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Screening for Breast Cancer: a Review

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INTRODUCTION

WITH THE availability of the 18 year follow-up results of the Health Insurance Plan (HIP) Study of Greater New York, attention has shifted from questions of whether benefit from screening can be expected in women under the age of 50 to why has such benefit not yet been seen in any of the European studies? This has led to considerations of sensitivity and specificity of screening, periodicity of rescreening and to a lesser extent, the modalities to be used in screening. Underlying this ferment of discussion and activity have been attempts to evaluate the type of women who should be included in the screening program and the cost effectiveness of different approaches. Many are working on mathematical models to try and simulate the results of different approaches, though as these are generally based on case detection rather than impact of screening on mortality, they are not very useful guides to future policies as yet.

In this update I shall review the results of the screening studies which have reported on mortality from breast cancer, consider the ongoing studies and what may be expected of them in the future, review our current understanding of the women to be included in screening programs and the periodicity of rescreening and conclude with a summary of the UICC screening project consideration of these issues a year ago and remind ourselves of their conclusions which, I believe, still stand [1].

THE HIP STUDY

The design and results of this study have been extensively reported [2–4]. It is remarkable that we continue to learn from it even though by modern standards it was relatively small and used what is now regarded as old fashioned mammography in combination with skilled physical examination of the breasts offered annually for four examinations. Table 1 shows the percentage reduction in breast cancer deaths by 5 year age at entry groups and the year when the difference between the study and the control group first became apparent. Also included is the difference first reported at 5 years. This table is based on the cases of breast cancer diagnosed in the first 5 years after initiation of screening. The conclusion would be the same if one considered those diagnosed in the first 7 years. Several things are apparent from this table. First, the early lack of effect in women under the age of 50 was later replaced by almost equivalent benefit to that in women over the age of 50. Second, the apparent large benefit for women aged 50–59 appeared to fall subsequently and third, the benefit first became apparent in those aged 50–59 and much later in those under the age of 50, particularly those aged 40–44. As has been repeatedly emphasized, the HIP study was not designed to assess a possible differential effect of screening at different ages. That it was used for this was a reflection of the importance of attempting to obtain as much information as possible from expensive and difficult to run studies. If at 5 years the results that became apparent at 18 had been available, the controversy as to whether or not there was benefit for women under the age of 50 would never have arisen.

Table 1. Percentage reduction in deaths from breast cancer in the HIP study (source, Ref. [4])

Age at entry	Percentage reduction in breast cancer deaths: At 5 years	At 18 years	Year reduction began
40–44	(18)	36	9
45–49	(0)	16	6
50–54	65	22	3
55–59	(30)	24	3
60–64	(50)	17	3

Parentheses indicate observations based on 20 or fewer breast cancer deaths in study and control groups combined.

A less well recognized aspect of the controversy

Table 2. Potential years of life saved in study group in comparison to control group, HIP study (source Refs [4] and [5])

Age at entry	Life years saved per 1000 women	
	Over 18 years [4]	Over lifetime [5]
40–44	17	51
45–49	6	20
50–54	30	44
55–59	23	29
60–64	29	35
All ages	20	36

is depicted in Table 2. In this table two different approaches to assessing potential years of life saved as a result of screening are presented. Both are based on the cases diagnosed within the first 7 years. One, that of Habbema *et al.* [5], was based on the results available at 14 years of follow-up and with person years of life saved calculated for the duration of the expected life span using life table techniques. The other, based on the 18 year results [4], gives the life years saved during the actual period of 18 years of follow-up, the calculations performed by the principal investigators. The fact that these are based on different points in the follow-up is far less relevant than the approach to calculating person years. In the approach of Habbema *et al.* [5], one gets a completely different impression of the benefit of screening women under the age of 50 to that in the approach of Shapiro *et al.* [4]. This is a reflection of whether one is aiming to get fairly immediate rewards, in which case one would tend to place one's resources on screening women over the age of 50, or whether one is really looking for lifetime benefits, in which case one would tend to put at least as much resources into screening women aged 40–49. Expressed another way, if we start screening women in their 40s we will not influence deaths from breast cancer that would occur while these women remain in their 40s; however, we will influence some of the deaths which would occur in the absence of screening in these women in their 50s as a result of the breast cancers that would have been diagnosed while they were in their 40s. For women in their 50s we can promise a benefit that will accrue to them in the same decade.

The final aspect of the HIP study which deserves to be re-emphasized is the question of modalities used in screening and which may have benefited the participants. Table 3, based as it must be on case detection, emphasizes the important contribution of physical examination to the yield from screening. This and other analyses suggest that physical examination must have made an important contribution to reduction in mortality in all age groups.

THE EUROPEAN STUDIES

As these studies are being updated at this meeting and as their updates were not available to me in preparing this paper, I shall refer to them relatively briefly, though my impression from the abstracts is that the conclusions I draw from published results have probably changed little.

Three programs, the two in the Netherlands [6, 7] and that in Florence [8], have been assessed by the case-control approach. The three show important reductions in mortality from breast cancer in women over the age of 50, two as a result of programs using mammography alone (Nijmegen and Florence) and one using the combination of mammography plus physical examination. The published results of the Nijmegen study indicate no benefit in women under the age of 50, though a new analysis makes a plea for consideration of possible benefit in these women. There was some non-significant reduction in mortality in women under the age of 50 in the Florence study, possibly a reflection of a longer follow-up time.

In the Swedish WE randomized trial, the initial results again showed no benefit in women aged 40–49 but important benefit in women over the age of 50 [9]. In this trial single-view mammography was used. Other trials are ongoing in Sweden but no mortality results are yet available.

The lack of benefit in women under the age of 50 in all these studies may be explained by the same factors that resulted in the delayed occurrence of benefit in the HIP study. If this is so, these studies must all be on the verge of showing mortality reduction in the under 50 age group. If not presented at this meeting one may begin to wonder whether or not there are other explanations. One possible explanation could be relative lack of sensitivity of the screen. All these studies have incorporated mammography and none which have so far studied women under the age of 50 in Europe have used physical examination. In Utrecht the study was originally planned with different objectives than demonstrating benefit [10] and therefore women under the age of 50 were not screened initially as it was expected that little benefit would accrue to them. Although the investigators subsequently screened women under the age of 50, mortality results from this are not yet available [11]. I have already indicated that I believe it likely that the physical examination component of the HIP screen contributed to reduction in mortality in all age groups. Its absence in the European studies could have contributed to lower sensitivity of the screen. That the screening was less sensitive in women aged 40–49 than in women over the age of 50 has, in fact, been demonstrated for the Swedish WE trial [12].

The second possible explanation is that the

Table 3. Breast cancer cases histologically confirmed by modality of detection on screening (source Ref. [4])

Age at entry	Total	Percent detected by: Mammography alone	Clinical alone	Mammography and clinical
40–49	40	25	58	18
50–59	67	39	40	21
60–64	25	32	36	32
All ages	132	33	45	22

periodicity of rescreening was too low in women aged 40–49. There was no difference in the periodicity of rescreening in the Nijmegen and Florence studies but there was in the Swedish study with the younger women being screened more frequently than the older. An attempt to assess the sojourn time of pre-clinical lesions in the Swedish study has suggested that this is not much less in younger women than in older women [12]. Thus, too infrequent a repeat screen in younger women may not be the answer to a lack of effect in them. That lack of sensitivity in younger women may be important has, in fact, already been suggested by an analysis in the Nijmegen study [13].

ONGOING STUDIES

There are three important studies ongoing that will provide guidance on screening for breast cancer. The first is the United Kingdom study incorporating women aged 45–64 using bi-annual mammography and annual physical examination in two centers and BSE in two more with four control districts [14]. In one of the mammography screening centers there is randomization by family practices. Time will tell whether this study is sufficiently powerful to provide much additional evidence on the benefits to be expected from this screening approach. For example, it is not clear whether we can expect any elucidation of the age issue as women aged 40–44 were not incorporated into the study. Further, it is not clear whether the study will be sufficiently powerful to give us any information on effectiveness of breast self-examination. Mortality results are not yet available but should become available within a year.

The National Breast Screening Study in Canada was designed specifically to provide additional information on the benefit of the combination of mammography, physical examination and breast self-examination given annually in women aged 40–49 and the incremental effect of mammography over and above physical examination and BSE in women aged 50–59 [15]. This study should have the power to answer both objectives yet it is now apparent that we admitted a highly selected group of women who have shown the expected numbers of breast cancers but so far a much lower mortality from breast cancer than expected. Some of this could be due to a benefit of physical examination in women aged 50–59 but it does not explain the lack of deaths in women aged 40–49. If this continues, our expectation that results might be available within 2 years may be disappointed. We may have to continue follow-up for at least a further three before we are in a position to report mortality results. We are currently in the process of re-evaluating the power of the study in the light of the trends in breast cancer deaths so far and hope to have a more precise prediction of the time when results could be anticipated within a few months.

The third ongoing study, of critical importance in those countries which so far have tended to rely on breast self-examination, is a randomized trial based on factories in Moscow and polyclinics in Leningrad evaluating team teaching of breast self-examination [16]. This trial will eventually include over 200,000 women but results will probably not be available for between 8 and 10 years. A geographically controlled comparison of BSE is underway in East Germany and there are plans to attempt to evaluate the program introduced by Dr. Gastrin in Finland, the Mama program, about 14 years ago [17]. Some evidence on effectiveness of BSE could, therefore, become available within the next few years.

SELECTION OF WOMEN TO BE SCREENED

It is clear that the most important risk indicator for breast cancer screening is age. However, many have attempted to evaluate the contribution of other risk factors particularly those recognized as being relevant in terms of etiology of breast cancer in attempting to identify women who should be screened. Other difficulties with this approach are that these are risk indicators for etiology of breast cancer, not necessarily for death from breast cancer and secondly, it is clear in all attempts to perform such discriminant studies that a proportion of women without risk factors for breast cancer develop it and many women with risk factors do not. Using the standard risk factors it was our experience that the discrimination was least good when we attempted this on the basis of a simple risk factor count

[18]. However, with a logistic regression analysis including symptoms of possible breast problems we developed a discriminant which enabled us to identify 86% of the breast cancers and only screen 40% of the participants. This approach reduced the program sensitivity from 90% if all were screened to 77% if only those labelled as high risk were screened, increased the program specificity from 98% to 99% and the positive predictive value from 18 to 33%. Others are also working on this approach, some incorporating decisions not only on whether or not to include women in screening programs but how often to rescreen them.

THE IMPORTANCE OF DIAGNOSTIC CENTERS

Screening is a process whereby the potentially abnormal are distinguished from those assessed to be normal. Screening is not diagnosis, those found to be abnormal on the test have to be referred elsewhere for diagnosis and management. This requirement for centers where the necessary skills in radiology, surgery and pathology will be available has been well recognized in the recommendations for the U.K. screening program [19] as it has been in Sweden and in the report of a WHO Consultation on Imaging Technologies in Breast Cancer Control [20]. In countries where health care systems permit the direct referral of a participant with an abnormal finding through a diagnostic center this approach can be well controlled. But in countries such as in North America with a less controlled approach to health care considerable difficulties are likely to ensue. This is reflected in the substantially different benign to malignant ratios for biopsies in the National Breast Screening Study in Canada compared to, for example, the experience in the WE trial in Sweden. In Sweden it was possible for the screening center to devote a great deal of time with more complete mammography and other aids to diagnosis before a biopsy was recommended [21]. Similar approaches were possible in the U.K. In Canada, at least initially, such an approach was not possible even though an attempt was made to make an informed recommendation on appropriate management following consultation between the study surgeon and radiologist to the woman's family physician. Interestingly our own attempts at cost effectiveness analyses suggests that the additional costs incurred by a high biopsy rate have far less impact that one might have anticipated. The major cost relates to the potential benefit and the numbers who are going to be screened.

POSSIBLE POLICIES FOR BREAST CANCER SCREENING

There will never be a point in time when we know everything we should like to know about the effectiveness of any particular medical approach. Therefore, inevitably decisions on policy have to be based on incomplete knowledge. Most commentators have echoed the conclusions of the project on screening for cancer of the International Union Against Cancer that mass screening reduces mortality from breast cancer with a consistent benefit for women aged 50 or more. Many would also agree that the effect in women aged 40–49 is less clear, at least in terms of making policy decisions. For this reason in the U.K. the recent policy decision has been to initiate screening in women aged 50–64 while in Finland the initial approach will be to screen women aged 50–59. In Sweden, on the other hand, the national policy is to screen women aged 40–69. These differing policies, at least in part, reflect resource implications as exhibited by the different periodicity of rescreening recommended every 3 years in the U.K., 2 years in Finland, 1 year to 18 months for women aged 40–49 and 2 yearly in women aged 50 or more in Sweden. In the United States the US NCI has incorporated recommendations for screening women aged 50 or more with annual mammography and physical examination as part of its planned objective to reduce cancer mortality by 50% by the year 2000 [22]. In Canada there is no national policy, though within Ontario there has been a recent decision to initiate a pilot screening project in one area using mammography and physical examination in women aged 50–69 given every 2 years. It is of substantial interest that none of these policies, with the possible exception of the US NCI approach, use the same periodicities of rescreening as was investigated in the screening trials. All of them appear to have been influenced by other considerations, concern over lack of sensitivity, particularly for the screen in women aged 40–49 in Sweden and possibly too long an interval for women aged 50 or more in that country, while economic considerations are clearly influencing the decision in the U.K. and possibly those in Finland and the pilot study in Canada as well.

The UICC project on screening concluded that in countries where breast cancer is common and where the necessary resources are available, screening using mammography alone or mammography plus physical examination is applicable as public health policy [1]. However, the greatest initial benefit will be obtained by concentrating screening on women aged 40–69. The ambiguity of the modality to be used is obvious in this recommendation. Although most people tend to concentrate on mammography, we and some others maintain that the benefit of physical examination either with mammography or in partial substitution for mammography could be considerable. Our own experience in Canada, in contradistinction to that of the U.K.

[23], is that a policy based on physical examination could be less expensive rather than more. Whether or not this is confirmed by a full cost–benefit analysis is likely to be resolved by the Canadian trial within the next few years.

REFERENCES

1. Day NE, Baines CJ, Chamberlain J, Hakama M, Miller AB, Prorok P. UICC project on screening for cancer: report on the workshop on screening for breast cancer. *Int J Cancer* 1986, **38**, 303–308.
2. Shapiro S, Strax P, Venet L, Venet W. Changes in 5-year breast cancer mortality in a breast cancer screening program. Proc. 7th National Cancer Conf., 1972, 663–678.
3. Shapiro S. Ten to fourteen-year effects of breast cancer screening on mortality. *J Natl Cancer Inst* 1982, **69**, 349–355.
4. Shapiro S, Venet W, Strax P, Venet L. Current result of the breast cancer screening randomized trial: the Health Insurance Plan (HIP) of greater New York study. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, Hans Huber, in press.
5. Habbema JDF, van Oortmarssen GJ, Van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of greater New York study. *J Natl Cancer Inst* 1987, **77**, 317–320.
6. Collette HJA, Day NE, Rombach JJ, deWaard F. Evaluation of screening for breast cancer in a non-randomized study (the Dom project) by means of a case-control study. *Lancet* 1984, **1**, 1224–1226.
7. Verbeek ALM, Hendriks JHCL, Holland R, Mravunac M, Sturmans F. Mammographic screening and breast cancer mortality: age-specific effects in Nijmegen project, 1975–82. *Lancet* 1985, **1**, 865–866.
8. Palli D, Del Turco MR, Buiatti E *et al.* A case-control study of the efficacy of a non-randomized breast cancer screening program in Florence (Italy). *Int J Cancer* 1986, **38**, 501–504.
9. Tabar L, Fagerberg CJG, Gad A *et al.* Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985, **1**, 829–832.
10. de Waard F, Collette HJA, Rombach JJ, Baanders-van Halewijn EA, Honing C. The Dom project for the early detection of breast cancer, Utrecht, The Netherlands. *J Chron Dis* 1984, **37**, 1–44.
11. Collette HJA, Rombach JJ, de Waard F, Collette G. An update of the Dom project for the early detection of breast cancer. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, Hans Huber, in press.
12. Day NE, Walter SD, Tabar L, Fagerberg CJG, Collette HJA. The sensitivity and lead time of breast cancer screening: a comparison of the results of different studies. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, Hans Huber, in press.
13. Verbeek ALM, Straatman H, Hendriks JHCL. Sensitivity of mammography in Nijmegen women under age 50. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, Hans Huber, in press.
14. U.K. trial of early detection of breast cancer group. Trial of early detection of breast cancer: description of method. *Br J Cancer* 1981, **44**, 618–627.
15. Miller AB, Howe GR, Wall C. The national study of breast cancer screening. *Clin Invest Med* 1981, **4**, 227–258.
16. The USSR/WHO Study. Protocol of the study of the role of breast self-examination in reduction of mortality from breast cancer. In preparation.
17. Gastrin G. *Breast Cancer Control*. Stockholm, Almqvist & Wiksell International, 1981.
18. Schechter MT, Miller AB, Baines CJ, Howe GR. Selection of women at high risk of breast cancer for initial screening. *J Chron Dis* 1986, **39**, 253–260.
19. Working group. Screening for breast cancer. *Lancet* 1987, **1**, 575–576.
20. Miller AB, Tsechkovski M. Imaging technologies in breast cancer control: summary of a World Health Organization meeting. *Am J Roentgenol* 1987, **148**, 1093.
21. Fagerberg CJG, Tabar L. The results of periodic one-view mammography screening in a randomized, controlled trial in Sweden. Part 1: Background, organization, screening-programme and tumour findings. In: Day NE, Miller AB, eds. *Screening for Breast Cancer*. Toronto, Hans Huber, in press.
22. Greenwald P, Sondik EJ, eds. *Cancer Control Objectives for the Nation:* 1985–2000. NCI Monographs. No. 2, 1986.
23. Chamberlain J, Clifford RE, Nathan BE, Price JL, Burn I. Error-rates in screening for breast cancer by clinical examination and mammography. *Clin Oncol* 1979, **5**, 135–146.