke at several African-American churches in an attempt to get women involved. Unfortunately, low minority representation is a phenomenon that is seen in all clinical trials.

My interest in breast cancer prevention preceded my joining the trial. Having lived through seeing my mother and aunt dying of breast cancer, I saw how devastating this disease is to a woman and how it affects her whole family.

My goddaughters, at the ages of 4 and 8, lost their mother to breast cancer. If we can do anything to prevent this breast cancer, we must.

This is why this study is so important. The BCPT was the first step, which will lead to a next step, and a next step in successfully preventing breast cancer. I feel that my experience is not that different than my colleagues' on the participant advisory board and in the study as a whole and hope that I have been able to reflect their point of view as well as my own in this testimony.

If I had the opportunity to say anything to women considering participating in a clinical trial, it would be this: It is important to evaluate where you are. Take a stand and make an effort to improve your health and the outlook for future generations. When you participate in a clinical trial, you receive excellent medical care. You are working toward making a difference.

Women need to stand up and be counted, and it is important to do something proactive to improve women's health.

If you participate, do so in a rational fashion. Know the risks, know the benefits, and become involved.

PREPARED STATEMENT

Again, I wish to thank you, Mr. Chairman, for the opportunity to discuss this important issue and I would be pleased to answer any questions that you may have about my participation.

Senator SPECTER. Thank you very much, Ms. Wilson.

[The statement follows:]

PREPARED STATEMENT OF HELENE WILSON

Good morning Mr. Chairman and members of the Subcommittee. My name is Helene Wilson. Thank you for inviting me to testify here today about my experience as a participant in the NSABP Breast Cancer Prevention Trial.

I am 48 years old and reside in North Wales, Pennsylvania. I am a mother of two children (a daughter age 30 and a son age 26). I am currently employed by Merck and Company where I am a senior manager in clinical research, specializing in clinical trials using Merck agents. This career has provided me with experience and an understanding of the conduct and efficacy issues surrounding clinical trials. I became a participant of the Breast Cancer Prevention Trial (BCPT) in October 1992, and finished my 5 years of tamoxifen therapy in October 1997.

When I discovered that I was eligible to participate in the BCPT, I felt as though I had won the lottery. I was elated that I was being offered a chance to take a proactive step toward preventing breast cancer. My maternal grandmother, my mother, my mother's sister, and my father's sister had all died of breast cancer; and as if this were not enough devastation for one family to endure, early signs of this dreadful disease began afflicting me. I had approximately seven biopsies, most of which were benign; however, the last few biopsies showed signs of atypical hyperplasia and microcalcifications, both thought to be strong indications of impending breast cancer. In my doctor's words, I was a "walking time bomb."

WHY I JOINED THE TRIAL

Before hearing about the BCPT, I was seriously considering undergoing a procedure called prophylactic mastectomy, where both breasts and the surrounding tissue

would be removed, in an attempt to escape from this fear of breast cancer. Since even this drastic step did not offer complete confidence that I would not develop breast cancer, I decided to forego the prophylactic mastectomy until I heard more about the BCPT. Because of my strong family history, and what was beginning to be a personal history, I felt that enough is enough! I met with individuals at the Montgomery Cancer Center who extensively explained the study, the consent form, and the risks and benefits of tamoxifen and participating in a clinical trial. I completed a risk assessment form used to evaluate my relative risk for developing breast cancer, underwent blood tests, a physical, a gynecologic exam, a mammogram, and finally, was accepted into the trial as a participant.

Being a participant in the BCPT has been a very positive experience for me. I feel that I am doing something proactive in my own care, which is important to me. I did not want to sit back and just wait for breast cancer to strike. Participating in this clinical trial has allowed me to become more aware of my own health—and at the same time, I am taking a step forward for future generations.

HOW I WAS INFORMED AS THE TRIAL PROGRESSED

Shortly after the trial started, the NSABP committed to informing participants of any new information before the media and before the general public. The NSABP also appointed a Participant Advisory Board (PAB), of which I am a member. This Board consists of a group of 16 participants whose purpose is to offer a voice for all participants, and to assist in communicating the concerns and thoughts of the women in the trial. The NSABP also implemented other tactics to strengthen the commitment they had promised to the participants of this trial. They developed a newsletter which is used to update participants between office visits, and there was always a phone number available where questions could be answered or concerns could be addressed. Additionally, women in the trial were reconsented when any new information about tamoxifen emerged. During my reconsenting process, additional risks were identified and explained to me, and I was given the option to withdraw my consent or to continue my participation in the trial.

The NSABP has truly kept its promise, and made a great effort to keep participants informed every step of the way in this trial. Throughout the conduct of the trial, I feel that I was given all new information with full explanations and in a timely manner.

MY JOY AT LEARNING THE RESULTS

As a Participant Advisory Board member, I was told of the initial results during a conference call with all PAB members. It is my understanding that other participants received a call from their study coordinator, or they received a letter which explained that initial results of the BCPT were available. The letter that came to me as a participant in the trial contained instructions for me to contact my study doctor to learn which arm of therapy had been assigned to me. The letter also explained that the results were initial and that more information would be forthcoming at a later date once the data was more fully analyzed. Although there are no concrete prevention guidelines, I feel that this information adequately explained the initial findings of the BCPT to the participants who made it possible. As a participant, the type of data that I am most interested in is the decreased rate of breast cancer. There is hope.

TIMING OF THE RELEASE OF INFORMATION

Personally, as a participant I was very happy to hear the results first. I know that if the information were not statistically significant, the NSABP would not have released the information. Additionally, participants needed to know. It would be unethical to keep a participant on placebo, an inactive agent, when the comparative arm, tamoxifen therapy, does show a benefit. Also, the process for obtaining an indication from the FDA for tamoxifen and the prevention of breast cancer could not start until the trial information was complete.

Although the manner used to release this information was unorthodox, I truly believe it was handled in an appropriate way. By that I mean, in other clinical trials the results were published in a peer reviewed journal first, a process that has not been followed for this trial. In a sense, the entire trial is unorthodox because it is evaluating a prevention rather than a treatment. The use of a Participant Advisory Board was also new and unconventional in clinical trials. All of these elements are different from the norm but they worked. Different does not always have to be wrong.

MINORITY RECRUITMENT TO CLINICAL TRIALS

I am an African-American. I have been asked on a number of occasions about the concern that the results may not apply to African-Americans because of the low minority representation in the BCPT. I am not concerned that the results may not apply to women of color. We did have a small representation percentage in the BCPT, but I am sure that as the analyses of the data continues, researchers will look at the women of color to see if there was any difference in this subgroup. The thing that concerned me most was how difficult it was to recruit women of color to a clinical trial. I think there are cultural reasons why people of color do not participate in clinical trials. I also believe that women of color do not get exposed to medical care at the level that most of the general population does nor do they have the same opportunities to participate in trials. The NSABP attempted to change this by developing programs specifically intended for increasing minority representation on the BCPT. Nancy Wilson became a national spokesperson, and similar efforts were attempted at each local level. I personally talked at several black churches to try to get women involved. Unfortunately, low minority representation is a phenomena that is seen in all clinical trials.

ADVICE TO OTHER WOMEN CONSIDERING PARTICIPATION IN CLINICAL TRIALS

My interest in breast cancer prevention preceded my joining the trial. Having lived through seeing my mother and aunt dying of breast cancer, I saw how devastating this disease is to a woman and how it affects her whole family. My god-daughters (ages 6 and 8) recently lost their mother to breast cancer, and if we can do anything to prevent breast cancer—we must. This is why this study is so important. The BCPT was the first step which will lead to a next step in successfully preventing breast cancer. I feel that my experience is not that different from my colleagues on the Participant Advisory Board and hope that I have been able to reflect their point of view as well as my own in this testimony.

It is important to evaluate where you are. Take a stand, and make an effort to improve your health and the outlook for future generations. When you participate in a clinical trial, you receive excellent medical care. You are working toward making a difference. Women need to stand up and be counted, and it is important to do something proactive to improve women's health. If you participate, do so in a rational fashion. Know the risks, the benefits, and become involved.

Again, I wish to thank you, Mr. Chairman, for the opportunity to discuss this important issue. I would be pleased to answer any questions the subcommittee may have.

ATTACHMENT A

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT [NSABP]

BREAST CANCER PREVENTION TRIAL SHOWS MAJOR BENEFIT, SOME RISK

Six years after its inception, the Breast Cancer Prevention Trial (BCPT) shows a 45 percent reduction in breast cancer incidence among the high-risk participants who took tamoxifen (Nolvadex®), a drug used for the past two decades to treat breast cancer.

As a result, investigators released the initial study results about 14 months earlier than expected and notified the 13,388 women participants of the findings so those women who had been taking a placebo could consider starting tamoxifen therapy after consulting with their personal physicians. Participants will continue to be followed by the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Pittsburgh-based research network that conducted the trial with support from the National Cancer Institute (NCI).

In this trial, healthy women assigned to take tamoxifen developed 85 cases of invasive breast cancer compared to 154 cases in the women assigned to the placebo.

Tamoxifen did increase the women's chances of three rare but life-threatening health problems: there were 33 cases of endometrial cancer (cancer of the lining of the uterus) in the tamoxifen group versus 14 cases in the placebo group; there were 17 cases of pulmonary embolism (blood clot in the lung) in the tamoxifen group versus six cases in the placebo group; and there were 30 cases of deep vein thrombosis (blood clots in major veins) in the tamoxifen group versus 19 cases in the placebo group.

Among these women at increased risk for breast cancer, women under age 50 appeared to suffer no excess risk of adverse effects from use of tamoxifen.

"Women who are at an increased risk of breast cancer now have the option to consider taking tamoxifen to reduce their chances of developing breast cancer. As with any medical procedure or intervention, the decision to take tamoxifen is an individual one in which the benefits and risks must be considered," said Leslie Ford, M.D., associate director for early detection and community oncology in NCI's Division of Cancer Prevention. The choice will vary depending on a woman's age, personal history, family history, and how she weighs the benefits and risks.

"Even if a woman is at increased risk of breast cancer, tamoxifen therapy may not be appropriate for her," continued Ford. "NSABP and NCI are developing information for individual decisionmaking that will help women at increased risk of breast cancer consult with their health care providers to answer the question, 'Is tamoxifen the right choice for me?'"

The BCPT is a clinical trial designed to see whether the drug tamoxifen prevents breast cancer in women who are at an increased risk of developing the disease. Women in the study were randomly assigned to receive tamoxifen or a placebo pill and neither participants nor their physicians were aware of the treatment assignment, a process called "double-blinding."

Launched in April 1992, the BCPT also looked at whether taking tamoxifen decreases the number of heart attacks and reduces the number of bone fractures in these women. There was no difference in the number of heart attacks between the tamoxifen and placebo group, but women in the tamoxifen group had fewer bone fractures of the hip, wrist, and spine (47 cases in the tamoxifen group versus 71 cases in the placebo group).

As part of the study design, the BCPT data were regularly reviewed by an independent Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC). At its regularly scheduled meeting on March 24, 1998, the committee recommended that the participants and their physicians be told what pills each participant had been taking because of the clear evidence that tamoxifen reduced breast cancer risk.

NSABP presented the data to NCI on March 26 and, together both NSABP and NCI researchers concurred with the committee's recommendation. This decision was based upon their joint assessment that a reduction of breast cancer had been demonstrated. It was agreed that any additional information that might be gained from continuing the study did not outweigh the benefits of making the treatment available to the participants in the placebo group and other women at increased risk of breast cancer.

The women in the trial have taken tamoxifen or placebo daily for about four years. In spite of extensive efforts to enroll minorities in the BCPT, African American, Asian American, Hispanic, and other groups together made up only about three percent of the participants.

About 40 percent of the participants were ages 35 to 49, 30 percent were ages 50 to 59, and 30 percent were age 60 or older. All age groups showed similar reductions in breast cancer incidence from tamoxifen. There was a suggestion that the breast cancer benefit from tamoxifen could be greater in women over age 50, but older women are also at increased risk for some of the serious side effects (endometrial cancer, pulmonary embolism, and deep vein thrombosis).

Women on tamoxifen also had fewer diagnoses of noninvasive breast cancer, such as ductal carcinoma in situ (31 cases in the tamoxifen group versus 59 cases in the placebo group). Eight participants have died of breast cancer, three in the tamoxifen group and five in the placebo group.

"This advance represents the results of a long-term investment in research," said NCI Director Richard Klausner, M.D. "This is a real advance, but it is no magic bullet. Only through continued research will we find preventions that are even more effective and with fewer side effects."

At the inception of the study, the investigators made a commitment to notify study participants of major results prior to any public announcement. The BCPT Participant Advisory Board, a group of 16 women in the trial, was notified by conference call. Letters were sent to BCPT researchers, and they in turn mailed letters or made other plans to notify the participants at their sites.

"Our heartfelt gratitude is extended to the study participants," said Norman Wolmark, M.D., chairperson of NSABP. "It is only because of their commitment that we were able to answer a question of extreme importance to many women."

Sandy Kanicki, co-chair of the Participant Advisory Board, said simply, "The results are so profound that I'm speechless. We don't know where we are going to go from here but we have taken a major step to help women reduce their incidence of breast cancer."

Women in the study will continue to be monitored by BCPT investigators. Post menopausal women who had been taking the placebo may have the option to participate in an upcoming trial that will compare tamoxifen to another drug that could

have similar breast cancer prevention properties, but which might be associated with fewer adverse effects. Women of any age on placebo also have the option of seeking tamoxifen from their health care providers.

The BCPT researchers will be evaluating the study's results in great detail in coming weeks. The final analysis will be published in the scientific literature.

The study began recruiting participants in April 1992 and closed enrollment in September 1997. Researchers with the NSABP are conducting the study in more than 300 centers across the United States and Canada.

"Since 1990 when I and my NSABP colleagues, together with members of NCI, designed this study, there has been an unprecedented display of teamwork by the participants, their physicians, study support staff, numerous government agencies, and medical centers," said Bernard Fisher, M.D., scientific director at NSABP. "That commitment to scientific investigation has resulted in this landmark accomplishment. I am delighted to have had an opportunity to make a contribution."

Only women at increased risk for developing breast cancer participated in the study. Because the risk of breast cancer increases with age, women 60 years of age and older qualified to participate based on age alone. At age 60, about 17 of every 1,000 women are expected to develop breast cancer within five years. Women between the ages of 35 and 59 who demonstrated an increased risk of breast cancer equivalent to or greater than that of an average 60-year-old woman were also eligible. This breast cancer risk was determined by a computer calculation based on the following factors:

- Number of first-degree relatives (mother, daughters, or sisters) who had been diagnosed as having breast cancer;
- Whether a woman had any children and her age at her first delivery;
- The number of times a woman had had breast lumps biopsies especially if the tissue was shown to have a condition known as atypical hyperplasia;
- The woman's age at her first menstrual period.
- Whether a woman had had a type of noninvasive breast cancer known as lobular carcinoma in situ.

One of the most widely prescribed cancer drugs in the world tamoxifen has been the focus of more than 25 years of research on its actions, benefits, and risks. Zeneca Pharmaceuticals, Wilmington, Del., manufactures tamoxifen and provided both the drug and placebo pills for the prevention study without charge.

For information on the BCPT and easy access to all clinical trials information from NCI, go to: <http://cancertrials.nci.nih.gov>

For information on NSABP clinical trials, including, future prevention trials, go to: <http://www.nsabp.pitt.edu>

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QUESTIONS AND ANSWERS: PRELIMINARY RESULTS FROM THE BREAST CANCER PREVENTION TRIAL

BACKGROUND AND STUDY DESIGN

What is the breast cancer prevention trial?

The Breast Cancer Prevention Trial (BCPT) is a clinical trial (a research study conducted with people) designed to see whether taking the drug tamoxifen (Nolvadex®) can prevent breast cancer in women who are at an increased risk of developing the disease. The BCPT is also looking at whether taking tamoxifen decreases the number of heart attacks and reduces the number of bone fractures in these women. The study began recruiting participants in April 1992 and closed enrollment in September 1997; 13,388 women ages 35 and older are enrolled. Researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting the study in more than 300 centers across the United States and Canada. The study is funded by the National Cancer Institute (NCI), the United States' primary agency for cancer research.

What is tamoxifen?

Tamoxifen is a drug, taken by mouth as a pill. It has been used for 25 years to treat patients with advanced breast cancer. Since 1985 it has also been rec-

ommended in the United States for adjuvant, or additional, therapy, following surgery and/or radiation for early stage breast cancer. Tamoxifen works against breast cancer, in part, by interfering with the activity of estrogen, a female hormone that promotes the growth of breast cancer cells. For this reason, tamoxifen is often called an “anti-estrogen.” In treatment, the drug slows or stops the growth of these cancer cells.

Why was tamoxifen tested to prevent breast cancer?

Research has shown that taking tamoxifen as adjuvant therapy for breast cancer not only helps prevent the original breast cancer from returning but also helps to prevent the development of new cancers in the opposite breast. Researchers believed that tamoxifen might have a similar beneficial effect for women at increased risk of breast cancer. While tamoxifen acts against the effects of estrogen in breast tissue, it acts like estrogen in other body systems. Tamoxifen’s estrogen-like effects include the lowering of blood cholesterol and the slowing of bone loss that may lead to osteoporosis and bone fractures.

Who participated in the BCPT?

Women at increased risk for developing breast cancer participated in the study. These included women 60 years of age and older who qualified to participate based on age alone, and women between the ages of 35 and 59 with an increased risk of breast cancer equivalent to or greater than that of a 60 year old woman. At age 60, about 17 of every 1,000 women are expected to develop breast cancer within five years.

Of the 13,388 women on the trial, about 40 percent were ages 35 to 49, about 30 percent were ages 50 to 59, and about 30 percent were age 60 or older. About 3 percent of the participants were minorities, including African American, Asian American, Hispanic, and other groups.

Did every woman in the study receive tamoxifen?

No. Participants in the BCPT were randomized (selected by chance) to receive either tamoxifen or a placebo (an inactive pill that looked like tamoxifen). In a process known as “double blinding,” neither the participant nor her physician knew which pill she was receiving. Setting up a study in this way allowed the researchers to clearly see what the true benefits and side effects of tamoxifen are without the influence of other factors. According to the design, all women in the study were to take two pills a day for five years, either a 20-mg dose of tamoxifen (two 10-mg pills) or placebo pills.

Why were women 60 years of age or older eligible for the BCPT based on age alone?

Many diseases, including breast cancer, occur more often in older persons. The risk of developing breast cancer increases with age, so breast cancer occurs more commonly in women over 60 years of age. The risk of developing heart disease or osteoporosis also increases with age, and those diseases are also being studied in the BCPT.

What factors were used to determine increased risk of breast cancer for the participants aged 35 to 59?

To enroll in the study, women between 35 and 59 years of age needed to have a risk of developing breast cancer within the next five years that was equal to or greater than the average risk for 60-year-old women. This increased risk was determined in one of two ways. Women diagnosed as having lobular carcinoma in situ, a condition that is not cancer but indicates an increased chance of developing invasive breast cancer, were eligible based on that diagnosis alone. The risk for other women was determined by a computer calculation based on the following factors:

- Number of first-degree relatives (mother, daughters, or sisters) who had been diagnosed as having breast cancer;
- Whether a woman had any children and her age at her first delivery;
- The number of times a woman had had breast lumps biopsied, especially if the tissue was shown to have a condition known as atypical hyperplasia; and
- The woman’s age at her first menstrual period.

For example, a 35-year-old woman would have to have two or more first-degree relatives with breast cancer AND a personal history of at least one benign breast biopsy, OR a diagnosis of lobular carcinoma in situ.

A 45-year-old woman would have to have one or more first-degree relatives with breast cancer AND a personal history of at least one benign breast biopsy, OR a diagnosis of lobular carcinoma in situ.

A 55-year-old woman would have to have one or more first-degree relatives with breast cancer OR a personal history of at least one benign breast biopsy OR a diagnosis of lobular carcinoma in situ.

What proportion of women in the United States are estimated to be at the level of risk required for participation in the BCPT?

At age 35, about three women in 1,000 would have qualified for the study based on their estimated breast cancer risk or 0.3 percent.

At age 40, the proportion is about 27 women in 1,000, or 2.7 percent.

At age 45, the proportion is about 71 women in 1,000, or 7.1 percent.

At age 50, the proportion is about 93 women in 1,000, or 9.3 percent.

At age 55, the proportion is about 125 women in 1,000, or 12.5 percent.

At age 60 and beyond, all women would have met the breast cancer risk criteria.

Did other factors affect eligibility for the study?

Certain existing health conditions affected eligibility for the study. For example, women at increased risk for blood clots could not participate. Also, women taking hormone replacements and women using oral contraceptives ("the pill") could not take part in the trial unless they stopped taking these medications. Those who stopped taking these hormones were eligible for the study three months after they discontinued the drugs.

Women who were pregnant or who planned to become pregnant were not eligible to participate. Animal studies have suggested that the use of tamoxifen during pregnancy might harm the fetus. Premenopausal women participating in the BCPT were required to use some method of birth control other than oral contraceptives. Oral contraceptives may change the effects of tamoxifen and may also affect the risk of breast cancer.

Were the participants required to have any medical exams?

Participants were required to have blood tests, a pelvic exam, a mammogram, and a physical exam before being accepted into the study. Women 55 years of age and older needed to have an electrocardiogram or ECG (a test to measure the heart's muscular activity), in addition to the other tests. Screening endometrial sampling (an examination of cells from the lining of the uterus) was required at entry for participants joining the study beginning in October 1994 and was strongly recommended annually for all women in the study. These tests were repeated periodically.

Who paid for these medical exams?

Most physicians' fees and the costs of medical tests were charged to the participant as if she were not part of the study; however, the costs for these tests were often covered by the participant's insurance company. Screening endometrial samplings were provided without charge. For women over 55, the required electrocardiograms were also done at no cost. Every effort made to contain the costs specifically associated with participation in this study.

How much did the tamoxifen cost the participants?

There was no charge to participants for the tamoxifen or the placebo. The company that manufactures tamoxifen, Zeneca Pharmaceuticals Group, of Wilmington, Del., (formerly ICI Americas, Inc.) provided both the tamoxifen and the placebo without charge.

PRELIMINARY TRIAL RESULTS/NOTIFICATIONS

What are the initial results of the BCPT?

At this point (data to Jan. 31, 1998), women on the trial have been followed on the study for about four years. Results show 45 percent fewer diagnoses of invasive breast cancer in women who were randomized to take tamoxifen compared to women who were randomized to take the placebo (85 cases in the tamoxifen group versus 154 cases in the placebo group). Women on tamoxifen also had fewer diagnoses of noninvasive breast cancer, such as ductal carcinoma in situ (31 cases in the tamoxifen group versus 59 cases in the placebo group). Eight women have died of breast cancer, three women in the tamoxifen group and five women in the placebo group.

Women in the tamoxifen group had fewer bone fractures than women in the placebo group (47 cases in the tamoxifen group versus 71 cases in the placebo group). There was no difference in the number of heart attacks between the two groups.

Tamoxifen did increase the women's chances of three rare but serious health problems: endometrial cancer (cancer of the lining of the uterus) 33 cases in the

tamoxifen group versus 14 cases in the placebo group; pulmonary embolism (blood clot in the lung) 17 cases in the tamoxifen group versus 6 cases in the placebo group; and deep vein thrombosis (blood clots in major veins) 30 cases in the tamoxifen group versus 19 cases in the placebo group.

What were the participants' chances of developing endometrial cancer?

BCPT participants who were randomized to the tamoxifen group had more than twice the chance of developing endometrial cancer compared with women on placebo (based on 33 cases in the tamoxifen group versus 14 cases in the placebo group). The increased risk of endometrial cancer was equal to the risk that was expected and is in the same range as (or less than) the endometrial cancer risk for postmenopausal women taking single-agent estrogen replacement therapy. Estrogens and agents that act like estrogens are known to increase the risk of endometrial cancer.

All the participants were informed about the possibility of increased risk of endometrial cancer before they entered the study. Like all cancers, endometrial cancer is potentially life-threatening. All but one (in the placebo group) of the endometrial cancers that occurred during the study were found at an early stage, when treatment is very effective. However, one participant (also in the placebo group) died of endometrial cancer. About 37 percent of BCPT participants in both groups had a hysterectomy (surgery to remove the uterus) for a variety of health reasons before joining the study. Therefore, these women were not at any risk for endometrial cancer.

What was done to help diagnose endometrial cancer early?

Pap smears are very effective at detecting cancer in the cervix but are not useful for detecting endometrial cancer. Therefore a screening endometrial sampling—removal of cells in the lining of the uterus for examination under a microscope—was used in the BCPT to detect abnormalities in the endometrium. Women who joined the study after October 1994 were required to have a screening endometrial sampling before entering the study if their uterus had not been removed. All women in the study were strongly urged to have screening endometrial sampling done annually throughout the study (at no cost to them), but could decline if they chose. In addition to these annual tests, women in the BCPT were told to see their physicians if they experienced abnormal vaginal bleeding or pain. The vast majority of the endometrial cancers that were diagnosed in the BCPT caused such symptoms.

What were the participants' chances of getting blood clots?

Women taking tamoxifen had almost three times the chance of developing a pulmonary embolism (blood clot in the lung) as women on placebo (based on 17 cases in the tamoxifen group versus 6 cases in the placebo group). Two women died from these embolisms, both in the tamoxifen group. Women in the tamoxifen group were also more likely to have deep vein thrombosis (a blood clot in a major vein) than women on placebo (30 cases versus 19 cases). Blood clots occur more often in people with high blood pressure (hypertension), diabetes, smokers, and in those who are obese.

Is there a relationship between tamoxifen use and the development of eye problems?

Women in the tamoxifen group, in general, had no more eye problems than women taking the placebo. However, women taking tamoxifen may be at a slightly increased risk for developing cataracts (a clouding of the lens inside the eye) according to other research.

As women age, they are more likely to develop cataracts whether or not they take tamoxifen. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few breast cancer patients in tamoxifen treatment trials.

Was tamoxifen associated with any other cancers?

Tamoxifen was not associated with an increased risk of any other cancer other than endometrial cancer.

What were the other adverse effects of tamoxifen?

Like most medications, whether over-the-counter medications, prescription drugs, or drugs in research studies, tamoxifen causes adverse effects in some women. The effects experienced most often by women in the tamoxifen group were hot flashes and vaginal discharge. Women in both groups reported sometimes having side effects—even though the placebo itself would not cause any symptoms. The side effects that some women in both groups reported included: vaginal dryness, itching, or bleeding; menstrual irregularities; depression; loss of appetite; nausea and/or

vomiting; dizziness; headaches; and fatigue. Treatments that could minimize or eliminate most side effects were available to the participants.

Did any group of women benefit more from tamoxifen than others?

It is possible that the breast cancer benefit from tamoxifen could be greater in women over age 50, but older women are also at increased risk for some of the serious side effects (endometrial cancer, pulmonary embolism, and deep vein thrombosis).

Why was the study "unblinded," and who made that decision?

As part of the study design, the BCPT data were regularly reviewed by an independent Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC). At its regularly scheduled meeting on March 24, 1998, the committee recommended to NSABP that the study be unblinded (inform the participants and their physicians what pills the participants had been taking) because of the clear evidence of a reduction of breast cancer incidence in the tamoxifen group. The NSABP presented the data and recommendation to the NCI on March 26 and together, NSABP and NCI researchers concurred with the committee's recommendation. This was based upon the assessment of all three groups that the effect of tamoxifen in the reduction of breast cancer had been demonstrated. It was agreed that any additional information that could be gained from continuing the study in its current form did not outweigh the benefits of making the treatment available to the participants in the placebo group and other women at an increased risk of breast cancer.

How were the participants notified?

At the inception of the study, the NSABP made a commitment to make every effort to notify the participants of major results prior to any public announcement. After notification to the BCPT Participant Advisory Board, a group of 16 women in the trial, a letter announcing initial results, and details for participant "unblinding" was rapidly sent to BCPT investigators so that they could convey this information to BCPT participants.

What will the participants do now?

All participants are being asked to continue with their follow-up examinations. Women who have been randomized to the tamoxifen group who have not completed five years of tamoxifen therapy will have the opportunity to continue on therapy. Postmenopausal women who had been taking the placebo are being invited to participate in an upcoming trial that will compare tamoxifen to a different drug that could have similar breast cancer prevention properties, but might be associated with fewer adverse effects. Women of any age on placebo also have the option of seeking tamoxifen from their private health care providers.

Would it be beneficial for women to take tamoxifen for more than five years?

Not necessarily: Results of another NSABP study in which women with early stage breast cancer took tamoxifen for 5 years versus 10 years (called the B-14 trial) showed no greater benefit from the longer duration of tamoxifen and showed a trend toward more adverse effects.

PUBLIC CONCERNS

Was any special effort made to include minority women on the trial?

Throughout the trial, several strategies were used to increase participation of women from racial and ethnic minority groups. These strategies included placing study-related recruitment materials in businesses and churches located in minority communities; collaborating with a minority-owned public relations firm to develop a structured media campaign targeting racial and ethnic minorities; developing and broadly disseminating a Public Service Announcement that featured singer Nancy Wilson; and communicating information to study sites about how other sites successfully reached racial and ethnic minorities.

When the early strategies did not attract sufficient numbers of minority participants, the NSABP launched the Pilot Minority Recruitment Program in August 1996. The goal of the program was to increase participation by increasing awareness and educating minority populations about the trial. A multidimensional approach was used: Community Outreach Coordinators employed at five BCPT sites offered personalized presentations on breast cancer risk factors, incidence, and survival rates, and on clinical trial research at African American churches, community hospitals and health clinics, health fairs, public housing sites, businesses, and local chapters of sororities, the Urban League, and minority medical societies. In less than a year, these strategies enabled the coordinators to establish many relation-

ships in their communities. As a result of these efforts, the number of Risk Assessment Forms submitted by minority groups increased, and during this period, the BCPT experienced the highest level of randomizations from racial and ethnic minority groups since the trial began. The Pilot Minority Recruitment Program has been the most effective strategy to date and will serve as the model for minority recruitment for future prevention trials.

Will the study results be published?

Further analyses of the data are under way. A manuscript will be prepared and submitted to a peer-reviewed journal.

Based on the BCPT results, should women who are at increased risk of breast cancer take tamoxifen?

Women who are at increased risk of breast cancer now have the option to consider taking tamoxifen to reduce their chances of developing breast cancer. As with any medical procedure or intervention, the decision to take tamoxifen is an individual one in which the benefits and risks of the therapy must be considered. The balance of these benefits and risks will vary depending on a woman's personal health history and how she weighs the benefits and risks. Therefore even if a woman is at increased risk of breast cancer, tamoxifen therapy may not be appropriate for her. Women who are considering tamoxifen therapy should talk with their health professional.

How can a woman learn more about the next breast cancer prevention trial?

The NSABP is planning a new breast cancer prevention trial, tentatively scheduled to begin in fall 1998. The trial would involve postmenopausal women who are at least 35 years old and are at increased risk for developing breast cancer. The study would compare tamoxifen to another drug.

There are several ways to be placed on a mailing list for more information on this upcoming trial—by Internet, by mail, or by fax. On the Internet, the NSABP homepage (www.nsabp.pitt.edu) has a form available. By regular mail, send a letter or post card with name, mailing address, and a note specifying interest in future breast cancer prevention trials to: NSABP, Box 21, Pittsburgh, PA, 15261. Or fax the same information to NSABP at 412-330-4664. When information about the next prevention trial is available, it will be mailed to the people on this list.

How does a woman determine whether she is at increased risk of breast cancer?

BCPT participants had their risk for developing breast cancer calculated using age, family history, and medical information in a computer program that also estimated their likelihood of developing heart disease, endometrial cancer, and blood clots. Some private physicians use computer calculations in their practice to assess breast cancer risk, but because these are not identical to the program used in the BCPT, it is unclear how well those programs would identify women at increased risk. The NSABP and NCI plan to make information available which will assist a woman and her health care provider to determine whether her risk is comparable to the women who participated in the BCPT.

Will women with breast cancer gene alterations (BRCA1 and BRCA2) benefit from tamoxifen?

These two breast cancer gene alterations, which increase a woman's risk of the disease, were first identified after the BCPT began. Using blood samples taken from participants, analyses are under way to determine whether tamoxifen has the same relative effects on women whether or not they carry alterations in these genes. To maintain strict confidentiality, samples in this study have no identifying labels that could link them to individual women. Therefore, researchers will not be able to give individual results to a participant or her health care provider.

Is tamoxifen a good substitute for hormone replacement therapy?

No. Every woman has individual health risks that affect her need for interventions such as hormone replacement therapy or tamoxifen therapy. Hormone replacement therapy is intended to help women maintain bone density. It may also reduce the risk of heart disease in postmenopausal women, and many women benefit from a reduction in hot flashes and other problems that can affect quality of life. Some studies have suggested that hormone replacement therapy increases a woman's chances of developing breast cancer.

The BCPT results show that tamoxifen reduces breast cancer risk and may help slow or reduce bone loss, as evidenced by the reduced number of hip fractures, but it did not decrease heart disease risk. A woman with a large risk of heart disease

but no increased risk of breast cancer may not have the same benefit from tamoxifen as from hormone replacement therapy.

Should women who are not at a demonstrated increased risk of breast cancer consider taking tamoxifen?

This question has not been studied. At this time, there is no evidence that tamoxifen is beneficial for women who do not have an increased risk of breast cancer.

Are there any women who should not take tamoxifen?

Animal studies have suggested that the use of tamoxifen during pregnancy might harm the fetus. Women who were pregnant or who planned to become pregnant were not eligible to participate in the BCPT. Premenopausal women participating in the BCPT were required to use some method of birth control other than oral contraceptives ("the pill") while taking tamoxifen. Oral contraceptives and hormone replacement therapy may change the effects of tamoxifen and may also affect the risk of breast cancer.

Women with a history of blood clots, hypertension, diabetes, and cigarette smoking must also consider that tamoxifen increases the risk for serious blood clots.

How much does a standard dose of tamoxifen cost?

A month's supply of tamoxifen costs about \$80 to \$100.

How much did the study cost?

The trial had been projected to cost \$70 million, but the total cost is estimated at \$50 million, including \$10 million for two more years of followup. All except \$3.5 million from the National Heart, Lung, and Blood Institute, was provided by NCI.

Why is the breast cancer prevention trial so important?

This year, more than 178,000 women in the United States alone will be diagnosed as having breast cancer, and about 43,500 will die of the disease. For many years, women at increased risk for developing breast cancer had no proven means to reduce their risk. Women had to rely on frequent checkups and periodic mammograms to detect breast cancer at an early stage. Doctors sometimes suggest that certain women at very high risk have preventive (prophylactic) mastectomies, which is surgery to remove breast tissue before cancer develops. However, the operation does not guarantee that breast cancer will be avoided, because it is almost impossible to remove all the breast tissue and the impact of prophylactic mastectomy on breast cancer risk is not known.

Because tamoxifen was successful in reducing the incidence of breast cancer, women at increased risk for developing the disease will have a choice other than more frequent exams or major surgery (although regular mammography should continue even if a woman decides to use tamoxifen). In order to prove its value, tamoxifen had to be tested in a large research study to determine whether the benefits outweighed the risks.

What is the national surgical adjuvant breast and bowel project?

The National Surgical Adjuvant Breast and Bowel Project is a cooperative group with a 40 year history of designing and conducting clinical trials, the results of which have changed the way breast cancer is treated, and now, potentially prevented. Results of research studies conducted by NSABP researchers have been the dominant force in altering the standard surgical treatment of breast cancer from radical mastectomy to lumpectomy plus radiation. This group was also the first to demonstrate that adjuvant therapy could alter the natural history of breast cancer, thus increasing survival rates. When a breast cancer prevention study was initially conceived, more than 30,000 women with breast cancer had participated in treatment studies conducted by NSABP investigators. A research study to prevent breast cancer was a logical next step for this research group.

NSABP was recently incorporated under the aegis of the NSABP Foundation, Inc., a Pennsylvania nonprofit membership organization with nearly 300 members in the United States, Canada, and Australia. More than 6,000 physicians, nurses, and other medical professionals in the NSABP located in member institutions and their satellites are involved in the conduct of treatment and prevention trials. NCI provides funding for the two headquarters components of NSABP: the NSABP Operations Center at Allegheny University of the Health Sciences, Allegheny Campus, and the NSABP Biostatistical Center at the University of Pittsburgh, both located in Pittsburgh, PA. NCI also provides funding directly or indirectly, to the medical center Members of the NSABP Foundation, Inc., who are responsible for implementation of NSABP studies.

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NSABP BREAST CANCER PREVENTION TRIAL (BCPT) SPEAKERS' BIOGRAPHIES

Norman Wolmark, M.D., is the Chairperson of the National Surgical Adjuvant Breast and Bowel Project (NSABP), a cooperative clinical trials group funded primarily by the National Cancer Institute. Dr. Wolmark is also the Principal Investigator of the NSABP Operations Center located on the Allegheny campus of Allegheny University of the Health Sciences.

Dr. Wolmark received his bachelor's and medical degrees from McGill University in Montreal, Canada. After completing his surgical residency at the University of Pittsburgh, he received additional fellowship training in surgical oncology at the National Cancer Institute in Bethesda, Maryland, and at the Memorial Sloan-Kettering Cancer Center in New York City, New York. He is currently Professor and Chairman of the Department of Human Oncology at Allegheny University of Health Sciences.

D. Lawrence Wickerham, M.D., has been the Associate Chairman of the NSABP since 1995 and is the Protocol Officer for the Breast Cancer Prevention Trial. As the Protocol Officer, Dr. Wickerham oversees the conduct and medical review of the protocol and coordinates committee activities. Dr. Wickerham has worked for the NSABP in several capacities since 1981.

Dr. Wickerham received his bachelor's degree from Washington and Jefferson College in Washington, Pennsylvania, and received his medical degree from the University of Pittsburgh. He is also currently an Associate Professor of Human Oncology at the Allegheny campus of the Allegheny University of the Health Sciences.

Bernard Fisher, M.D., is a founding member and former chairperson of the NSABP from 1967 to 1994. He has devoted his career to exploring the biology of cancer and providing new treatments for women with breast cancer. Dr. Fisher's laboratory and clinical investigations have resulted in major alterations in the use of surgery and systemic therapy for breast cancer management.

Beginning in 1990, Dr. Fisher and his NSABP colleagues, working with the NCI and numerous government agencies, designed and implemented the first breast cancer prevention trial in the United States. In addition to determining the value of tamoxifen in breast cancer prevention, the study was to be directed toward addressing questions related to the genetics of the disease. Dr. Fisher is past-president of the American Society of Clinical Oncology and a former member of both the President's Cancer Panel and the National Cancer Advisory Board. He is currently Scientific Director of the NSABP and professor at the Allegheny campus of the Allegheny University of the Health Sciences.

H. Samuel Wieand, Ph.D., has been the Director of the NSABP Biostatistical Department since 1995. He is also a Professor in and the Associate Chairman of the Department of Biostatistics at the University of Pittsburgh. Prior to joining the NSABP, he was Director of Biostatistics of the Mayo Clinic Cancer Center and of the North Central Cancer Treatment Group (NCCTG).

Dr. Wieand received his Ph.D., from the University of Maryland in 1974. He is a Fellow of the American Statistical Association.

Joseph Costantino, Dr. P.H., is the Associate Director of the NSABP Biostatistical Center and the Coordinating Statistician of the NSABP Breast Cancer Prevention Trial. He is also an Associate Professor of Biostatistics at the University of Pittsburgh's Graduate School of Public Health. Dr. Costantino has been with the NSABP and the University of Pittsburgh since 1984. Before joining the NSABP, he was employed as the Director of Health Effects Research for the BCR National Laboratory. Prior to this position, he was the Deputy Director of the Allegheny County Health Department in Pittsburgh, Pennsylvania.

Dr. Costantino received his bachelor's degree from Bethany College in Bethany, West Virginia and his doctoral degree from the University of Pittsburgh in Pittsburgh, Pennsylvania.

BIOGRAPHICAL SKETCH OF ELSIE ANDERSON

I am now finished with my 5 years on the tamoxifen/placebo Breast Cancer Prevention Trial. When you are told that you will be on this trial for 5 years, it seems so long, but the years have gone by so quickly. I am so happy that I never gave up. I had one breast tumor removed and a needle biopsy during the trial; neither were malignant. I also had other illnesses, not due to tamoxifen (if that is what I was on), but mostly due to my age, such as thyroid disease and colitis. My breast surgeon did not approve of this trial, and neither did the mammogram technician. Both firmly told me their opinions, but because someone has to take a stand, as others have before me and others will after me, why not me? We all have responsibilities and I believe "I am my brother's keeper." Because my three daughters have lost one aunt and two sisters to cancer (one to breast cancer), and have another aunt who is a survivor of breast cancer, and I have eight granddaughters who are at high risk and many friends who have breast cancer, and because of the knowledge of what my two grandchildren have had to go through because they had no mom, I would go on another trial if possible. I don't want to see any more moms who have to leave their children behind as they face death.

I have been appreciated and looked after so well by the NSABP staff, and also by our local cancer clinic. I have had the best care possible. Thank you everyone.

I believe we have to prevent cancer besides finding a cure, and I have had the opportunity to do that.

BIOGRAPHICAL SKETCH OF JUDITH ANN BINGHAM

I was born at Baptist Hospital in New Orleans, Louisiana on Tuesday, July 10, 1951. I have three sisters and three brothers. Throughout my school years, I enjoyed singing in the church choir and teaching roller skating lessons for the Jefferson Parish Recreation Department.

From 1969 to 1997, I worked at Sears Roebuck and Co. I am currently a Collection Supervisor for First Commerce Corporation. In 1976, I married Donald Bingham, and we currently reside in Slidell, Louisiana. We don't have children, but we have 8 nieces and 9 nephews.

I enjoy bowling, skating, walking, arts and crafts, shopping, and collecting koala bears of any shape, size, or form. I also enjoy helping others, and that is one of the reasons I decided to participate in the BCPT. I am committed to the study and its success.

BIOGRAPHICAL SKETCH OF BARBARA CAPUZELO

I am originally from southwestern Pennsylvania and moved to Kansas City, Missouri in 1980 after having lived in Washington DC, Los Angeles, New York, and Boston. I became a single parent in 1982 of a 10-year old girl. When I realized that I was her sole support, and that I was in a dead-end job, I decided to pursue my childhood dream of becoming a nurse. I graduated from Avila College with a BSN and many honors, with a job waiting at the local Veterans Administration. I stayed there until 1993 when I moved to St. Luke's in June. Since then, I have served as Chair of the Unit-based Education Committee and am presently co-chair of the Unit-based Quality Committee. I work on a medical-surgical oncology, blood and transplant unit, I am active in the local and national chapters of the Oncology Nursing Society, and I am a Eucharistic minister and rector at my parish. I have completed a three year New Wine Program and am presently pursuing a master's degree in clinical counseling.

I am very proud of raising an independent daughter, who has made me a mother-in-law and grandmother of a 10-month old baby girl. I have two cats, love dogs, cry at sad movies, like to travel (I worked for TWA in Los Angeles) and meet people, read, enjoy the theater, and love ice cream. I have been a BCPT participant since October 1993.

BIOGRAPHICAL SKETCH OF MARY ELLEN GORMAN

Two words that summarize my life are competitive and generalist. I do many things well but am an expert at nothing! Over the years I have been a full-time mom to three daughters, divorced, single working parent, remarried, retail business partner with my spouse and finally a ski instructor! I have always enjoyed competing in sports from tennis, to ski racing, to indoor rowing. Skiing is my bliss! Now

we are retired and enjoy the outdoor life of Montana. Other hobbies we enjoy together are cooking, collecting wine, and classical music.

I am very fortunate, as my father is approaching his 100th birthday and my mother, age 93, is a 33-year breast cancer survivor. I consider it a privilege to be a participant in the BCPT. It raised my knowledge and commitment to many breast cancer issues. I feel very rewarded by my advocacy work, both locally and nationally, for this most important clinical trial.

BIOGRAPHICAL SKETCH OF SANDRA KAY KANICKI

I am the mother of four sons and I have four daughters-in-law. I serve on the school board, and participate in breast cancer awareness activities in my community. The catalyst to my participating in this very important trial was that my grandmother, mother, and sister are all 8-year survivors of breast cancer. My number one priorities are my husband and my family, and I believe that I have contributed greatly to future generations by participating in this trial.

BIOGRAPHICAL SKETCH OF ELIZABETH (BETTY) LEE

I was born in Huntingdon, West Virginia and was the 7th daughter and 11th child of the late Pearl William and Luana Dortch Adams. My family migrated to Syracuse, New York in the late 40's for a visit, and remained. I am married to Fred Lee, and together we have four children, 14 grandchildren, and one great-grandson. I am a 1995 Syracuse University Master's of Social Work graduate. While working on my degree, I became the first humble and proud winner of the Vivian Teal Howard (former first lady of Hopps Memorial C.M.E. Church) Graduate Student Award. Prior to my entry to graduate school, (May, 1994) I retired from 25 years of public service. However, I completed most of my college education while working full-time and raising a family, and have started a second career with the Syracuse Community Health Center as a certified social worker in the capacity of counselor/therapist.

Because my spiritual life is of the utmost importance to me, I am active in Hopps Memorial Church where I am a 50-year plus member and perform many duties ranging from Church clerk to a member of the Gospel Chorus and president of the Missionary Society. I am also an active member of the 6th District Prince Hall Masonic Family.

I thank God for His grace, my husband, children, and other family members and friends for their love and support and intend to continue working for the betterment of mankind as long as God sees fit to use me, and being in this trial is one of the ways I feel He has chosen to use me.

BIOGRAPHICAL SKETCH OF JEANNIE MORICE

To my closest friends, I am considered outgoing, fun-loving, and a little eccentric—I attribute all the above to my Irish Catholic upbringing. My Canadian-born husband Dale and I have survived 27 years of marriage with never a dull moment. Dale is a Scorpio and yours truly a Leo. Our three children, ages 21 to 25, currently attend University. Hopefully, with a decent education, we can enjoy the true meaning of "empty nesters." We love Calgary, Alberta and being close to the beautiful Rockies. My hobbies include wine making, tai-chi, and walking my gorgeous golden retriever, Murphy.

I joined the BCPT having lost my mother to breast cancer. I remain confident that the results of this trial will benefit not only myself, but my daughters and women everywhere.

BIOGRAPHICAL SKETCH OF BEVERLY MUNN

I am the mother of three and grandmother of four. My mother had breast cancer for 10 years before she passed away in 1991. My sister and only sibling has had two separate incidences of breast cancer. This is why I am a high-risk participant. I work part-time as a secretary in a doctor's office. I enjoy traveling and antiques.

My reason for entering the program is to help in the research for breast cancer so that the information gained might be of help, not only to me, but to future generations of women. I am grateful for the opportunity this trial has given me.

BIOGRAPHICAL SKETCH OF RICI RUTKOFF

My mother, grandmother, and two aunts died from breast cancer. I have had several close friends develop the disease—some with a family history; others without. Breast cancer truly does not discriminate.

I live in Rockville, Maryland with my family and am a coordinator for The Event Network, a Washington, DC, destination management company. Being part of the BCPT and any future similar clinical trials is my way of being involved in helping to find a prevention for breast cancer rather than just waiting to develop it. The experience has been exciting and extremely rewarding. I sincerely encourage others that fit within the participant criteria to be part of future trials.

BIOGRAPHICAL SKETCH OF MARY SANKOLEWICZ

I am currently in the process of moving back to Easthampton, Massachusetts from a small town in Northern Maine where I have lived for the last 2 years. I am a grandmother to a beautiful 4-month old baby girl named Tia-Lynn. I have studied early childhood education and taught nursery school. My last job I was employed as a personal care attendant. I found working with numerous clients very rewarding. I had considered entering a nursing program so I could do private duty nursing, at one point in my life. Unfortunately, I was in a car accident almost 4 years ago which left me disabled and altered my future plans in the nursing profession.

The accident has not affected my commitment to the trial though. Personally, I joined the BCPT because breast cancer runs in my family. It is my hope that my involvement in the study will benefit my daughter and granddaughter so they will not go through the endless worrying and wondering.

BIOGRAPHICAL SKETCH OF MARTY SMITH

I am a licensed property/casualty insurance agent who enjoys live theater, writing, and cross country skiing. I have a 19 year old son, and have been married for 25 years. My sister died last year of breast cancer. My mother is a breast cancer survivor. I feel there is a tremendous need for cancer prevention, and encourage every woman to keep an open mind, and never stop looking for breast cancer prevention and a cure.

BIOGRAPHICAL SKETCH OF LONNIE WILLIAMS

I am a native Oklahoman. I have been married to the same man for 49 years. My hobbies are golf, aerobics, bridge, crossword puzzles, and reading. I have a B.A. degree from Oklahoma State University. I worked as a Service Representative for Southwestern Bell Telephone Company for 4 years after graduation. Since my children were born, my activities have been strictly volunteerism. These included various PTA offices, as well as president of our high school PTA. I spent 5 years on the woman's committee of the Oklahoma City Symphony. I spent 13 years as head of a box office committee for the Oklahoma City Lyric Theater. I served on the board of the American Cancer Society for 15 years. I am a member of the D.A.R. My daughter was a doctor and I acted as the office manager once a week.

I became a participant in the BCPT in 1992 because my daughter was diagnosed with breast cancer at age 35. I was not aware until then how many young women were getting breast cancer and how devastating it was to the family. My daughter was still in her medical residency and had a 5-month old baby. My daughter died in 1996 at the age of 42 of metastatic breast cancer. That is much too young to die. I was even more deeply committed to the prevention trial after her death. It is so important that we do something to prevent this from happening to our young women. I still have one daughter and one granddaughter about whom I am very concerned. From the beginning of the trial, I felt that I wanted to be a part of a program that was dedicated to prevention of this terrible disease. If some way can be found to prevent this disease, I want to be part of it.

BIOGRAPHICAL SKETCH OF HELENE WILSON

As a registered nurse who has elected to continue my career managing clinical trials for a major pharmaceutical company, I have taken my involvement in drug development and disease management and prevention to the personal level by participating in the BCPT. My daughter and I were interviewed for the Philadelphia

Inquirer and I was involved in a television commercial for the Fox Chase Cancer Network.

I have an Associates Degree in Applied Sciences in Nursing from Montgomery County Community College. When my children were old enough to be in school, I went back to college part-time and received my B.S. in Nursing from Gwynedd Mercy College. Because of my family history for breast cancer—my maternal grandmother, aunt, mother, and my fraternal aunt have all died of breast cancer—I have developed a strong interest in oncology that was manifested throughout my nursing career. I was the nurse manager of the original oncology unit at a local hospital. In my current position, I am responsible for the management of several large drug development trials.

I am a divorced mother of two children, Bernadette and Joel, and am very interested in community and Church activities. I serve as a member of the Mt. Zion A.M.E. Church Chancel Choir, Community Health Education Committee, and the after school tutorial program, as well as volunteer for the American Cancer Society. I enjoy reading, needlepoint, sewing, traveling, and, most recently, scuba diving.

When I first became a participant in this study and a member of the Participant Advisory Board, I hoped to increase women's awareness of issues relating to breast cancer and the importance of early diagnosis and treatment, especially in the African-American community. Over the last five years, I have become even more committed to those causes. I have lost a close friend and mother of my two young Goddaughters to breast cancer and have heard of numerous other women who have received a diagnosis of breast cancer. I know first-hand how breast cancer affects the family, and I believe that identification of a means to prevent the development of breast cancer is very important. I believe that the results of this trial will be beneficial, not only to me, my daughter, my new granddaughter, and my Goddaughters, but to all women today and future generations to come. I am proud to have been a participant in this study.

WHAT IS THE NSABP?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is a cooperative group that was formed in 1971 to conduct clinical trials in breast and colorectal cancer research. The members of this cooperative group had been involved in collaborative research as early as 1958. The cooperative group now comprises the membership of the NSABP Foundation, Inc. headquartered in Pittsburgh, Pennsylvania.

Current membership includes nearly 300 medical centers in the United States, Canada and Australia. Over 6,000 physicians, nurses, and other medical professionals in the NSABP member institutions and their satellites conduct NSABP treatment and prevention trials. Members as a group represent a wide range of institutional types: major medical centers, university hospitals, large oncology practice groups, and health maintenance organizations. The majority are non-university centers which can make state-of-the-art clinical trials available to patients near their homes. Each member institution has, at a minimum, a designated principal investigator who is responsible for overall conduct of the study at his or her site, and a program coordinator who is designated as the primary contact for all NSABP-related administrative and logistical matters.

Institutional members conduct NSABP clinical trials including enrollment, protocol treatment, and submission of data for subjects and participants. Both the geographic accessibility to NSABP trials and the NSABP's track record of conducting clinically relevant, important, well-designed studies have contributed substantially to its success. In 1997, NSABP treatment trial members enrolled more than 3,000 breast and colorectal cancer patients in 7 treatment trials. During the height of recruitment to the Breast Cancer Prevention Trial, more than 9,000 participants were enrolled during a 12-month period.

The National Cancer Institute is the primary source of funding for NSABP Member institutions to conduct NSABP clinical trials. NCI funding also supports two headquarters components of the NSABP: the NSABP Operations Center at Allegheny University of the Health Sciences, Allegheny Campus; and the NSABP Biostatistical Center at the University of Pittsburgh. The Foundation also receives support from other sources for ancillary studies, training and educational programs.

Since 1958, the NSABP has played a vital role in improving the treatment of women with breast cancer. More recently, it has made contributions in the management of colon and rectal cancers. During this 40-year period, over 50,000 women and men were enrolled in NSABP clinical trials.

Results from NSABP clinical trials have been a major factor in altering breast cancer management. The most obvious change in the treatment of the disease has been the reduction in the extent of the operative procedures. NSABP trials were the first to demonstrate that the radical mastectomy was no more effective than less extensive procedures. After 10 years of follow-up, an NSABP study shows that patients treated by lumpectomy (a breast-conserving procedure) followed by breast irradiation have a survival prognosis similar to those treated by mastectomy. Due in large part to these findings, a National Institutes of Health consensus conference recommended that lumpectomy and breast irradiation be the procedure of choice for women with primary breast cancer.

The NSABP trials were among the first to evaluate the worth of systemic adjuvant chemotherapy for the treatment of breast cancer. Subsequent studies have evaluated hormonal therapies as well. Results from these trials indicated that such therapies reduce the recurrence rate of breast cancer and improve survival.

The NSABP is conducting studies to evaluate the use of preoperative therapy in the treatment of breast cancer. The aim of these trials is not only to improve survival rates but also to reduce or eliminate the need for breast cancer surgery. In addition, the NSABP is evaluating therapies for noninvasive breast cancer and has enrolled 13,388 women in a Breast Cancer Prevention Trial to determine the effectiveness of tamoxifen in preventing the occurrence of breast cancer in women at high risk for the disease.

Thus as the NSABP enters its fortieth year, it can look back on a proud history of changing the way breast cancer is treated * * * and now, potentially, prevented. This cooperative group has established a long history of successfully conducting large-scale, randomized clinical trials for the treatment and, most recently, for the prevention of breast cancer. The group already has in place the supporting components including an NSABP Operations Center, an NSABP Biostatistical Center, and a dispersed membership necessary to conduct large clinical trials and related studies. Each of these components are necessary but the most important, and the one unique to this cooperative group, is a membership with demonstrated capabilities and commitment to complete the research studies undertaken.

BCPT participant distribution

| The United States: | |
|----------------------------|-----|
| Alaska | 1 |
| Alabama | 169 |
| Arkansas | 13 |
| Arizona | 159 |
| California | 840 |
| Colorado | 128 |
| Connecticut | 96 |
| District of Columbia | 30 |
| Delaware | 55 |
| Florida | 385 |
| Georgia | 174 |
| Hawaii | 112 |
| Iowa | 289 |
| Idaho | 4 |
| Illinois | 764 |
| Indiana | 216 |
| Kansas | 215 |
| Kentucky | 253 |
| Louisiana | 102 |
| Massachusetts | 310 |
| Maryland | 112 |
| Maine | 43 |
| Michigan | 520 |
| Minnesota | 340 |
| Missouri | 377 |
| Mississippi | 40 |
| Montana | 96 |
| North Carolina | 412 |
| North Dakota | 60 |
| Nebraska | 84 |
| New Hampshire | 86 |
| New Jersey | 191 |
| New Mexico | 37 |

BCPT participant distribution—Continued

| | |
|------------------------|-------|
| Nevada | 48 |
| New York | 601 |
| Ohio | 663 |
| Oklahoma | 170 |
| Oregon | 108 |
| Pennsylvania | 786 |
| Rhode Island | 36 |
| South Carolina | 172 |
| South Dakota | 31 |
| Tennessee | 122 |
| Texas | 1,037 |
| Utah | 44 |
| Virginia | 175 |
| Vermont | 188 |
| Washington | 329 |
| Wisconsin | 295 |
| West Virginia | 90 |
| Wyoming | 7 |
| Canadian Provinces: | |
| Alberta | 330 |
| British Columbia | 138 |
| Manitoba | 134 |
| Ontario | 242 |
| Quebec | 878 |
| Saskatchewan | 40 |
| Other locations: | |
| Bahamas | 1 |
| Mexico | 2 |
| Puerto Rico | 7 |
| Virgin Islands | 1 |

ATTACHMENT B

SAMPLE LETTER FOR BCPT PARTICIPANTS

DEAR (PARTICIPANT'S NAME): This letter contains important information about the NSABP Breast Cancer Prevention Trial (BCPT); the initial study results are going to be released! As a participant in the trial, you have made a major contribution to this research project and these findings would not be possible without the involvement of you and the other 13,000+ women in this trial.

The important findings will be shared with the general public at a national press conference being held on Wednesday, April 8 in Washington, DC. Members from the BCPT Participant Advisory Board (an NSABP advisory board comprised of 16 women who are participating in the BCPT) will attend the press conference, along with the study organizers and officials from the National Cancer Institute. Until the public announcement occurs, we would appreciate all participants honoring our request for keeping this information confidential; please do not share it with other individuals until after April 8.

On March 24, 1998, the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC) responsible for monitoring the trial, held a regularly scheduled meeting to review the data to date from the study. The ERSMAC, formed before the start of the BCPT, is comprised of individuals with different areas of expertise such as medical oncology, biostatistics, and ethics. They are not affiliated with the NSABP and, thus, can provide a non-biased review of the trial. The ERSMAC meets every 6 months to review data on the study and to ensure the safety of the participants in the trial.

After each meeting, the committee provides a recommendation about the study. Based on the most recent analysis of the data, this is now the first study in the world to show that a drug can reduce the incidence of breast cancer. Specifically, the study has shown that tamoxifen is effective in reducing the rate of breast cancer by an estimated 45 percent for the study population of women at increased risk for developing breast cancer. For example, this means that in a group of women similar to the BCPT population, rather than 100 breast cancers developing in the first 3½ years after taking tamoxifen, there would be 55 cases of breast cancer.

The researchers are still analyzing all of the data to further understand the other potential benefits and the potential risks of taking tamoxifen to prevent breast can-

cer, and to determine if the drug works better in some groups of women than others. For example, tamoxifen use has historically been associated with an increased risk of developing endometrial cancer in women who have not had a hysterectomy (surgical removal of the womb). It has also been associated with an increased risk of deep vein thrombosis (blood clots in large vein, which could potentially travel to the lungs), and pulmonary embolism (a blood clot that has traveled to the lungs). The overall BCPT data indicate that these are still possible risks; however, the data show that the rate of these risks does not exceed what has been originally predicted for the study. As more information about the specific benefits and risks becomes known, you will be informed.

The medical recommendations that will be available from this data are still being developed and will be made available to your BCPT doctor. In general:

- If you have been on tamoxifen for less than 5 years and have not had problems, you may consider continuing tamoxifen therapy until you take the drug for 5 years.
- If you were on tamoxifen for all 5 years, there is currently no evidence indicating that additional tamoxifen therapy beyond 5 years is beneficial.
- If you have been on a placebo, you may consider starting tamoxifen therapy after consulting with your doctor. You may also be eligible for a new study being planned that will compare tamoxifen to another drug for the prevention of breast cancer in post-menopausal women. This study is planned to begin in Fall 1998.
- If you are among the group of women who have developed breast cancer during the BCPT, your treatment plans have already been determined. Your contribution to helping others at risk for breast cancer cannot be overstated.

The availability of these findings does not mean that “the study is over.” The only difference in the trial is that participants will know what therapy they were taking. The follow-up examinations that are required in this trial represent good health care for women at increased risk for developing breast cancer. It is important that participants continue to receive this follow-up care, either at their BCPT center or through their own health care provider. Regardless of who performs your follow-up examinations, the NSABP is still interested in receiving data about your health status. This additional data will answer more questions about tamoxifen’s effectiveness in reducing the incidence of breast cancer. Presently, the NSABP would like to collect information about your follow-up for at least the next 2 years.

Although this letter may seem impersonal, it was the most effective way to get information to you and your 13,000+ partners in this research study before it is shared with other researchers, the medical community, and the general public. We and the NSABP made a commitment that every effort would be made to share the study results with the trial participants as soon as possible after they became available. In the next week or so, it is likely that you will hear the results described and discussed on television and in the newspapers. The NSABP has promised to provide us with updated study information as it becomes available. We will continue to keep you informed.

You can be very proud that you have been an important part of this project and we thank you for your contribution.

Sincerely,

APPROPRIATE BCPT PHYSICIAN AND COORDINATOR.

INSTRUCTIONS FOR UNMASKING OF THERAPY ASSIGNMENT FOR BCPT PARTICIPANTS

As part of this mailing you will find a listing which provides the unmasked therapy assignment for all participants attributable to your BCPT subcenter (i.e., according to records at the NSABP Biostatistical Center these participants have been followed on protocol by staff at your subcenter). The listing is sorted alphabetically by the participant’s last name (with “consent withdrawals” grouped at the end of the list).

NOTIFICATION TO BCPT PARTICIPANTS

The method by which you elect to provide this information to participants is at your discretion. However, every effort should be made to notify the participants prior to the national press conference scheduled for April 8, 1998. In your communication to the participants, the information that is provided in the enclosed sample letter should be conveyed to each participant.

If you decide to notify your participants by mail, the enclosed sample letter may be provided to them after it is personalized for your BCPT site. If you decide to no-

tify your participants by mail, the NSABP has provided (enclosed in this mailing) participant-specific notifications which identify the therapy to which each participant was assigned; your use of these participant-specific notifications is optional. These participant-specific sheets have been provided for all participants followed by your site except those who are consent withdrawals, lost to follow-up, or who are deceased. [While participants or their survivors in those categories should be notified, it is unlikely that the information will be relayed by mail.] These participant-specific sheets are sorted alphabetically by the participant's last name.

If you decide to notify participants by telephone, please be certain to emphasize the following important points:

- Without their contribution to this study through their enrollment, these results would not be available in such a timely fashion.
- It is important that they continue to receive follow-up examinations and follow-up care.
- More information about the impact of these results on their future course of therapy will be forthcoming in the near future.
- Their decision about whether to begin or continue tamoxifen therapy should be made in consultation with their BCPT physician.

With either method of notification, be sure to include documentation in the participant's study record when they were notified, by whom, and by what method (mail, phone, personal visit).

NOTIFICATION TO THE INSTITUTIONAL REVIEW BOARD

Please convey a copy of the Sample Letter to Participants and the March 31, 1998 Confidential Memorandum Regarding Initial BCPT Results to your IRB Chairperson as soon as possible. The NSABP has consulted OPRR, and OPRR concurs that the information to participants should be conveyed as quickly as possible in order to eliminate the immediate hazards associated with participants receiving incorrect, incomplete, or distressing information through the media. If possible, please speak with your IRB Chairperson personally about this and stress the importance of maintaining confidentiality until April 8, 1998. This IRB notification should not delay the immediate dissemination of the information to your participants.

We realize that our request for this information to be disseminated before the press conference may be difficult to meet, however, we feel it is important that every participant be made aware of the upcoming results, and that they hear about this information from the investigators whom they have become familiar with over the course of their participation.

ATTACHMENT C

STATEMENT OF PRESIDENT BILL CLINTON

BREAST CANCER PREVENTION TRIAL

Today's new research findings about the potential use of the drug tamoxifen to prevent breast cancer are an historic step in the ongoing fight against this deadly disease. Breast cancer strikes one in eight American women, and about 180,000 women in the United States will be diagnosed with breast cancer in 1998. Each of us has a sister, a daughter, a friend, or in my case, a mother, who has fought against it.

The landmark Breast Cancer Prevention Trial gives us new hope that some women at high risk for breast cancer may actually be able to reduce their risk of getting this life threatening disease. It is an important contribution to our national battle to detect, prevent, treat and finally cure breast cancer for generations of women to come.

STATEMENT OF DONNA E. SHALALA, SECRETARY OF HHS ON THE BREAST CANCER PREVENTION TRIAL

Despite all of our efforts to detect, prevent and treat breast cancer over the last few years, women have had no proven means to reduce their risk of getting this deadly disease. Instead we have relied on frequent check ups and mammograms to detect breast cancer at an early stage. Today's new research findings are an historic step toward more effective prevention of breast cancer.

This stunning result does not come without its limitations, however, and those who will choose to consider tamoxifen should consult with their doctors in order to weigh the risks and benefits for themselves.

The Food and Drug Administration is committed to a priority review of this new use of tamoxifen. And the National Cancer Institute will develop tools for women and their physicians to help them in weighing the risks and benefits.

While the results of the Breast Cancer Prevention trial may not have an immediate impact on all women, the study designers have given women more options to deal with the risk of breast cancer. Continued participation by women in trials like this will greatly aid researchers in developing newer and better methods of fighting breast cancer as well as other types of cancer.

We must also remember that high-quality mammography is the most effective technology currently available to detect breast tumors. Regular mammography screening starting at age 40 can decrease the chance of dying from breast cancer. In addition, early detection may prevent the necessity of removing lymph nodes and in some cases may prevent the need for removing the entire breast. This is especially important for older women, for whom Medicare coverage of annual mammograms is so important.

STATEMENT FROM FDA LEAD DEPUTY COMMISSIONER MICHAEL A. FRIEDMAN, M.D.,
ON THE NCI BREAST CANCER PREVENTION TRIAL STUDY

The Food and Drug Administration applauds research efforts conducted on important issues like breast cancer prevention. For the tens of thousands of women who are diagnosed with breast cancer each year, this landmark study is encouraging news.

While initial reports about the potential utility of tamoxifen in preventing breast cancer are certainly positive, like all drugs, there are also some risks. Although tamoxifen has been approved for the treatment of breast cancer patients, FDA must first review the clinical trial data before approving it for the prevention of breast cancer. We are already in contact with the NCI and the study sponsors to obtain the data. Once we receive it, we are committed to a thorough review within six months.

The federal government has been dedicated to investing time and resources into breast cancer research. This study is another example of the importance of continued research in our fight against this life threatening disease.

ZENECA COMMENDS THE NCI/NSABP IN LIGHT OF BREAST CANCER PREVENTION
TRIAL RESULTS

Zeneca commends the National Cancer Institute (NCI) and National Surgical Adjuvant Breast & Bowel Project (NSABP) for their leadership in conducting the Breast Cancer Prevention Trial which showed that women at increased risk of developing breast cancer who took tamoxifen (also known as the brand name Nolvadex (tamoxifen citrate) were 45 percent less likely to develop breast cancer than women who received placebo. "The news that tamoxifen is shown to provide significant preventive benefits in women who are at increased risk of developing breast cancer is a long-awaited development in the fight against breast cancer. The women who participated in this trial are to be applauded for their role in this historic study," says Gerard T. Kennealey M.D., Vice President of Medical Affairs, Zeneca Pharmaceuticals. "Zeneca is prepared to work closely with the NCI, NSABP, and the Food and Drug Administration to determine the appropriate next steps." This trial is the largest of three prevention trials being conducted worldwide. In each trial, Zeneca provided free of charge both the active drug, Nolvadex, and the matched placebo, as well as regular information updates from our extensive data base which reflects about 10 million patient-years of experience. Zeneca has committed to provide Nolvadex to study participants for up to five years. We will continue to provide the product to women (through the NCI/NSABP) in the Nolvadex arm for the balance of the five-year duration of the study and to provide the drug to women in the placebo arm should they and their physician choose this option. Nolvadex is among the world's most studied cancer medications with clinical data accumulated for more than 25 years. The efficacy and safety profile of Nolvadex reflects more than 10 million patient-years of experience in 110 countries. Zeneca Pharmaceuticals is a business unit of Zeneca Inc., a \$3.4 billion bioscience business with approximately 7,200 employees in the United States. Zeneca Inc. is a wholly-owned subsidiary of the U.K.-based Zeneca Group PLC (NYSE:ZEN), a major \$8.6 billion international bioscience business engaged in the research, development, manufacturing, and market-

ing of ethical (prescription) pharmaceuticals, agricultural and specialty chemical products, and the supply of health care services.

TAMOXIFEN BREAST CANCER PREVENTION TRIALS, PENNSYLVANIA BREAST CANCER COALITION, BOARD OF DIRECTORS

Pat Halpin-Murphy, President and Founder of the Pennsylvania Breast Cancer Coalition (PBCC), serves on the board of the National Surgical Adjuvant Breast and Bowel Project (NSABP) which is conducting the tamoxifen prevention trials nationally. Norman Wolmark, M.D., chairman of the NSABP, also serves on the board of the Pennsylvania Breast Cancer Coalition.

Ms. Halpin-Murphy is a breast cancer survivor who founded the PBCC in order to educate the public about the need for research, education and outreach. Pennsylvania First Lady Michele Ridge serves as honorary chairperson of the PBCC.

"Results from the tamoxifen prevention trials are very encouraging," says Ms. Halpin-Murphy, "because, for the first time, a clinical trial has shown that under certain circumstances, the use of a drug can help prevent breast cancer. The women who participated in the trials were considered at high-risk for breast cancer because of a family history of the disease. This is the breakthrough we have been waiting for."

CLINICAL TRIALS

Senator SPECTER. Before we move on to Ms. Pearson, what suggestion would you have here? You have identified yourself as being African-American and have said that women of color do not participate in these clinical trials. What suggestion would you have, if any, as to how to encourage other African-Americans to be participants?

Ms. WILSON. My suggestion would be to get more people involved at the grassroots, to actually go into the community and to encourage them on a 1-to-1 basis.

I hope that women, the minority women who were in this study, will have the opportunity to go out and encourage other women to do what they had done, to set an example and just to encourage others to repeat what we have done.

Senator SPECTER. Thank you very much, Ms. Wilson.

SUMMARY STATEMENT OF CYNTHIA PEARSON

I would like to turn to Ms. Cynthia Pearson, executive director of the National Women's Health Network. She has long been involved in women's health issues, served as executive director of a community based women's health clinic, is on the board of directors of the National Breast Cancer Coalition and the Steering Committee of the National Action Plan on Breast Cancer.

Ms. Pearson is a graduate of the University of California at San Diego.

Welcome, Ms. Pearson. We look forward to your testimony.

Ms. PEARSON. Thank you, Mr. Chairman. I appreciate the opportunity to testify today.

I think I have been invited to come today to provide a note of balance in some respects and also caution.

First, it is clear that we do not yet know what the long-term risks and benefits of tamoxifen are, nor do we know whether the short-term benefits, which were recently announced and are summarized on the posters over here are likely to make a difference in the lives of most women who would eventually develop breast cancer.

Although these results show clearly that tamoxifen can prevent breast cancer for a few years, at least, in women at high risk, they also show very clearly that tamoxifen causes serious complications.

But what they do not show, although scientists have made these data available publicly, but what we believe is not getting enough attention, is that, even within this trial of high risk women, there were a group of women for whom the risks outweighed the benefits or at least were just a wash-out. Those are the women who Dr. Klausner described as being over 50 when they started the trial and having a uterus.

Senator SPECTER. That was over 50 and what?

Ms. PEARSON. And also having a uterus, so that they could be at risk for the development of uterine cancer.

In every thousand women in that category, for every 20 breast cancers that were prevented, 22 life threatening complications were caused. You might have heard arguments that these other risks are not so bad. However, as has been said already, they can potentially be fatal. Some women, two women, did die of tamoxifen caused complications in the trial and probably the only reason why there were not more tamoxifen caused deaths is that this trial was done at the highest standard with extremely careful monitoring, far beyond what happens in the real world for most women.

Now we hope as hard as anyone does that tamoxifen will be shown to have long-term benefits. But we need to acknowledge that we don't know that yet and there are at least two possible reasons why that might not turn out to be true.

Now we do know that women who take tamoxifen for breast cancer treatment for 5 years have a long-lasting benefit that lasts after the 5 years. But we don't know yet whether that lasting effect after you stop taking the drug will be present in healthy women.

We also know that tumors which occur in women previously treated with tamoxifen may be less treatable because tumors can become resistant to tamoxifen or even feed on it. This was shown in another NIH supported study in which breast cancer patients who took tamoxifen for more than 5 years were actually more likely to die of breast cancer than those who took tamoxifen for only 5 years.

I have attached NIH's, NCI's own clinical announcement so that you can look for more details.

Even recognizing, though, these significant risks, the possibility that many women will not benefit in the terms of trading one risk for another, and the unanswered questions, the National Women's Health Network strongly supports women's right to choose this drug if they are properly informed of the risks and benefits.

We are concerned, though, that probably for the majority of women who will eventually develop breast cancer, given what we know now, the risks may well outweigh the benefits, and we are concerned that this information is not being communicated as clearly and forcefully as it needs to be.

We know from experience that patients are often not well informed about risks and benefits by many physicians and that many physicians will casually overprescribe drugs to people who don't need them. There is the recent tragic misuse of the diet drug combination phen-fen and the brand new websites for the male impo-

tence drug, where all you need is a click on a mouse and a credit card number and you can get your prescription. That is a tragic misuse waiting to happen.

Given this, we have two recommendations. One: Women and doctors urgently need accurate, realistic information about tamoxifen that makes it clear that the known risks outweigh the short-term benefits potentially for relatively many women. It is true when Dr. Klausner says there are many women at very high risk. But relatively there are more women not at that high level of risk, and even though you have heard very balanced statements today, we believe that NCI's first descriptions of the trial results as remarkable with no qualifying words in those first sentences means that NCI and NIH need a little bit of help from the outside, from public health and prevention experts, from consumer advocates in developing and getting the final format of the educational materials about risks and about tamoxifen worked out. We recommend that you encourage that process.

Finally, to wrap up, I would just like to say that our second recommendation is that NCI should immediately commit itself to lifetime followup for all the women that were so committed to the cause that they participated in this trial, and immediately stop recruiting women who were on the placebo group in this trial to the new trial being proposed for tamoxifen versus raloxifene. Preventing breast cancer is good in and of itself, but saving lives by the use of tamoxifen is better.

If tamoxifen only delays breast cancer, instead of preventing it, or if it creates a more deadly strain of breast cancer resistant to treatment, it won't save lives. The only way to know is to continue the followup of Ms. Wilson and all the women who participated in the trial for many more years, not the 2 years that were in the original protocol.

This will require additional funding which we wholeheartedly support and encourage Congress, with your leadership, to provide.

PREPARED STATEMENT

It will also mean that this group of women should not be actively encouraged, although, of course, they have the right to do so. But they should not be actively encouraged to participate in studies of hormone drugs which would then make it difficult to tell.

[The statement follows:]

PREPARED STATEMENT OF CYNTHIA PEARSON

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to testify today. I am Cynthia Pearson, Executive Director of the National Women's Health Network, the only national public interest membership organization in the United States that is devoted solely to the health of all women. Unlike many other health advocacy organizations, we do not receive any financial support from the Federal government, pharmaceutical companies, trial lawyers, or any other organization with a financial interest in the provision of health care services.

I am here today to urge caution about the use of tamoxifen to prevent breast cancer. The study you are hearing about today was stopped early, so we do not yet know what the long-term benefits or risks are. Even the short-term benefits shown in this study are unlikely to make a difference in the lives of most women. Although the results of the Breast Cancer Prevention Trial indicate that tamoxifen can prevent breast cancer for a few years in women at high risk, the study also indicates that tamoxifen causes very serious, even fatal, complications. The risks of tamoxifen may outweigh the benefits for most women at risk of breast cancer.

Let me be specific: For every 1,000 women (with a uterus) over the age of 50, 20 breast cancers were prevented and 22 potentially life-threatening complications occurred. Of the 20 breast cancers prevented, 17 would have been invasive and 3 would have been non-invasive. Of the 22 life-threatening complications, 10 were blood clots and strokes and 12 were uterine cancers. You may have heard arguments that these risks, especially, uterine cancer, are somehow “not so bad.” However, uterine cancers can be fatal, and the reason why the uterine cancers in this study were caught early is because women were monitored much more carefully than they would have been in the real world.

We hope that tamoxifen will have long-term benefits, but we’re not sure. Breast cancer patients who take tamoxifen for 5 years have a long-term benefit, but we don’t know if it will have the same long-lasting effects for healthy women who have never had breast cancer. Women need to know if this drug can truly prevent, and not delay, breast cancer. Also, tumors which occur in women previously treated with tamoxifen may be less treatable. Apparently, tumors can become resistant to tamoxifen, or even learn to feed on the drug.

A previous NIH study shows that breast cancer patients who took tamoxifen for more than 5 years were more likely to die of breast cancer than those who took tamoxifen for only 5 years. In fact, that study was stopped early because of the clear danger of long-term tamoxifen use. NCI had originally planned to compare 10 years of tamoxifen with 5 years of use, but determined that it would be unethical to do so because of these deaths. I have attached to my testimony NCI’s own announcement, which showed that 9 years after beginning treatment, 92 percent of the women who took tamoxifen for only 5 years were alive and free of disease, compared to 86 percent of the women who took the drug continuously for the entire 9 years.

What about those women who take tamoxifen to prevent breast cancer and who later get breast cancer anyway? Will they be resistant to tamoxifen and therefore unable to use it to treat their breast cancer? That would be potentially disastrous because tamoxifen is normally such an effective treatment for breast cancer.

And let’s remember that there are other potential problems. Including quality or life issues that will prevent many women from choosing it. It can’t be taken by women who want to become pregnant, and in fact, causes side effects similar to menopause.

We support women’s right to choose this drug if they are properly informed of the risks and benefits. We believe that the benefits may well outweigh the risks for women with an extremely high risk of breast cancer, such as women with the breast cancer gene or women who have had a diagnosis of non-invasive cancer. These women potentially have a 30 percent risk of developing, breast cancer within the next 20 years. However, most women who develop breast cancer are not in this ultra-high-risk population—most, in fact, have no known risk factors. In the general population, risks will outweigh benefits. We are also very concerned that age alone not be considered sufficient risk to justify using tamoxifen for prevention, especially because the risks of tamoxifen are higher for older women. Unfortunately, we know from experience that patients are often not well informed of the actual risks and benefits. For example, the recent tragic misuse of the diet drug combination phenfen shows that doctors will prescribe drugs to hundreds of thousands of patients who are not likely to benefit. One of our major concerns is that the recent hype regarding, this study will result in millions of women taking tamoxifen with little likelihood of short-term benefit and before we even know what the long-term benefits are and that the long-term risks are.

We have the following recommendations.

- Women and their doctors urgently need accurate, realistic information about tamoxifen which makes it clear that the known risks outweigh the short-term benefits for most women. Given NCI’s inappropriate public announcement of the results as “remarkable” and a “breakthrough”, we cannot count on the NIH for unbiased information. We recommend that Congress advise the NIH to create a process which involves public health experts and consumer advocates in the development and final format of educational materials about tamoxifen.
- NCI should immediately commit itself to life-time follow-up for all women who participated in the Breast Cancer Prevention Trial. NCI should also immediately stop its unethical recruitment of women in the placebo group to their new trial comparing tamoxifen to raloxifene. While preventing breast cancer is good, what is really important is determining, whether tamoxifen actually saves lives. If it only delays breast cancer instead of truly preventing it, or if it creates a more deadly strain of breast cancer resistant to treatment, it won’t save lives. The only way to know whether or not tamoxifen saves lives is to continue the follow-up of women participating in the trial for many more years. This will require additional funding, which we wholeheartedly support and encourage Con-

gress to provide. It will also mean that this Group of women should not be asked to participate in other studies of hormone drugs. Currently, NCI is actively encouraging women who were given placebo pills to take part in a study of tamoxifen compared to raloxifene. Obviously, this destroys any possibility of finding out whether or not tamoxifen saves lives. This is outrageous.

The nation has invested 50 million dollars in the Breast Cancer Prevention Trial. While the results clearly indicate that tamoxifen offers a new and welcome option for a small group of women in dire need, it is a blip, not a breakthrough, in our shared efforts to eradicate breast cancer. We need to work together to ensure that women and their physicians are appropriately informed about the true implications of this study. And women deserve a commitment to finding out whether or not preventive tamoxifen saves lives.

TAMOXIFEN

Senator SPECTER. Ms. Pearson, there can be no disagreement about the maximum amount of information and lifetime followup certainly sounds desirable. Your cautionary words are obviously very important, I would like your opinion, your judgment, on this. If you have a woman under 50, who does not have a uterus—you had said if you were over 50 and if you had a uterus, there is a real risk potential, a high one. For someone who is a high risk cancer patient under 50, without a uterus, what would you suggest—that tamoxifen is good?

Ms. PEARSON. I would suggest looking very carefully about what that high risk is. You are very educated about cancer. You use that term carefully.

Many people in the community, including many community doctors, use it casually to mean someone who maybe gave birth to their first child in their late thirties.

Senator SPECTER. Well, if you have a high risk of breast cancer and I am about to ask Dr. Wolmark to define high risk, then what?

Ms. PEARSON. If a woman has been diagnosed with precancerous conditions through the biopsy, if a woman has an extremely strong family history, the discussion about tamoxifen between her and her doctor is absolutely a good idea and we are glad that there is this new option.

Senator SPECTER. OK. But beyond the discussion, if you have the high risk characteristics, if you are under 50, if you do not have a uterus, then do you think that it is wise to prescribe and take—

Ms. PEARSON. It is a reasonable choice—

Senator SPECTER. Let me finish the question. Do you think it is wise to prescribe and take tamoxifen?

Ms. PEARSON. It is a reasonable choice for a woman to make in that situation.

Senator SPECTER. Would you define high risk for us, Dr. Wolmark, so that we have that on the record?

Dr. WOLMARK. I think that is not a straight-forward formula, which I think makes the issue a little bit more complex.

Senator SPECTER. Dr. Wolmark, there are a lot of doctors listening to C-SPAN and a lot of doctors following you. It may not be easy, but this is a unique opportunity to convey a lot of information as best you can as to what high risk means.

Dr. WOLMARK. Well, the original study was formulated on the premise that the women who would enter into this study would have the risk equivalent to a 60-year-old patient or participant.

That implied that over the next 5 years, her likelihood of developing breast cancer was 1.7 percent.

So those women who are under 60 years of age must have a risk equivalent to that to have been eligible for this study.

Also, there are many combinations of risk factors that would make a woman eligible for this study or equivalent to a risk of 60 years of age or greater. And for those who are listening on C-SPAN, if you had a 35-year-old woman, if she had two first degree relatives plus a history of a personal breast biopsy, she would qualify. But the criterion that made her of a risk equivalent to a 60-year-old woman is not necessarily the same and is not the same for a woman who is age 40. In that category, for example—

Senator SPECTER. Dr. Wolmark, let me interrupt you. You can transmit that to the doctors. Maybe they will understand it.

Is there anything you can say that would give some general parameters to a woman who worries as to whether she is high risk and what that means to her?

Dr. WOLMARK. Well, as she approaches age 60, she requires fewer factors and fewer discriminants to qualify for that high risk. If she is younger, then she will require more factors.

DEFINING HIGH RISK CATEGORY

Senator SPECTER. Dr. Klausner, let me ask you. We don't have a whole lot of time. They are going to start a series of votes, three votes, in just a few minutes and I am going to have to face a choice as to how far we have gone as to whether we come back and keep you waiting. These are very important questions.

Would you try your hand at defining a high risk category?

Dr. KLAUSNER. For women who are concerned they are at high risk, the two most important issues are their family history and family history specifically in close relatives—first degree relatives are mothers, sisters, daughters—and whether they personally have a history of breast disease—an abnormal biopsy, for example, or a precancerous lesion. Those are the two highest risk considerations.

There are other factors, but they have to be calculated, we believe, with their physician. So would be the two issues that women could know themselves. But they have to check it out. We have done studies.

Senator SPECTER. Obviously, they have to go to a doctor and have a fuller explanation than you can give them here on a sound byte.

Dr. KLAUSNER. Yes, right. That is exactly right, sir.

APPROVAL OF TAMOXIFEN USE

Senator SPECTER. Let me move to a number of other subjects because, as I say, our time is limited. Let's explore this a little more fully. I did not want to take the time out before we had finished giving everybody a chance to testify. On tamoxifen, it is currently approved by the FDA for secondary breast cancer treatment, that is, following a mastectomy or radiation therapy. It is also used for metastatic disease.

Let me follow up with you, Dr. Varmus, because we had started to discuss it. If a doctor wishes to use it for breast cancer prevention, which the doctor may do. However, the company which makes

it, Zeneca, cannot advertise or market tamoxifen as a preventive. Is that a summary statement of it?

Dr. VARMUS. That is correct at the present time.

Senator SPECTER. Moving into somebody else's field, why does it take the FDA 6 months to make a determination on tamoxifen so that there can be more information in the field and there can be advertisements for it and more information to women as a preventive?

Dr. VARMUS. Senator Specter, the statement that was made by Dr. Friedman was that within 6 months this would happen.

What has to occur is that the paperwork for submission to FDA needs to be prepared after the study is carefully reviewed. Zeneca then would submit the application for this additional indication. Experts would then be assembled to review the data.

That will be done, I would say, in somewhere between 3 and 6 months, and I think Dr. Friedman was cautiously giving an outside boundary.

Senator SPECTER. The question which arises here in the Congress is whether it could be done faster.

We recently had changes in the Food and Drug Administration law. In Ms. Wilson's testimony, she expresses her feelings of being a walking time bomb for cancer and that she really welcomed the opportunity to be in this test group. I think there are many women who would like to have the availability of tamoxifen.

Dr. VARMUS. It is available.

Senator SPECTER. Yes; they can get it now because a doctor can prescribe it since it is OK for some collateral use. But there are many women out there who do not know about it and will not know about it in the absence of advertising or a real promotion of tamoxifen.

Dr. VARMUS. We are trying to provide a great deal of information. We believe that a very, very large segment of the physician population and the patient population will be aware of these new findings as a result of this hearing.

Senator SPECTER. I think you have done a good job with that and I will reserve that question for the FDA.

Dr. VARMUS. I think that will be wise.

Senator SPECTER. We will contact them and we will ask them why not sooner, what is the soonest they can do this?

Dr. VARMUS. Right now, they are waiting for the application.

Senator SPECTER. Dr. Wolmark, did you have a point you wanted to make?

Dr. WOLMARK. Senator, in all fairness, I have had discussions with Mike Friedman, who said that he would do whatever is necessary to expedite this as quickly as possible. I think that we can have it done sooner than 6 months.

Senator SPECTER. Would you care to give an estimate as to how soon?

Dr. WOLMARK. Well, we would like it tomorrow——

Senator SPECTER. That's good.

Dr. WOLMARK [continuing]. But I don't think it will be by then. [Laughter.]

Senator SPECTER. We'll take it up with him and we will encourage him to do it as fast as he can.

What more will be done on tamoxifen, Dr. Wolmark, with respect to the research and the study which your very distinguished group has undertaken?

Dr. WOLMARK. We think we need to refine some of the risk-benefit models, as Dr. Klausner has said, and that is currently ongoing to provide the best information relative to the risk-benefit to a particular woman who is at increased risk for the development of the disease.

Having said that, ultimately the decision will be an individual one based on having accurate information of risk benefit.

I think Ms. Pearson clearly underscored that example. She looked at the data relative to women over 50 and said that, in her conclusion, the risks were equivalent to the benefits.

I think other people looking at that would conclude something very different and state that they would wish to avail themselves of tamoxifen seeing exactly the same data set.

RALOXIFENE AND TAMOXIFEN

Senator SPECTER. With the limited time we have, let me move for a moment or two to raloxifene.

Dr. Klausner, could you give a distinction between tamoxifen and raloxifene. We just heard of raloxifene in the media yesterday. What is the difference?

Dr. KLAUSNER. Raloxifene and tamoxifen are similar drugs and they act on estrogen receptors, either turning them on or turning them off in different tissues. Raloxifene recently has been approved by the FDA for use in postmenopausal women to prevent osteoporotic fractures.

The recent reports in the news relate to analysis of the several studies looking at women that took raloxifene for prevention of osteoporotic fractures to see whether—

Senator SPECTER. So raloxifene is for osteoporosis primarily.

Dr. KLAUSNER. That is what it has been approved for.

Senator SPECTER. But testing has shown, according to the New York Times today that raloxifene does not appear to raise the risk of uterine cancer as a side effect contrasted with tamoxifen.

Is that an accurate report?

Dr. KLAUSNER. That is what the New York Times says. We are concerned that those studies—

Senator SPECTER. I'm not asking you if I have accurately quoted the New York Times. I'm asking you if the New York Times is correct.

Dr. KLAUSNER. We are not sure. That is why we think this has to be studied.

In those studies, women were observed for only about 2 years, 28 months, I think, total. Very few women were actually specifically looked at in terms of what was happening in their uterus. We are interested in terms of the possibility, and I think it is that. It is a possibility that raloxifene is similar to tamoxifen in some respects and may be different in having less of a stimulatory effect on the uterus. That is exactly why we want to do a clinical trial to compare them.

We won't know the answer until we directly compare them. There has not been long enough experience to say that for sure. It is just a suggestion.

Senator SPECTER. So your judgment is the clinical trials, which you conducted with tamoxifen, move you far ahead in that analysis and you have not had the clinical trials in raloxifene to give you the same kind of assurances.

Dr. KLAUSNER. That is exactly right.

Senator SPECTER. Even though there may be some preliminary indicators that tamoxifen does not cause uterus cancer, you really don't know about that.

Dr. KLAUSNER. I think that's right.

Senator SPECTER. So tamoxifen is the better of the two given the limitations which have already been described.

Dr. KLAUSNER. It's the only drug for which we have evidence, the best type of evidence, which is from a randomized clinical trial.

Senator SPECTER. Dr. Klausner, in the past I have asked you how much you would like to have by way of funding for research. Let me try again.

My sense is—and I have said this to you before and to Dr. Varmus—with a Federal budget of \$1.7 trillion, we can take care of our priorities. I believe that it has been modestly stated to double NIH's funding over 5 years, which would be more than \$2.5 million a year.

We have seen what has gone to the National Cancer Institute. But if you had your druthers, what would the figure be?

I'm about to ask Dr. Varmus the same question for the whole National Institutes of Health. So I give you just a little warning there.

What is your figure, Dr. Klausner?

Dr. KLAUSNER. According to the law, I am asked what my druthers would be in the formal NCI bypass budget, and in that bypass budget we asked for a budget of \$3.191 billion in order to attempt to do the many things we very much would like to do and cannot.

Senator SPECTER. Dr. Varmus, what would the NIH budget be? First of all, this is a two-part question. What would you like the NIH budget to be? Second, what would the NIH budget have to be to give Dr. Klausner his druthers?

Dr. VARMUS. They are related questions, obviously, Senator Specter.

The NIH, as you know, has requested an increase of about 8.4 percent for this coming year. That is the President's budget request for the NIH. We believe that the NIH can do well with that.

You requested a few weeks ago, before our appropriation hearing, that I ask all the Institute Directors what each would like to spend in an ideal world where there were not other constraints upon the budgetary process. The aggregate number, the average for the whole of NIH—was a 23-percent increase, which would bring us up to—I don't have the numbers with me—something close to \$17 billion for the coming year.

Senator SPECTER. Well, we are going to take a close look at those figures as to fiscal year 1999 and future years. I do believe that the NIH is the crown jewel of the Federal Government, maybe the only jewel of the Federal Government. You have had such spectacular results on this breakthrough on tamoxifen.

Dr. Wolmark, to what extent has the funding for the National Institutes of Health enabled these remarkable tamoxifen breakthroughs to have occurred?

Dr. WOLMARK. Without that funding, these trials clearly could not have been done. They take a significant amount of money to carry out and they take a significant amount of commitment from the participating members, the data managers, and the patients who do far more than what the budget pays them to do.

We estimate that the budget provides only for two-thirds the actual costs in time and effort, and that does not take into account the medication which is provided free of charge by the companies.

Senator SPECTER. Is your research budget adequate?

Dr. WOLMARK. Our research budget can always be greater and we would be able to bring more patients into these trials if our budget were larger.

Senator SPECTER. How much more?

Dr. WOLMARK. Well, we would want a 40-percent increase.

Senator SPECTER. If you brought more patients in for the clinical trials, do you think you would have better answers to some of the obviously unanswered questions?

Dr. WOLMARK. They would certainly be more rapid answers, and that would enable us to move on to the next trial, which could test a more interesting and a more effective agent.

Senator SPECTER. That is something that this subcommittee is very interested in, how rapid it can be and how fast we can provide these answers. There are many, many women out there who want the answers.

SUMMARY STATEMENT OF DR. BERNARD FISHER

We have in the hearing room today Dr. Bernard Fisher. Although he is not on the official witness list, Dr. Fisher, would you mind stepping forward. I would like to get your appraisal of this hearing today.

Dr. Fisher was chairman and principal investigator of the national surgical adjuvant breast and bowel project for 27 years. In 1992, he initiated the world's first study to determine whether tamoxifen can prevent breast cancer in women at high risk.

There have been some professional questions raised and Dr. Fisher has emerged the victor. Sometimes the courts have to adjudicate medical controversies, and there was a very sizable award in addition.

Our question today is on the medical aspect. Dr. Fisher, you were in my office along with others trying to mediate and trying to find an answer to some of those problems. Today the focus is on trying to prevent breast cancer.

The subcommittee would like your evaluation of these studies.

Dr. FISHER. Well, Senator Specter, I thank you very much for allowing me to make a few comments. I consider the current findings to be the most important of the contributions which I and my colleagues have made during my 40 years of using large, randomized clinical trials to improve the status of women with breast cancer. The results presented here today permit the opening of a new door which permits us to move forward in an entirely new direction of breast cancer research.

Where that journey will take us remains to be determined. But it will take us forward in our common effort to eliminate breast cancer. This situation is entirely similar to that which has occurred as a result of identification of the changes in BRCA I and BRCA II genes. In both situations, a multiplicity of new questions have been raised which must be answered. In both the precise way in which the findings will be integrated into strategies that will better women must be and will be defined.

From my perspective, I see a nexus between these two recent developments, the BRCA I and BRCA II genes and the identification of these alterations which put a woman at high risk for the disease and the presence of agents which can possibly markedly decrease that risk.

For these events now there exist possible alternatives for women who are considering removal of both breasts to prevent a breast cancer. Just as it is likely that there will be observations of other genes—

Senator SPECTER. Dr. Fisher, permit me to interrupt you for one question. Do you think there are circumstances under which removal of both breasts is an appropriate effort made to prevent breast cancer?

Dr. FISHER. I think there are circumstances, but in my view they are few and far between.

Senator SPECTER. It sounds very drastic to me. You say there are a few cases, but they are very rare.

Dr. FISHER. Very rare.

I think, just as there will be more genes discovered which relate to breast cancer, as we have said here today, there are going to be other drugs which will come along about which we need to know their relative merits.

Senator SPECTER. Dr. Fisher, I am going to have to ask you to summarize in 2 minutes because there are about 3 minutes left to the vote.

Dr. FISHER. Then I will just give it to you in 50 seconds.

Senator SPECTER. Perfect.

Dr. FISHER. Senator Specter, I am grateful for the funding that I have received from the Federal Government over the past 40 years which made it possible for me and my associates to demonstrate that mutilating operations for breast cancer could be replaced by lumpectomy, that post-operative chemotherapy and hormonal agents can prolong the lives of many patients with breast cancer, and that now some women can have their breast cancers prevented.

New lines of investigation are available. Much work must be done and ample funding is necessary to accomplish the goals. The goals of eliminating breast cancer as a terrible public health issue can only be achieved if we keep our collective eyes on the goal and work together without inappropriate divisiveness.

Thank you, sir.

Senator SPECTER. Thank you very much, Dr. Fisher, and thank you for all the service you have given to America and the world on this important subject.

Dr. FISHER. Thank you.

Senator SPECTER. We are going to conclude the hearing at this point rather than interrupting. We have what we call three back-to-back-to-back votes and it will take about 45 minutes. There is too much talent in this room to ask you to wait.

We may have another hearing on this subject. In the interim, I would like to ask Dr. Klausner, Dr. Wolmark, and Dr. Varmus to submit to the subcommittee a definition as to a high risk patient so that we can have it on the record and we can promulgate it.

I would also like you to give the subcommittee a written answer, Dr. Klausner and Dr. Wolmark, as to what might be done as to Ms. Wilson's suggestion. First, as to whether you agree with her that we need more minority participants and, second, as to how we can go about getting them.

Ms. Pearson, I would appreciate it if you would submit to the subcommittee the qualifications you have articulated of the circumstances where you would opt on the side of giving tamoxifen. You have given some good cautionary signals. I would like you to amplify the answer which you had been giving as to where you would recommend that tamoxifen be given.

Finally, Dr. Klausner, I would like as much specification as you can give as to what you think you could do at the National Cancer Institute if you had that figure which matched your druthers.

I have already done this with Dr. Varmus, where he had a very distinguished assemblage of the directors of the various institutes in this room several weeks ago. To the extent that you can quantify it, Dr. Klausner, tell us where we might go with both tamoxifen and raloxifene. The subcommittee would appreciate that.

[The information follows:]

MINORITY PARTICIPATION

Throughout the trial, several strategies were used to increase participation of women from racial and ethnic minority groups. These strategies included placing study-related recruitment materials in businesses and churches located in minority communities; collaborating with a minority-owned public relations firm to develop a structured media campaign targeting racial and ethnic minorities; developing and broadly disseminating a Public Service Announcement that featured singer Nancy Wilson; and communicating information to study sites about how other sites successfully reached racial and ethnic minorities.

In the beginning of the study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) tried several minority recruitment approaches on the BCPT which were marginally helpful. In August 1996, the NSABP began a Pilot Minority Recruitment Program (PMRP) for the BCPT. The goal of the PMRP was to increase minority enrollment in the BCPT by increasing communities' awareness of, and educating racial and ethnic minority populations about, the trial. This was thought to be best accomplished by funding a half-time community outreach coordinator (COC) dedicated to conducting community outreach. Selected sites employed a part-time COC who was representative of and had an understanding of the barriers to participating in clinical trials faced by various minority groups. The COCs fostered many relationships in their communities by offering personalized presentations on breast cancer risk factors, incidence, and survival rates and on clinical trials research. In less than a year, collaborations were formed as a result of presentations given at African American churches, community hospitals and health clinics, Hispanic health fairs, local chapters of Chi Eta Phi and Delta Sigma Theta Sororities, the Urban League, YWCA, AARP, and minority medical societies. Additionally, the COCs heightened awareness about the BCPT via an article that appeared in Essence magazine and via newsletters that reached thousands of physicians in Chicago and the constituents of state representatives in Pennsylvania.

The PMRP has been the most effective recruitment strategy to date and will serve as the model for minority recruitment for future prevention trials. The NSABP has recently received approval for full funding of these currently half-time COCs and

hopes to add more minority sites that will reach not only the African American community, but also the Hispanic community as they continue to strengthen minority outreach for the upcoming breast cancer prevention trial with raloxifene.

HIGH RISK

The following information will outline what the NSABP used as a standard to classify what constitutes "high risk" for breast cancer among women ages 35 to 59:

- To enroll in the study, women between 35 and 59 years of age needed to have a risk of developing breast cancer within the next five years that was equal to or greater than the average risk for 60-year-old women. This increased risk was determined in one of two ways. Women diagnosed as having lobular carcinoma in situ, a condition that is not cancer but indicates an increased chance of developing invasive breast cancer, were eligible based on that diagnosis alone. The risk for other women was determined by a computer calculation based on the following factors:
- Number of first-degree relatives (mother, daughters, or sisters) who had been diagnosed as having breast cancer; whether a woman had any children and her age at her first delivery; the number of times a woman had breast lumps biopsied, especially if the tissue was shown to have a condition known as atypical hyperplasia; and the woman's age at her first menstrual period.
- For example, a 35-year-old woman would have to have two or more first-degree relatives with breast cancer and a personal history of at least one benign breast biopsy or a diagnosis of lobular carcinoma in situ.
- A 45-year-old woman would have to have one or more first-degree relatives with breast cancer and a personal history of at least one benign breast biopsy or a diagnosis of lobular carcinoma in situ.
- A 55-year-old woman would have to have one or more first-degree relatives with breast cancer or a personal history of at least one benign breast biopsy or a diagnosis of lobular carcinoma in situ.
- Women 60 years of age or older were eligible for the BCPT based on age alone because many diseases, including breast cancer, occur more often in older persons. The risk of developing breast cancer increases with age, so breast cancer occurs more commonly in women over 60 years of age. The risk of developing heart disease or osteoporosis also increases with age, and those diseases are also being studied in the BCPT.

The NCI is in the process of developing and testing a risk/benefit assessment tool for physicians to use in counseling their patients about whether or not to take tamoxifen for breast cancer prevention. This will be posted on the NCI Cancer Trials web site and will also be available through the Cancer Information Service. In the meantime, health care providers who want information about how to assess the breast cancer risk of an individual woman may contact NCI via email at cisocc@nih.gov or by calling the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) and following the prompts for ordering materials. The model will be refined over time, and requesters may sign up to be notified when a more refined version is available.

RALOXIFENE

The NSABP is planning a second breast cancer prevention trial, tentatively scheduled to begin in the fall of 1998. The trial would involve 20–25,000 postmenopausal women who are at least 35 years old and are at increased risk for developing breast cancer. The study would compare tamoxifen to raloxifene, a drug that was recently approved by the FDA for treating osteoporosis and is thought to have the same benefits as tamoxifen but possibly fewer side effects. The primary aim of the trial is to test whether long-term raloxifene therapy is effective in preventing the occurrence of invasive breast cancer in postmenopausal women having an increased risk of developing the disease. A secondary aim is to establish the net effect of raloxifene therapy. Data will also be collected on cardiovascular and fracture endpoints and for all toxicities and side effects. This information will allow a comprehensive benefit/risk assessment to be derived for the use of raloxifene as a chemopreventive agent. We estimate that the cost of this study will be approximately \$80 to 100 million. Women will be informed about the study through similar channels as were used for the BCPT. In addition, we will be strengthening the minority enrollment programs as outlined earlier.

CONCLUSION OF HEARING

Senator SPECTER. Dr. Varmus, did you have one more word?

Dr. VARMUS. Just that Dr. Klausner, of course, was in the room at that time and submitted along with other Institute Directors a statement about his ambitions with increased funds.

Senator SPECTER. Well, if you have any supplement, we will take that.

Thank you all very much for being here, we appreciate it, that concludes our hearing. The subcommittee will stand in recess subject to the call of the Chair.

[Whereupon, at 2:50 p.m., Tuesday, April 21, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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