Attachment No. 2

October 18, 1977

NIH/NCI CONSENSUS DEVELOPMENT MEETING ON BREAST CANCER SCREENING

Bethesda, Maryland - September 14-16, 1977

ISSUES AND RECOMMENDATIONS

In 1973-74 Breast Cancer Detection Demonstration Projects (BCDDP) were initiated at 29 locations around the country under the auspices of the National Cancer Institute and the American Cancer Society. Their purpose was to demonstrate the feasibility of periodic screening of large numbers of women for breast cancer, using clinical history, physical examination, mammography, and thermography. Following inception of this program, however, questions were raised about the relative values of the screening components when compared to possible risks involved with the ionizing radiation from mammography. Critics suggested that the radiation used to detect cancers might also induce malignancies at a later date. No concern was expressed or intended regarding the obvious value and importance of diagnostic x-ray examination of the breast in women with signs and/or symptoms which might be related to breast cancer.

In October 1975, the National Cancer Institute appointed three experts to lead investigations into various aspects of these issues, by analysis of data generated by a study conducted by the Health Insurance Plan (HIP) of Greater New York, which began in 1963. A group headed by Dr. Lester Breslow of UCLA was to examine the benefits as determined by the HIP Study results; a group chaired by Dr. Arthur Upton, at the time Dean of Basic Sciences, Health Sciences Center, State University of New York, Stony Brook, was to consider and estimate radiation risks; and a group headed by Dr. Louis Thomas of NIH was to reexamine the pathology of cancers found in the HIP Study. Subsequently--in January 1977--a working group under Dr. Oliver Beahrs of the Mayo Clinic, was charged with reviewing in-depth the findings generated by the BCDDP.

Recently, the National Institutes of Health and the National Cancer Institute convened a meeting, the NIH/NCI Consensus Development Meeting on Breast Cancer Screening, with the objective of developing a set of recommendations on the major issues and questions which have arisen concerning breast cancer screening and the BCDDP, including mammography.

The Panel (see attachment) appointed to deliberate on these issues met in open forum at NIH on September 14, 15, and 16, 1977, and reviewed the reports of the four study groups mentioned above, heard testimony from interested professionals, associations, BCDDP project directors, and members of the public. The questions, and a summary of the recommendations formulated by the Panel, follow.*

*Throughout its deliberations, the Panel repeatedly emphasized the distinction between mammography used for diagnosis--the value of which was not in question--and mammographic screening to detect possible disease in women who have no symptoms or physical findings whatsoever.

QUESTION 1:

Is there evidence that early detection of breast cancer leads to reduced mortality from breast cancer? Which of the available screening modalities or combination of modalities is most effective in early detection?

ANSWER:

The only sound scientific evidence which demonstrates a favorable benefit in breast cancer screening is derived from the HIP Study. The data from this randomized controlled trial--which formed the rationale and stimulus for the BCDDP--indicate that periodic breast cancer screening can decrease the number of deaths due to breast cancer by about 40% in women who are over 50 years of age. The age suggests that this may be related to menopause but the data in the HIP Study do not permit any definition of this question. However, the HIP Study thus far shows no decrease in breast cancer mortality attributable to screening women below the age of 50.

The evidence indicates that the benefit of the screening program rests on the use of physical examination and mammography, in combination. The Panel noted that there are no rigorous scientific data showing to what extent either physical examination alone or mammography alone may be beneficial. The efficacy of physical examination as a screening procedure for breast cancer (e.g., by well-trained nurse practitioners) has not been examined.

The Panel acknowledged that mammographic techniques have improved markedly in recent years, with smaller, and presumably earlier, lesions now being detected. The advantage of mammography lies in the fact that appropriate therapy may be administered at an earlier stage of breast cancer, presumably improving prognosis. Moreover, radiation dosage has been decreased significantly. Nonetheless, there are insufficient data to indicate that these advances have resulted in decreased mortality for women under age 50 at the time of screening.

QUESTION 2:

What are the risks of each of the available screening modalities for early detection of breast cancer?

ANSWER:

Neither physical examination nor techniques such as thermography or ultrasound are known to have harmful effects upon the body. The use of mammogrphy, however, is associated with an inherent risk of radiation exposure, and studies indicate that breast tissue is particularly susceptible to radiation damage.

The precise radiation risk is difficult to quantify, but current evidence strongly suggests that risk increases linearly with increasing dose and is linear down to the lowest dose.

At the present time, the average surface radiation exposure in the BCDDP centers is 1.2 (0.2 to 2.5) roentgens. It is estimated that every rad of exposure raises a woman's risk of breast cancer by about 1%. Thus, if a woman in the general population has about a 7% chance of developing breast cancer in her lifetime, one rad will increase her risk by 1% of 7%, or from 7% to 7.07%. The Panel observed that even with the cumulative dose that would result from a series of five yearly mammograms in the BCDDP--about 4 rads total with the newer techniques--the increased risk of breast cancer is so little that it could not be demonstrated in long-term follow-up studies of the BCDDP group.

With repeated examinations of one cohort of women, the likelihood of finding new cancers progressively declines after prevalent cancers are detected while the total radiation given each woman progressively rises. This puts an obvious limit on the advisability of repeated re-screening of the same population.

QUESTION 3:

Do the potential risks versus benefits differ for different methods of breast cancer detection and at different ages of patients screened?

ANSWER:

The question of risk, in this context, applies only to mammography. Data from several studies indicate that the risk of radiation, in general, may decrease with age although data from the analysis of A-Bomb survivors show an excess of cancer in the age group over 50. Data suggest that the peak age of susceptibility is between 10 and 19 years and that the danger drops gradually thereafter. This possibility, too, argues for confining radiation, in this case mammography, to older age groups, but there is no conclusive evidence.

QUESTION 4:

If it is not possible to answer any or all of the foregoing questions, what data need to be generated to provide adequate answers?

ANSWER:

New diagnostic/screening techniques are needed. The Panel recommended greater emphasis on research with noninvasive techniques, such as

thermography, ultrasound, and biologic markers.

Because the potential benefits of thermography remain undocumented, the Panel recommended that thermography be discontinued as a routine part of the BCDDP screening program except in those centers where sufficient expertise is available to justify further clinical investigation and research. Because thermography in the BCDDP was not set up as a research study, its continued use should require the development of a research design.

The Panel deplored the lack of clear-cut data on the efficacy and the risk-benefit ratio of screening for women under 50, but they did not come to an agreement about the feasibility and logistics of randomized clinical trials to resolve such issues. However, clinical trials would be important in order to resolve certain questions concerning the efficacy of periodic breast screening.

The BCDDP should continue to monitor all women in whom breast cancer has been diagnosed. Although the Panel was unable to assess the feasibility of following all women who have had a mammogram in the BCDDP, there seemed to be general agreement that such followup would be important and that this question deserves further consideration.

QUESTION 5:

What are the practical and ethical considerations for implementing demonstration projects in cancer detection and how does the BCDDP comply with these considerations?

ANSWER:

Demonstration programs by definition utilize proven and practical methods to project new information to the medical community. However, from its inception the BCDDP has of necessity incorporated certain practices of assumed but unconfirmed value.

As a demonstration program with investigational components, therefore, the BCDDP must come to grips with several important ethical concerns. The Panel recommended that the BCDDP's Informed Consent Form indicate the radiation dosage to be delivered to the patient, and assure that all information gained through the program will be disclosed to the screenee, as well as to her physician.

The Panel proposed that the screenee receive the Informed Consent Form and appropriate background materials beforehand, so that she would be able to discuss the proposed procedure with her family and her physician.

The Panel recommended that the histology of any lesion smaller than one centimeter in diameter, or any papillary or intraductal proliferation originally interpreted as malignant, be reviewed by at least two pathologists prior to definitive therapy.

Women who have been screened already and who have had a diagnosis of cancer should be notified promptly if there has been a change in diagnosis.

Any new experimental study should take into consideration a variety of issues, e.g., its justification from a cost-benefit point of view, the informed consent process, the way in which research subjects are selected, and the development of guidelines for compensation of individual participants who are injured in the course of the study. Furthermore, more women, both professional and consumer representatives, should be included in the design and planning of any future studies.

QUESTION 6:

What can the Consensus Panel recommend as to the type and frequency of breast cancer screening and who should provide the screening?

ANSWER:

Based on the available evidence, with the understanding that no new participants are being added to the program and that limits be set on radiation exposure, the Panel recommended that BCDDP screening, using mammography and physical examination in combination, be continued for those women 50 and older who are currently enrolled. Regardless of the location for mammographic screening, upper limits should be set on radiation exposure consistent with best current data. Women subjected to mammography should ask for such information and should be urged to maintain their own personal exposure records.

The Panel found no convincing justification for routine mammographic screening for women under the age of 50. This does not imply, however, that physical examination and breast self-examination are not important for women of any age.

The Panel recommended that routine mammography for women 40 through 49 enrolled in the BCDDP be restricted to women having a personal history of breast cancer, or whose mothers or sisters have a history of breast cancer.

Mammographic screening of women below the age of 40 should be limited to those women having a personal history of breast cancer.

Ethical considerations, however, led the Panel to concede that women under 50 who are already participating in the BCDDP should be afforded the opportunity to continue having mammograms if they wish--so long as they are informed that there is no proven benefit and there is presumed risk, and that the Panel does not recommend screening mammography in this age group. (Again, the Panel went to great length to distinguish between mammographic screening and mammography used as a diagnostic tool. Thus, for example, if a woman under the age of 50 in the BCDDP develops symptoms or findings suggestive of breast cancer, she may well require mammographic examinations as part of her medical evaluation by her own physician).

Attachment

Attachment

LIST OF PANELISTS

1. Samuel Thier, M.D., CHAIRMAN
   Professor and Chairman
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2. Virgil Loeb, M.D., VICE-CHAIRMAN
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October 18, 1977

NIH/NCI Consensus Development Meeting on Breast Cancer Screening

Bethesda, Maryland

September 14 - 16, 1977

Background Discussion and Recommendations

The National Institutes of Health inaugurated a new approach to evaluation of therapeutic and diagnostic procedures with a mid-September "Consensus Development Conference" on breast cancer screening. The conference, first in a continuing series, was held September 14-16, 1977 at the NIH in Bethesda.

The goal of consensus development conferences is to speed up the decision making process in research as well as in health care policy. Central to the mechanism is a carefully selected panel of scientists, health professionals, legal experts, ethicists and representatives of the lay public. The panel hears comprehensive presentations of available data on the issue under consideration and whatever differing interpretations may exist concerning these data. In addition, comments on the societal implications are solicited and heard by the panel. Following full presentation of the issues the panel is asked to engage in open discussion for the purpose of reaching consensus on as many facets of the problem as possible.

Results of the conferences, -- the points on which consensus is reached, as well as the points of disagreement -- are to be made widely available for the information of the general public, for health professionals and for use in policy and regulation development by the appropriate funding or regulatory agencies.

Large scale breast cancer screening, surrounded by controversy, was an appropriate and challenging topic for the first NIH Consensus Development Conference.

The Panel

The Breast Cancer Screening Consensus Development Panel was made up of 16 leading scientists, epidemiologists and physicians from various disciplines, including radiology, medical oncology, surgery, and general medicine, together with distinguished representatives of the clergy, the legal profession and the lay public. Besides aiming at a broad representation, criteria for

selection of the panel members included the fact: 1) that they were not known to have taken a public position either for or against mammography or wide-scale breast cancer detection applied to asymptomatic women; (2) that they were not significantly involved in either the development or operation of the Breast Cancer Detection Demonstration Projects (BCDDP), jointly sponsored by the National Cancer Institute and the American Cancer Society (ACS); and (3) that they were not federal employees or staff members of the ACS. A further goal was to include a significant proportion of women on the panel. As finally constituted the panel included four women. The Chairman was Dr. Samuel O. Thier, Professor and Chairman of the Department of Internal Medicine, Yale University School of Medicine.

Prior to the meeting the panel was provided with technical information on the issues involved, including a detailed history of the creation of the BCDDP, the manual of procedures and operation of the BCDDP, copies of minutes of selected meetings of the Cancer Control and Rehabilitation Advisory Committee, a collection of publications dealing with screening and mammography and other relevant materials.

Background

Historic background for the meeting stretches back at least to 1973, when the 27 Breast Cancer Detection Demonstration Projects (BCDDP) were activated at 29 centers around the country under the auspices of the National Cancer Institute and the American Cancer Society. The purpose of the project centers was to demonstrate the feasibility of periodic screening of large numbers of women for breast cancer using clinical history, physical examination, mammography and thermography. By this means it was hoped that the early detection of breast cancer would reduce the mortality from this disease.

Critics of the BCDDP have long questioned whether the radiation designed to detect cancers might not itself trigger development of malignancies at a later time.

The Consensus Development Meeting

The consensus meeting was held to coincide with the completion of a report from the Working Group for the Review of the BCDDP chaired by Dr. Oliver Beahrs, Professor of Surgery at the Mayo Medical School, Rochester, Minnesota. This group was formed in January 1977 by the NCI and charged with analyzing the data currently available from the BCDDP and determining what information

could be added to that already existing from the reports and reviews of the earlier breast cancer detection screening program conducted by the Health Insurance Plan (HIP) of New York which began in early 1960's.

The review of the HIP data and information on the risk of radiation to the breast[1] was requested in October of 1975 following criticism of the BCDDP which suggested that the radiation designed to detect cancers might also be triggering the development of malignancies[2]. Three groups were appointed to the investigation. Two reviewed data from the HIP screening program: the group headed by Dr. Lester Breslow, Dean of the School of Public Health, University of California at Los Angeles examined the benefits of mammographic screening as determined from the HIP data; the group headed by Dr. Louis B. Thomas, Chief of the Laboratory of Pathology, NCI re-examined the pathology of cancers found in the HIP study. The third group, headed by Dr. Arthur Upton at the time Dean of Basic Sciences, Health Sciences Center, State University of New York, Stony Brook, evaluated the relationship between benefit and risk in mammographic screening using data from several studies of women exposed to radiation from various sources.

The principal finding from the HIP data was that in women over the age of 50 years, those in the screening group had a 40 percent lower mortality from breast cancer than the unscreened controls. However, in women below 50 there was no similar decrease in breast cancer mortality. The second point was viewed as important since there is some finite though undetermined risk from the exposure to radiation.

The HIP review studies, which were completed in March 1977, led the NCI to issue interim guidelines for the BCDDP limiting routine mammography in asymptomatic women to those who had a personal or close family history -- sisters or mothers -- of breast cancer.

At the Consensus meeting, Dr. Beahrs presented his working group's analysis of the BCDDP data[3]. Up to June 30, 1976, a total of 445,048 screening examinations had uncovered 1810 breast cancers among those who had an initial examination and up to three subsequent annual re-screenings. The evidence from the BCDDP is that physical examination and mammography combined is an effective procedure in detecting early disease among women under 50 years of age as well as those over 50.

Over one-third of the total cancers discovered were minimal, i.e., less than one centimeter in size, and at least 70 percent had no nodal involvement. This is regarded as promising in view of the evidence from many clinical sources that the treatment of early disease leads on the average to better survival.

These minimal cancers were a special concern of the Beahrs group. Mammography detected 95 percent and physical examination 33 percent of a total of 592 minimal cancers. Four pathologists in the Beahrs working group reviewed 506 of these and from their findings it is clear that there were numerous difficulties in pathological interpretation. The review of these 506 lesions originally classified as malignant, resulted in 66 (13%) being re-classified as benign and a further 22 (4%) as borderline or uncertain. (These findings may be modified following a further review of pathology material.)

It should be noted that the BCDDP is not involved in decisions concerning treatment or determining the management of carcinomas discovered in the project. Rather patients who have lesions discovered are referred to their personal physicians for followup and treatment. However, 58 of the 66 women were subsequently treated by some form of breast surgery, 27 of them by a radical procedure. Of the 22 cases re-classified as borderline, 20 were also treated with breast surgery.

The Beahrs group also recommended that clinical trials be conducted on questions which remain unanswered from the BCDDP Program, e.g., benefit-risk ratio and the magnitude of the benefit from mamography, effect of increasing the interval between screening, etc.

Directors of many of the centers involved in the BCDDP, professionals directly or indirectly involved in breast cancer diagnosis and management, and individual members of the public made statements to the panel. Prior to the meeting a total of 280 letters had been sent from NIH inviting statements from public interest groups, private interest groups and concerned professionals. Speakers included strong critics as well as proponents of the BCDDP. Attendance at the six sessions of the meeting averaged some 350 and many members of the audience participated in the discussion periods following the individual presentations.

After hearing the many presentations and discussions, the panel proceeded to carry out its assigned role, i.e., to determine what degree of consensus might be achieved in its responses to a series of questions which had formed its initial charge:

1. Is there evidence that early detection of breast cancer reduces mortality from breast cancer? Which of the available screening modalities or combination of modalities is most effective in early detection?

2. What are the risks of each of the available screening modalities for early detection of breast cancer?

3. Do the potential risks versus benefits differ for different modalities of breast cancer detection and at different ages of patients screened?

4. If it is not possible to answer any or all the questions 1, 2, or 3, what data need to be generated to provide adequate answers?

5. What are the practical and ethical considerations for implementing demonstration projects in cancer detection and how does the BCDDP comply with these considerations?

6. What can the consensus Panel recommend as to the type and frequency of breast cancer screening and who should provide this screening?

As a preliminary step the Panel divided itself into three subgroups to discuss and develop recommendations on: (1) the benefits; (2) the risks; and (3) the ethics involved in screening in general and as used in the BCDDP in particular. The Panel then reconvened to deliberate as a body.

It should be noted that throughout these deliberations the Panel repeatedly emphasized the distinction between mammography used for diagnosis--the value of which was not in question--and mammographic screening to detect possible disease in women with no symptoms or other physical findings.

With this in mind the Panel came to the following conclusions and recommendations:

- Based on the available evidence, with the understanding that no new participants are being added to the program and that limits be set on radiation dosage, BCDDP screening using mammography and physical examination in combination, should continue to be available on request to women 50 years of age or older. But there is no basis for such routine screening for women under the age of 50. (This does not mean, however, that these women could not benefit from physical examination for breast cancer, and breast self-examination.)

- Mammography for women aged 40 to 49 years in the BCDDP should be restricted to women having a personal history of breast cancer, or whose mothers or sisters have a history of breast cancer.

- Mammographic screening of women aged 35 to 39 years should be limited to those women having a personal history of breast cancer.

- Because of ethical considerations, women under 50 who are already participating in the BCDDP should not be denied the opportunity to continue having mammograms if they wish--so long as they are informed that there is no proven benefit and there is presumed risk, and they are told that the Panel does not recommend mammography for them.

- The only sound scientific evidence to demonstrate the value of breast cancer screening comes from the HIP study. The evidence indicates that the benefits of the screening program rests in the use of physical examination and mammography, in combination. There are no rigorous scientific data to show to what extent either physical examination alone or mammography alone is beneficial.

- Mammographic techniques have improved markedly in recent years with smaller, and presumably earlier, lesions now being detected; moreover radiation dosage has been decreased significantly. Nonetheless, there are no data to indicate that these advances result in decreased mortality in women under age 50.

- Neither physical examination nor techniques such as thermography or ultrasound are known to harbor any risks. The use of mammography, however, is associated with an inherent risk of radiation exposure, and studies indicate that breast tissue is particularly sensitive to radiation. The precise risk is difficult to quantify, but current theory holds that the risk increases with increasing dose and decreases with age.

Evidence has been accumulated from survivors of the atomic-bomb radiation in Japan; from women exposed to multiple fluoroscopic examinations during treatment for tuberculosis; and in women treated with X-rays for post-partum mastitis, that there is a linear, nonthreshold relationship between the dose of radiation to which these women were exposed and the subsequent development of breast cancer.

At the present time the average radiation dose per mammogram in the BCDDP centers is less than one rad. It is estimated that each rad raises a woman's risk of breast cancer by about 1 percent. Thus, if a woman in the general population has about a 7 percent chance of developing breast cancer in her lifetime, one rad will increase this risk by 1 percent of 7 percent, i.e., from 7 percent to 7.07 percent.[1] The cumulative dose that would result from a series of five mammograms in the BCDDP is about 4 rads with the newer techniques. This increased risk of breast cancer is so small that it could probably never be domonstrated in long-term followup studies of the BCDDP group.

- Clearly new diagnostic and screening procedures are needed. Therefore, there should be a renewed emphasis on research on noninvasive techniques, such as thermography, ultrasound, and biologic markers. However, because the potential benefits of thermography remain undocumented, this modality should be discontinued as a routine part of the BCDDP screening although it should be retained by those centers doing it as a research endeavor.

- There is a lack of clear-cut data on the risk-to-benefit ratio of screening for women under 50. Although there was agreement that further study to define this risk to benefit ratio, no consensus could be reached on precisely what kinds of further studies are needed. It was suggested that the question of the design of new studies warranted more discussion.

- The BCDDP should continue to follow all women in whom breast cancer has been diagnosed. The Panel felt that some form of followup of all BCDDP screenees was desirable, but there was no agreement on the method by which these women should be followed.

- Demonstration programs, by definition, utilize proven and practical methods. Mammography had not been validated as a screening procedure for women under 50 years old prior to the inception of the BCDDP, hence the projects have included research elements. Any experimental study should have taken into consideration its justification from a risk-benefit viewpoint, the informed consent process, the way in which subjects are selected. Thus

the BCDDP must come to grips with several important ethical concerns. The BCDDP's Informed Consent Form should indicate the radiation dosage delivered to the patient and assure her that all information gained through the program will be disclosed to her and to her physician. This Informed Consent Form and appropriate background materials should be provided a prospective screenee beforehand in sufficient time to enable the woman to discuss the proposed procedure with her family and her physician. Guidelines should be developed for compensating individual participants who sustain injury during the course of study. Furthermore, there should be greater participation of women, both professional and consumer representatives, in the design and interpretation of any such studies.

- The histology of any lesion smaller than one centimeter in diameter, or any papillary or intraductal proliferation originally interpreted as malignant, should be reviewed by two consultant pathologists prior to definitive therapy. Screenees should be notified if their diagnosis is changed following pathologic review. The recommendations re pathology should also be included in the informed consent form.

The Panel recommendations have been conveyed to the NCI for consideration and possible implementation. That Institute is already engaged in verifying the pathology diagnoses of the minimal cancers with a view toward prompt notification of women in whom the diagnosis had been changed.

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