Bimodal Age-Frequency Distribution of Epitheliosis in Cancer Mastectomies

Relevance to Preneoplasia

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A census of epitheliosis in 500 consecutive cancer mastectomies has been carried out. The probability of concurrence of this phenomenon with cancer has a bimodal age-frequency distribution. It is high in cancer mastectomies from women in their early 40s, low in the late 50s and high again in the elderly. Epitheliosis during the reproductive life span is regarded as a reversible ovary-dependent abnormality. It is greatly increased in the premenopausal cancerous breast and it is thought that it carries increased risk for cancer initiation. In contrast the probability of epitheliosis in the breast in the elderly cancer patient is only slightly greater than in "noncancerous" post mortem breasts of similar age. Much of this "epitheliosis" may represent, in fact, indolent autonomous cancer though a small proportion could be epitheliosis supported by extraovarian estrogen.

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PATHOLOGISTS, both classical[1,2] and modern,[3,4] have noted transitions from mammary epithelial 'hyperplasia' (epitheliosis[5]) to neoplasia in some cases of breast cancer.

Jensen and her colleagues[4,6–8] (see also complementary discussion by Cardiff *et al.*[9]) have made exceptionally detailed dissections of cancer and autopsy breast tissue to reach important conclusions on the anatomical aspects of this association. Of particular interest is her study of the frequency and distribution of so-called "atypical lobules." These nodules of excess epithelium seen by the dissecting microscope correspond to epitheliosis in routine histopathologic studies. She found these structures more common in mammary tissue ipsilateral and contralateral to cancer. This suggests that cancer does not initiate in a normal mammary epithelium, but rather after a series of epithelial proliferations.

As the above concept stands in 1981, there is difficulty in the credible application of the (focal) epitheliosis–neoplasia concept to the generality of human breast cancer. The problem is summarized in conclusion 5 of Sir Robert Muir's article on the genesis of mammary cancer written in 1941.[2] He wrote "in a large proportion of cases of carcinoma of the breast, the stages of evolution of malignancy within ducts and acini cannot be followed and in some of these there is evidence that malignancy arises *de novo* without the occurence of preliminary hyperplastic changes." Many pathologists would agree with this. It is easy to verify, certainly at ordinary levels of sampling, that many breast cancers reside in atrophic rather than "epitheliotic" breast tissue. In 1979, Gray,[10] concluded from the examination of 178 cancer mastectomies that epithelial hypoplasia was present in 75 and "hyperplasia" in (only) 62.

We regard age as an important variable in all mammary indices and, thus, we decided to define the age-frequency distribution of epitheliosis in 500 consecutive Glasgow Royal Infirmary cancer mastectomies in the hope that it would give information on cancer pathogenesis.

Methods

A name and age list was prepared of 500 consecutive cases of breast cancer treated at Glasgow Royal Infirmary between 1974 and 1979. The filed histopathologic sections relating to these cases were assembled for review. The two pathologists (H.W.S. and F.M.) reassessed the slides covering about 20 cases at a session using a twin-headed microscope. During this review they were

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FIGS. 1–6. Selected sections from cancer mastectomies performed at Glasgow Royal Infirmary from 1975–1979. The diagnosis of invasive cancer was made from other sections of the breast tissue. The six sections illustrated exemplify lesions that were assessed as "epitheliosis" and not carcinoma *in situ*. The cases were unselected for age but fell as expected into two groups: paramenopausal and the elderly.

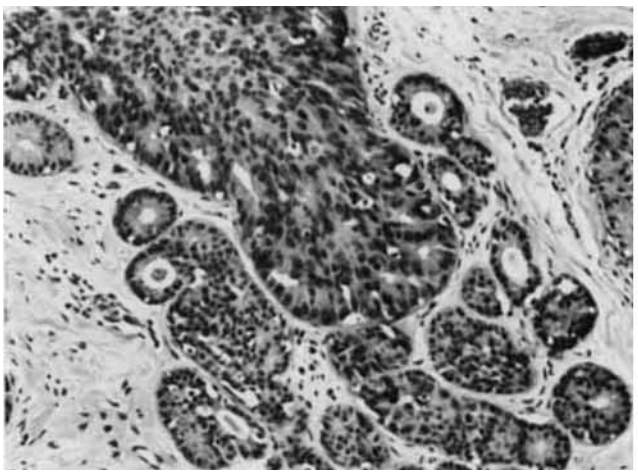

FIG. 1. Section from a 43-year-old woman at mastectomy. *Para* 4 + 0. Expansion of lobular alveolar units by epitheliosis with atypia from mild to severe.

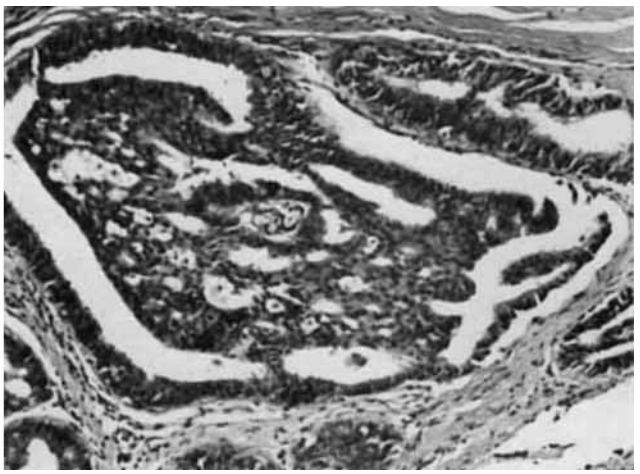

FIG. 2. Section from a 44-year-old woman at mastectomy, considered to represent cribriform epitheliosis. While the spaces represent shrinkage artefact in some parts, in others the appearances are of a semilaminar construction.

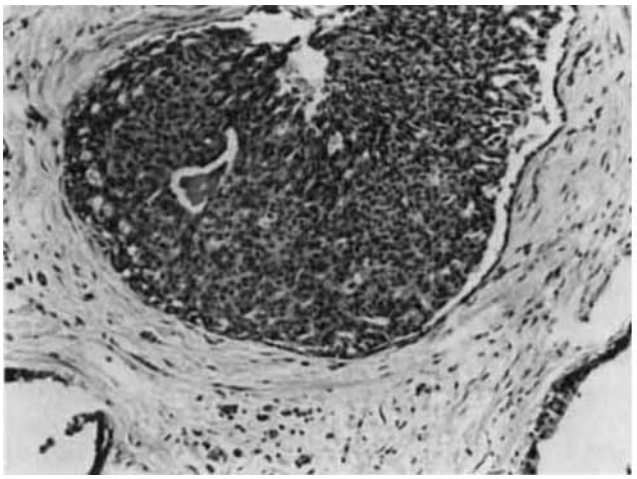

FIG. 3. Section from a 46-year-old woman at mastectomy considered to represent "solid type" epitheliosis with only mild atypia.

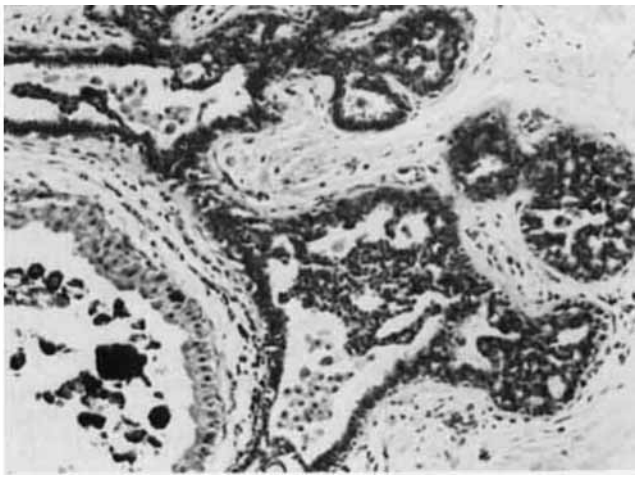

FIG. 4. Section from a 55-year-old nulliparous woman at mastectomy. Cribriform epitheliosis with apocrine metaplasia and microcalcifications. In our experience the juxtaposition of epitheliosis, metaplasia, and cystic change was a definite entity suggesting a common origin for each or a time-dependent transition.

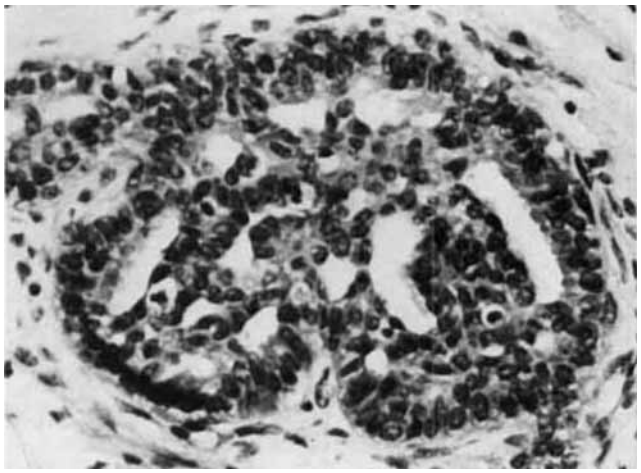

FIG. 5. Section from a 71-year-old woman at mastectomy who currently has a contralateral breast lump. Cribriform epitheliosis with mild atypia suggesting either a neoplastic pathogenesis or an extra ovarian source of estrogen, *e.g.*, adrenal.

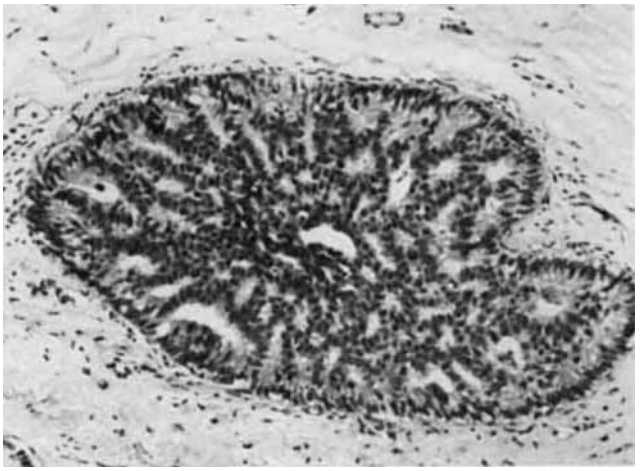

FIG. 6. Section from a 74-year-old woman at mastectomy. Section represents cribriform epitheliosis.

unaware of the age of the particular patient. All sections relating to each case were examined. Normally they contained diagnostic "cancer areas," uninvolved breast (including a block taken specifically away from the tumor) and a section through the nipple. All of the noncancerous breast tissue was assessed for epitheliosis except the tissue from the region of the nipple and the lactiferous sinuses. With these exclusions an average of two tissue sections of material from breast parenchyma proper was available for scoring. This was on a simple all-or-none basis. The pathologists sought to determine if the breast tissue showed unequivocal epitheliosis or not, *i.e.*, "regular typical epithelial proliferations in ducts or lobules" (WHO AIII lesions).[11] In the literature, the term epitheliosis has been used synonymously with this definition. Dawson,[5] who originated the term, described it as a "multiplication of epithelial cells within existing ducts and ductules without the formation of new glandular elements." As she said, this proliferation may be of

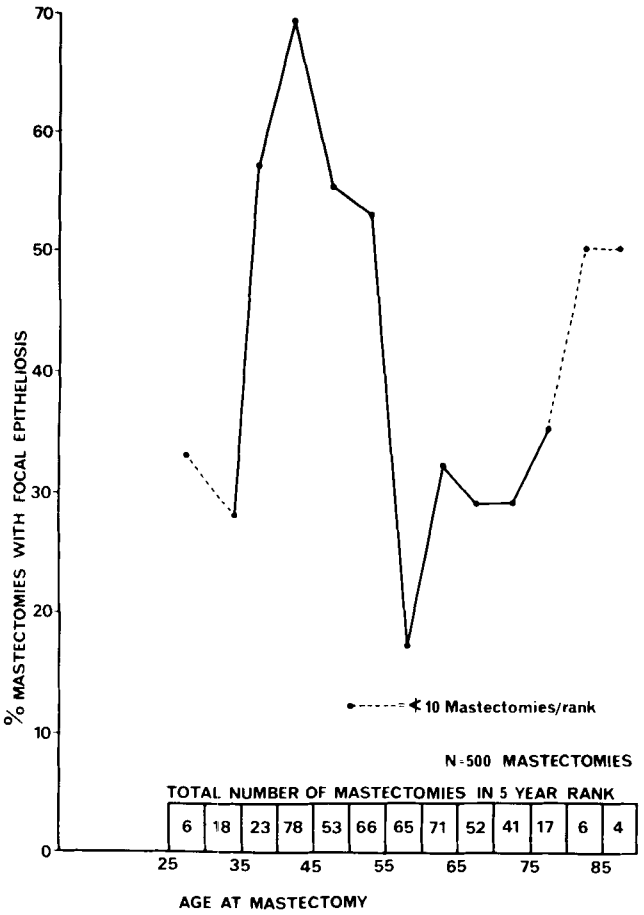

FIG. 7. Age-frequency distribution of epitheliosis in cancer mastectomies performed at the Glasgow Royal Infirmary 1974–1979. Illustrated are the results of the census for the presence or absence of epitheliosis in 500 consecutive cancer mastectomies. For the purpose of plotting, the mastectomies were allotted to a five year rank depending on the patient's age at operation. However this information was not available to the pathologists carrying out the census until the data were collated. Note the bimodal age-frequency distribution.

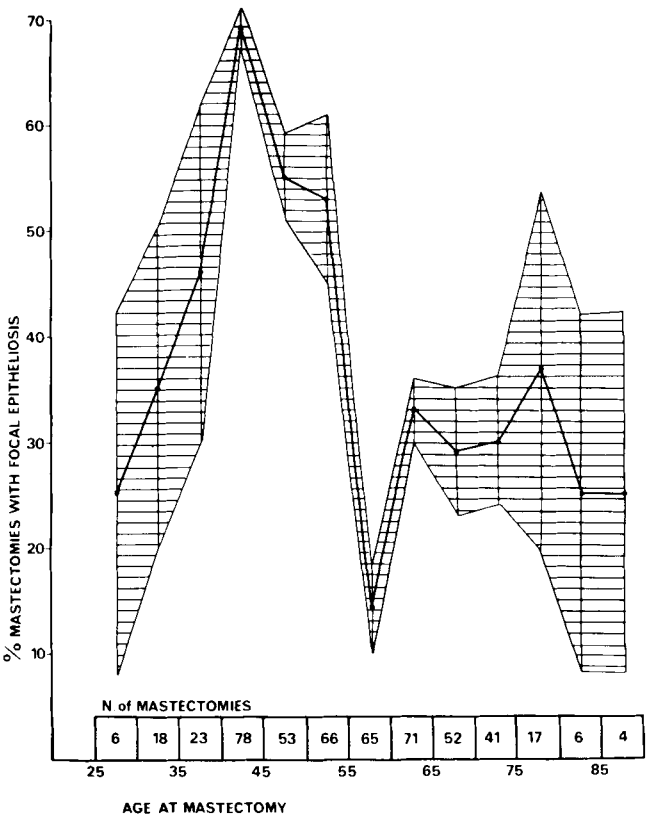

FIG. 8. Reassessment of data by computing means and standard errors from percentage totals for each year (1974–1979) to obtain dispersion indices. Of course, standard errors based on percentages have to be viewed with caution.

"solid or papillary character or may form a multilayered cell lining." During the census it was an absolute rule that all decisions on the presence or absence of epitheliosis were made at the time of looking at the slides and no changes were made thereafter. Doubtful cases were scored as negative for epitheliosis. Typical examples of cases scored positively for epitheliosis are illustrated in Figures 1–6. It should be noted that all epithelia (including apocrine or other metaplastic types) were scored positive for epitheliosis if they fulfilled Dawson's criteria (we have not found a specific reference as to whether metaplastic epithelia are included in her definition).

Results

Results are presented as a graph (Fig. 7). They confirm and extend our earlier conclusions[3,12,13] of a peak frequency of epitheliosis in cancer mastectomies from patients in the 41–45-year age rank and a trough in the 56–60-year rank. The increased number of specimens now studied has enabled us to define a second peak in the elderly (80–90 age group). This is significant at the 2.5% level by a Spearman test for a monotonic increase with age. The evidence for a sharp fall of cancer associated epitheliosis in mastectomies from patients aged

TABLE 1. Comparison Between the Observed Frequency of Epitheliosis in the Nonneoplastic Tissue of Cancer Mastectomies and the Expected Frequency as Found in the Mammary Tissue of Consecutive Autopsies

Age (yr)	Percent breasts with epitheliosis: Cancer mastectomies	Autopsy* breasts	Observed *vs* expected
26–30	33%	8%	×4.1
31–35	28	7	×4.0
36–40	57	6	×9.5
41–45	59	27	×2.6
46–50	55	14	×3.9
51–55	53	17	×3.1
56–60	17	23	×0.7
61–65	32	27	×1.2
66–70	29	27	×1.1
71–75	29	27	×1.1
76–80	35	35	×1.0
81–85	50	33	×1.5
86–90	50	No data	—
$\bar{x}$	41%	21%	×2.8

* Sandison, 1962.

in their middle 40s to late 50s is discussed here *in extenso*, as we think it is a new and important finding.

The authors examined an estimated average of two paraffin blocks of noncancerous mammary tissue per case, and 69% of the 78 mastectomies falling into the 41–45-year age group contain such foci of epitheliosis. An estimate of the reliability of this percentage *vis-à-vis* a universal population, can be obtained from estimating this figure from each year's (1974 through 1979) cases separately. New means and their standard errors can then be calculated from the six estimates (Fig. 8). The individual yearly estimates are 69%, 58%, 67%, 71%, 73%, and 75%, respectively. In other words, the overall average (69%) is a reasonably reliable indicator of the "universal" population. This high frequency of epitheliosis is in sharp contrast to the low frequency found in the 65 mastectomies falling into the 56–60-year age group. Here the average incidence of epitheliosis was found to be only 17% with the individual estimates being scattered as follows: 8%, 21%, 29%, 30%, 0%, and 14%.

It is reaffirmed that these estimates were made by two pathologists with no knowledge of the patient's age at mastectomy. We conclude that a sharp fall in the epitheliosis incidence in cancer mastectomies from the 41–45-year age group to the 56–60-year age group does characterise the data and that there is a bimodality.

Discussion

The question arises as to whether the bimodal distribution of the frequency of epitheliosis is an age-related trend of normal mammary tissue or whether cancerous breasts exhibit an altered frequency. For comparison, we have a substantial census of the "normal" age-frequency distribution of epitheliosis estimated from 800 consecutive autopsies (unselected for diagnosis) at an adjacent Glasgow hospital by our colleague Dr A. T. Sandison.[14] The sample size of tissue examined in each case of Sandison's study was of a similar order to that of our own and therefore it forms a valid comparison especially in regard to age trends. His tabulated data have been plotted so that a comparison may be made between the observed and expected frequency (Table 1;

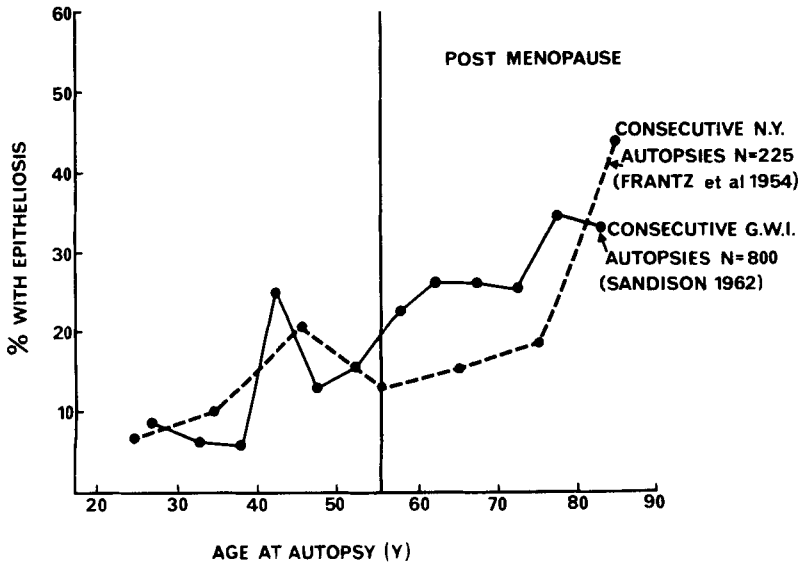

FIG. 9. Comparative estimates for the age-frequency distribution of epitheliosis in New York[15] and Glasgow[14] hospital consecutive autopsy populations. The sets of data are in good agreement.

compare Figs. 7 and 9). The graph also summarizes a similar "control" census of epitheliosis frequency derived from a New York autopsy population published by Frantz and colleagues.[15] Perusal of these three studies show that, premenopausal *cancer* mastectomies contain a substantial increase of epitheliosis above the expected. It can be seen from Table 1 that cancerous breasts from patients aged 26–55 years contain 2.6–9.5 times the expected frequency. In contrast, postmenopausal cancerous breasts evidenced an observed frequency of epitheliosis above but yet remarkably close to that expected from the autopsy studies.

Jensen and colleagues showed by subgross dissection of 52 breasts that there was, on average, an increase in "atypical lobules" in cancer-associated tissue (that is above autopsy controls; 65 breasts dissected); and, further, that there was an age-related increase in this phenomenon until the seventh decade.[4]

Our data confirm that there is an overall increase in epitheliosis in cancer-associated breast tissue (×2.8; table 1) and that over selected age ranges there are systematic increases with age, (*i.e.*, age 26–40 years and 61 years upward).

However, our finding of a bimodal age-frequency distribution of epitheliosis in cancer-associated breast tissue is in partial conflict with her conclusions and a discussion is pertinent. First it is important in this context that there are between-country differences in the presence or absence of the so-called menopausal "hook" in the incidence of the disease.[16–18] In high-incidence countries this fall or plateau seen, in medium-incidence countries, is obscured by steadily increasing rates; high-incidence countries are predominantly characterised by an increase in postmenopausal cases; thus, although the Scottish incidence of breast cancer is relatively high in world terms,[19] in the current instance it is substantially less than in California where Jensen's study was carried out.[19] Second, Jensen's sample size was relatively small being less than a quarter of our own and it is clearly an important principle in assessing population trends that the sample size is reasonably large. Third, in our own study a relatively constant amount of tissue was examined, and discrepancies could occur with conclusions from subgross dissection because in the latter the whole breast is examined. In the former, a block of a "fatty" breast would contain proportionally less epithelial tissue. Estimates for the age-frequency distribution of epitheliosis in postmortem material do exhibit modest falls (13%[14] and 8%[15]) at the time of menopause (Fig. 9), but these are small compared with the peak–trough difference in cancer-associated epitheliosis. The possibility that the bimodal distribution is due to a dilution of epithelial tissue by fat in the early post menopause is not a major explanation of our findings.

We are convinced that a bimodal age-distribution of epitheliosis does characterize the Glasgow population of cancer mastectomies.

Mammary epithelium is a hormone supported tissue and on first principles a pathologist would expect involution to occur at the menopause. Our data are consistent with this expectation. In contrast to the epitheliosis-laden breast tissue of the premenopause cancer mastectomy, the same tissue from early postmenopausal women exhibits no significant increase of epitheliosis above autopsy controls. It can, therefore, be reasonably assumed that the autonomous cancer in this early postmenopausal group, having initiated in a focus of epitheliosis some years earlier, is now left without evidence of its origin.

With regard to the elderly (aged 80–90 years), our data suggest that at the very minimum half of the mastectomies contain lesions recognised as epitheliosis by the histopatholgist (Table 1). However, Sandison[14] finds only a slightly lower probability in his breast autopsy series. If this difference is real it must be small; it could represent an effect of nonovarian estrogen. But the primary conclusion is that 'epitheliosis' in the elderly would seem to have little or no predictive value for cancer risk. A secondary conclusion might be that breast cancer in the elderly is a closely age-linked phenomenon, *c.f.*, skin cancer, and that ordinary histopathology cannot discriminate between benign and malignant disease, *i.e.*, that many of the lesions in this group diagnosed as epitheliosis represent indolent malignancy.

In summary, we postulate two primary populations of breast cancer differing in pathogenesis: (1) a "prime of life group" age 25–60+ at diagnosis initiated in epitheliosis supported by ovarian estrogen; and (2) an elderly group with some difference in etiologic causes of disease.

We believe it may be possible to identify the "prime of life" group by surface heat changes. Gautherie[20] has described a thermographic signal associated with increased risk for the subsequent development of clinical breast cancer. It is interesting that patients exhibiting this Stage III thermogram fall into the age group of the first peak of the bimodal distribution of epitheliosis described herein. Vascular changes associated with epitheliosis could be a morphologic explanation of his signal. In this context we have developed the 16-channel thermochronobra which takes into account the ultradian, circadian, and menstrual rhythms of breast temperature in an attempt to obtain a better description of this signal in breasts considered to be at increased risk.[3]

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