

CORRESPONDENCE



RADIATION THERAPY FOR IN SITU OR LOCALIZED BREAST CANCER

To the Editor: In the study by Fisher et al. (June 3 issue)¹ of lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer, more than 20 institutions enrolled 818 women, and the diagnosis of breast cancer was made by institutional pathologists. There was apparently no central pathology review. The ability of pathologists to categorize in a reproducible way proliferative lesions of the breast and the distinction between intraductal breast cancer and ductal hyperplasia are matters of concern.² We believe that misclassification of patients has not been excluded as a possible explanation for the benefit reported in the group treated with radiotherapy.

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1. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993;328:1581-6.
2. Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. *Am J Surg Pathol* 1992;16:1133-43.

To the Editor: The study by Fisher et al. demonstrates the efficacy of radiation therapy for intraductal breast cancer in a generic sense. The study does not, however, indicate which

subgroups of ductal carcinoma require in situ radiation therapy. Neither the article nor the accompanying editorial¹ considers a large body of evidence that women with small and non-comedo types of ductal carcinoma in situ may be treated acceptably by surgical excision alone.

The benefit of radiation therapy in reducing the number of local recurrences after excisional biopsy for intraductal breast cancer has been documented repeatedly. This benefit appears to decrease with a longer follow-up period. In studies with a follow-up period of more than 5 years, recurrences appear to double between 5 and 8 years and are even more frequent after 10 years.

In an analysis of the influence of the histologic grade on local recurrence, Solin et al.² noted a recurrence rate of 20 percent for high-grade intraductal breast cancers, as compared with a rate of 5 percent for low-grade lesions, after 87 months of follow-up. These results are similar to those of one of our studies,³ in which the recurrence rates were projected to be 28 percent for similarly defined high-grade intraductal cancers and 6 percent for low-grade cancers after 120 months of follow-up.

Fisher et al. reported a postirradiation local-recurrence rate of 7 percent after a mean follow-up period of 43 months. This is not substantially different from the results of surgery alone after a comparable follow-up period.³

Radiation may have a role in the treatment of some types of intraductal breast cancer, but whether it does anything more than delay recurrences of incompletely removed lesions remains to be demonstrated.

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1. Swain SM. In situ or localized breast cancer — how much treatment is needed? *N Engl J Med* 1993;328:1633-4.
2. Solin LJ, Yeh I-T, Kurtz J, et al. Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation: correlation of pathologic parameters with outcome of treatment. *Cancer* 1993;71:2532-42.

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We are unable to provide prepublication proofs, and unpublished material will not be returned to authors unless a stamped, self-addressed envelope is enclosed. Receipt of letters is not acknowledged, but correspondents will be notified when a decision is made.

3. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ: frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer* 1989;63:618-24.

To the Editor: The studies by Fisher et al. and Veronesi et al. (June 3 issue)* provide important evidence of reduced local recurrence of in situ or localized breast cancer in patients who received radiation therapy after tumor excision. However, despite the statistical significance of the differences, the absolute benefit was relatively small. After lumpectomy for intraductal breast cancer, radiation reduced the annual incidence of recurrences of intraductal breast cancer in the ipsilateral breast from 2.6 percent to 1.5 percent and of invasive cancer from 2.6 percent to 1.6 percent. Similarly, in the Milan study, the incidence of local recurrences was 8.8 percent for the patients treated with quadrantectomy without radiotherapy, as compared with 0.3 percent for those treated with postsurgical radiotherapy.

Neither report stressed that it is too early to evaluate the overall effects on survival of adding radiotherapy. If survival proved to be identical, regardless of the use of radiotherapy, then these studies would show that approximately 75 percent of patients with intraductal breast cancer and 90 percent of those with invasive tumors under 2.5 cm in diameter could be spared irradiation without compromising the ultimate outcome. This approach would be contrary to the unequivocal recommendations for radiation therapy made by both study groups and by Dr. Swain in her editorial. A more cautious interpretation is that radiation therapy after total excision of intraductal breast cancer or small invasive carcinomas reduces the risk of a local recurrence but that a survival advantage has not yet been demonstrated.

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*Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993;328:1587-91.

The authors reply:

To the Editor: The comment by Verhoeven et al. that there was no central pathology review is incorrect. Reference to such a review appears in our paper on page 1585 and in a footnote to Table 2. The pathologist was unaware of both the treatment received and the outcome. Since, as we stated, "discordant diagnoses were few and were distributed between the two groups," misclassification cannot explain our findings.

Lagios and Page's inference that our paper is faulty because it includes no information about the relation of comedo necrosis or other clinical characteristics to outcome is inappropriate. We do not share their conviction that "a large body of evidence" indicates that small and noncomedo intraductal cancers can be treated by excision without irradiation. There are no data from a randomized trial to substantiate their claim.

With respect to the characteristics of the study patients, the tumor sizes listed in Table 2 of our paper require clarification. Those that were under 0.1 cm should have been more accurately labeled "no palpable mass." All other tumor sizes listed in the table (i.e., 0.1–1.0 cm, 1.1–2.0 cm, and

>2.0 cm) represent the sizes of palpable tumors reported by the investigators.

Dr. Sinoff minimizes the benefit of radiation therapy by choosing to present only the average annual incidence of intraductal cancer. When expressed as the cumulative incidence through five years of follow-up, the reduction after radiation was not trivial. Overall, the cumulative incidence of second tumors was reduced from 20.8 to 10.4 percent, noninvasive tumors from 10.4 to 7.5 percent, and invasive tumors from 10.4 to 2.9 percent. These reductions indicate that mastectomy is inappropriate treatment for localized intraductal carcinoma. Survival was not a primary end point of our study. Even if a survival difference is never demonstrated, the improved local disease control gained by eliminating mastectomies and the need for second ipsilateral-breast operations justifies the use of irradiation.

The view that five years of follow-up is insufficient to make our findings acceptable is reminiscent of the same criticism after our earlier reports^{1,2} indicating no benefit from radical mastectomy over simple mastectomy and from modified radical mastectomy over lumpectomy with or without radiation — findings that prevail after more than 15 and 10 years, respectively. Although we cannot predict the outcome beyond five years, we consider the five-year results to be firm and more appropriate for therapeutic decision-making than retrospective anecdotal information, which currently dictates the choice of therapy for localized intraductal carcinoma.

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1. Fisher B, Montague E, Redmond C, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. *Cancer* 1977;39:Suppl:2827-39.
2. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985;312:665-73.

To the Editor: In reporting the results of our study, we stated that survival rates at four years were similar in patients treated with and without radiotherapy after quadrantectomy. It is therefore likely that radiotherapy immediately after surgery has no survival advantage over radiotherapy at the time of a local recurrence. However, we believe that any strategy linked with a high risk of local recurrence, which is a dramatic event for the patient, should be avoided. Moreover, a local recurrence often leads to a mastectomy, thereby frustrating the objective of breast conservation.

For these reasons, we recommend radiotherapy after partial surgery for small breast carcinomas, at least in women less than 55 years of age. However, the rates of local recurrence after quadrantectomy remain lower than 10 to 12 percent in certain subgroups, and if the recurrences are successfully treated with radiotherapy, then immediate postsurgical radiotherapy in these subgroups may be avoided. This hypothesis applies only to breast quadrantectomy, which is not a disfiguring operation as Dr. Swain incorrectly states in her editorial, but involves a wider resection and requires more skill and competence than lump excision. Lumpectomy, on the other hand, if not supplemented by radiotherapy, leads

to local recurrences in some 50 percent of patients, making it appear to be a sort of debulking operation that cannot be justified without radiotherapy.

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VITAMINS AND BREAST CANCER

To the Editor: In their analysis of the effect of vitamin E supplementation on the risk of breast cancer, Hunter et al. (July 22 issue)¹ appear not to have taken into account the cardioprotective effect of vitamin E supplementation found by Stampfer et al. (May 20 issue)² in the same cohort. Vitamin E supplements resulted in a 52 percent decrease in major coronary disease and a 15 percent decrease in overall mortality.² Without information on the age distribution of the cohort, it is not possible to do a complete life-table analysis; however, in the simplest terms, if 15 percent more women taking vitamin E supplements survive, then 15 percent more will incur the risk of breast cancer. Thus, instead of an average 7 percent higher risk of breast cancer among supplement users, perhaps the real, survival-adjusted, risk is 8 percent lower. This lowered risk would be no more statistically significant than the reported higher risk. However, a longer follow-up period, as the cohort members enter the age groups with the highest risk for heart disease and breast cancer, will perhaps clarify the influence of vitamin E on the risk of breast cancer.

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1. Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. *N Engl J Med* 1993;329:234-40.
2. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993;328:1444-9.

The authors reply:

To the Editor: Drs. Ennever and Paskett argue that if vitamin E reduced mortality, then more women who took it would survive to be at risk for breast cancer. This argument could have been relevant if we had presented our data in terms of the lifetime cumulative incidence of breast cancer at various levels of vitamin E intake (as Ennever and Paskett imply in their informal calculation). Our data were calculated as incidence rates over the eight-year follow-up period. Thus, women who may have avoided death from coronary disease by taking vitamin E supplements continued to contribute person-time to the denominator of the incidence rate; this compensates for increased survival. Therefore, no bias was introduced into our interpretation of the relation of vitamin E and breast-cancer incidence because of the protective association between use of vitamin E supplements and coronary disease and overall mortality. Furthermore, death from cardiovascular disease was much less frequent than incident breast cancer in this cohort (the number of cardiovascular deaths was less than 300 in the base-line cohort of 89,494, whereas 1439 incident breast cancers

were documented). The absolute number of cardiovascular deaths prevented by the use of vitamin E supplements was thus relatively small and would have had little impact on the relative risks for vitamin E and breast cancer even if we had used cumulative incidence as a measure of disease frequency.

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WOMEN'S DECISIONS ABOUT ABORTION

To the Editor: As one of the dissenting members of the Human Fetal Tissue Transplantation Research Panel, I believe that Kassirer and Angell (Nov. 26, 1992, issue)¹ too easily dismissed our concern that transplantation therapy using tissue from induced abortion would encourage abortion.

Many women are ambivalent about abortion, and many find the decision difficult to make.^{2,3} About one third change their mind at least once.^{3,4} Women may vacillate because the decision is normally based on more than one factor.^{4,5} For these women, "the pros and cons of the decision [are] somewhat evenly balanced,"⁴ and abortion is only a marginal good. For some women, knowledge that their fetal tissue could save someone's life can only tip the balance toward having the abortion.

Kassirer and Angell make two other critical errors. First, they claim that the National Institutes of Health guidelines would ensure that a woman's decision about abortion would be "totally independent" of her decision about tissue donation. In fact, if fetal-tissue transplantation became successful, it would be common knowledge that fetal tissue could be used to save someone's life. That abortion clinics do not mention this does not prevent women from considering it in their abortion decision.

Second, Kassirer and Angell claim that, even if women knew about the therapeutic use of fetal tissue, they would not be swayed, because they would be considering only "powerful personal factors, not abstract generosity toward anonymous patients with Parkinson's disease." In fact, women considering abortion are motivated not only by self-interest but also by concern for others. In one study more than 20 percent of women had abortions because their husbands or partners wanted them to,⁵ and more than 25 percent of minors were influenced by their parents' wishes.⁵

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1. Kassirer JP, Angell M. The use of fetal tissue in research on Parkinson's disease. *N Engl J Med* 1992;327:1591-2.
2. Kerenyi TD, Glascock EL, Horowitz ML. Reasons for delayed abortion: results of four hundred interviews. *Am J Obstet Gynecol* 1973;117:299-311.
3. Bracken MB. The stability of the decision to seek induced abortion. In: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research on the fetus: appendix. Washington, D.C.: Department of Health, Education, and Welfare, 1975:16-1-16-23. (DHEW publication no. (OS) 76-128.)
4. Bracken MB, Klerman LV, Bracken M. Abortion, adoption, or motherhood: an empirical study of decision-making during pregnancy. *Am J Obstet Gynecol* 1978;130:251-62.
5. Torres A, Forrest JD. Why do women have abortions? *Fam Plann Perspect* 1988;20:169-76.