

Spread to the Nipple and Areola in Carcinoma of the Breast

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In 40 breasts with primary carcinoma, the nipple and areola were cut horizontally in order to investigate the frequency of intraductal and invasive cancer. In 20 of these breasts the nipple and/or areola were found to be involved at a depth of 1 cm (50%; 95% confidence limits: 33.8–66.2%). Eleven neoplasms were purely intraductal, eight intraductal as well as stromal, and only one purely stromal. By means of clinical or physical findings, it was not possible to select the breasts in which the nipple and/or areola were *not* involved. It is concluded that the general use of surgical methods preserving the nipple and areola in treating breast cancer leaves a focus of invasive or intraductal carcinoma in about half the patients. The implications of this are not known.

SEVERAL AUTHORS HAVE recently advocated surgical methods for preserving the nipple and areola in the treatment of breast cancer^{5,9,10,14,16,17,28,29}, viz. subcutaneous mastectomy, restorative mammoplasty and extended local removal of the tumor.

A knowledge of the frequency with which the nipple and areola are involved in breast cancer must obviously be a presupposition for performing these conservative surgical procedures. Among the advocates of preserving the nipple and areola, only one group, Millard et al., has approached this problem, doing so by an unsubstantiated quotation (from the pathologists Boulton and Haukohley) that 90% or more of all breast cancers do not involve the nipple and if they do, this is evident clinically as well as pathologically.¹⁹

In the literature we find three studies elucidating this aspect,^{11,21,26} reporting involvement of the nipple by 8, 11.1, and 12.2% of all primary breast cancers. However, these studies were not satisfactory, as they comprised at most two sagittal sections from each nipple. On the assumption that the reported figures are too low, we performed a prospective study which seemed technically more sufficient, as the nipple and subareolar tissue were cut into horizontal sections.

Method

The study comprised 40 consecutive mastectomy specimens from 40 women, mean age 61.0 years, under-

going operation during the period April 1, 1977 to October 4, 1977. Our Pathology Department serves five hospitals, in all of which, the surgical method is simple mastectomy with removal of the inferior axillary lymph nodes.

A detailed macroscopic study was made of the operative specimens by the same author (R.P.) throughout the study period. In this connection special emphasis was placed on elucidating the objective clinical findings which might influence the assessment of nipple and areola involvement. These include the size of the tumor and its site, the possible presence of nipple retraction, skin retraction, *peau d'orange* and *Paget* changes of the nipple.

Tumor size was taken as the greatest dimension of the cut tumor; its site as compared with the nipple judged by the middle of the scar after tumor biopsy. Using the method described by Haagensen,¹⁸ the tumor site is divided into four quadrants and a central area. The central area is circular and comprises everything within 1 cm from the areolar border.

The specimen was fixed for 24 hours in 10% buffered formalin (pH 7.2) at 4°. A cylindrical block containing the nipple and areola was removed (Fig. 1). This block is 1 cm deep, measured from the surface of the areolar epidermis. It was then fixed for another 24 hours at 4° to facilitate sectioning. The entire nipple/areola was cut into horizontal sections. However, the uppermost section at the nipple was cut vertically in order to detect *Paget* changes, if any. The areola was divided into 12 blocks, each about 3 mm thick. It was possible to relate the individual sections to the quadrants and to the first, second, and third level beneath the epidermal surface by a fixed numbering procedure (Fig. 1). A histological study was performed (an average of 45 paraffin blocks being taken from each breast) including 14 from the nipple/areola.

The same author (J.A.A.) studied and assessed all the histological preparations, recorded whether malignant involvement of the nipple and areola was present,

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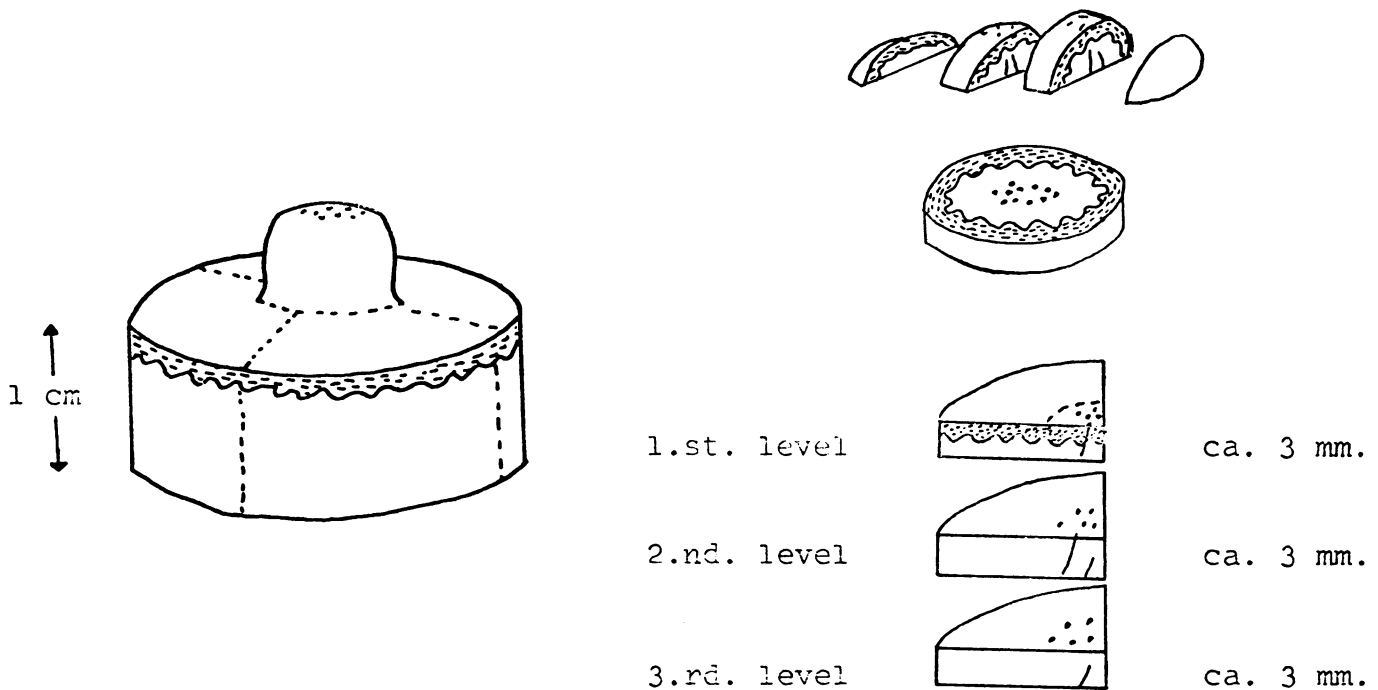


FIG. 1. Methods of cutting the nipple/areola into a 1 cm deep block. Thereafter, the areola is divided into 4 quadrants, and the nipple as well as areola are cut horizontally, as shown on the right.

whether it was intra- or extraductal (invasive), and at which depth beneath skin level such involvement was situated. As already mentioned, the uppermost section of the nipple was particularly intended for evaluating *Paget* changes, if any. These sections were stained, not only with HE, but also with PAS and van Gieson-alcian blue at pH 2.6.⁸

Classification of the tumors was by the principles set up by WHO.²⁵

Results

Among the 40 breasts studied, the nipple and/or subareolar tissue at a depth of 1 cm was found to be involved in 20 (50%). Using "exact" confidence limits, the 95% limits are 33.8% and 66.2% respectively. Of these 20 cases 11 were purely intraductal, eight intraductal as well as stromal, and only one purely stromal. Of the 11 purely intraductal cases five showed (Fig. 2) involvement of only one duct, five of two neighboring ducts, and in only one more than two ducts. In ten instances (25%) only the nipple was involved. In 15 specimens the nipple and/or the first level beneath the epidermis (about 3 mm) were involved. The nipple and/or the first and second levels were involved in 19 cases. In other words, 19 of the 40 breasts showed invasive or intraductal cancer of the nipple and/or a level of the areola 6–7 mm deep.

The intraductal growth in 10 specimens was of the ordinary ductal type (Figs. 3A and B and 4) whereas in nine cases it was lobular (Figs. 5A and B).² There was no case of lobular carcinoma *in situ*.¹

Pathological and clinical data for the groups with and without involvement of the nipple and areola were compared. The comparison of tumor size and tumor site are shown in Tables 1 and 2. The type of tumor was distributed on 30 infiltrating ductogenic carcinomas, six infiltrating lobular carcinomas, one infiltrating lobular and ductogenic carcinoma, one medullary carcinoma,

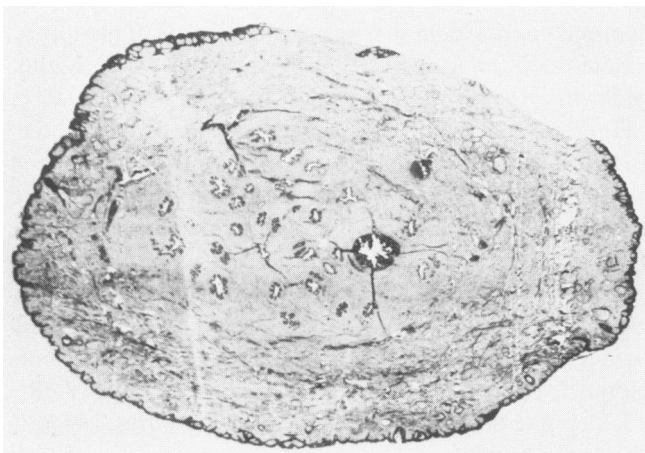
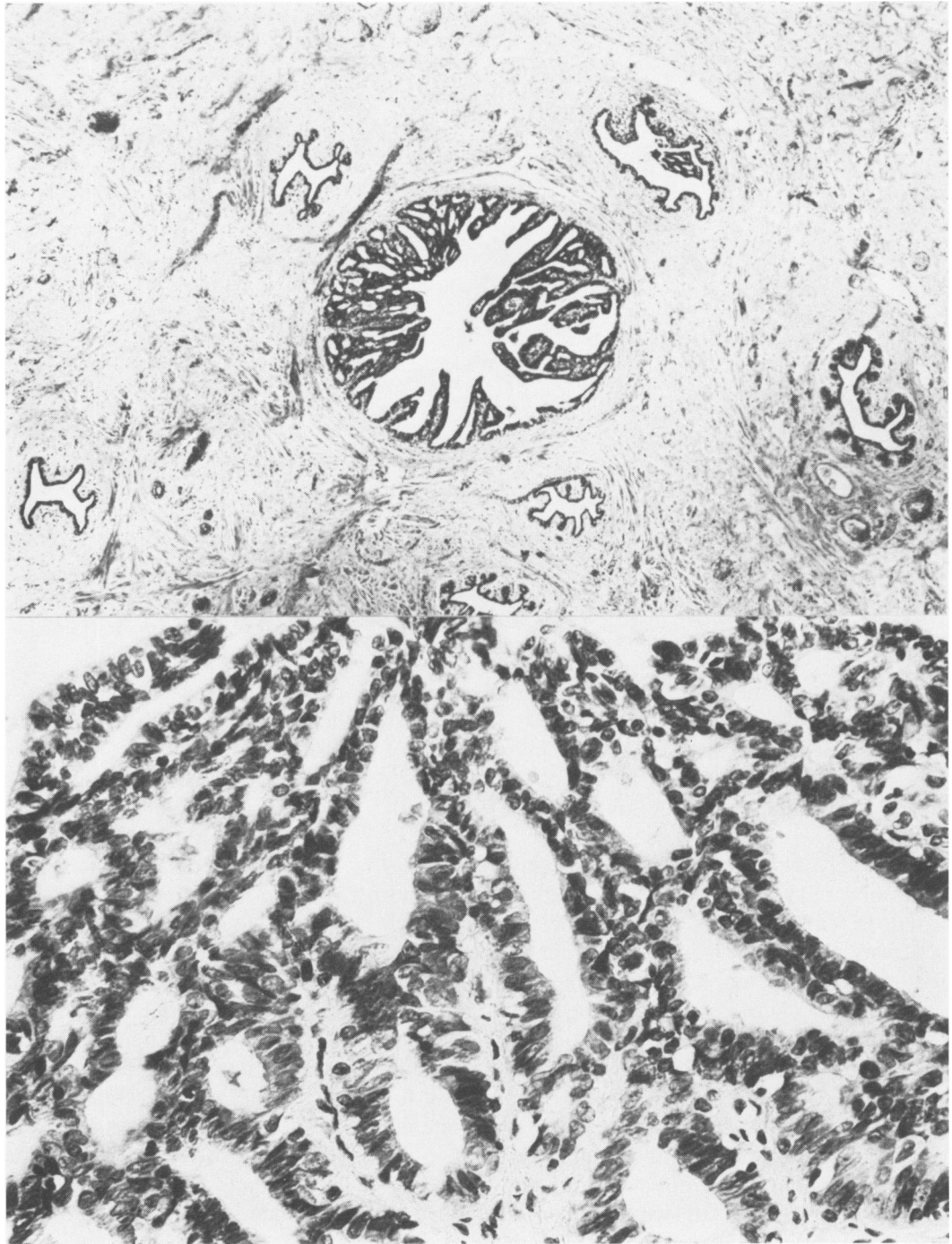


FIG. 2. Cross section of a nipple in which only one duct houses carcinomatous changes. This photomicrograph illustrates why sagittal sections may entail underdiagnosing of malignant foci of the nipple. Hematoxylin-eosin $\times 6$.



FIGS. 3a and b. (a top). Intraductal carcinoma of an ordinary ductal type, papilliferous growth. The lesion is surrounded by normal lactiferous ducts. Horizontal section of the nipple. Hematoxylin-eosin $\times 33$. (b, bottom) Same lesion as Figure 3a. Hematoxylin-eosin $\times 330$.

one tubular carcinoma, and one cystosarcoma phylloides with a malignant ductogenic carcinoma.

It has been claimed that spread to the nipple is more common when: 1) the tumor is central; 2) the tumor is 3 cm or larger; and 3) the nipple is clinically involved. Exclusion from the material of all breasts fulfilling one or more of the above-mentioned criteria reduces it to 18 specimens. Among them microscopic involvement

of the nipple and/or the uppermost 6–7 mm of the areola was found in seven or 38.8%.

Discussion

The 50% involvement of the nipple and/or areola in breast cancer demonstrated by our study is greater than previous findings. Our material is not extensive, but even when using the lowest 95% limit according to

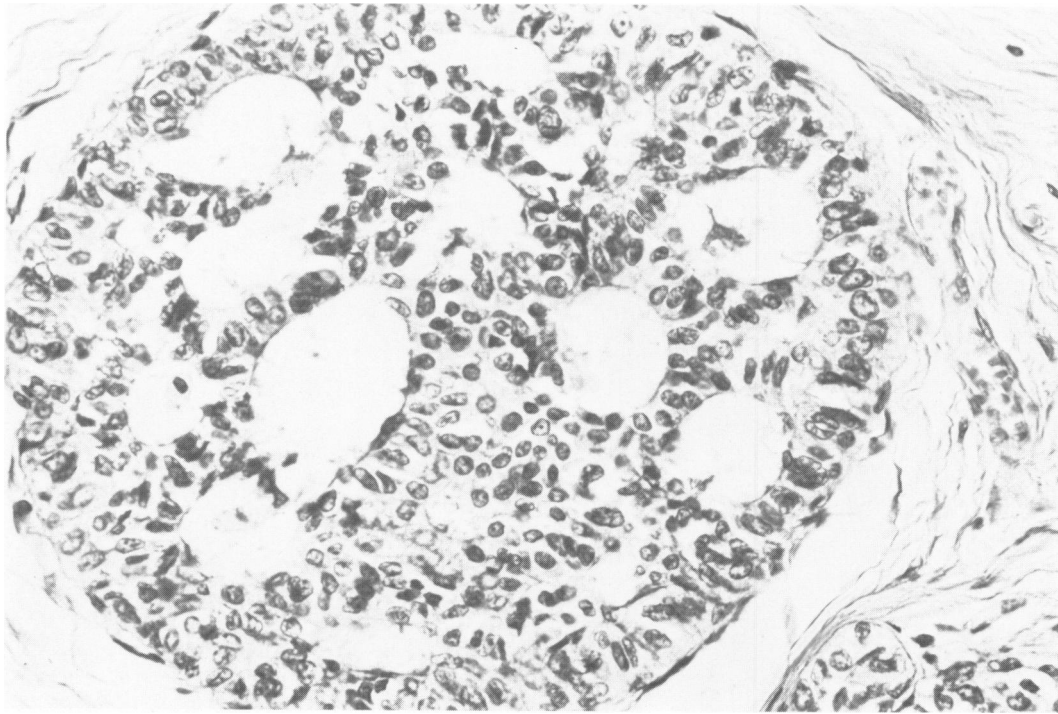


FIG. 4. Intraductal carcinoma of ordinary ductal type, cribriform growth. Horizontal section of the areola. Hematoxylin-eosin $\times 330$.

current statistical methods, this value is considerably higher than those reported by Smith et al.,²⁶ Fisher et al.,¹¹ and Parry et al.²¹ who found involvement of the nipple in 12.2, 11.1, and 8% respectively of primary breast cancers, while our lowest 95% limit was 33.8%.

Presumably there are several reasons why our findings are different: 1) Our studies are based upon a block 1 cm deep. Only Smith et al. state precisely how much tissue was examined, *viz.* a block 0.5 cm deep. Involvement merely in the nipple was found in 25%, and when including the uppermost 3 mm of the areola this value increases to 37.5%. 2) Our sections are horizontal and therefore include all lactiferous ducts. All other studies have been on saggital sections. 3) All the tissue of the nipple and areola was embedded. In the event of even slight epithelial atypia, serial sections were cut.

Previous authors have not stated the number of sections or else they have cut two sections—saggital in all cases—from each nipple.²⁶ Such a diagnostic method

must entail under-diagnosing, considering that intraductal cancer involvement often affects only one lactiferous duct (Fig. 2).

Millard et al. claim that involvement of the nipple is clinically evident.¹⁹ Like Smith et al.,²⁶ we do not agree. True, it may be clinically evident in some cases, but even when the nipple is clinically uninvolved there is often a microscopic focus, in our study in 38.8%. Thus, it does not seem possible, even with strict criteria, to preserve the nipple and areola without leaving a malignant or potentially malignant focus in about one-third of these selected patients.

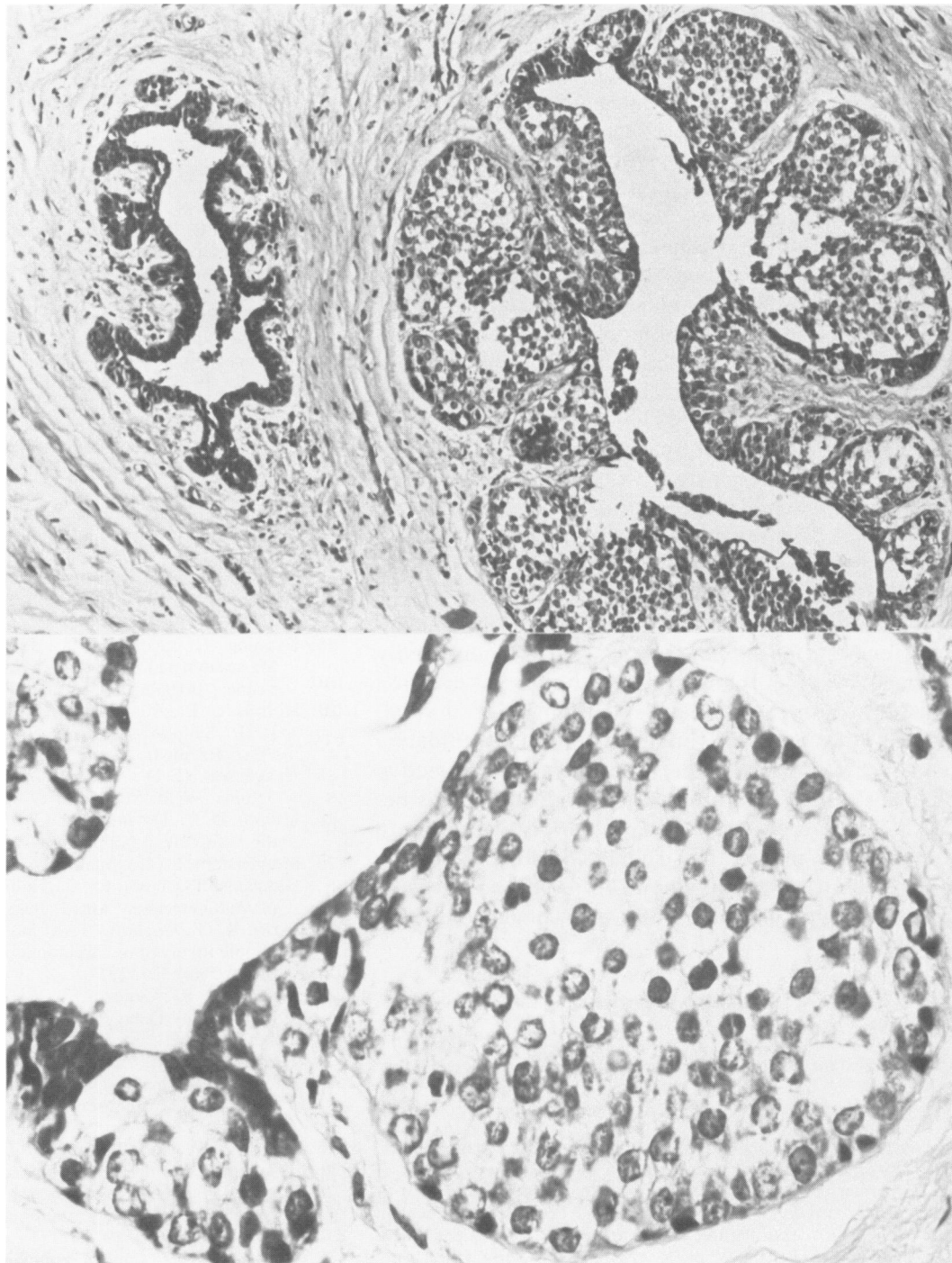
There have been many descriptions of the technique of subcutaneous mastectomy.^{3,6,12,13,24,27} Only one of these publications states in detail how much of the areola was left, *viz.* Angelchik and Wohl who felt it was necessary to leave a rim of subcutis 4–5 mm thick.³ This means that about 7–8 mm of the areola is left, calculated from the epidermal surface. This easily corresponds to the first and second level in our study.

TABLE 1. Tumors Distributed by Size and by Carcinomatous Involvement and Noninvolvement of the Nipple and/or Areola

Size of Tumor, cm	Involvement of Nipple and/or Areola	Noninvolvement of Nipple and/or Areola	Total
<2	13	10	23
2–4	5	10	15
>4	2	0	2
Total	20	20	40

TABLE 2. Tumors Distributed by Central and Noncentral Site in Cases with and without Carcinomatous Involvement of the Nipple and/or Areola

Site	With Involvement of Nipple and/or Areola	Without Involvement of Nipple and/or Areola	Total
Central	6	1	7
Noncentral	14	19	33
Total	20	20	40



FIGS. 5a and b. (a, top). Intraductal carcinoma of lobular type. Normal lactiferous duct to the left. Horizontal section of the areola. Hematoxylin-eosin $\times 132$. (b, bottom) Same lesion as Figure 5a. Hematoxylin-eosin $\times 528$.

Several authors have used the nipple/areola as a free graft. Only a few have taken a horizontal section of the subareolar tissue for histological examination.¹⁴ Such a microscopic examination must be a minimum demand, although it does not by any means guarantee against an intraductal focus at a higher level (13 cases in our study) while presumably it will most often catch stromal invasion.

According to Horton et al., it is possible to isolate lactiferous ducts in a small bundle at the base of the

nipple.¹⁷ While working on our sectioning technique we found that this is correct. It seems possible, therefore, to isolate the ducts to a small bundle and cut this bundle as high up as possible, thereby minimizing the problem under consideration.

The pathogenesis of nipple and areolar involvement differs. In principle, three mechanisms are possible: 1) Direct extension of the primary tumor, intraductal or stromal. 2) Dissemination by way of the ducts. 3) Malignant changes independent of the primary tumor

and representing the tendency of breast cancer to be a multicentric disease.

All three mechanisms may occur, but it is our impression that the majority of the intraductal growth represent multicentricity. On horizontal sectioning we often came across one or more uninvolved levels between the tumor and the nipple affection.

Several workers have discussed the tendency of breast cancer to be multicentric.^{4,15,20,22,23} The most detailed studies have been carried out by Qualheim and Gall²³ and by Gallagher and Martin.¹⁵ Both are based upon whole organ-sectioning of breasts containing cancer. Qualheim and Gall found that 54% contain more than one nidus of cancer, whereas according to Gallagher and Martin more than 75% of breasts with invasive carcinoma also include areas with intraductal carcinoma or intraductal hyperplasia with epithelial atypia. In a study on intraductal "noninfiltrating" breast cancers, Brown et al. found that 33% were multicentric and that 30% affected the subareolar lactiferous ducts.⁷ This result is fairly close to ours.

What are the implications of possibly leaving a malignant focus in the nipple and/or areola? Undoubtedly most authors feel that a focus with stromal invasion constitutes a threat to the patient's chances of survival. On the other hand, the implications of an intraductal focus are not clear. There have been no prospective studies showing how often intraductal carcinomas become invasive and how long a period elapses until they possibly invade the stroma. The current opinion is that all intraductal carcinomas will become invasive sooner or later, providing that the woman lives long enough.

Acknowledgments

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References

1. Andersen, J. A.: Lobular Carcinoma In Situ of the Breast. *Cancer*, 39(6):2597, 1977.
2. Andersen, J. A.: Lobular Carcinoma In Situ of the Breast with Ductal Involvement: Frequency and Possible Influence on Prognosis. *Acta Pathol. Microbiol. Scand.*, (A) 82:655, 1974.
3. Angelchik, J. P. and Whol, R. H.: Subcutaneous Mastectomy with Prosthetic Reconstruction. *Ariz. Med.*, 32(10):794, 1975.
4. Ashikari, R., Huvos, A. G. and Snyder, R. E.: Prospective Study of Noninfiltrating Carcinoma of the Breast. *Cancer*, 77(39):435, 1977.
5. Atkins, H., Hayward, J. L., Klugman, D. J. and Wayte, A. B.: Treatment of Early Breast Cancer a Report After Ten Years of a Clinical Trial. *Br. Med. J.*, 2:423, 1972.
6. Berens, J. J. and Stapley, L. A.: Breast Tumors Treated by Mastectomy (Subcutaneous) with Mammary Replacement. *Ariz. Med.*, 26:651, 1969.
7. Brown, P. W., Silverman, I., Owens, E., et al.: Intraductal "Noninfiltrating" Carcinoma of the Breast. *Arch. Surg.*, 111:1063, 1976.
8. Eskelund, V.: Mucin Staining with Alcian Blue. *Acta Pathol. Microbiol. Scand.*, 40:107, 1957.
9. Esselstyn, C. B.: A Technique for Partial Mastectomy. *Surg. Clin. North. Am.*, 55:1065, 1975.
10. Esselstyn, C. B., Hermann, R. E., Crile, G., et al.: The Results of Selective Conservative Treatment in Breast Cancer. *Bull. Soc. Int. Chir.*, 34(6):513, 1975.
11. Fisher, E. R., Remigio, M., Gregorio, M.D., et al.: The Pathology of Breast Cancer. A syllabus derived from finding of the National Surgical Adjuvant Breast Project, (Protocol no. 4). *Cancer*, 36:1, 1975.
12. Freeman, B. S.: Subcutaneous Mastectomy for Benign Breast Lesions with Immediate or Delayed Prosthetic Replacement. *Plast. Reconstr. Surg.*, 30:503, 1962.
13. Freeman, B. S.: Technique of Subcutaneous Mastectomy with Replacement; Immediate and Delayed. *Br. J. Plast. Surg.*, 22:161, 1969.
14. Freeman, B. S.: Subcutaneous Mastectomy for Central Tumors of the Breast, with Immediate Reconstruction. *Plast. Reconstr. Surg.*, 51:263, 1973.
15. Gallagher, H. S. and Martin, J. E.: The Study of Mammary Carcinoma by Mammography and Whole Organ Sectioning. *Cancer*, 23(4):855, 1969.
16. Gynning, I., Jacobsson, S., Linell, F., et al: Subcutaneous Mastectomy in 80 Patients with Breast Tumors. *Acta Chir. Scand.*, 141:488, 1975.
17. Horton, C. E., Adamson, J. E., Mladick, R. A. and Carraway, J. H.: Simple Mastectomy with Immediate Reconstruction. *Plast. Reconstr. Surg.*, 53(1):42, 1974.
18. Haagensen, C. D.: Diseases of the Breast. Second ed. Philadelphia, W. B. Saunders, 1971. 380-382.
19. Millard, D. R., Devine, J. and Warren, W. D.: A Plea for Saving the Uninvolved Nipple. *Am. J. Surg.*, 122:763, 1977.
20. Morgenstern, L., Kaufman, P. A. and Friedman, N. B.: The Case Against Tylectomi for Carcinoma of the Breast. The Factor of Multicentricity. *Am. J. Surg.*, 130:251, 1975.
21. Parry, R. G., Cochran, T. A. and Wolfort, F. G.: When is the Nipple involved in carcinoma of the breast? *Plast. Reconstr. Surg.*, 59(4):535, 1977.
22. Pennisi, V. R., Capozzi, A. and Perez, F. M.: Subcutaneous Mastectomy Data. *Plast. Reconstr. Surg.* 59(1):53, 1977.
23. Qualheim, R. E. and Gall, E. A.: Breast Cancer with Multiple Sites of Origin. *Cancer*, 10:460, 1957.
24. Rubin, L. R.: The Cushioned Augmentation Repair After a Subcutaneous Mastectomy. *Plast. Reconstr. Surg.*, 57(1):23, 1976.
25. Scarff, R. W. and Torloni, H.: Histological Typing of Breast Tumors. World Health Organization, Geneva 1968.
26. Smith, J., Payne, W. S. and Carney, J. A.: Involvement of the Nipple and Areola in Carcinoma of the Breast. *Surg. Gynecol. Obstet.*, 143:546, 1976.
27. Theogaraj, S. D.: Cancer Prophylaxis by Subcutaneous Mastectomy. *VA. Med. Mon.*, 100:545, 1973.
28. Watts, G. T.: Reconstruction of the Breast as a Primary and Secondary Procedure Following Mastectomy for Carcinoma. *Br. J. Surg.*, 63:823, 1976.
29. Watts, G. T.: Restorative Prosthetic Mammoplasty in Mastectomy for Carcinoma and Benign Lesions. *Clin. Plast. Surg.*, 3:177, 1976.