

Terminal Duct Lobular Units are Scarce in the Nipple: Implications for Prophylactic Nipple-Sparing Mastectomy

Terminal Duct Lobular Units in the Nipple

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Background: The use of nipple-sparing mastectomy (NSM) for both breast cancer treatment and risk reduction is increasing. There is no randomized data comparing nipple-sparing mastectomy with standard mastectomy techniques. There is evidence to suggest that ductal and lobular breast cancer arises in the terminal duct/lobular unit (TDLU). This study was undertaken to determine whether TDLUs exist in the nipple and if so, to what extent.

Methods: At the time of mastectomy the nipple papilla was excised and submitted for separate pathological examination. The presence or absence of TDLUs was noted.

Results: Thirty-two nipples were studied in 22 patients. There were no TDLUs in 29 specimens. Three of 32 nipple specimens were found to contain TDLUs. The three nipples contain one, two, and three TDLUs respectively. All TDLUs were found at the base of the nipple, with none located near the tip.

Conclusions: The infrequent occurrence of TDLUs in the nipple papilla supports the use of NSM for risk reduction surgery, including for those women with BRCA1/2 mutations.

Key Words: Prophylactic mastectomy—BRCA1/2—Breast anatomy—Breast cancer.

As breast cancer tumor size has decreased during recent decades, the extent of surgery for breast cancer has shown similar reductions. Radical mastectomy with routine skin grafting evolved from radical mastectomy with primary skin closure, into modified radical mastectomy, then into lumpectomy. However, mastectomy is still being carried out for a variety of indications including extensive cancer and prophylactic mastectomy for risk reduction, as well as patient choice. As breast reconstruction, both with synthetic implants and autologous tissue, entered the mainstream, it was obvious that retention of the

breast skin envelope resulted in a superior cosmetic result. Multiple nonrandomized series of skin-sparing mastectomies (SSMs) have now been published suggesting similar recurrence rates to those of mastectomy done using the more classical mastectomy incisions.^{1–4} The evolution continues, with the appearance of several relatively small series of nipple-sparing mastectomies (NSMs) undertaken both for cancer and risk reduction.^{5–8}

The sequencing of the BRCA1 and BRCA2 genes has allowed women, in many instances, to obtain an accurate estimation of breast cancer risk. Many women who test positive for a deleterious mutation elect to undergo prophylactic mastectomy.^{9–11} Whether nipple-sparing mastectomy should be utilized in these instances is unknown. Without published randomized trial data, surgeons will depend on surrogate information to make decisions as to

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whether NSM is oncologically sound. Germane to this subject is the anatomic origin of breast cancer and to what extent this anatomy exists in the nipple. This study was designed in an attempt to answer these questions.

METHODS

Following mastectomy, the nipple was grasped with a straight-jawed non-crushing clamp and transected using a scalpel or straight scissors at the junction of the nipple papilla and the areola (Fig. 1).

The nipples were serially sectioned vertically, using 2 mm thickness, and the sections were entirely submitted for routine haematoxylin and eosin (H and E) microscopic examination for the presence or absence of terminal duct lobular units (TDLUs).

RESULTS

Nipple anatomy was studied in 22 patients. Ten patients had bilateral procedures, giving a total of 32 nipple specimens. The indications for surgery can be seen in Table 1. Twenty-two mastectomies were undertaken for prophylaxis, four for invasive ductal carcinoma, four for ductal carcinoma in situ, and one for invasive lobular carcinoma. Three patients undergoing four mastectomies tested positive for a BRCA1/2 gene mutation. Patient ages ranged from 37 to 76 with a mean age of 52.5 years.

Sections of nipples show skin and abundant interlacing fascicles of smooth muscle fibers. The nipple skin contains sebaceous glands and apocrine glands. The dilated lactiferous sinuses and branching lactiferous ducts are seen. Three of 32 nipple specimens (9%) were found to contain TDLUs. The three nipples contained one, two, and three TDLUs respectively. No TDLUs were identified in the remaining 29 specimens. All TDLUs were located at the base of nipples. No evidence of atypical ductal hyperplasia, ductal carcinoma in situ, or invasive ductal carcinoma was identified in any of the 32 nipple specimens.

DISCUSSION

Occult nipple involvement in underlying cancer has been described. Anatomic and pathologic features increasing the risk of nipple involvement have also been noted.^{12,13} Guidelines, however, do not exist when considering NSM in the risk reduction or pro-

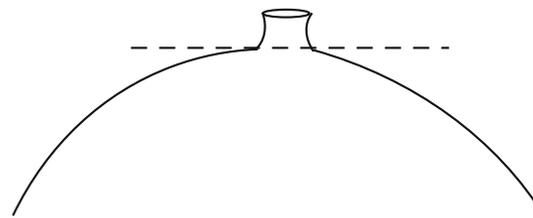


FIG. 1. The nipple is transected at the base of the nipple papilla.

TABLE 1 Indications for surgery

Indications for surgery	Number (%)
Prophylactic	22 (69)
Invasive ductal carcinoma	4 (12)
Invasive lobular carcinoma	1 (3)
Ductal carcinoma in situ	5 (16)
Total	32

phylactic setting. It is in this setting that knowledge of the anatomic origin of breast cancer may be helpful in determining the risk of subsequent new breast cancers. Much of the work on the anatomic origin of breast cancer was carried out by Wellings, Jensen, and associates.^{14,15} Utilizing whole-mount methodology, and subgross microscopic examination, they evaluated 196 breasts, 119 of which were suitable of quantitative morphologic study. They concluded that “the basic reacting unit in practically all dysplastic, metaplastic, hyperplastic, anaplastic and neoplastic lesions of the human breast is the terminal ductal-lobular unit.” The only exceptions they cite are intraductal papillomas and rarely occurring epithelial hyperplasia arising in larger ducts. In 1959 Parks also concluded that breast cancer arises in the TDLUs.¹⁶ Although the existing evidence is not entirely conclusive, it seems reasonable to conclude that both ductal and lobular carcinoma share a common origin in the TDLU.

Are TDLUs found in the nipple? Clearly, the answer to this question is important when considering the use of NSM performed for risk reduction. In a very detailed histologic study of the nipple by Montagna there is an extensive discussion of the lactiferous ducts and sebaceous gland structures in the nipple with no mention of TDLU.¹⁷ Similarly, in histological studies by Going and Moffat,¹⁸ Love and Barsky,¹⁹ and Taneri et al.²⁰ focus almost exclusively on the anatomy of the lactiferous system and the number of ducts emptying onto the nipple. Again there is no mention of TDLUs in the nipple. Only one study, by Rosen and Tench, addressed the presence of TDLU in the nipple.²¹ They found that TDLUs existed in only 17 of 101 cases studied. In five cases

where no TDLUs were found, the nipples were sectioned more extensively and reexamined. No TDLUs were found in these five cases leading them to conclude that “lobules are absent from some nipples.” Most importantly, Rosen and Tench defined the nipple in histological terms as being represented by the presence of lactiferous ducts. In our study, we defined the nipple in surgical terms; being the actual papilla that is elevated above the level of the surrounding areola. This distinction is of more than just passing interest. In considering NSM, the surgical anatomy is more meaningful than the histologic anatomy. It is the elevated portion of the nipple, the papilla, which is spared, with tissue deep to the papilla being removed. Moreover, it seems clear from the work of Going and Moffat that the lactiferous ducts extend below the nipple papilla (Fig. 2). In our study we found that 91% (29 of 32) of nipples studied contained no TDLUs. In the three cases where TDLUs were identified, their distribution was sparse.

Without TDLUs, the nipple would be an unusual site to develop a primary cancer. A review of the pathologic studies from the National surgical adjuvant breast project (NSABP) B-04²² and B-06,²³ as well as a search of the literature, failed to yield a single mention of primary breast cancers originating in the nipple. Even in patients with BRCA1/2 mutations, it is likely that NSM might still yield results comparable to the 90–95% risk reduction that is currently reported.^{24–26}

The distinction between our own work and that of Rosen and Tench is also important when considering whether surgeons should attempt to remove tissue from within the nipple papilla. How thoroughly ductal tissue is removed from the nipple using current techniques is not known. The earliest mention of the term “coring” appears to be by Randall et al. in 1979.²⁷ They referred to the process as “apple coring” and described a method by which the entire tip of the nipple is removed with nipple contents, thereby assuring removal of all ducts. Our current approach, as well as that of others,⁸ is much less radical and does not include removal of the tip of the nipple. It would seem reasonable to conclude that the low prevalence of TDLUs in the nipple papilla might obviate the need to radically remove nipple contents. In this current study we also observed that when TDLUs were present, they were universally located near the base of the nipple, with no TDLUs found at the tip. Therefore we would also suggest that removal of tissue from the nipple be limited to the region near its base.

What is the risk of Paget’s disease of the nipple in patients undergoing prophylactic NSM? A literature

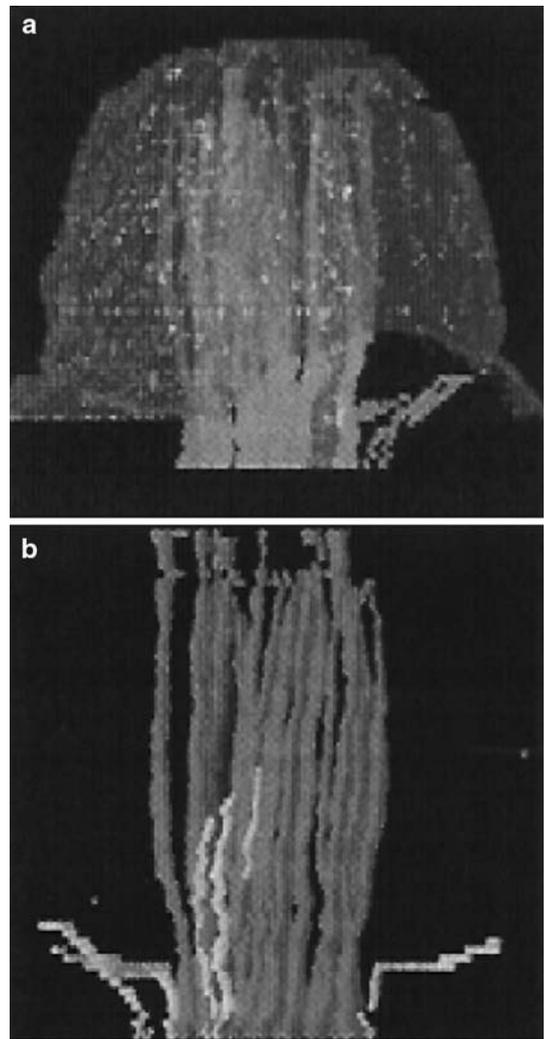


FIG. 2. Digital model of nipple duct anatomy. Note the extension of the lactiferous ducts below the base of the nipple. From Going JJ, Moffat DF.¹⁶ Reproduced with permission by John Wiley & Sons Ltd on behalf of PathSoc.

search fails to reveal any studies examining this specific problem. The great preponderance of cases are associated with underlying breast carcinoma. In one of the largest series of Paget’s disease, Ashikara et al. studied 214 cases and found that only 2.8% of cases not to have an associated breast cancer.²⁸ In a study from Guy’s Hospital, 35 consecutive patients undergoing mastectomy for Paget’s disease were found to have either invasive ductal carcinoma or ductal carcinoma in situ.²⁹ Further supporting the connection between Paget’s and underlying breast cancers are studies using immunohistochemistry to characterize and compare the nipple disease and the underlying cancer.³⁰ Though one must consider the possibility of

pagetoid spread of cancer to the nipple when performing NSM for cancer, it seems unlikely that Paget's disease originating in the nipple would significantly affect risk of future breast cancer.

One might consider cancers arising in papillomas as an exception to the origin of cancers in the TDLU. Two types of papillomas have been described. One, termed "peripheral," arises from the TDLU. The other type is "central" and arises in the large central ducts.³¹⁻³³ Page et al. reported a relative risk of developing cancer in a papilloma of 7.5 when atypia is present.³¹ Since most papillomas are asymptomatic, the actual risk of cancerous transformation is difficult to ascertain. The risk of malignant transformation of a papillary lesion has been shown to be higher in peripheral lesions compared to central. In the pathological review of cases from NSABP B-04 (Radical mastectomy versus simple mastectomy versus simple mastectomy plus radiation), Fisher et al. noted that only 0.4% of cases had pure papillary histology.²² Again, without reports of primary breast cancer arising in the nipple the actual incidence is unknown. One might reason, however, that this risk is exceptionally low.

CONCLUSIONS

It is likely that the number of mastectomies performed for risk reduction is rising. The advent of genetic testing, the good results demonstrated in risk reduction studies and the improvements in breast reconstruction techniques are likely to be responsible. It is also likely that most breast cancers arise from the TDLU. The infrequent occurrence of TDLUs in the nipple papilla would therefore make the development of a primary cancer in this area unusual. Although this study does lend support to the use of NSM for risk reduction surgery, including in those women with BRCA1/2 mutations, only prospective studies can accurately define its indications and safety.

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