

The prevalence of the precancerous lesions in breasts contralateral to clinical cancer

A morphological comparison with breasts containing a benign lump

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Summary: Two small series (nine cases each) of human female breasts were collected to compare the morphological changes of mammary glandular trees contralateral to primary breast cancer and those collateral to symptomatic benign lump. Each whole mammary gland was analysed by a submacroscopic scrutiny method using a stereomicroscope. Interesting and suspicious samples were removed for routine histology. Benign subclinical lesions were indifferently present in both series: Spheric cysts (5:5), sclerosing adenosis (3:3), intraductal papillomas (1:1), fibroadenomas (3:1). On the contrary, proliferative epithelial lobular lesions with various degree of atypia i.e. atypical lobules (Grades IV-V according to Wellings), were detected only in the first series ($p < 0.01$). These data agree completely with the hypothesis of a systemic nature of breast cancer and support indirectly, the possible predictive value of atypical lobules detected in bioptic specimens for the subsequent development of cancer in collateral and/or contralateral breasts.

Key words: Breast; Breast cancer; Precancerous lesions.

INTRODUCTION

The systemic nature of breast cancer, suggested by multicentricity, bilaterality and local recurrence of clinical tumors, was explained by the different morphologic backgrounds of cancerous versus non-cancerous breasts^(1, 2). The purpose of the present study is a morphological comparison between the mammary glandular tree of asymptomatic breasts contralateral

to clinical cancer derived from autopsies and mammary glands removed either by subcutaneous mastectomy from women affected by symptomatic benign breast pathology, or by total mastectomy for a breast pathology, or by total mastectomy for a breast lump which was likely to be malignant on the basis of clinical criteria. The expected results are: 1) a further confirmation of the systemic nature of breast cancer in both mammary glands by the discovery of asymptomatic preneoplasias and/or subclinical carcinomas in the mammary glandular tree contralateral to primary cancer; 2) the rareness or substantial absence of precancerous lesions in the mammary glandular tree collateral to symptomatic benign tumor; 3) the diffuse presence in both breast series of subclini-

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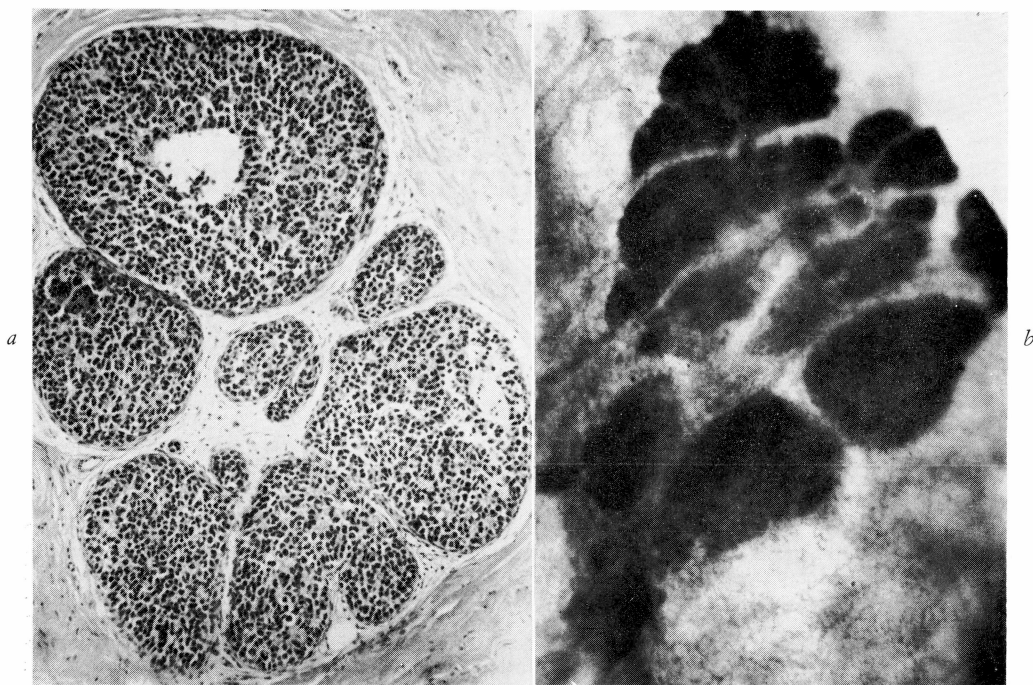


Fig. 1. — *a*) Histologic view of a atypical lobule type A, Grade V according to Wellings (ALA), showed at submacroscopic level in *b*). Haematoxylin-eosin, $\times 80$.

cal proliferative changes which, taken together, configure the so-called fibrocystic condition.

MATERIALS AND METHODS

Two series of human female breasts were collected: Group I, nine breasts contralateral to clinical cancer and Group II, twelve breasts affected by benign pathology. Breasts contralateral to clinical cancer were removed by subcutaneous mastectomy during routine autopsy. Six breasts with benign disease were surgically removed by bilateral subcutaneous mastectomy from three women affected by the clinical symptoms of the fibrocystic condition. Breasts removed from the same woman were considered as a single mammary glandular tree (three cases). The six remaining breasts were surgically removed by total mastectomy according to a clinical diagnosis of cancer not confirmed after subsequent histologic examination. This material was collected many years ago when frozen section diagnosis was not yet the rule for surgeons.

The entire mammary glandular tree of each breast was analysed by a submacroscopic scrutiny

method^(3,4) which allows a three-dimensional view of serial thin slices (2-3 mm thickness) with a dissecting microscope. Each slice was fixed in 10% formalin and then treated by subsequent passages: defatted in acetone, hydrated, stained in 50% Harris' haematoxylin (for nuclear staining), dehydrated, cleared, stored in cedar oil and finally observed. The most interesting and suspicious samples were removed in order to be processed for routine histology. The terminology used here for morphological changes is that described in detail by Wellings⁽⁵⁾.

RESULTS

A) Group I

Clinical and autopsic data

The age range of the nine autopsied women was 61-83 years, the average age being 72 years. All women were in postmenopausal status. The causes of death were as follows: 1) postoperative complications after mastectomy (4 cases); 2) cardiovascular disease (2 cases); 3) malignant

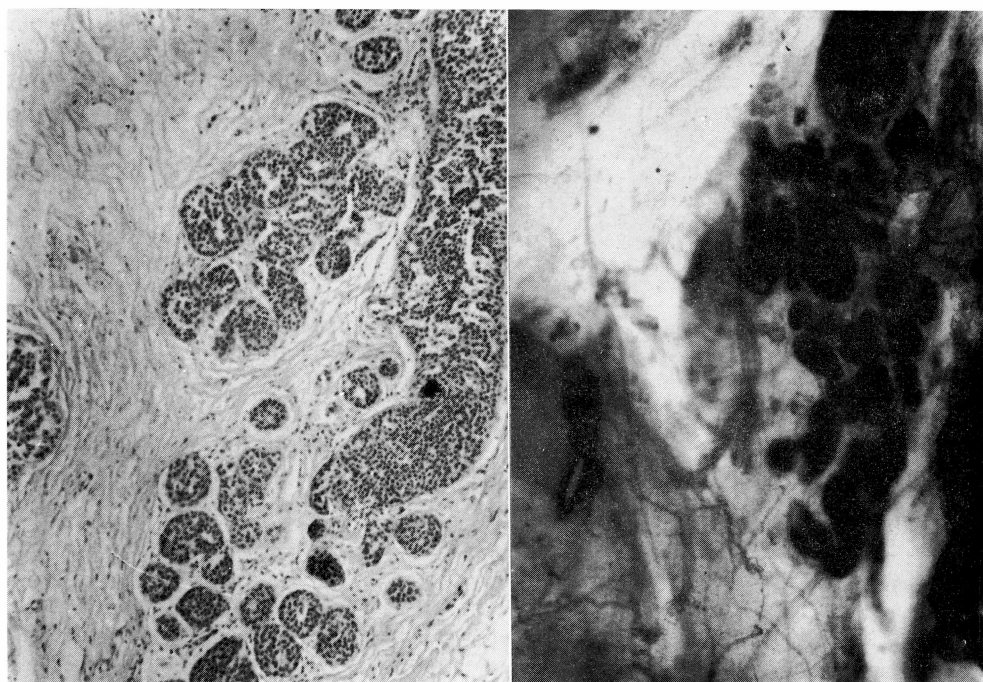


Fig. 2. — *a*) Histologic view of an atypical lobule type B, Grade V according to Wellings (ALB), showed at submacroscopic level in *b*). Haematoxylin-eosin, $\times 80$.

neoplasm different from breast cancer (1 case); 4) breast cancer recurrence (1 case); 5) sepsis (1 case). In conclusion, only 55% of the patients died because of their breast cancer.

The stage grouping according to the pathological TNM classification system was the following: Stage I, 3 cases; Stage IIA, 3 cases; Stage IIIB, 2 cases; Stage IV, 1 case.

Histologic diagnosis was as follows: *a*) infiltrating ductal carcinomas, 6 cases (66%); *b*) infiltrating lobular carcinoma, 1 case (11%); *c*) medullary carcinoma, 1 case (11%); anaplastic carcinoma, 1 case (11%).

Morphological findings of the breast contralateral to clinical cancer.

Only one breast (11% of cases) showed a well developed adenotic mammary gland

dular tree, i.e. with normal lobules. The remaining 89% cases were more or less completely atrophic.

Benign asymptomatic elementary lesions showed the following prevalence: spheric cysts, 5 cases (55%); apocrine lobules, 4 cases (45%); sclerotic lobules, sclerosing adenosis and fibroadenomas, 3 cases (33%); cystic lobules and intraductal papillomas, 1 case (11%). Epithelial lobular atypical hyperplasia, i.e., atypical lobules (AL), was present in 5 cases (55%). Morphological precursors of ductal carcinoma, i.e., AL Type A (ALA) according to Wellings (Fig. 1) were observed in four instances. In all four cases these findings were in the breast contralateral to an infiltrating ductal mammary cancer. In one case morphological precursors of lobular carcinoma, i.e., AL Type B (ALB) according to Welling (Fig. 2) were present in

Table 1. - Distribution of AL positive cases in 9 autoptic breasts contralateral to clinical cancer on the basis of patients' age decades, clinical stage and histologic type of contralateral cancer.

Patients' age decades	Total cases	AL+	AL-
6th	1	1	0
7th	2	1	1
8th	4	2	2
9th	2	1	1

Clinical stage	Total cases	AL+	AL-
I	3	2	1
IIA	3	1	2
IIIB	2	1	1
IV	1	1	0

Histologic type of breast cancer	Total cases	AL+	AL-
Infiltrating Ductal Ca.	6	4	2
Infiltrating Lobular Ca.	1	1	0
Medullary Carcinoma	1	0	1
Anaplastic Carcinoma	1	0	1

the mammary glandular tree contralateral to an infiltrating lobular carcinoma. The distribution of positive cases for AL (ALA, ALB) on the basis of patients' age, clinical stage and histologic type of breast cancer is shown in Table 1.

B) Group II

Clinical data and histologic diagnosis

The age range of the nine patients studied in this group was 37-68 years, the average age being 52 years. Five women were in postmenopausal status. The pathological diagnosis in the six patients submitted to monolateral total mastectomy was as follows: fibrocystic disease, 2 cases (33%); isolated cyst, 1 case (16.5%); localized fibrosis, 1 case (16.5%); granulomatous mastitis, 1 case (16.5%); fibroadenoma, 1 case (16.5%). Fibrocystic disease was diagnosed by routine biopsy in the remaining three women operated by bilateral subcutaneous mastectomy.

Morphological findings of the whole mammary glandular tree collateral to the main lump.

After submacroscopic study three breasts appeared as atrophic (33%) and the remaining six (77%) as adenotic. These data may be explained by the advanced age of the patients under study. The mammary gland collateral to the main clinical lump was found to be diffusely affected by the following benign elementary subclinical lesions: sclerotic lobules, 6 cases (66%), cystic lobules, apocrine lobules, spheric and apocrine cysts, 5 cases (55%), sclerosing adenosis, 3 cases (33%), intraductal papilloma and fibroadenoma, 1 case, (11%). Preneoplastic lesions such as AL were never detected.

C) Comparison between Groups I and II

Benign subclinical lesions, such as sclerosing adenosis, intraductal papillomas, fibroadenomas and spheric cysts were indifferently present in both types of mammary glandular trees, either contralateral to clinical cancer or collateral to benign breast lump (Table 2). Only atypical lobules were significantly associated with contralateral breast cancer (chi square = 6.923, $p < 0.01$).

DISCUSSION

The morphological analysis of the entire mammary glandular tree by a submacroscopic-histologic method can provide us detailed information on the background in which breast cancer develops in comparison with the general appearance of noncancerous breasts. Pathologists, generally, derive cancerous breasts from surgical mastectomies and noncancerous breasts from routine autopsies. Morphological studies carefully carried out on both bioptic and autoptic whole breast specimens contribute: 1) to better demonstrate the systemic nature, i.e., the multi-

centricity of breast cancer (^{6, 7}); 2) to confirm the hypothesis that breast cancer originates from terminal ductal-lobular units (^{8, 9, 10, 11, 12}); 3) to show a higher incidence of preneoplastic lesions (ALA-ALB) in the morphologic background of cancerous breasts with respect to that of non cancerous breasts (^{1, 2}); 4) to indicate that all other elementary morphofunctional fibrocystic changes are distributed in both cancerous and noncancerous breasts. In our previous submacroscopic-histologic comparison between mammary glandular trees collateral to clinical cancer and autotptic derived asymptomatic breasts (²), AL and/or subclinical cancers showed a significant correlation ($p < 0.01$) with clinical cancer. On the contrary, benign subclinical changes showed no correlation with clinical cancer. Our previous pathological data agreed indirectly with the results of the retrospective studies carried out in patients submitted to curative breast biopsy for benign lumps (^{13, 14}). According to these studies, only women with high grade AL showed a moderately increased risk of future breast cancer development.

Our present results offer a morphological explanation of the results of clinical follow-up studies. Preneoplastic lesions were absent in the whole mammary glandular tree collateral to a benign lump. Accordingly, precancerous lesions were seldom observed in noncancerous whole breasts obtained at autopsy (^{15, 16, 17, 18}). On the contrary, the analysis of whole breasts contralateral to clinical cancer showed an increased prevalence of atypical lobules including borderline lesions and "in situ" carcinomas (55%). The prevalence of these lesions is even higher than that previously detected by us in two series of breasts containing clinical cancer, in which preneoplastic lesions were found in 36% cases (⁷) and in 46% cases (²). Moreover, the increased risk for the development of a new cancer in the breast contralateral to

the primary tumor can be justified by the morphological observation concerning the prevalence in both breasts of cancer precursors. On the contrary, all the other subclinical fibrocystic changes detected at submacroscopic-histologic level were found either in mammary glands contralateral to primary cancer or in mammary parenchyma collateral to a benign lump. In a previous study (²) we have shown that subclinical fibrocystic changes were detected with no statistical difference either in completely asymptomatic or in cancerous breasts.

In conclusion, our previous and present data suggest that, as far as the prevalence of preneoplastic lesions is concerned, the morphological background of cancer-containing and contralateral breasts is substantially different from that of asymptomatic and benign lump-containing breasts, with preneoplastic lesions prevailing in the former group. On the contrary, there are no significant differences in the distribution of all other fibrocystic changes at the submacroscopic-histologic level. The predictive value of high grade AL for the future development of clinical breast cancer appears to be explained and indirectly confirmed by these morphological studies.

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