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PRECLINICAL STUDY

Breast duct anatomy in the human nipple: three-dimensional patterns and clinical implications

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Abstract

Background The anatomy of the nipple has become clinically relevant. Diagnostic techniques access the breast through nipple ducts and surgeons offer nipple-sparing mastectomy. There is variation in the number of ducts reported and little is known about the spatial location of ducts, their size, and their relationship to orifices on the surface.

Methods Nipple specimens were taken from 129 consecutive mastectomies. Each was sectioned coronally into 3 mm blocks and one section was prepared from each block. The number of ducts and cross-sectional areas of nipple and duct 'bundle' were recorded. Three nipples were sectioned at 50 μm intervals and digitally reconstructed in three dimensions.

Results The median number of ducts was 23 (interquartile range 19–28). Reconstructions and summary data from 25 nipples show a central duct bundle narrowing to form a 'waist' as the ducts enter breast parenchyma. A three-dimensional reconstruction focusing on one nipple tip demonstrated 29 ducts arising from 15 orifices. Beneath the skin, most ducts are very narrow, gradually becoming larger deeper within the nipple.

Conclusions This work demonstrates that many ducts share a few common openings onto the surface of the nipple, explaining the observed discrepancy between number of ducts and of orifices. Neither duct diameter nor position predicts whether a duct system will terminate close to the nipple or pass deeper into the breast. These new insights into nipple anatomy will be of use in considering the reliability of a ductal approach to diagnosis and in planning nipple-sparing mastectomy.

Keywords Anatomy · Breast · Cancer · Ductal lavage · Ductoscopy · Ducts · Mastectomy · Nipple-sparing · Reconstruction

Introduction

There are compelling reasons to understand the anatomy of the nipple, yet there are still several areas of controversy. Uncertainty about the number of ducts in the nipple dates back to 1840 and Sir Astley Cooper's book 'On the Anatomy of the Breast' in which he states: "The greatest number of lactiferous tubes I have been able to inject, has been twelve, and more frequently from seven to ten. But the greatest number of orifices I have been able to reckon has been twenty-two; however, some of these might have been follicles only, and not open ducts". Cooper [1]

More recent investigations have shown 17 and 27 ducts [2, 3] and 5–9 orifices [4], raising questions about the anatomical relationship between ducts and orifices. These have important implications for intraductal approaches to diagnosis such as ductography, ductoscopy and ductal lavage, which rely on the nipple for access

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to the duct systems [5–8]. Duct cannulation is based upon the premise that each duct has a separate orifice on the nipple or that the ducts that can be cannulated branch to form the majority of the glandular tissue in the breast. All in vivo studies have counted fewer ducts than histopathological studies and it is essential to understand the reasons for this and the consequent limitations these may impose on ductal diagnostic techniques.

Another reason to investigate nipple anatomy stems from developments in surgical techniques. Patients who require or choose mastectomy have reconstructive options that are continually evolving. Evidence that skin-sparing mastectomy is an oncologically safe procedure in selected patients [9–11] has led to increasing interest in the possibility of conserving the nipple [12–15]. The advent of genetic testing has helped to identify women at high risk of developing breast cancer. Many of these women choose prophylactic mastectomy and, since they are young and undergoing ablative surgery in the absence of malignancy, they often seek the best cosmetic option available. The number of ducts, their position within the nipple and their relationship to the vasculature and to the overall nipple shape are very relevant to surgical technique as these will determine the optimal method of excision of ductal tissue when performing a nipple-sparing mastectomy. To date, however, nipple-sparing mastectomy has been carried out based on limited information about the microscopic ductal and vascular anatomy of the nipple.

Finally, studying the anatomy of the nipple may help to optimize techniques that can then be applied to understanding ductal anatomy elsewhere in the breast [16].

This study aims to document the number of ducts within the nipple and relate these to the number of orifices on the nipple surface. Data obtained from three-dimensional reconstructions of nipple specimens provide new insights into the arrangement of ducts within the nipple. These will be of relevance to ductal approaches to diagnosis and in planning nipple-sparing mastectomy.

Materials and methods

Patients and specimens

Institutional Review Board approval was obtained to study discarded tissue from mastectomy specimens. Consecutive non-nipple-sparing mastectomy specimens were collected between January 1st and June 30th 2006. Male specimens and those in which the nipple was grossly involved by tumor were excluded. In addition, if the nipple was inverted or had been sectioned in the sagittal plane for pathology purposes, the case was excluded. Diameter and height of both the whole breast and the nipple were recorded. Breast volume was approximated to a cylinder and calculated. Nipple specimens were cut to contain the nipple and sub-areolar tissue and to measure approximately $2 \times 2 \times 2$ cm when fresh. These were fixed in formalin, measured, and cut into blocks approximately 3 mm thick, perpendicular to the axis of the nipple (in the coronal plane). One hematoxylin and eosin (H&E) section was prepared from each block. These ‘block sections’ were reviewed by a pathologist (EFB) to confirm that they did not contain information that would affect staging or clinical management decisions.

Images and duct number

An Epson Perfection 4990 Photo flatbed scanner was used to scan microscope sections at a resolution of 9600 pixels per inch. Images were saved in ‘tif’ format at maximum detail. Using Reconstruct software [17], these images were calibrated using an image of a ruler scanned in the same manner.

Ducts were counted on one ‘block section’ from the nipple papilla of each specimen. The best quality section with visible circumferential skin was selected. The mean and median number of ducts were calculated. The range and the interquartile range were also noted. Correlations between number of ducts and age of patient, breast volume and nipple diameter were tested.

Three-dimensional reconstructions

After examining block sections of all nipple specimens, two specimens were selected for serial sectioning. These represented the best examples of anatomical patterns that could be observed in all specimens. Serial 5 μm sections were taken and every 10th section was mounted and stained with H&E. Scanned images of the step-sectioned nipple specimens were uploaded in order and aligned by eye and using software alignment capabilities. Structures were traced in the two-dimensional scanned images. The ducts were easily visible in most sections though, for some, corroboration of the scanned image with microscopic examination of the original section was required. The 50 μm step between sections was small enough to allow ducts to be followed from section to section parallel to the axis of the nipple. Reconstruct software was used to create a three-dimensional image.

Quantification of the duct bundle

Each 'block section' image from 25 consecutive specimens was uploaded into the Reconstruct program and the outline of the nipple and duct bundle was drawn by hand. An example is shown in Fig. 1. The duct bundle was not drawn more than 1 cm beneath the areola since this would represent size of the cut specimen rather than the true extent of duct spreading. The software was used to calculate cross-sectional areas. These areas were approximated to circles and the radius was calculated for ease of comprehension. The depth to which the block section corresponds was calculated relative to the skin (positive within the papilla, negative beneath the areola). Since the overall morphology of nipples varies, the 25 nipples were divided into two groups by nipple height (gross measurement of greater than or less than 0.5 cm). Within each group, radius values were ranked by corresponding depth and grouped in tens. The means of each group of 10 radii were plotted against means of the corresponding 10 depths to produce graphical representations that resemble sagittal sections through two schematic nipples.

Duct termination within the nipple specimen

Most ducts could be traced throughout their length from the skin to their termination within the nipple specimen or at the cut edge. Sections at two levels of a reconstructed nipple were color-coded according to their termination in an attempt to identify patterns of size or position that might be associated with early termination.

Duct diameter

An important factor in determining ability to cannulate a duct is its diameter at the tip of the nipple. Most ducts are crenellated in cross-section suggesting that, when cannulated, the diameter could expand significantly. Trace length is recorded in the Reconstruct program and duct diameter was calculated from the length of the traced duct edge. By approximating the trace to a circle, duct diameter equals trace length divided by pi. The average duct diameter in sections at 0.5 mm intervals of depth was calculated for the three reconstructed nipples and an overall average diameter by depth was also plotted.

Relationship between ducts and orifices

The first two reconstructions did not provide sufficient detail to be certain of the relationship of ducts to orifices. In order to understand the arrangement whereby many ducts appear to connect to fewer orifices, the uppermost block (2.9 mm) of a third nipple was embedded upside-down. This eliminated the problem of tissue loss at the tip during preparation of the block. Step-sectioning began at the deep margin and proceeded at 50 μm intervals from proximal to distal through to the very tip to allow closer scrutiny of the ducts and orifices at the tip. Staining and reconstruction were performed as

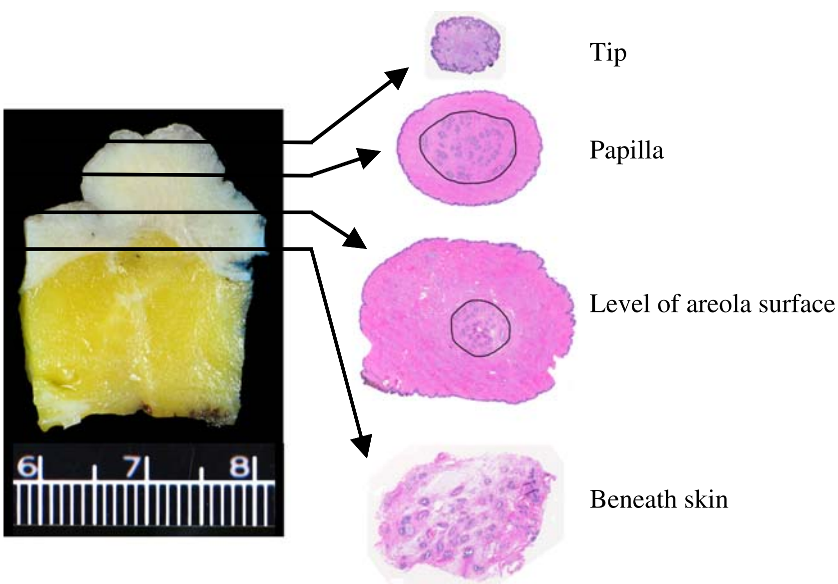

Fig 1 Photograph of a sagittal section through a nipple with coronal block sections from a different nipple. The sagittal section illustrates the approximate location of tissue sections. Block sections from a coronally sectioned nipple show differences in morphology with depth. The duct bundle is outlined in black. The beginnings of the waist can be seen at level of the areola

described above. Microscopic corroboration was essential for this step.

Data analysis

Reconstruct software [17] was used for all measurements of length and area in the reconstructed nipples. Calculations of medians, interquartile ranges and means, assessment of correlations and production of graphs were performed using Microsoft Excel.

Results

One hundred twenty nine nipple specimens were collected. The mean age of the patients was 52 years (range 35–82 years). Breast diameters and height were recorded in 128 specimens and were used to calculate volume. Nipple diameter and height were recorded in 125 and 115 specimens respectively. The number of ducts was counted for all 129 specimens. The median number of ducts was 23 with an interquartile range of 19–28. The mean number was 24 and the range was 5–50. These data are summarized in table 1. There was no correlation between duct number and age, breast volume or nipple diameter (R^2 = 0.004, 0.011 and 0.022 respectively).

Three-dimensional reconstructions

Five important anatomical facts emerge from examining the two fully reconstructed nipples (see Fig. 2). First, the ducts are arranged in a central bundle with a peripheral duct-free rim. Second, the bundle narrows to a 'waist' just beneath the skin, possibly at the level of the superficial fascia. Third, some ducts originate on the areola or part way up the nipple. Fourth, most ducts are very narrow as they approach the tip of the nipple and finally, many of the ducts originate within a smaller number of clefts in the nipple surface.

Quantification of the duct bundle

In order to confirm that the first and second features (the apparent duct bundle and waist) seen in the three-dimensional reconstructions were not unique to the two reconstructed nipples, nipple area and duct bundle areas were measured in sections from each block of 25 consecutive nipples. Figure 1 shows a gross photograph of a sagittally-sectioned nipple and block sections from a coronally-sectioned nipple specimen to illustrate the approximate level of block sections. Figure 3 illustrates schematic diagrams of two nipples created from data derived from 25 nipple specimens. These confirm the appearance of the three-dimensional reconstructions in which the ducts appear to converge in a 'waist' approximately 2 mm beneath the level of the areola.

Areolar ducts

Some ducts were noted originating at the base of the papilla and the areola. Comparison of the two complete reconstructions found that this group comprised approximately 10% of ducts in one reconstructed nipple and 46% in the other. These areolar ducts are morphologically different from the majority of the ducts that form the central duct bundle within the papilla, tending to be narrower and without crenellations.

Duct termination within the nipple specimen

In the three-dimensional reconstructions, ducts were traced from their origin at the skin to their termination within the nipple or their cut-off point at the base or edge of the specimen. Figure 4a shows the outline of a nipple that was reconstructed (Fig. 4a) and two example sections (Fig. 4b, c). Ducts traced in black ended within the specimen either as lobular tissue or as a blind-ending sinus. Ducts shown in gray reached the cut edge of the specimen either as a duct or as significant amounts of lobular tissue. The sections illustrate that many ducts ended within the nipple specimen. Most did so in association with a small area of lobular tissue, though some were blind-ending sinuses. Figure 4b shows that larger ducts near to the tip of the nipple do not necessarily pass deep into the breast. Most of the larger ducts in that section terminated within the specimen. Figure 4c suggests that the central

Table 1 Quantitative information obtained from 129 consecutive nipple specimens

Dimension	Number of specimens	Median (Interquartile range)	Mean (Range)
Breast volume (calculated from diameters and height of breast)	128	970 cm^3 (612–1942)	1398 cm^3 (215–7466)
Nipple diameter	125	1.25 cm (1.1–1.3)	1.2 cm (0.7–1.9)
Nipple height	115	0.6 cm (0.3–0.7)	0.6 cm (0–1.9)
Number of ducts	129	23 (19–28)	24 (5–50)

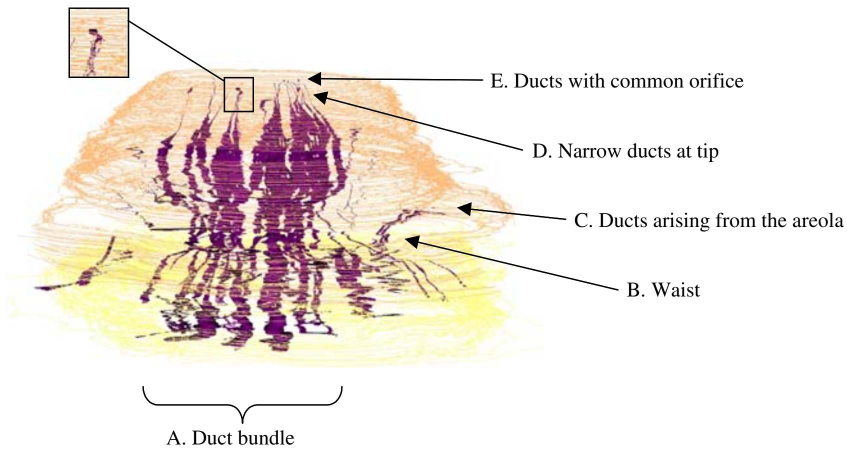

Fig. 2 Three-dimensional reconstruction of a nipple. Skin in tan, cut edge in yellow and ducts in purple. (A) the ducts are arranged in a central bundle (B) the bundle narrows to a waist just beneath the skin (C) some ducts originate on the areola or part way up the nipple (D) most ducts narrow as they approach the tip of the nipple (E) many of the ducts originate from a few clefts

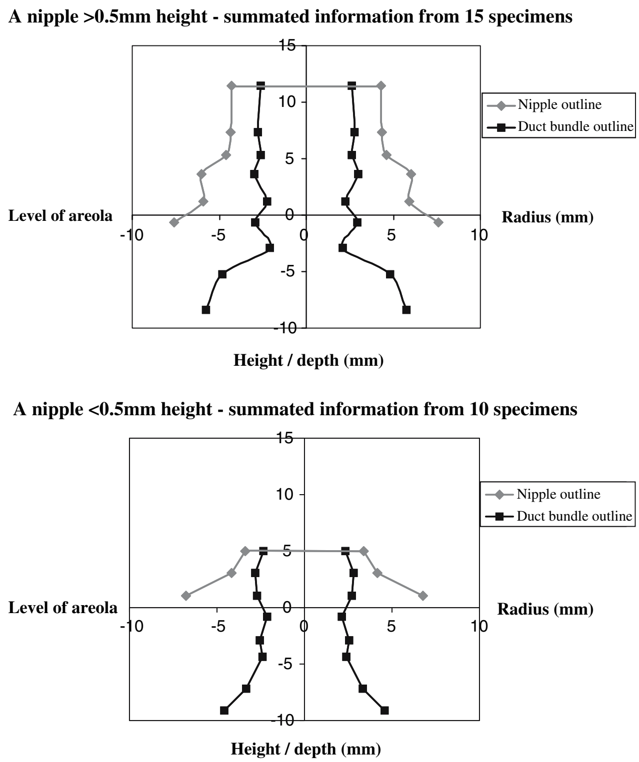

Fig. 3 Graphic illustration of a sagittal section through two schematic nipples. This was created by aggregation of measurements of nipple and duct bundle area from 15 nipples greater than or equal to 0.5 mm in height and 10 nipples less than 0.5 mm in height

or peripheral location of a duct within the duct bundle does not predict early termination. Eleven ducts do not appear on these images because their terminations could not be identified.

Duct diameter

The mean duct diameter for each section was plotted against depth of section for each nipple, see Fig. 5. There was good concordance between the three specimens. At 1 and 1.5 mm beneath the tip, the average duct diameter was 0.06 mm. This increased more than ten-fold to 0.7 mm at 3 mm depth.

Relationship between ducts and orifices

Figure 6 illustrates the three-dimensional reconstruction resulting from the nipple tip reconstruction. Twenty-nine ducts in this specimen could be traced from 15 openings on the surface. Nine of the 29 ducts had an individual opening while 20 of the 29 ducts arose from six common openings at the surface of the nipple. Two of these common openings were clefts in the tip of the nipple with many narrow ducts arising independently from one another in the depths of the cleft. The other common openings were smaller invaginations of squamous epithelium with only two or three ducts arising at the deep aspect. Some openings were dilated by keratin debris and associated with a sebaceous gland. Since the nipple has a round tip (rather than a flattened or cut-off end), not all openings appear in the tip section. Openings were present in sections between 0.2 and 1.7 mm depth below the tip section.

Discussion

This work adds a significant amount of information to the literature on nipple anatomy. Details of the spatial arrangement of the ducts within the nipple will be useful in guiding improvements in surgical techniques for nipple-sparing mastectomy. Data on diameter of ducts and the finding that multiple ducts arise from a single cleft in the surface of the nipple tip lead to concern about the reliability of ductal approaches to diagnosis.

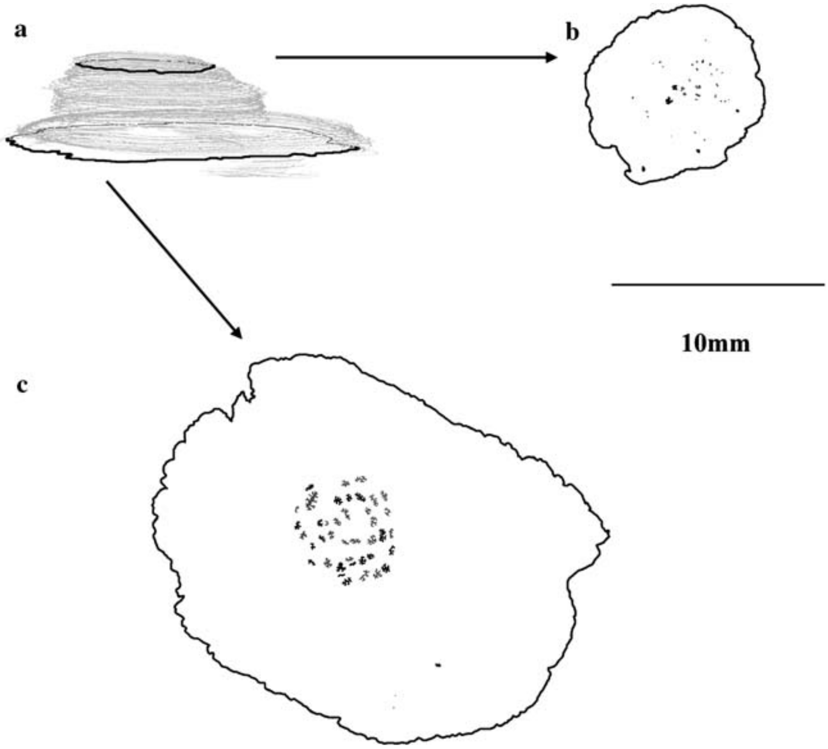

Fig. 4 Illustration of duct termination within the specimen. **a** shows the outline of a nipple that was reconstructed and the levels at which the sections seen in **b** and **c** were taken. In **b** and **c**, ducts that could be traced to their termination within the nipple specimen are shown in black and ducts that were traced to their cut-off at the edge or base of the specimen are shown in gray

Position of the ducts within the nipple

Duct arrangement is best seen in a three-dimensional image of a reconstructed nipple (Fig. 2). The majority of ducts form a central bundle that occupies 21–67% of the cross-sectional area of the papilla. This configuration would allow surgical excision of the central duct bundle in cases in which it is deemed advisable to remove all ductal tissue, such as patients with extensive DCIS. Lagios et al. [18] found a 20% risk of occult involvement of the nipple in therapeutic mastectomy in patients with this pathology. In such cases a frozen section of the duct core could be examined to ensure that the affected duct had been successfully removed. It might seem unnecessary to remove the duct core in prophylactic mastectomy since most tumors develop in the terminal ductal lobular units. However, it has been reported that 17% of nipples do contain lobular tissue [19] and this was also identified in our series.

The changing cross-sectional area of the duct bundle forms a 'waist' as shown in the three-dimensional reconstructions (Fig. 2) and in the summated schematic nipples (Fig. 3). This is unlikely to be an artifact of fixation. It may have a developmental origin: Sagittal sections illustrate that the narrowest point of the duct bundle occurs at the level of the superficial fascia, perhaps indicating that in-growing ducts pierce this fascia together before dispersing into the developing breast. The waist may also correspond to the operative finding that the plane between breast and subcutaneous fat becomes more fibrous at the border of the nipple and this must be freed before the nipple can be inverted.

Going and Moffat [3] classified nipple ducts into three categories according to their origin and size. We confirm the finding of a subset of ducts joining the main duct bundle from around the base of the papilla as they described. They also described a group of ducts characterized by a relatively wide, funnel-shaped opening onto the surface of the nipple and a more numerous group of ducts which taper down to a minute lumen at their origin from the deep aspect of the nipple epidermis on the apex of the papilla. We find that, though a few ducts are enlarged at the tip, they narrow to become indistinguishable from the other ducts as they traverse deeper into the papilla. Going and Moffat [3] logically hypothesized that larger ducts might, in general, be connected to larger duct systems. However, our three-dimensional reconstruction demonstrated that there is no organized relationship between size of duct and whether it terminated within the nipple or passed deeper into the breast. Nor does there seem to be a pattern linking position within the duct bundle cross-section to early termination within the nipple. Illustrative sections are shown in Fig. 4.

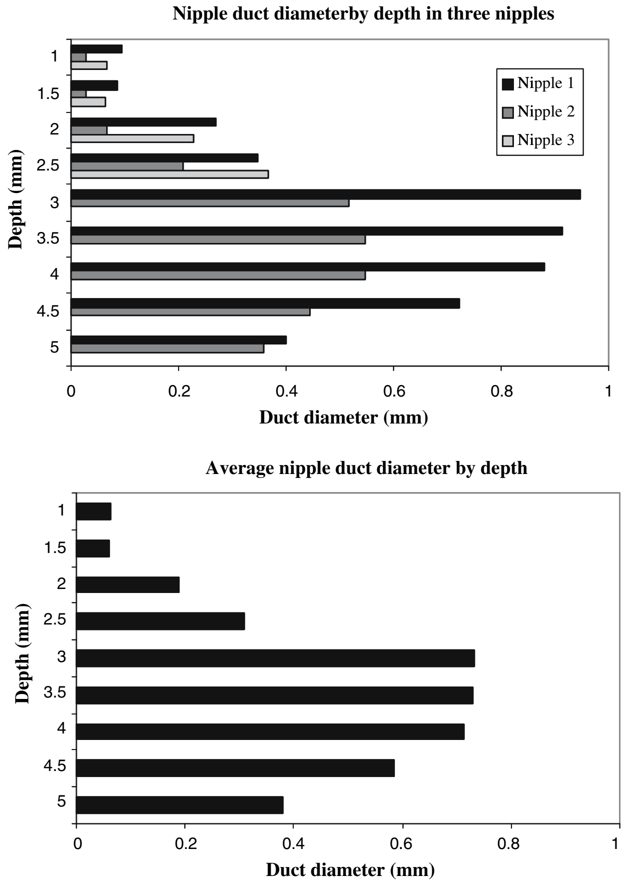

Fig. 5 Pattern of duct diameter by depth from nipple tip. The average diameter is less than 0.1 mm at 1 mm and 1.5 mm depth. The diameter then gradually enlarges to a maximum at 3 mm depth

Number of ducts

In this series of 129 nipples, the median number of ducts was 23 and the interquartile range (IQR) was 19–28. This is in close agreement with Going and Moffat [3] who examined a single coronal section through the base of 72 nipples and found a median of 27 (IQR 21–30) collecting ducts. Similarly, Taneri et al. [2] sampled 226 mastectomy nipples histologically and found a mean of 17 ducts (range 18–30). The mean in our series was 24 (range 5–50). Another method that has been used to study breast ducts beneath the nipple is ultrasound. Ramsay et al. [20] performed an ultrasound study of 21 lactating women. They found a mean of 9.6 ducts in the left breast and 9.2 in the right. However, the equipment had insufficient resolution to identify ducts of less than 0.5 mm in diameter. In a section at the base of a serially-sectioned nipple, we noted that 26 of 55 ducts are of this small size suggesting that the ultrasound method would miss a significant number of ducts if it were employed to count ducts within the nipple.

Love and Barsky [4] employed several approaches to the study of ductal orifices. Using serial sectioning and cytokeratin immunocytochemistry of 10 nipples they identified 5–9 duct orifices per nipple. They noted a mean of five duct orifices by direct in vivo observations of lactating women and 6–8 orifices by observation of passive conduction of lymphazurin from a subareolar injection to the nipple tip in mastectomy specimens. These findings are restricted to the number of ductal orifices and do not establish the number of underlying ducts or their interconnections.

Relationship between ducts and orifices

Three groups using histological techniques have noted the discrepancy between duct number and orifice number and postulated that duct branching may be responsible [2–4]. Going and Mohun [21] tried to elucidate the path of the 19 identifiable ducts in a 2.2 mm thick block at the tip of a nipple using episcopic fluorescence image capture (EFIC). However, they found that EFIC has insufficient resolution to discriminate reliably between keratin plugging and discontinuity between the duct and the skin surface. By modifying embedding technique to allow preparation of standard H&E sections from an entire nipple tip and reconstructing this tip specifically to examine this possibility, we have shown that several ducts arose in the same cleft of the nipple, accounting for the discrepancy between the number of ducts in the nipple and the number of openings that can be counted externally.

Duct diameter

Taneri et al. [2] found a mean duct diameter of 0.57 mm in their series of 226 nipples. However, their measurement was of the greatest diameter of the cross section of the ducts in one of three histological sections. In our study, duct diameter was calculated from circumference since this is more likely to reflect potential size of the duct and is therefore of more relevance to cannulation. Furthermore, Taneri et al chose the section in which the ducts were largest. This may not represent the area of difficulty for cannulation techniques, which need to access the ducts at the orifice. Estimating diameter at different levels showed that most ducts are very narrow at the tip of the nipple with only a few ducts of a size that could be cannulated. Although the presence of a pathological lesion and nipple discharge may cause a duct to expand and thus become easier to cannulate, in the absence of discharge the small size of many of the ducts at the tip of the nipple will almost certainly prevent cannulation.

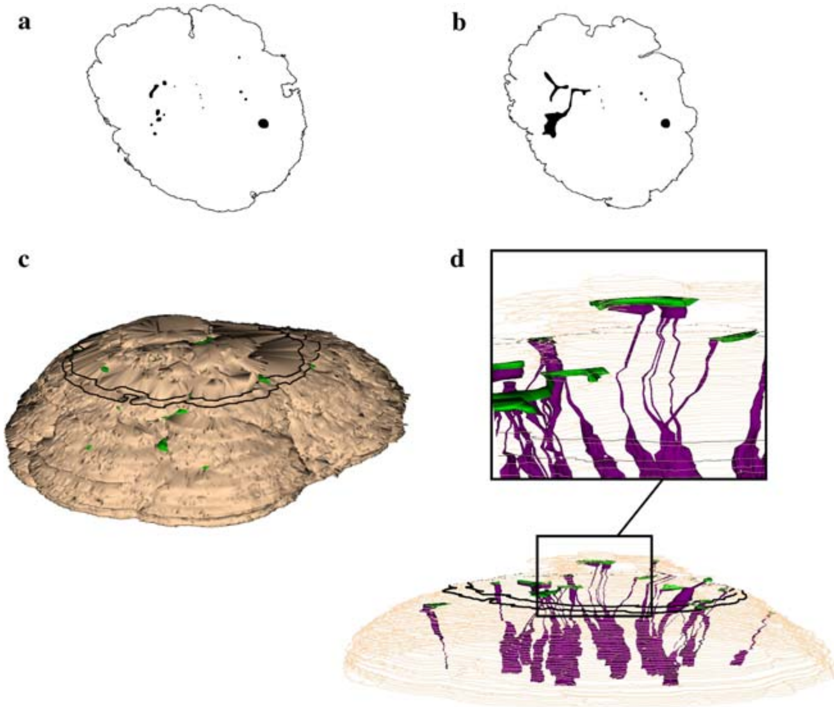

Fig. 6 **a**, **b**: Two sections of the nipple tip. Many small ducts in upper left quadrant of section **a** arise from a cleft in section **b**, 100 micrometers nearer the tip. **c**, **d**: three-dimensional reconstruction of a nipple tip. In both **c** and **d** the sections used in **a** and **b** are shown in black. **c** shows duct openings in green. **d** illustrates purple ducts arising from a cleft in the nipple tip

The finding that many ducts arise deep within a cleft of the nipple leads to the conclusion that all techniques relying on cannulation are at risk of uncontrolled cannulation of the few ductal orifices which are of a size sufficient to permit entry of a guide wire, and that selective passage into one of several ducts which originate within a particular cleft is impossible to achieve without direct vision. This may explain the poor sensitivity of ductal lavage reported in the literature [7, 8]. Ductoscopy has the advantage of selectivity at branch points, but since dilation by a probe is necessary prior to insertion of the ductoscope, smaller orifices are likely to be bypassed before a view is obtained through the ductoscope. Nipple aspiration fluid cytology may have utility as a method of detection of abnormalities in ductal epithelial cells but its application is limited by difficulties in locating the site of pathology within the breast.

Conclusions

In conclusion, this study goes beyond a description of the number of ducts within the nipple and provides an explanation for the discrepancy between histological techniques and other methods of assessment of duct number. Demonstration of the shared opening of many ducts on to the surface of the nipple and the narrow caliber of most ducts close to the nipple tip has profound impact on the clinical application of ductography, ductal lavage and ductoscopy.

From a surgical perspective, this study provides a detailed illustration of the location of the duct bundle within the nipple suggesting that excision is feasible should it be deemed necessary. The rate of occult involvement of the nipple stated in the literature and the finding that a proportion of nipples contain terminal ductal lobular units suggest that this may be advisable when performing a nipple-sparing mastectomy. A future step in understanding surgical anatomy involves the elucidation of the relationship between the ducts and vasculature of the nipple.

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