Europ. J. Cancer Vol. 15, pp. 311–315

0014-2964/79/0301-0311 $02.00/0

Mammography in Mass Screening

D. W. VAN BEKKUM
Radiobiological Institute TNO, the Netherlands

Abstract—*The statement on X-ray mammography in screening for breast cancer which was released by the National Cancer Institute in August* 1976 *is critically evaluated. The considerations which have led to the discontinuation of the use of mammography for screening of healthy women under* 50 yr *of age in the U.S. are analysed. There is no reason to adopt these NCI recommendations in the Netherlands, provided that certain specific requirements, in particular the use of low dose techniques for mammography in mass screening programs are met.*

INTRODUCTION

IT IS generally accepted that the recognition of breast cancer at an early stage increases the chances for a cure. Therefore, many techniques have been used in an attempt to improve the methods for the detection of small tumors in the breast. One of the very promising procedures is mammography.

In the United States, recommendations restricting the mass application of this detection method to women above 50 yr of age have been recently published by NCI. This has caused some confusion with respect to the strategy of mass screening for mammary carcinoma. Since the introduction of mass screening for breast cancer in several European countries is just beginning, it seems opportune to examine whether these American guidelines should be applied over here.

The aim of the present paper is to analyse the problems under discussion in the United States. In order to do this, it is necessary to understand the history and the background of the developments in the United States.

In 1963, an investigation involving 62,000 women in the age group of 40–64 yr was started under the auspices of the Health Insurance Plan (HIP) of greater New York [1, 2]. Half of the women were screened for breast cancer four times at intervals of one year by means of physical examination and mammography. The other 31,000 women were not screened for breast cancer; they received the normal medical care—that is, they were examined according to the complaints they came in with. They formed the control group in this study. The screening revealed 132 cases of breast cancer. At least 44 (33%) cancers would not have been discovered without mammography, 29 tumors were discovered by a combination of physical examination and mammography, so that the percentage of tumors diagnosed as a result of mammography may be estimated at about 50. In the period of 7 yr after the beginning of the study, the death rate from breast cancer in the screened group was 30% lower than in the control group; this gain was exclusively in the age group above 50 yr. Using decrease in mortality as a criterium, mammography offered no advantage to women under 50 yr of age.

In 1973, the "Breast Cancer Detection Demonstration Project" was organized in the U.S. as a cooperation between the National Cancer Institute and the American Cancer Society. Twenty-seven breast cancer detection centers, each of which were to screen 10,000 women, were established. In March 1976, 258,000 women had been registered in this program, among whom 1083 breast cancers were discovered. In the age group between 35 and 49 yr (129,712 women) 308 cancers were discovered; of these, 223 were revealed at the first screening. One-hundred of these 223 cases were detected by mammography only. This experience is in agreement with that of two recently conducted breast cancer screening pilot programs in the Netherlands (in Nijmegen and Utrecht) where approximately 50% of the tumors appeared not to be palpable. In the screening program in Cincinatti, about 2/3 of all minimal breast cancers (*in situ* and stage 1 tumors smaller than 5 mm) were discovered by means of

Accepted 21 August 1979.

mammography [3]. In a similar program in Atlanta, including 5810 women under the age of 50, 70% of the cancers in this age group were detected by xeromammography [4].

THE RECENT NCI GUIDELINES

In 1976, criticism was aroused in certain scientific circles in the U.S. concerning the mass application of mammography to "healthy" women, especially in connection with the possible risks of development of breast cancer due to low dose irradiation. Recent calculations and extrapolation seemed to indicate that the risk was greater than previously thought. After a period of fierce discussions between those in favour and those against the mass application of mammography, the NCI issued new interim guidelines [5] to the 27 detection centers. Among these directions were the following main statements:

1. Mammography remains an accepted part of the complete diagnostic investigation when suspicion of breast cancer is under consideration, regardless of the age of the woman.
2. It has been demonstrated that the application of mammography during the screening for mammary carcinoma (next to physical examination) is of clear advantage in women over 50 yr of age. Mammography is indicated as part of the screening program for this age group.
3. The routine use of mammography in the screening of women between 35 and 49 yr of age cannot be recommended at this time. It is, however, not advised to withhold a mammography examination from a woman under 50 yr when she and the doctor are in agreement that it (mammography) is of direct importance for her, taking into consideration the very small assumed risk of mammography for the individual woman.
4. The presently available refined methods of mammography have not been in general use long enough to determine their effectiveness in decreasing mortality (from breast cancer) through the screening of asymptomatic women between 35 and 49 yr of age. Neither has it been shown that mammography is of no benefit in this connection. In younger women with a specific risk of breast cancer, mammography is of value for the early detection.

These are the most important parts of the recommendations. They represent a rather complicated means of telling the profession that, at present, mammography should not be used as a part of the mass screening of women under 50. It is remarkable that these guidelines were issued less than 2 months after the American College of Radiology had made the following recommendation:

"For asymptomatic women, the initial mammography investigation should be performed between 31 and 40 yr of age . . ." [6]. Recent comments in the medical press [7, 8] have, through inadequate representation of the basic data, increased rather than decreased the confusion. What can be the reasons for the ambivalent wording of the NCI recommendations? One is probably the apprehension of the American authorities that a straightforward rejection of mass mammography for women below 50 yr of age (for screening) might lead to protests and perhaps even to legal actions by some women under 50 who have been participating in the detection programs. Another motive may well be the concern of the authorities for the development of reservations by the public to cooperate in screening programs in the future. After all, during the past years, more than 100,000 women have undergone a procedure they were told was to be for their benefit, which is now being discontinued because it may involve risks.

THE INDUCTION OF MAMMARY CARCINOMA BY IRRADIATION

Most likely, there is still another reason for the obscure wording in the reports. The actual data on which the presently published guidelines for safer application of mammography are based have been available since 1969. In drafting the screening procedure in 1973, insufficient consideration was given to these data. Also, they were evaluated differently at that time; the precise interpretation of the data by the various committees established for that purpose was completed at the beginning of 1977 [9].

These studies deal with the frequency of breast cancer after irradiation in 3 groups of exposed women:

(a) more than 3700 Japanese women who received a dose of 10–600 rad (average 81 rad) of mixed gamma and neutron irradiation during the atomic bomb attacks [10, 11].

(b) a group of 300 women who were treated for tuberculosis between 1944 and 1955, during which they underwent a great number of fluoroscopic examinations (average

number 162; average accumulated dose to the mammary tissue estimated at 1200 rad; average dose per fraction 8 rad) [12, 13].

(c) 600 women who were treated in the same period for postpartum mastitis by X-ray irradiation [14]. These patients were aged from 20 to 34 yr and received an average dose of 200 rad on both breasts.

In all these groups, an increased incidence of mammary carcinomas was registered as compared to the appropriate control groups; in 2 of the 3 studies, an increase in tumor incidence with the radiation dose was also evident. The minimum latent period was 15 yr. Especially the Japanese data clearly suggest an increase in mammary cancer in the groups receiving a dose of less than 100 rad. In the 27 American detection centers, the average dose on the mammary gland tissue was 1 rad per mammographic investigation. To calculate the risks involved in mammography, the most unfavourable model for the extrapolation from high to low dose is employed, namely, that of a linear relationship between dose and effect. This method of extrapolation has been subject to criticism, but it is generally accepted by the international forum of radiation experts. This method results in practically identical risk factors whichever of the three exposed groups of women are used for the calculations [15]. The number of extra mammary carcinomas that can be expected yearly amounts to 6 for 10^6 women per rad received; in other words, if 10^6 women each undergo one or more examinations resulting in a total dose of 1 rad on the breast tissue, six radiation induced mammary carcinomas may occur per year beginning 10–15 yr after the exposure. This risk calculation implies that, assuming a latent period of 10 yr, annual mammographic examinations (1 rad per mammography) beginning at 35 yr of age, will increase the frequency of mammary carcinoma after 10 yr from $1300/10^6$ to $1306/10^6$ (age 45 yr), after 20 yr, from 1800 to $1860/10^6$ (age 55 yr), and after 40 yr, from 2300 to $2480/10^6$ (age 75 yr)* [16, 17]. Another presentation of the thus calculated risks runs as follows: if a group of 10^6 women undergo mammographic investigation annually (1 rad per breast per examination) beginning at 35 yr of age, and if they should all reach the age of 75 it can be expected that 61,000 natural and, in addition, a maximum of 2520 radiation induced mammary carcinomas will appear during that period of 40 yr in that group of women. If the screening begins at 40 yr of age and a latent period of 15 yr is assumed, then one can expect 59,000 natural and 1260 induced tumors per 10^6 women in the interval from 40 to 75 yr old. According to such calculations, some of the benefits of the screening in terms of human life would be lost particularly if one limits the benefits to those tumors that are revealed exclusively by mammography. This consideration, the unimproved 3-yr survival in the screened women between 35 and 49 yr of age in the HIP program and the evidence that the radiation dose on the mammary gland in some American detection centers appeared to be higher than 1 rad, were the primary reasons for the recommendation that mammography should no longer be used for the screening of women below 50 yr of age. In case mammography is started at the age of 50, the loss of benefit from the screening will, naturally, be much smaller. However, the age limit of 50 is rather arbitrary and, from the point of view of early cancer detection, not attractive. In the screening programme conducted in West London [18] more than half of the carcinomas were discovered in women under 50 yr of age [19].

REDUCING THE RADIATION DOSE

The next question to arise is whether the calculated risks due to mammography can be lowered to such an extent that younger women may also receive the benefits of this type of screening. The American considerations are based on the measured average dose of 1 rad on the mammary gland tissue per mammogram in the detection centers of NCI/ACS, but the dose varied between 0.3 and 6.5 rad. Since 1976, it has been stipulated that the skin dose for mammography in the detection centers should not exceed 1 rad per examination (equivalent to 0.2–0.3 rad to the mammary gland tissue). The technical developments of mammography are such that, while the average dose per mammogram amounted to as much as 7 rad in the HIP study, reliable techniques are

*On the basis of the figures for The Hague and Friesland (1965–1969), Report of Staff of Dept. of Epidemiology and Information, Ministry of Public Health and Environmental Hygiene, the Netherlands, these numbers are as follows: 45 yr of age, 1380 (+6 induced); 55 yr, 1430 (+60 induced); 70 yr, 2280 (+150 induced). No data for 75 yr are given in this report.

now available by which the dose per examination remains much less than 1 rad [20]. For the screening on breast cancer in Nijmegen, the Netherlands, use is presently made of the Kodak Min R film-screen combination, by which the average dose on the mammary gland tissue is limited to approximately 0.1 rad per mammogram. With such low doses, the risks of regular (even annual) mammography for younger women can be ignored.*

It is regrettable that NCI has not more clearly explained why a procedure which seemed acceptable in 1973 must now temporarily remain in abeyance—that is until the modern low dosage procedures have been generally adopted. It is not uncommon that insights and interpretations of data change through further study and it is perfectly proper to adjust prevailing procedures to such changes.

RECOMMENDATIONS

In our opinion the guidelines of NCI should not be adopted in the Netherlands because the American situation, with respect to the application of mammography in mass screening for mammary carcinoma, is totally different from that in our country. In its "Advice concerning the early diagnosis of cancer" of 1974 [21] the Dutch Health Council agreed that "the clinical and diagnostic techniques of mammography are also applicable to the early diagnosis of breast cancer in mass screening of the population, provided that methods delivering a very low radiation dose are used". In the light of the data presently available, the following recommendations are proposed:

(1) All mammographics for screening purposes be so performed that the dose per examination per breast does not exceed an average of 0.1 rad on the mammary gland tissue. These conditions should be safeguarded through regular checks by means of dosimetry. Subsidized screening centers should be required to exclusively use systems which deliver the lowest possible radiation dose.

(2) A program of research should be initiated with the objective of determining the benefits of regular screening with mammography in terms of follow-up and mortality, particularly concerning the age group of 35–50 yr.

(3) In all programs of mass screening for mammary carcinoma, it is desirable that the scientific design and guidance guarantee the evaluation of the screening on a long term basis. For this purpose, the necessary financial support should be made available. From the point of view of limiting the radiation risks with regard to its carcinogenic effects, the tissue dose must be controlled. This holds equally for other current methods for mass screening with radiography, e.g. thorax examinations.

*With annual mammography, a maximum of 250 induced cancer cases in the period of 35–75 yr as compared to 61,000 spontaneous carcinomas per 10^6 women.

Acknowledgements—The author acknowledges the contributions of Prof. Dr. W. Penn, Head of the Dept. of Diagnostic Radiology, University Hospital, Nijmegen, the Netherlands, for the risk calculations and thanks Prof. Dr. L. M. van Putten and Prof. Dr. G. W. Barendsen for critical evaluation of the manuscript.

REFERENCES

1. S. Shapiro, P. Strax and L. Venet, Periodic breast cancer screening in reducing mortality from breast cancer. *J. Amer. med. Ass.* **215,** 1777 (1971).
2. S. Shapiro, P Strax, L. Venet and W. Venet, Changes in 5-yr breast cancer mortality in a breast cancer screening program. *Proc. nat. Cancer Conf.* **7,** 633 (1973).
3. M. Moskowitz, S. Pemmaraju, J. A. Fidler, D. J. Sutorius, P. Russell, P. Scheinok and J. Holle, On the diagnosis of minimal breast cancer in a screence population. *Cancer (Philad.)* **37,** 2543 (1976).
4. A. H. Letton, J. P. Wilson and E. M. Mason, The value of breast screening in women less than 50 yr of age. *Cancer (Philad.)* **40,** 1 (1977).
5. J. B. Hartman, Statement on X-ray mammography in screening for breast cancer, NCI HEW-News, March (1977).
6. *Bull. Amer. Coll. Radiol.* **32,** 8 (1976).
7. D. S. Greenberg, Medicine and public affairs. *New Engl. J. Med.* **295,** 739 (1976).
8. B. J. Culliton, Breast cancer: second thoughts about routine mammography. *Science* **193,** 555 (1976).

9. Final Reports of National Cancer Institute ad hoc working groups on mammography screening for breast cancer and a summary report of their joint findings and recommendations. DHEW Publication No. (NIH) 77–1400 March 1977.
10. C. K. WANEBO, K. G. JOHNSON, K. SATO and T. W. THORSLUND, Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. *New Engl. J. Med.* **279,** 667 (1968).
11. S. JABLON and H. KATO, Mortality among A-bomb survivors, 1950–1970. JNIH-ABCC Life Span Study, report 6. Technical Report 10 (1971).
12. I. MACKENZIE, Breast cancer following multiple fluoroscopies. *Brit. J. Cancer* **19,** 1 (1965).
13. J. A. MYRDEN and J. E. HILTZ, Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmonary tuberculosis. *Canad. med. Ass. J.* **100,** 1032 (1969).
14. F. A. METTLER, L. H. HEMPELMANN, A. M. DUTTON, J. W. PIFER, E. T. TOYOOKA and W. R. AMES, Breast neoplasms in women treated with X-rays for acute postpartum mastitis. A pilot study. *J. nat. Cancer Inst.* **43,** 803 (1969).
15. BEIR REPORT, Report of the Advisory Committee on the Biological Effects of Ionizing Radiations. The effects on populations of exposure to low levels of ionizing radiation. Division of Medical Sciences, National Academy of Sciences, National Research Council, Washington, D.C. (1972).
16. H. SEIDMAN, *Ca-A Cancer Journal of Clinicians.* Published by the American Cancer Society, **27,** 66 (1977).
17. J. A. H. LEE, P. G. CHIN, W. A. KUKULL, R. S. TOMPKINS and A. F. WEATHERALL, Relationship of age to incidence of breast cancer in young women. *J. nat. Cancer Inst.* **57,** 753 (1976).
18. J. CHAMBERLAIN, P. ROGERS, J. L. PRICE, S. GINKS, B. E. NATHAN and I. BURN, Validity of clinical examination and mammography as screening tests for breast cancer. *Lancet* **ii,** 1025 (1975).
19. B. E. NATHAN and J. L. PRICE. *Brit. J. Radiol.* **49,** 817 (1976).
20. D. L. ASBURY and P. G. BARKER, Radiation dosage to the breast in well-women screening surveys. *Brit.J. Radiol.* **48,** 963 (1975).
21 Dutch Health Council, Advice in early diagnosis of cancer, No. 1933, Rijswijk, The Netherlands (1974).