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Cancerous versus noncancerous breasts

A comparative morphological analysis of the entire glandular tree of the breast*

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Summary. Cancerous and clinically normal autopsy obtained breasts were collected in order to compare the physiopathological profile of both types of glandular tree. Each breast was visualized by whole thin sections and observed under a stereomicroscope with removal of the more interesting changes for histology. The comparison was made between 67 atrophic cancerous breasts and 88 atrophic control breasts. The results were as follows: 25% of the cancerous breasts versus 47% of control breasts showed no changes, atypical lobules, microfoci of "in situ" and/or infiltrating cancer were present in 46% of cancerous breasts and in 16% of control breasts, showing a significant correlation with clinical cancer. All other types of functional and proliferative changes, variously associated each other, were found in 29% of cancerous and in 37% of control breasts. Our morphological data agree completely with the statements in follow-up studies carried out on benign breast biopsies. The significant differences in the physiopathological profile of the glandular tree between "normal" and cancerous breasts, confirms that some changes are causally related to clinical cancer.

Key words: Breast – Breast cancer – Precancerous lesions

Introduction

Multicentricity of breast cancer has been widely demonstrated by many Authors using different methods of investigation (Egan 1982; Gallager and Martin 1969; Lagios 1977; Sarnelli and Squartini 1986; Schwartz et al. 1980). Atypical lesions, "in situ" and infiltrating microcarcinomas were often found near or far from the clinical tumour, topographically and morphologically independent from it (Fisher et al. 1975; Lesser et al. 1982; Sarnelli and Squartini 1984; Schwartz et al. 1980). This supports the hypothesis of the systemic nature of breast cancer (Wellings and Jensen 1973; Wellings 1980). Follow-up studies suggest that some focal proliferative atypical changes occasionally found in breast biopsies for benign pathology are predictive of clinical cancer (Page et al. 1978). In this case, women with high morphological risk of developing breast cancer could be selected (Cancer Committee of the College of American Pathologists 1986). Comparative morphological analysis between clinically normal mammary glandular trees and those collateral to the clinical cancer might confirm the hypothesis that breast cancer is closely related to a specific microenvironment (Sarnelli et al. 1980; Sarnelli and Squartini 1983; Squartini and Sarnelli 1981; Squartini 1983; Squartini et al. 1986). For this purpose a submacroscopic-histological comparison between cancerous and clinically normal autopsy derived breasts has been undertaken in the present study.

Materials and methods

Two series of human female breasts were collected: (1) a consecutive series of 106 breasts removed surgically for clinical cancer, by total or radical mastectomy (women age range 25–84 years); (2) a control consecutive series of 212 clinically normal breasts removed by bilateral subcutaneous mastectomy from 106 autopsied women (age range 32–90 years) without evidence of breast pathology during life. In all cases of both series, the gynaecological history was negative for previous neoplastic disease. Moreover, no significant gynaecological disease was observed during the routine autopsies on the control women. In order to compare two homogeneous groups, we excluded from our study the youngest women of the first series (25–31 years) and the oldest women of the second series (85–90 years). In this way only 32–84 age range women in both series were con-

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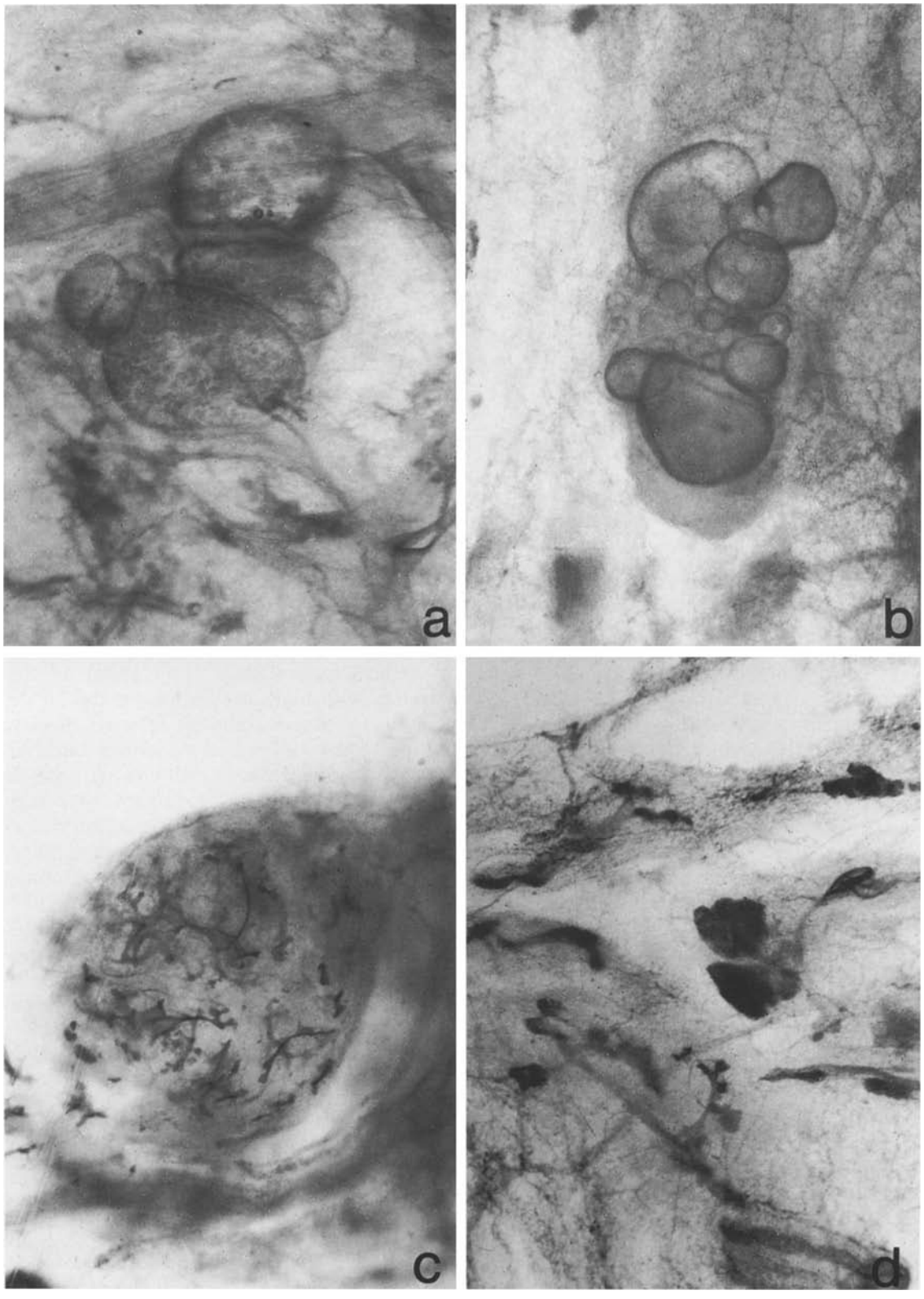

Fig. 1. Submacroscopic view of apocrine cysts (**a**), spherical cysts (**b**), fibroadenoma (**c**) and atypical lobules (**d**). Harris' Haematoxylin, × 10

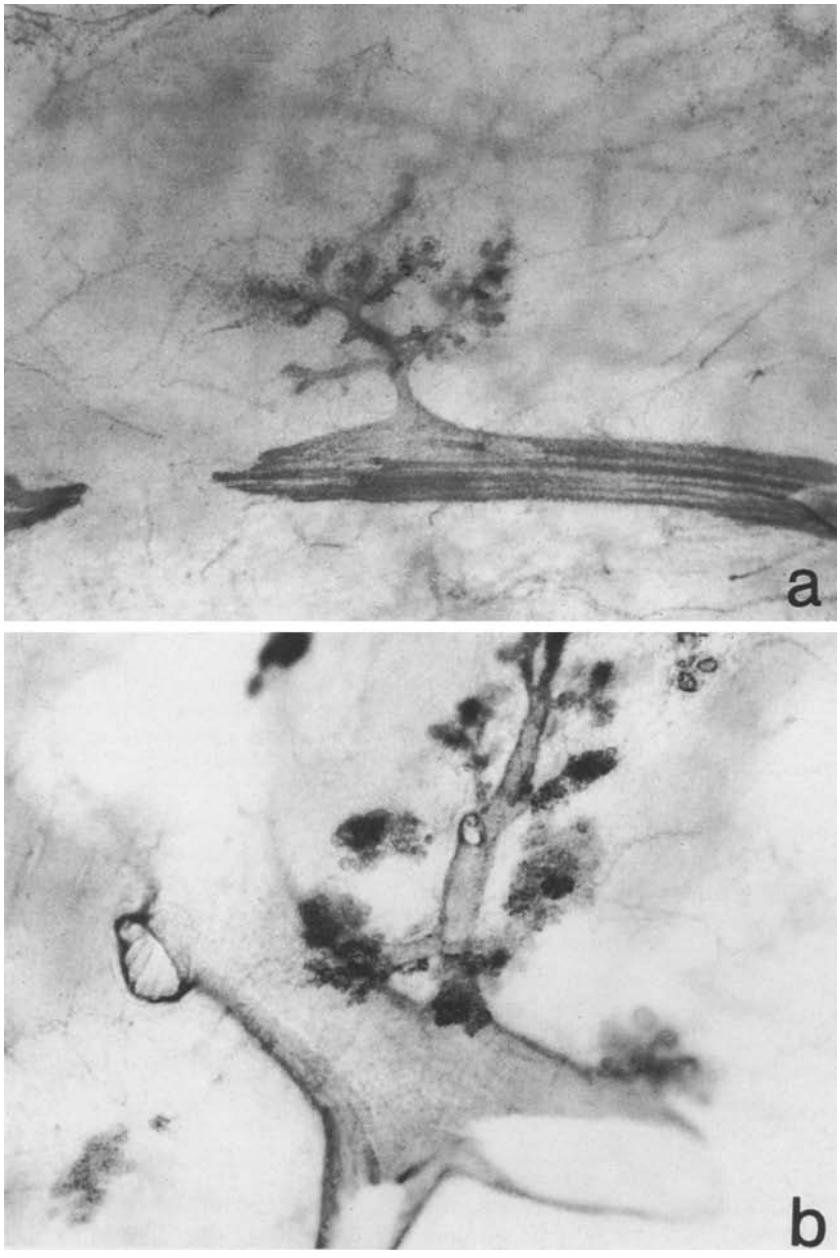

Fig. 2. Subgross detail of terminal ductal-lobular units of an atrophic (**a**) and an adenotic (**b**) mammary glandular tree in three dimensional view. Harris' Haematoxylin, ×10

sidered. Age was distributed by decades as follows: 4th) 4 operated women (O) and 2 autopsied women (A); 5th) 18 (O) and 3 (A); 6th) 18 (O) and 10 (A); 7th) 21 (O) and 27 (A); 8th 6 (O) and 46 (A). A further criterion used to ensure comparable materials was the endocrine status. The hormonal status was evaluated on the basis of the morphological expression of endocrine responsiveness at the mammary level. There was no absolute correspondence between age and presence-absence of menstrual cycles on the one hand and mammary submacroscopic profile (adenosis-atrophy) on the other. Thus, after the subgross scrutiny of the mammary glandular tree we selected 67 cases from the first and 88 from the second series for the statistical comparison. Both series showed the same morphological expression of hormonal status, that is to say, atrophic mammary glands, generally corresponding to a post-menopausal state. We excluded from this study adenotic breasts, because they were insufficient in number for statistical purposes.

The mammary glandular tree of each breast was analysed by a submacroscopic method of scrutiny under a stereomicroscope (Migliori 1975; Sarnelli et al. 1980). First of all, in order to limit the microscopic effects of postmortal changes, each breast was cut as soon as possible into four–five thick slices, leaving the cutis out, and then was fixed in 10% formalin and kept in a refrigerator (−10° C). Breast specimens quickly became hard and could be cut into serial thin slices (2–3 mm) in order to ensure complete fixation. Eight random sections representative of all quadrants and one passing through the nipple have been taken from each specimen. The slices were defatted in acetone, hydrated, stained in 50% Harris' haematoxylin, dehydrated, cleared, stored in cedar oil and observed under a dissecting microscope equipped for microphotography. The method allows a three dimensional view of the mammary gland, therefore the discrimination of many lesions does not give any problems, as for example between cysts and ectatic ducts (Figs. 1a, b and 2b, respectively). After being photographed (Figs. 1–3), the more interesting or suspicious samples

were removed for routine histology. The sampling of the specimens for histology in cancerous breasts was widespread, both near and far from the clinical tumour. However, we distinguished two different areas: (1) less than 3 cm from the clinical tumour and (2) 3 cm or more from its edges. Only the submacroscopic foci of infiltrating cancer located at least 3 cm from the main tumour mass were considered in our study, because they appeared more significant as small subclinical "de novo" cancers rather than as intramammary metastases. Finally, there were no significant physiopathological differences between the right and the left breast of each woman in the control series. Therefore, both breasts have been considered as a single entity.

The terminology of elementary lesions was derived by Wellings et al. (1975). Statistical comparison of groups was performed by the chi-square test.

Results

The mammary glands observed at subgross level were adenotic (rich in lobules) or atrophic (with scanty lobules consisting of a few ductules). Each series of breasts (surgical and autopsy) was subdivided in two groups, adenotic and atrophic, on the basis of their submacroscopic profile (Fig. 2a–b). There was no absolute correspondence between pre- or postmenopausal status and morphological expression of endocrine responsiveness of the breast. Therefore, the submacroscopic profile of the mammary gland was finally considered to be a better criterion of choice rather than the presence-absence of the menstrual cycle for a correct comparison between two homogeneous groups. Moreover, the statistical comparison was here limited to atrophic breasts, since they were prevalent in the surgically removed material for clinical cancer, as well as in the control autopsy material.

The frequency (%) of the elementary lesions in each group of breasts is reported in Table 1. Many changes were significantly associated with clinical cancer, namely: atypical lobules, "in situ" and infiltrating carcinomas, spherical cysts, apocrine cysts, sclerotic lobules, cystic lobules, and cystic ducts. Other changes were not significantly associated with cancer, including persistent lobules, apocrine lobules, sclerosing adenosis, fibroadenomas, duct hyperplasia, intraduct papillomas.

75% of cancerous breasts and 53% of control breasts showed elementary physiopathological changes variously associated each other (Table 2). Atypical lobules characterized by various degree of atypia, including "borderline" lesions and "in situ" carcinomas (Fig. 3a–d), and/or infiltrating carcinomas were detected in 46% of cancerous breasts and in 16% of control breasts. The distribution of these lesions was significantly different in cancerous versus noncancerous breasts; atypical lobules and microcarcinomas were more frequent in the first group ($p<0.01$). All the other physiopathological changes were variously associated each other in 29% of cancerous breasts and in 37% of noncancerous breasts. The glandular tree was completely atrophic and without any lesions in 25% of cancerous breasts. The same occurred in 47% of autopsy breasts. "Normal" status was significantly associated with control breasts, as expected ($p<0.01$).

Table 1. Frequency (%) of the physiopathological changes in 67 cancerous breasts, compared with 88 clinically normal autopsy obtained mammary glandular trees, as controls. Statistical comparison by chi-square test

Physiopathologic changes	Cancerous breasts %	Control breasts %	$p<$
"In situ" carcinomas	28	0	0.000001
Atypical lobules	39	11	0.00001
Cystic lobules	46	11	0.00001
Infiltrating carcinomas	19	0	0.0001
Cystic ducts	30	6	0.0001
Spherical cysts	19	4	0.005
Sclerotic lobules	43	20	0.05
Apocrine cysts	26	9	0.01
Persistent lobules	31	19	0.10
Large lobules	6	2	0.50
Sclerosing adenosis	18	12	0.75
Fibroadenomas	13	10	0.75
Duct hyperplasia	13	10	0.75
Apocrine lobules	25	27	0.90
Intraduct papillomas	4	4	0.99

Table 2. Frequency (no. and %) of three possible types of mammary glandular tree in 67 cancerous breasts versus 88 clinically normal, autopsy obtained mammary glandular trees as controls. Statistical comparison by the chi square-test*

Type of the mammary gland	Cancerous breasts		Control breasts	
	no.	%	no.	%
A) No changes	17	25	41	47
B) Atypical lobules, microcarcinomas	31	46	14	16
C) All the other changes	19	29	33	37

* A—B—C; $p<0.0001$
A—B+C: $p<0.01$
B—A+C: $p<0.00007$

Discussion

The present study confirms that breasts surgically removed by radical mastectomy for clinical cancer frequently show multiple focal changes. However, the submacroscopic-histological analysis of the entire glandular tree removed at autopsy from women with a negative history for any breast disease suggests that changes of different types are also present in autopsy material, as previously reported

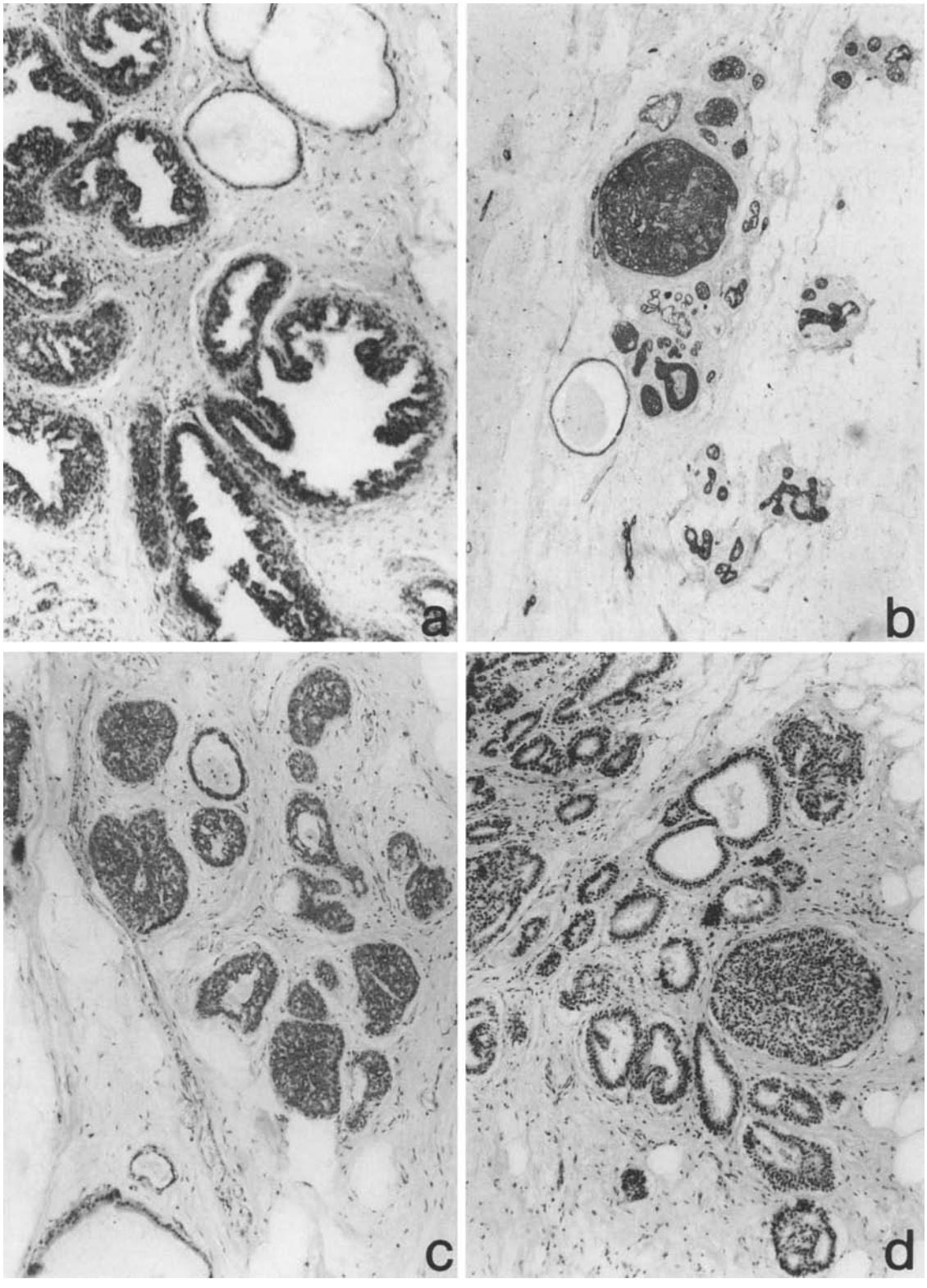

Fig. 3. Histological appearance of atypical lobules detected by submacroscopic analysis, with different degrees of atypia; mild, ×160 (**a**), intermediate, ×100 (**b**), high, ×100 (**c**) and (**d**). Haematoxylin-eosin

by others (Jensen 1981; Rush and Kramer 1963). Nevertheless, the comparison between the physiopathological changes in cancerous breasts and control material clearly indicates that the frequency of focal changes associated with clinical cancer is invariably higher than in so-called normal breasts and that the difference is always significant for lesions at moderately increased risk of cancer, such as atypical proliferative lesions, and for lesions at high risk of clinical cancer such as microfoci of "in situ" and infiltrating carcinomas. It is very interesting to notice that submacroscopic foci of cancer were not detected in control breasts. Moreover, in this series atypical lobules were present but they were scanty in the glandular tree and with a low degree of atypia. In only three cases were "borderline" lesions. The data give further confirmation that proliferative atypical lesions and microfoci of cancer are not common findings in the elderly female (average age of our population being 70 years). These lesions can therefore be considered to be predictive of clinical neoplasia when found casually in benign breast biopsies, at any age – but especially in pre- and perimenopausal women. Some changes without a documented increased risk for subsequent cancer were significantly associated with clinical cancer, for example spherical and apocrine cysts. Such lesions might be interpreted as an expression of the benign microenvironment from which cancer can develop.

In conclusion, the data reported here suggest that the background from which breast cancer arises is different from that of so-called normal breasts, that atypical lobules and microfoci of cancer occasionally detected in the mammary glandular tree may be causally related to the development of clinical cancer and that a more precise definition of the risk of future tumour development can be determined using morphological variables.

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References

Cancer Committee of the College of American Pathologists (1986) Is "fibrocystic disease" of the breast precancerous? Arch Pathol Lab Med 110:171–173

Egan RL (1982) Multicentric breast carcinoma. Clinical-radiographic-pathologic whole organ studies and 10-year-survival. Cancer 49:1123–1130

Fisher ER, Gregorio R, Redmond C, Vellios F, Sommers SC, Fisher B (1975) Pathologic findings from the national surgical adjuvant breast project (Protocol no. 4). I. Observations concerning the multicentricity of mammary cancer. Cancer 35:247–254

Gallager H, Martin JE (1969) The study of mammary carcinoma by mammography and whole organ sections. Early observations. Cancer 23:855–873

Jensen HM (1981) Breast pathology, emphasizing precancerous and cancer associated lesions. In: Bulbrock and Taylor (eds) Commentaries on research in breast disease. Alan R Liss Inc, New York 2:41–86

Lagios MD (1977) Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. Cancer 40:1726–1734

Lesser ML, Rosen PP, Kinne DW (1982) Multicentricity and bilaterality in invasive breast carcinoma. Surgery 91:234–240

Migliori E (1975) Un metodo di studio submacroscopico della mammella umana intera. Tumori 61:357–363

Page DL, Zwaag RV, Rogers LW, Williams LT, Walker WE, Hartmann WH (1978) Component parts of fibrocystic disease complex and breast cancer. J Natl Cancer Inst 61:1055–1063

Rush BF Jr, Kramer WM (1963) Proliferative histologic changes and occult carcinoma in the breast of the aging female. Surg Gyn Obstet 117:425–432

Sarnelli R, Orlandi F, Migliori E, Squartini F (1980) Morfologia submacroscopica della mammella: reperti semeiologici, nomenclatura e possibilità di applicazione del metodo. Pathologica 72:139–187

Sarnelli R, Sabo' C, Squartini F (1980) Subgross physiopathology of the breast associated with clinical cancer. Tumori 66:565–582

Sarnelli R, Squartini F (1983) The microenvironment of human breast with clinical cancer. Applied Pathol 1:323–332

Sarnelli R, Squartini F (1984) Independent submacroscopic foci of infiltrating carcinoma in breast removed for clinical cancer. Tumori 70:169–178

Sarnelli R, Squartini F (1986) Multicentricity in breast cancer: a submacroscopic study. In: Sommers SC, Rosen PP, Fechner RE (eds) Pathology Annu. Appleton Century-Crofts Norwalk, Connecticut 21:143–158

Schwartz GF, Patchefsky AS, Feig SA, Shaber GS, Schwartz AB (1980) Clinically occult breast cancer. Multicentricity and implications for treatment. Ann Surg 191:8–12

Schwartz GF, Patchefsky AS, Feig SA, Shaber GS, Schwartz AB (1980) Multicentricity of non palpable breast cancer. Cancer 45:2913–2916

Squartini F, Sarnelli R (1981) Structure, functional changes and proliferative pathology of the human mammary lobule in cancerous breasts. J Natl Cancer Inst 67:33–46

Squartini F (1983) The mammary lobule in cancerous breasts: human findings and experimental background. In: Hollman KH, De Brux S, Verley JM (eds) New Frontiers in Mammary Pathology. Plenum Publishing Corporation, New York 2:65–209

Squartini F, Bistocchi M, Sarnelli R, Basolo F (1986) Early pathological changes in experimental and human breast cancer: Facts and Comments. Ann NY Acad Sci 464:231–261

Wellings SR, Jensen HM (1973) On the origin and progression of ductal carcinoma in the human breast. J Natl Cancer Inst 50:1111–1118

Wellings SR, Jensen HM, Marcum RG (1975) An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst 55:231–273

Wellings SR (1980) Development of human breast cancer. In: Klein G, Weinhouse S (eds) Advances in Cancer Research. Academic Press, New York 31:287–314

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