SUPPLEMENTAL AND CONCLUDING REPORT
OF THE WORKING GROUP
TO REVIEW
THE NATIONAL CANCER INSTITUTE-
AMERICAN CANCER SOCIETY
BREAST CANCER DETECTION DEMONSTRATION PROJECTS

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Address reprint requests to Office of Cancer Communications, National Institutes of Health, Building 31, Room 10A17, Bethesda, Md. 20014.
INTRODUCTION

Since February 1977, the Working Group To Review the National Cancer Institute (NCI)-American Cancer Society (ACS) Breast Cancer Detection Demonstration Projects (BCDDP) under contract to NCI has examined various aspects and data regarding this demonstration program. On September 6, 1977, the Working Group submitted a preliminary report and recommendations to the Director of the Division of Cancer Control and Rehabilitation (DCCR), NCI. The report was complete in many respects. However, because of the need to discuss the report with the directors of the BCDDP on September 11, 1977, and to present it to the National Institutes of Health (NIH)-NCI Consensus Development Meeting on Breast Cancer Screening scheduled for September 14-16, 1977, a number of issues had not been fully explored by the Working Group. Subsequent to the Consensus Development Meeting and partially on the basis of the information exchanged during those sessions, the Working Group has continued its review, the results of which constitute this supplemental report.

The Working Group considers its review of the BCDDP based on available information completed with the submission of this supplemental report and recommends that it, the Working Group, terminate its activities.
Section III of the preliminary report presented data on the pathology review of minimal breast cancers detected in the BCDDP; minimal cancers are defined as all in situ cancers and invasive cancers less than 1 cm in diameter. The total number of cancers detected by June 30, 1976, was 1,810 in 445,048 screening examinations. Of these cancers, 592 (about one-third) were reported to be minimal. Specimens from 506 of these cancers were available for pathologic review. The Pathology Review Subgroup of the Working Group, after a retrospective study of the material (pathology slides) submitted to it, considered that the pathologic changes seen in 66 cases were not sufficient to diagnose cancer. The changes were interpreted by the panel as representing atypical ductal hyperplasia in 71%, atypical lobular hyperplasia in 11%, atypical ductal and lobular hyperplasia in 4%, and other changes in 14%. Twenty-two other cases about which there was a division of opinion were categorized as borderline.

At the time of the report to the Consensus Panel, all clinical facts and pathologic and other data that related to the 66 cases were not yet available. Subsequently, from the supplemental information discussed later, it appears that the representative slide from which the diagnosis of cancer was made was not always presented for the review reported in September 1977. In some instances, the mastectomy slides had been submitted only when the biopsy specimen may have contained the tumor or incorrect slides had been submitted for review. In other cases, assessment of record information by the Clinical Review Group indicates that a full review was not possible because the quality of the frozen section had deteriorated or because slides were held by consulting pathologists. In part, the report that follows is concerned with the findings of the additional inquiry into the 66 cases; the findings are based on clinical, pathologic, and other data that had been collected by the Clinical Review Group for these cases. A preliminary assessment of the 66 cases is contained in a letter dated November 21, 1977, from Dr. O. H. Behrs, Chairman of the Working Group To Review the BCDDP, to Dr. Diane Fink, Director of DCCR.

RESULTS OF ADDITIONAL INQUIRY INTO CASES CLASSIFIED AS NONMALIGNANT IN INITIAL PATHOLOGY REVIEW

Introductory Comments by Clinical Review Group

Medicine is a composite of many complex factors that lead to judgment-making in the management of disease. This is true in the evaluation of the historical and physical finding of a lesion of the breast with the possibility of its being cancer. Findings in clinical medicine or surgery and their interpretation are often not absolute.

In pathology, which is also an interpretive science, the pathologist, on the basis of training and experience, reports the significance of the changes seen through the microscope. Cell change from normal to abnormal (cancer) is a continuum, and exactly where the line is to be drawn between a benign and malignant condition is a matter of opinion. This is well illustrated not only by the variance of opinion, in some cases between the hospital pathologist or project pathologist and the review panel, but also by differences of opinion among the experts themselves that occurred in the pathology review of the “minimal” cases in the BCDDP. As reported in the preliminary report of the Working Group, 22 cases were classified as borderline. This category was established for cases that one or more of the pathologists classified as cancer and the others did not. Furthermore, the classification of 66 cases as “not cancer” involved resolution of differences among the pathologists in their initial, independent interpretations in a number of cases (i.e., initial interpretations by the four pathologists agreed with the consensus classification in 74.2, 93.0, 98.5, and 98.5% of the instances). If such variation exists even among experts, it may be expected to occur among practicing pathologists as well. Recognizing this, the treating physician must take into account not only pathologic facts but clinical information when he attempts to arrive at a decision regarding treatment.

One must also remember that most breast cancers currently diagnosed and treated are not of the minimal type but instead are larger cancers that present few problems in pathologic interpretation. A prior retrospective review of larger lesions of the breast found during the pathology review by the Health Insurance Program (HIP) of Greater New York demonstrated a high degree of accuracy in pathologic interpretation of larger lesions found during that study. Because of this accuracy with larger lesions, the Pathology Review Subgroup for the BCDDP did not review such cancers during the review of the BCDDP and confined its review to lesions less than 1 cm and to noninfiltrating cancers.

Subsequent to the presentation of the Pathology Review Subgroup Report on the BCDDP at the NIH-NCI Consensus Development Meeting on September 15, 1977, some BCDDP expressed concern that all pertinent histologic material may not have been submitted
for the unconfirmed cases. Because of this concern, the Clinical Review Group for the BCDDP initiated further requests to the BCDDP to secure additional slides from 66 cohort cases not classified as cancer. In response to these requests, additional sections were received for 36 of 66 cohort cases not classified as cancer. As previously indicated, slides were not available in other cases because the quality of frozen sections had deteriorated, slides had been retained by the consulting pathologist, or the available representative tissue was thought to have already been reviewed.

Additional Considerations by Pathology Review Subgroup

Supplemental Review

Section III of the preliminary report by the Working Group describes the results of a special pathology review of 506 cases that were classified in the DMC for the BCDDP as minimal breast cancers. The examination was based on histologic sections submitted by the 27 BCDDP and was performed by 4 pathologists appointed as a Pathology Review Subgroup. The purpose of the review was to achieve uniform pathologic classification of cases designated "minimal breast cancers" by multiple sources and thus provide a clearly defined group of minimal breast cancers that could be subjected to further analysis. During the course of the review, several cases were identified in which a diagnosis of carcinoma could not be confirmed on the basis of the slides that had been submitted initially. Supplemental requests were made twice to the BCDDP for additional materials on these cases because of the Pathology Review Subgroup's concern that the slides submitted originally might be incomplete. The Pathology Review Subgroup met subsequently to review these additional materials and incorporate the results into its report. The pathology report presented at the NIH-NCI Consensus Development Meeting in September 1977 discussed 66 cases in which a diagnosis of carcinoma was not confirmed as a result of these review procedures.

Subsequent to that meeting, some BCDDP expressed concern that all pertinent histologic material still might not have been submitted from the unconfirmed cases. Because of this concern, the Clinical Review Group initiated a further request to the BCDDP to secure additional slides from the 66 unconfirmed cases. In response to this request, additional slides from 36 cases were received. These subsequently were reviewed by three pathologists from the Pathology Review Subgroup who were available for this activity, and the results were used to update the previous report by the Pathology Review Subgroup. Table 1 displays the status of the 66 cases, and the information obtained from this supplemental review is taken into consideration.

Other Comments

In retrospect, it appears that several items in the Pathology Review Subgroup Report may require further clarification.

1) Performance of pathology review to obtain consensus classification for scientific purposes differs significantly in its mechanics, setting, and purpose from the private practice of pathology, which is oriented toward individual patient care. During the course of the pathology review, each pathologist examined all material from each case independently and recorded his diagnosis for each case on a separate standardized form (see Appendix fig. 1 in the preliminary report). Consensus sessions were also held daily, at which times these written diagnoses were compared and cases discussed. In most instances, the recorded diagnoses of the reviewing pathologist agreed and these findings became the review diagnosis of record. When disagreement occurred, the pathologists attempted to resolve the problem and achieve a consensus opinion. At times this process required rereview of selected slides. However, when no consensus could be obtained by this process, the cases were recorded as borderline. Of 506 cases, 22 fell in this borderline category. Table III.2 in the preliminary report by the Pathology Review Subgroup displays intragroup variability in these pathologists' review diagnoses.

2) It is appropriate to restate in more detail the process by which cases were selected for review and to indicate the source of the diagnoses with which the Pathology Review Subgroup's diagnoses were compared. Cases that were reviewed had been listed by the BCDDP as minimal breast cancers at the DMC, and all comparisons in the preliminary report of the Pathology Review Subgroup were based on these classifications. The Pathology Review Subgroup did not compare its diagnoses with those of community pathologists who submitted cases to the BCDDP for review by project pathologists working with the BCDDP. This review, therefore, should not be interpreted as an evaluation of diagnoses rendered by pathologists in a clinical practice setting, but instead it should be.

| Table 1.—Current status of 66 cases not previously classified as carcinoma on pathology review |
|-------------------------------------------------|--------|
| Status                                          | No. of cases |
| Total                                          | 66     |
| Reclassified as cancer                         | 11     |
| Reclassified as borderline                     | 5      |
| Error in case identification                   | 2      |
| Not classified as cancer                       | 48     |

*One or more of the reviewing pathologists interpreted the case as carcinoma; the others did not.
*Cases incorrectly selected for initial review.
*In response to the Clinical Review Group's request, additional slides were provided for review in 20 of these cases.
interpreted as an assessment of results reported during the course of a large demonstration project.

3) The differences observed between the BCDDP diagnoses and those resulting from pathology review reflect a significant current difficulty in the pathologic diagnosis of minimal breast cancer. This difficulty is also reflected in variations of opinion observed among members of the Pathology Review Subgroup. Because of this, it seems prudent to recommend that concurrent pathology review be conducted whenever possible prior to definitive therapy for borderline breast lesions, possibly cancer, or when unusual histopathologic changes of questionable significance are present in lesions detected by the BCDDP.

Context for Pathology Review and Assessment by Clinical Review Group of Information From Medical Records

Early in the deliberations of the Working Group, it became apparent that a high proportion of the breast cancers detected in the BCDDP was classified as minimal (noninfiltrating or infiltrating <1 cm in diameter). This observation was derived from reports received by the DMC from the projects on the results of histologic studies by numerous pathologists throughout the country. Because of the importance attached to the finding of a high proportion of minimal cancers, the Working Group established, as noted earlier, a panel of four pathologists with expertise in the examination of minimal lesions to determine the extent to which their reviews would sustain or change the classification of cases reported in the statistical tabulations as minimal cancers. The end sought was a histologic definition of a uniform group of minimal breast cancers that could be subjected to further analysis.

Consistent with this objective, the Pathology Review Subgroup for the BCDDP was concerned with the classification of cases listed by the BCDDP as minimal cancers, and the review was based on the examination of histologic sections that the projects submitted. The supplemental review maintained this approach by the use of the additional sections that became available subsequent to the initial review.

To obtain a more complete picture of circumstances that affected decisions on surgical therapy, the Clinical Review Group for the BCDDP analyzed in detail the clinical and pathologic records of the cases that had not been classified as cancer by the Pathology Review Subgroup for the BCDDP. Projects in which the 66 cases occurred were notified regarding their case(s) by the Clinical Review Group to obtain all clinical data related to them. The data that were received regarding the 48 cases which were considered not to be cancer by the Pathology Review Subgroup (postsupplemental review) indicate the following:

In 11 cases, only biopsies (9) or partial mastectomies (2) of the breast lesions had been done, whereas in 37 cases some form of mastectomy had been done (simple, modified, or radical). In 1 of the 11 cases, there is no project pathologic report. In the remaining 10 cases, both the hospital pathologist and the project pathologist considered the tumors to be cancers in only two instances. In 8 cases, one pathologist considered the lesions to be cancers and the other did not.

In the management of 29 of the 37 cases in which some form of mastectomy was done, the operation was performed in two stages. A biopsy was done on one day, and the tissue was studied by the hospital pathologist; in 16 cases, the record indicated that an outside pathologist was consulted. On the basis of the pathology information and other data received from the clinical record, the surgeon elected to do a mastectomy 1-113 days later (simple in 17 cases, modified in 11 cases, and radical in 1 case). In 22 of the 29 cases, both the hospital pathologist and the project pathologist considered the tumors to be cancers; only one or the other pathologist considered the lesions to be cancers in 7 cases. In 15 of 16 cases in which an outside consultant was used, he concurced with the hospital pathologists that the tumors were cancers.

In the remaining 8 of the 37 cases for which there was treatment, a one-stage surgical procedure was done, namely, biopsy followed by mastectomy on the same day (simple in 1 case, modified in 5, and radical in 2). In 7 of the 8 cases, the hospital pathologist considered the tumors to be cancers. In a retrospective review of tissue slides, the project pathologist concurred in the diagnosis of cancer in 1 case, tissue was not available for review in 2 cases, and he considered the lesions not to be cancers in 4 cases.

Concluding Comments by Clinical Review Group

Surgical therapy of nonminimal breast cancers ordinarily presents few difficulties. Histologic confirmation of carcinoma is obtained by frozen section, and mastectomy is accomplished without delay. However, minimal breast cancers create more difficulties in pathologic interpretation, and pathologists do not agree as to the exact point at which the abnormality becomes malignant. Frozen sections may often not afford an unequivocal pathologic diagnosis of carcinoma. In this circumstance, many surgeons use the procedure that was used with many of the minimal breast lesions under discussion in this report. The surgeon delays definitive surgery to permit further pathologic consultation and thereby avails himself of a carefully studied pathologic interpretation to use as a basis for further therapeutic decisions. Difficulties in prescribing therapy for minimal breast cancer arise when the pathologic diagnosis remains somewhat in doubt, even though pathologic consultation has been obtained.

As has been indicated, it is not unusual even among experts for one pathologist to interpret a minimal lesion as "benign," whereas his colleagues favor a

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5 Data recently obtained by the Clinical Review Group from a tabulation prepared by the DMC as of June 1978, for all cancers detected show that 74% of the invasive cancers and 32% of the noninvasive cancers were treated by a one-stage procedure. Thus the noninvasive cancers were treated by staged operations in 68% of the cases.
diagnosis of carcinoma. In this situation, as often happens in clinical medicine, correctness of therapy must depend on surgical judgment, which is based on a multitude of factors, including an estimate of the magnitude of risk, the degree to which cell change is evident, the personal attitude and desires of the patient, the evaluation of the patient's personal medical background and other factors that indicate increased risk of breast cancer, and the findings on physical examination of the patient. In some instances, after analyzing these various factors, the surgeon may believe that mastectomy is indicated even though the pathologic diagnosis is equivocal; in other circumstances, the same surgeon may prefer to follow the patient carefully without further immediate therapy. Sometimes, the disagreement in diagnosis and the risks are discussed with the patient and the patient herself may elect surgery (which is also considered by the surgeon and which appears to have occurred in at least 6 of the cases).

With respect to the cases in the supplemental review, on the basis of data available for this report, great care was apparently given to the diagnosis and management of the women who had possible breast cancer or significant pathologic changes in their breasts. In the opinion of the Clinical Review Group, which was based on information the medical record indicates was available to the surgeon at the time of management, the treatment was in almost all instances consistent with acceptable surgical practice.

### ADDITIONAL CONSIDERATIONS BY EPIDEMIOLOGIC-BIOSTATISTICS REVIEW WORKING GROUP IN MEASURING EFFICACY OF SCREENING

#### BARRIERS TO USE OF BCDDP'S EXPERIENCE FOR MEASURING EFFICACY

The preliminary report of the Working Group discussed several approaches to the measurement of benefit from screening as possible alternatives to randomized controlled trials (pp. 687-688). In each instance, the conclusion reached was that none of the questions related to the efficacy of screening (i.e., benefits in screening women less than 50 years of age, magnitude of benefit of including mammography, and effect of screening at intervals longer than 1 year) could be answered by means of BCDDP data that were currently available or that might become available through long-term follow-up. A basic reason for this negative conclusion was the absence of suitable comparison groups for judging whether mortality from breast cancer has been lowered in the screened population.

The proposition that the high proportion of breast cancers detected in an early stage of the disease among screened women provides definitive evidence of substantive benefit in the BCDDP was also not accepted. The reason is that we do not know when and at what stage of the disease the cases which were detected in a screening program would ordinarily be diagnosed. The uncertainty relates to lead time (average amount of time the diagnosis of cancer is advanced by screening) and length-biased sampling (the propensity of screening to detect cases that are more likely to be indolent than are cases found in clinical practice). These sources of bias, particularly length-biased sampling, cannot be estimated with any reasonable degree of precision. An additional complicating factor arises from the lack of knowledge about the natural history of cases classified as noninfiltrating cancers; for some of these the question may be raised whether they would ever have become clinically known. However, no data indicate that a noninfiltrating cancer is not a precursor to an invasive one.

Further consideration has been given to an approach originally considered and rejected by the Working Group but advanced by others since the report of September 1977. The underlying concept involves a comparison of the breast cancer mortality rates of two groups of BCDDP. The group that had a more "effective" detection program would be expected to have the lower mortality, after differences in personal background characteristics that were determined when women appeared for their first screening are taken into account. Indicators of "effectiveness" would be the proportion of breast cancers that are minimal and the detection rate during the initial rounds of screening. Projects that were rated high on both of these measures would be classified as more effective than would those that were rated low. The analysis would be aimed primarily at the efficacy of screening persons less than 50 years old for breast cancer; questions related to mammography and periodicity of screening could not be addressed.

Several factors have led the Working Group to reject the above model as a viable methodology for producing the needed information. First, it will not be possible on the basis of available data to adjust mortality data for differences in self-selection that may exist between the two groups of projects. Second, differential attrition rates among projects in screenee participation in successive reexamination cycles, particularly since mid-1976, will create a serious problem for comparisons of mortality. For example, a large drop in participation in the "more effective" projects might result in a sizable reduction in any underlying differential in mortality that may in fact be there. If the situation is reversed (i.e., larger attrition rates in the "less effective" projects), the result might be an exaggeration of differentials. Third, the categorization of
projects by effectiveness is based on two criteria—percent of breast cancers that are minimal and detection rate—that are expected to be highly correlated. However, there proved to be little consistency between these measures.

Finally, a large and costly effort would be required in the face of great uncertainty about the scientific validity of the approach in order to identify all interval breast cancer cases diagnosed after screening is completed and all deaths due to breast cancer, including those among women for whom confirmed evidence of breast cancer first becomes available when death occurs.

NEED FOR RANDOMIZED CONTROLLED TRIALS

In view of the preceding considerations and those presented in the document of September 6, 1977, the Working Group reaffirms its recommendation that randomized controlled trials be designed and conducted to answer the following questions about breast cancer screening:

1. the magnitude of benefit and net benefit-risk with the use of mammography for screening,
2. the benefit in screening women 40-49 years of age, and
3. the effect on the benefit from screening of increasing the interval between each screening.

A set of conditions and a research design for the conduct of randomized controlled trials that address the above issues are presented on pages 691-692 of the preliminary report. As stated on page 691, it is expected that when the NCI proceeds with the planning of new studies, a multidisciplinary advisory group will be formed to review the design described by the Working Group and also the alternative designs for randomized trials that may produce the needed information more efficiently. The Working Group's model provides for the following study and control group comparisons:

- $C_{(40-49)}$ vs. $S_1(40-49)$—BSE vs. MM+P
- $C_{(40-49)}$ vs. $S_2(40-49)$—BSE vs. P only,
- $C_{(50-59)}$ vs. $S_1(50-59)$—MM+P vs. P only, and
- $C_{(50-59)}$ vs. $S_2(50-59)$—(MM+P) (annual vs. biennial).

Under the conditions specified on pages 692-693 of the preliminary report, 240,000 women randomly allocated to six study and control groups would be required for this design. If the full scope of the design cannot be implemented, the Working Group recommends that the highest priority be given to the testing of the benefit of screening women 40-49 years of age and to the independent contribution of mammography. This set of objectives would set aside the issue of periodicity. The following study-control experimental design would require about 130,000 women, with approximately 100,000 eligible for four annual screenings:

- at ages 40-49 years, BSE vs. MM+P and
- at ages 50-59 years, MM+P vs. P only.

The first comparison is aimed at determining whether screening with mammography and physical examination reduces breast cancer mortality among women 40-49 years of age. The comparison provides a test of the negative finding in the HIP study. The second comparison addresses the question of how much benefit is attributed to the inclusion of mammography in screening women 50-59 years of age: results would be extrapolated to women 40-49 years of age if the first comparison showed that screening with both modalities was beneficial in that age group.

An alternative to the above option would include a test of the benefit from the use of mammography in the age group 40-49 years. The comparison groups, all consisting of women at these ages, would then be as follows:

- BSE vs. MM+P and BSE vs. P only.

The number of participating women in this design would be about 100,000, with about two-thirds involved in the periodic screening that consists of a minimum of four examinations at annual intervals.

SPECIAL STUDIES

The BCDDP present a unique opportunity to conduct special studies that would enlarge our knowledge of risk factors in breast cancer and our understanding of the natural history of noninfiltrating breast cancer. All of the studies identified by the Working Group depend on relatively small subsamples related to targeted subgroups of screeners and cancer patients.

Other proposals may be advanced as it becomes more widely known that the BCDDP are being viewed as a resource for special investigations. However, the Working Group recommends that the 280,000 women who entered the screening program of the BCDDP not be followed after the completion of the five rounds of screening, except for well-defined subsamples. The only justification for follow-up of the entire group would be a determination that the information obtained could answer questions still outstanding regarding the efficacy of screening for breast cancer. As indicated in the preliminary report and further considered in this supplemental report, answers to such

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4 $S_1$ = study group No. 1; $S_2$ = study group No. 2; C = control group; BSE = breast self-examination; MM = mammography; P = physical examination. Numbers in parentheses indicate the age group, in yr, of the women.
questions cannot be derived from the BCDDP. The follow-up program projected by NCI covered a 5-year period after completion of screening for all 280,000 women. The Working Group estimates the annual cost for this activity at 1-1.5 million dollars.

The discussion that follows defines several projects as a basis for later expansion by NCI, in most instances, into either requests for contract proposals or solicitations for grant proposals.

### EPIDEMIOLOGIC RISK FACTORS

Before the establishment of the Working Group, plans were developed by NCI to conduct case-control studies of risk factors in breast cancer on the basis of information collected through extensive interviews with subgroups of women screened by the BCDDP. These groups consist of all women with breast cancer and two matched comparison groups drawn as random samples of women who had benign biopsy specimens and women who did not have breast surgery. A major interest was in the investigation of hypotheses related to the risk of breast disease associated with various types of prescribed drugs. The large numbers of cases in BCDDP were also seen as providing an opportunity to extend the research in other risk factors that had already been conducted on the basis of more limited cases and controls. As originally proposed, the study was to be performed over a long period, during which new participants with breast cancer and their matched controls would be entered for inquiry into new hypotheses as they were advanced.

The Working Group reviewed the proposed case-control study of risk factors and reached the conclusion that the rationale for utilizing the screened population of the BCDDP for this type of inquiry was sound. In view of the past responsibility in the development of the project, an appropriate course would be for the study to proceed under the scientific direction of the Environmental Epidemiology Branch, Division of Cancer Cause and Prevention, NCI. The Working Group has therefore recommended to NCI that support be extended to women with breast cancer already identified and their controls. The objectives that require a long-term commitment for the accumulation of new cases and controls should be set aside at this time and reexamined when results from the current case-control study become available.

### BREAST PATTERNS ON FILM MAMMOGRAPHY OR XEROMAMMOGRAPHY

One of the more exciting developments in recent years in the identification of predictors of breast cancer has been the suggestion that the type of breast parenchymal patterns as depicted by film mammography or xeromammography can be used as a predictor of future breast cancer. There is widespread interest in investigating the issue, but few opportunities exist to do so with large numbers of cases and controls. The BCDDP offer the possibility for designing a study that would determine the reliability of various classifications that are being advanced and their predictive power. It is recommended, therefore, that NCI proceed rapidly with the issuance of a request for proposal (RFP) for the conduct of such a study. The Working Group has not developed approaches to the design and conduct of the research, but it is clear that sampling methods are indicated and that high-level biostatistic skills will be needed.

### NATURAL HISTORY OF MINIMAL BREAST CANCERS

The program of the BCDDP has produced an unusually large number of cases that are close to or on the border between being benign and malignant. Greater knowledge about the natural history of such cases is needed to reduce the area of uncertainty. The Working Group recommends that high priority be given to long-term follow-up (at least 10 yr) of all cases classified as minimal breast cancers or atypical duct or lobular hyperplasia.

### FOLLOW-UP OF OTHER GROUPS OF BREAST CANCER

Although patient survival rates for breast cancers detected in the screened population cannot be used to estimate benefit from screening, for the reasons previously given, there may be interest in information on the course of the disease under different circumstances of detection (e.g., screening-detected cases by different modalities vs. interval-detected cases). The Working Group recommends that women with breast cancer be included in a long-term follow-up program under appropriate research protocols. The mechanism to obtain research proposals could be the issuance of an RFP. If such studies are to be performed, follow-up should include cases detected through screening and interval-detected cases. Highest priority should be given to death as the end point, but other interests may lead to the inclusion of inquiries into the factors of recurrence and impairment of function.

### DEVELOPMENTS RELATED TO THERMOGRAPHY

The Working Group's assessment of the effect of including thermography as a routine screening procedure in the BCDDP led to the conclusion (pp. 648-649) in the report of September 6, 1977, that "...thermography does not appear to be suitable as a substitute for mammography for routine screening in the BDCCP." The recommendation (p. 648) was therefore made that "...thermography should be discontinued as a routine procedure in the BCDDP for women of all ages.

However, the Working Group also commented as follows in the preliminary report about the future of thermography:

"...thermography has no radiation risk and is less costly than mammography, and continued
developmental work on this procedure, as well as other techniques suitable for screening, is needed.” (p. 691)

Analysis of the experience with thermography in individual projects of the BCDDP suggests that several projects had results that were more favorable than was the picture for the BCDDP as a whole. This finding encourages investment in the development and testing of thermography under carefully controlled study conditions, and the Working Group recommends that high priority be given to such studies. Suitable sites appear to be available among the BCDDP, and proposals for the conduct of developmental studies should be solicited. At the same time, thermography should be discontinued as a routine screening procedure in the BCDDP.

ADDITIONAL CONSIDERATIONS

PATHOLOGY REVIEW

Concurrent pathology review of minimal cancers before definitive treatment was previously recommended by the Working Group’s report. The recommendation relates primarily to those minimal borderline lesions, possibly cancer, or those in which unusual histopathologic cellular changes of questionable clinical significance are present. Review of these lesions by more than one pathologist is encouraged so that multiple opinions regarding cellular changes can be obtained before treatment. In some surgical environments, multiple opinions are available at the time of frozen-section study, because many departments have more than one pathologist who can study the tissue immediately after biopsy and before definitive surgery.

RADIATION DOSAGE

Although a theoretical risk of carcinogenesis that results from exposure to radiation does exist with the use of mammography, the magnitude of this risk is most likely very low, and it is lower than previously projected because of new reduced-dose techniques. Also, recent measurements show that the dose to the midline of a 6-cm breast in all projects per two-view examination is well below 1 rad and averages 0.076 rad for film mammography and 0.58 rad for xeroradiography. However, because of the lack of data on a favorable benefit-risk ratio in screening that includes mammography for women less than 50 years old, the Working Group in the “Final Recommendations” of this report reaffirms its recommendation for limiting mammography for women at these ages.

FOLLOW-UP OF POSITIVE SCREENING FINDINGS

A comprehensive evaluation of the BCDDP as a demonstration program requires information concerning the extent to which recommendations for “surgical opinion” by the screenee’s physician (positive cases expected to need a biopsy) or aspiration were followed up, reasons for recommendations not being followed, the number of biopsies performed, and the proportion of women in whom cancer was confirmed. The reporting system from the projects does not call for all of these elements. Reports are being received for negative biopsy tissue, but the completeness of the information needs to be addressed. The Working Group urges that information on follow-up of recommendations be given high priority by DCCR. First steps would be to determine the correspondence between reports on the above type of recommendation and biopsies performed and the ascertainment of the extent to which the record system established by projects for follow-up of such recommendations can provide data on the follow-up.
THE FINAL RECOMMENDATIONS

The final recommendations of the Working Group vary little from those in the preliminary report and are as follows:

1. The BCDDP should be continued as a demonstration program for the remainder of the planned five annual screenings.
2. Physical examinations should be continued in the BCDDP as a routine screening modality for women of all ages.
3. Reduced-dose film mammography (or xeromammography) should be continued in the BCDDP as a routine screening modality for:
   a) all women 50 years of age and older,
   b) women 40–49 years of age, only when they have a personal history of breast cancer or a history of breast cancer in first-degree relatives (mothers or sisters), and
   c) women 35–39 years of age, only when they have a personal history of breast cancer.
4. Thermography should be discontinued as a routine procedure in the BCDDP for women of all ages and developmental work should be encouraged for this procedure under carefully controlled conditions.
5. Concurrent review or multiple pathologic opinions should be obtained in borderline lesions, possibly cancer, or when unusual histopathologic cellular changes of questionable clinical significance are present, and the BCDDP should encourage this practice. Monitoring of the quality of mammography and physical examination should either be instituted or continued. Existing monitoring and control measures for radiation dosage should be maintained, and the BCDDP should encourage the continuation of this practice.
6. The reporting system in BCDDP should include results of follow-up of recommendations for all women with positive findings on screening examination. Of particular interest is the group with recommendations expected to result in biopsy or aspiration.
7. The informed consent should provide women who are having routine mammography with a reasonable basis for weighing radiocarcinogenic risks (including dosage) against known benefits or against benefits that have not been established but that the BCDDP's experience suggests might result from the inclusion of mammography.
8. Follow-up after the planned five annual screenings should be restricted to women with breast cancers that have been detected through screening and to all women with interval cases; this effort should be made part of a defined research proposal. Follow-up should be for a minimum of 10 years after diagnosis: The minimal cancers represent a unique group of cases for the study of the natural history of breast cancer.
9. Further consideration should be given to other special studies that are based on subgroups of BCDDP screenees and directed at the epidemiology and natural history of breast cancer.
10. Randomized controlled studies in screening for breast cancer should be started on questions not answerable from the BCDDP. These questions include the magnitude of benefit and net benefit-risk in the use of mammography, the benefit in screening women 40–49 years of age, and the effect of increasing the interval between screenings. Net benefit-risk questions related to mammography screening of women 40–49 years of age rank high in priority.
11. The Working Group should discontinue its review of various issues related to the BCDDP at the end of the contract period.

/s/
Oliver H. Beahrs, M.D.
Chairman
Working Group To Review BCDDP

/s/
Mr. Sam Shapiro
Chairman
Epidemiologic-Biostatistics
Review Group

/s/
Charles Smart, M.D.
Chairman
Clinical Review Group

/s/
Robert W. McDivitt, M.D.
Chairman
Pathology Review Subgroup