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RADIATION AS A CAUSE OF BREAST CANCER*

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DESPITE recent great advances in medical care, the mortality rate for cancer of the breast in the United States is essentially unchanged.[1] Even if there has been some improvement in the survival of patients with cancer of the breast through modern, presumably more effective management, this improvement is hardly commensurate with the announced advances in therapy and early detection.

The latest announced advance in postoperative chemotherapy[2] has evoked an unusually enthusiastic editorial in the prestigious *New England Journal of Medicine*,[3] while in News and Comments of *Science*[4] the reports were considered greatly exaggerated.

There is no question that previously hailed advances have failed to affect the mortality rate. Thus, either these advances really are not

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effective or other factors are operating to increase the incidence of breast cancer. We propose to investigate the possible role of radiation as a factor in the causation of breast cancer.

Some variables said to be associated with a high risk of breast cancer include genetic factors, pre-existing breast disease, artificial menopause, family history of breast cancer, failure to breast feed, older than usual age at time of first pregnancy, high socioeconomic status, specific blood groups, fatty diet, obesity, and hormonal imbalances. To this list we must add ionizing radiation as an additional and serious risk factor in the causation of breast cancer.

Among the irradiated groups which have an increase in the incidence of cancer of the breast are:

1) Tuberculous women subjected to repeated fluoroscopy

2) Women who received localized x-ray treatments for acute postpartum mastitis

3) Atom-bomb survivors

4) Other x-ray exposures involving the breast, including irradiation in children and in experimental animals.

To this list we can add a group of women who were treated with x rays for acne or hirsuitism.[5]

In 1965 MacKenzie[6] reported that 40 cancers of the breast had appeared in women who had repeated fluoroscopic examinations in sanatoria for pulmonary tuberculosis. By the technique used, large doses of unfiltered radiation were delivered to the anterior chest wall. This study by MacKenzie had been suggested in 1961 when he observed a previously irradiated 43-year-old woman who presented with a rapidly growing tumor in the upper inner quadrant of the breast. In a later related work, Myrden and Hiltz[7] traced more than 1,500 tuberculous patients who were treated at a Nova Scotia sanatorium during the years 1940 to 1949. Of 300 female patients fluoroscoped during treatment by artificial pneumothorax, 22 developed carcinoma of the breast, while of 483 female patients who did not receive pneumothorax, breast cancer occurred in only four. Myrden and Hiltz estimated the expected annual incidence of breast carcinoma in Nova Scotia as 55 per 100,000 female population, while the 22 breast cancers developing in that group of 300 patients gave an incidence of 730 per 100,000 female population per annum. The study demonstrated a much higher incidence of breast carcinoma in those patients who had undergone repeated fluoroscopic

examination. The breast cancers developed about 17 years after treatment and in a younger group than is usual. The authors warned that patients who had received artificial pneumothorax treatment with fluoroscopy years ago should be examined frequently for cancer of the breast.

In a pilot study on breast cancers in women treated with x rays for mastitis, Mettler and his associates[8] surveyed by mail the incidence of benign and malignant tumors in more than 600 women. The follow-up period extended from 10 to 25 years after the radiation; 13 cases of breast cancer were observed instead of an expected 5.9 cases. In five of the 13 women with cancer only one breast had been treated; significantly, in all five women the cancer arose in the irradiated breast. The total radiation dose per breast was estimated to range from 75 rads to more than 1,000 R in this study. Even though the association between mastitis and irradiation and the subsequent development of breast cancer seems strongly evident, there still may be some uncertainty as to whether the radiation or the disease that was treated was the cause of the subsequent cancer. This question of association between cancer and other breast lesions including cystic mastitis was studied by Lewison and Lyons[9] in 385 women in a follow-up period of some 13 years; they found no evidence that mastitis is a precursor of breast cancer.

In 1950 Lorenz[10] of the National Cancer Institute irradiated mammals with dose levels ranging from 0.11 to 8.8 R per day and showed an increased incidence for mammary tumors in the chronically irradiated animals of both sexes over that of the nonirradiated controls. Subsequently, others confirmed this appearance of mammary cancer in irradiated animals.[11]

The Adult Health Study of 12,000 female survivors and controls who had lived in Hiroshima and Nagasaki at the time of the atomic bombing was reported in reference to breast cancer by Wanebo and associates;[12] a fairly definite carcinogenic effect of the atomic bomb radiation was established. It is not certain that the effect is a dose-response phenomenon, for the incidence of breast cancer is much lower than the incidence of the well-known and well-studied leukemogenic effect of the atomic bomb irradiation. Nevertheless, there seems to be a dose-effect relation when the breast or total body received more than 90 rads. Of great interest is the relatively young age at the time of the bombing in the patients with subsequent breast cancer who received

more than 50 rads. This influence of age on the incidence of cancer is not without precedent, for it is also true of the relation between irradiation in childhood and subsequent leukemia and cancer of the thyroid.

Exposure of the fetus to doses as low as 10 rads is enough to produce many common forms of childhood cancer.[13] In animals, sublethal whole-body x-ray exposure of young female rats caused early appearance of mammary neoplasm, the incidence of which seems linearly related to dose between 25 and 400 R. It also was observed that fission neutron irradiation had a very high relative biologic effectiveness (RBE) for mammary tumor production in rats.

Lowell[14] reported the case of a 46-year-old man who 35 years previously, when he was a child of 11, had therapeutic radiation to his right breast for prepubertal gynecomastia. The details of the treatment were given in exposure time of 133 kv radiation therapy, not in roentgens or rads.

Case Reports

Our patients with carcinoma of the breast who had received radiation to the breasts in the course of treatment of acne or hirsutism at or about the age of 20 developed cancers many years later.

Case 1. A 45-year-old mother of three children had a ductal carcinoma of the left breast with involved nodes at all levels of the axilla at mastectomy in March 1974. In June 1974 a mastectomy was done for carcinoma of the other breast, again with extensive involvement of the axillary lymph nodes. The patient went on to rapid demise, despite oophorectomy, chemotherapy, and radiotherapy. Significant in this case was the presence of severe and even active acne of the face, upper arms, and chest wall anteriorly and posteriorly. The patient had received an indeterminate number of x-ray treatments for acne during her teens, but there was no definite indication of radiation-induced skin changes from this treatment. The details of the therapy are not available because the treatment was administered by a dermatologist who has since died.

Case 2. A 49-year-old career woman had a radical mastectomy at The Mount Sinai Hospital, New York, for a Stage II infiltrating carcinoma of the medial half of the breast. This treatment was followed by radiotherapy over an L-shaped internal mammary and supraclavicular field. Metastases in bones and lungs appeared within 18 months, and

death occurred four years after mastectomy. The patient appeared healthy; she was a slender woman with tanned face and atrophy of the skin, with some telangiectasia of the face and anterior chest which was consistent in appearance with the late effects of radiation given for acne in 1945 when she was 24 years old. Again, as is understandable in such cases, the details of the acne treatment are unavailable, but, according to the patient's history, the acne had included the lower neck and presternal regions. The patient's skin was characterized as unusually dry. She had been very preoccupied with cosmetics for this dry condition over a period of recent years. In this instance, the mastectomy was done approximately 25 years after the radiotherapy for acne.

Case 3. A 48-year-old unmarried woman had cancer of the breast, with metastases and demise three years after mastectomy. Her skin was atrophic and pitted from acne scars. During her teens she had been treated by dermatologists for several years. Her skin showed telangiectasia and dryness, as seen after radiotherapy for acne. It is worthy of note that this patient's elder sister also died of cancer of the breast.

Case 4. A 75-year-old woman had cancer of the endometrium in June 1975, cancer of the colon in 1973, and cancer of the breast in 1970 at the age of 70, for which a right radical mastectomy was done. There was no evidence of cancer of the breast at the time we treated her for endometrial cancer. Noteworthy were the cutaneous changes of her face, viz., atrophy, scarring, telangiectasia, and shrinkage of the mouth and chin, all characteristic of late effects of radiation therapy. The patient had received radiotherapy for hirsutism; it was given over a period of months in the early 1920s when she was in her 20s. The treatment was administered in New York by a pioneer radiotherapist who is now deceased and the records are no longer available. From the practice of his day, it is likely that the anterior chest wall and breasts were irradiated, although the chief damage was to the lower face. A basals-cell cancer of the skin of the chin had been excised in 1972.

Case 5. A 61-year-old doctor's wife had a left radical mastectomy for cancer of the breast. Her skin showed telangiectasia of the face and infraclavicular regions. As a teen-ager she had received radiation for acne.

Case 6. A 60-year-old woman developed cancer of the left breast in the axillary tail. During her teens the patient recalls having many weekly x-ray treatments to the left axilla for hydradenitis.

Discussion

Details of radiation exposure given many years previously are difficult to obtain. Records are lost, therapists die, exact physical specifications of dose and fields are often unrecorded, and the treatment had been given under circumstances in which it was considered improbable that a detailed history would ever become important.

The evidence for the relation of radiation for acne to the subsequent occurrence of carcinoma of the breast is circumstantial. The latent period may be 25 years or more. Yet, this clinical observation of a relation between radiation and subsequent carcinoma is the way that some of the most important carcinogenic effects of radiation have been detected. As an example, a personal communication from Sir Brian Windeyer (formerly Director of Radiotherapy and Dean of the Middlesex Hospital Medical School, London) states that the pioneer studies showing the subsequent development of leukemia in patients who were treated with radiation for ankylosing spondylitis[15] began by the anecdotal observation of just a few patients who developed leukemia while attending the follow-up clinic for ankylosing spondylitis patients in London. Later, the epidemiological investigation of these patients established this important relation between radiation and leukemia.

Radiation for benign conditions such as acne in women may not, by itself, cause breast cancer, but it is possible that it affects the incidence of superimposing a carcinogenic factor on susceptible patients. In Case 3 the patient's relatives had breast cancer and the patient herself was an irradiated susceptible woman. It also is possible that many women have had potentially carcinogenic radiation of the breast—particularly during the 1920s and 1930s when radiation was used cosmetically for epilation, notably in big cities, and also when the radiotherapy of acne was more widely approved.

In assessing the potential carcinogenic effect of diagnostic radiation on the incidence of cancer of the breast, we must take into account the implications of either a threshold dose or linearity of effect. In the present state of our knowledge it is not possible to extrapolate a threshold dose. For this reason it is prudent from a public health point of view to think in terms of linearity of effect and to assume there is no threshold for carcinogenesis.

In the Silvanus Thompson Memorial Lecture delivered at the British

Institute of Radiology on April 18, 1974,[16] Mole reported on an exhaustive survey of the problem of ionizing radiation as a carcinogen; he pointed out the practical problems which arise from considering the carcinogenesis of diagnostic radiography. He stated that the selection of cases for radiography is outside the radiologist's hands and that the referring clinician, not the radiologist, has the responsibility for the use of x rays.

For all practical purposes, the decision on whether to order a diagnostic x-ray examination depends on the hypothesis to be used for extrapolation—threshold dose or linearity. The most prudent assumption is that there is no threshold for carcinogenesis, an important assumption for the estimation of risk. It is, as Mole says,[15]

> ... disquieting for physicians, who exploit the benefits of ionizing radiation, to recognize that their activities can also do harm. Unwanted side effects are commonplace throughout medicine. Radiation today is usually used in an exemplary and controlled fashion, and so is the care and assiduity with which its harmful side effects are looked for and recorded. So much has been learned in this way that acceptability of radiography is based on objective considerations and not merely on theoretical possibilities.

From the viewpoint of the surgeon, how helpful is mammography in a young woman? An attempt to answer this question was made by Lesnick[17] in a presentation to the Third International Symposium on Detection and Prevention of Cancer, showing that 63% of mammograms in young women with proved breast cancer failed to demonstrate the malignant tumor; 56% of these young women with cancer even had mammograms which failed to show any tumor at all. Lesnick's retrospective analysis showed further that 29% of these young patients who had mammograms had their operations for cancer delayed because of acceptance of the "negative" mammographic diagnosis. In this surgeon's experience, mammography in the young has been more deceptive than helpful. These data from the clinical investigation by Lesnick corroborate the previous impressions of many experienced mammographers that the benefits from mammography in the young are questionable.

Mammography and Radiation Exposure

If there is a linear effect of radiation for carcinogenesis of the breast,

the exposure of the breasts of young women to diagnostic x rays must be considered especially hazardous.

Why take up this problem of the linearity of carcinogenic effect of radiation on the breast at this time? The reason is that we are in the throes of enthusiasm for early diagnosis of breast cancer, and particularly for mammography as a most important method of detecting such tumors. Early diagnosis seems an obvious virtue, but the solid foundation of the great desirability of early detection of cancer of the breast for survival has become shaky. In an editorial in the *Journal of the American Medical Association* by Gardner,[18] the doubling time of tumor growth and its significance is discussed. Doubt is cast on whether a small tumor is an early tumor. The author suggests that 80% of the patients with cancer of the breast have either disseminated or local disease. This leaves only 20% with early nodal metastases which might be affected by the type of treatment. Consideration of this small number of breast cancers which are amenable to differences in treatment makes it important that any early diagnostic procedure be free of risk. That is the crux of the problem of mammography and radiation exposure.

In "An Overview of Research in Cancer Diagnosis," Berlin[19] states ". . . the most important yardstick for evaluating cancer diagnostic research programs is reduction of mortality." The reduction can best be measured by comparing survival in a population of cancer patients prospectively with that of a mass control population without cancer. Indeed, mammography may well establish its effect on increasing the survival of patients with cancer of the breast. At the same time, mammography *must* be demonstrated to be without risk of inducing cancer.

The amount of radiation received in mammography varies with the technique and equipment used.[20] The soft-tissue technique of mammography implies a much larger dose to the skin on the tube side than to the skin overlying the film or detector. There is difficulty in making accurate measurements of this low-energy radiation; the dose of radiation to the breast falls off sharply as the breast is penetrated, especially when low energies in the 20 to 30 kv range are used. In May 1970 Gilbertson and his associates[21] reported exposure of 10 to 20 R on the entrance side of the breast, depending on techniques. Crosby and Ty[22] describe Lo Dose film systems which reduce this skin dose to a range of 1.5 to 3.5 rads per exposure. The dose absorbed by breast tissue is less than these entrance doses.

It is to be expected that the modern thrust in the improvement of technique is toward decreasing the dose of irradiation to the young breast and toward vigilance in controlling radiation technique and methods.[23] Surveys on techniques applied have shown variation from less than one rad to as much as 50 rads in single examinations.[24] Little is said about the unnecessary exposures to radiation from repeated examinations made because of unsatisfactory technique, nor is there much mention of the hesitancy on the part of the radiologist to make a diagnosis in a dense young breast.

The dose of radiation received by the survivors of the atom bomb who subsequently developed cancer of the breast ranged from 80 to 800 rads, the tuberculous women who were fluoroscoped received an estimated 50 to 6,000 rads, the women who were treated for mastitis probably were exposed to 30 to 700 rads, and our patients with acne received 100 to 6,000 rads. These imprecise estimates are to be compared with mammographic doses in the range of 10s of rads to the breast at each examination—again, an imprecise estimate depending on technique and equipment.

However imprecise these estimates may be, it is apparent that younger women are more likely than older women to develop cancer from exposure to radiation. The American Cancer Society advises that women under 35 years should have mammography only for medical indication, not for so-called screening. The Food and Drug Administration also voiced its "word of caution" on mammography.[25]

Another prudent approach to mammography was a recent veto by Hugh Carey, Governor of New York, of a bill which advocated a large investment of state monies in an overly enthusiastic mammography project. Only recently has the unrestrained use of mammography in the young been recognized as potentially hazardous.

If we have had advances in the treatment of cancer of the breast in recent years, and if, indeed, the mortality rate has remained the same during this period, some other factor must be operating to account for this anomalous status, viz., improved diagnosis and treatment and an essentially steady mortality rate. The operating factor seems to be an increased incidence of the disease; if there is a real increase in incidence, it may be due to the iatrogenic effect of exposure to radiation. Such an increase in incidence associated with radiation is analogous to the increase in cancer of the thyroid following thymic irradiation of infants.

Radiotherapy has survived as a valuable modality of treatment for tumors, but its short history is dotted with uses which now seem to have risks exceeding their benefits. Also, more effective therapies have supplanted these pioneer uses of radiotherapy. Most of these uses, now associated with carcinogenesis, were administered to the young. Examples are irradiation for large tonsils or adenoids, epilation, acne, thymic enlargement, and rheumatoid arthritis. From a demographic standpoint, the dose applied to breasts during mammography and other diagnostic procedures may well exceed the dose used in the defunct therapeutic procedures enumerated above.

If linearity of effect of radiation exposure as a carcinogen holds, mammography and other diagnostic radiation to the chest of young women may even be contributing, along with other factors, to the apparent increase in the incidence of breast cancer.

How does one classify a young woman for purposes of interdiction of mammography for screening? Since the time lag between the development of cancer of the breast and radiation exposure seems to be more than 20 years, a young woman in this context is one whose life expectancy is more than 20 years. Perhaps the age of 50 years is a good cut-off age for the young category.

In these young women especially, the factors which limit the benefits and increase the risks from mammography may be listed as follows:

1) The hazard of radiation carcinogenesis is increased.

2) Dense breasts require greater exposure of radiation for penetration in mammography.

3) Diagnosis is difficult; a small tumor cannot be discerned in the midst of dense breast tissue.

4) The yield of cancer finds is low.

Lest the annals of medicine add more iatrogenically induced cancer, the prudent tenets of the Amrican Cancer Society and the American College of Radiology should be upheld, limiting mammography in young patients to those with medical indication. Mammography should *not* be used for screening in the young.

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