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Mammographic Patterns in Breast Cancer Chemoprevention with Fenretinide (4-HPR)

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In 1987 a chemoprevention trial was started at the Istituto Nazionale Tumori of Milan to evaluate the efficacy of fenretinide or 4-HPR (an effective agent against carcinogen-induced epithelial tumours in experimental animals) in reducing the incidence of contralateral breast cancer in women previously treated for an early breast cancer (pT1, pT2, N-). Patients were randomised into two groups: 4-HPR 200 mg/day vs. no treatment. We reviewed the mammograms of 149 patients who received 4-HPR for at least 4 years to examine whether changes seen in the mammary glands of rats could also be seen in women. For each patient, at least five mammograms (one at baseline and four annual controls) of the contralateral breast were classified according to Wolfe's parenchymal patterns (N1, P1, P2, DY). With the daily dosage of 200 mg and after follow-up, no changes in mammographic patterns were observed.

Key words: breast, mammographic parenchymal patterns, chemoprevention, retinoids
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INTRODUCTION

FENRETINIDE [*N*-(4-HYDROXYPHENYL)RETINAMIDE] or 4-HPR is a synthetic retinoid which has been shown to cause, in experimental animals, a reduction in the incidence of carcinogen-induced epithelial tumours. Among the synthetic retinoids tested against mammary and urinary carcinogenesis, 4-HPR seems to be the most promising in terms of its effectiveness relative to toxicity [1]. One of the advantages of 4-HPR is its ability to concentrate in breast tissue without accumulation in the liver [2, 3]. The effect of 4-HPR on prepuberal female rats has been investigated with regard to the development of buds in the ductal tree of the mammary gland. The reduction of ductal branching and end-bud proliferation with 4-HPR is more pronounced than after administration of retinyl acetate, a compound which in experimental animals prevents breast cancer induced by methyl-nitrosourea but is also toxic in animals fed chronically for 6 months [4–6]. For these reasons 4-HPR was chosen in a chemoprevention trial run at the Istituto Nazionale Tumori of Milan to evaluate its capacity to reduce the incidence of contralateral breast cancer in patients who had already been treated for an early breast cancer [7].

We reviewed the mammograms of 149 consecutive patients who received 4-HPR for at least 4 years, in order to test whether the experimental changes seen in female rat mammary glands could also be seen as modifications in human mammographic patterns.

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PATIENTS AND METHODS

Patients treated for an early breast cancer without axillary node metastases and aged between 35 and 65 were chosen as candidates for the clinical trial. With the exception of surgical treatment (quadrantectomy with or without radiotherapy; mastectomy), no other treatments were allowed. All patients were randomised into two groups; one received 200 mg/day of 4-HPR for 5 years, and the other, the control group, did not receive any treatment. As 4-HPR reduces retinol plasma levels, a 3-day drug holiday at the end of each month was prescribed to allow for partial recovery of plasma retinol levels. All patients underwent a clinical examination and were interviewed for randomisation. Eligible patients had to use measures to avoid pregnancy during the study and for 6 months after treatment interruption because of the potential teratogenicity of the retinoid. Mammography was performed at baseline and then once a year.

All mammographies were examined to exclude tumoral lesions; parenchymal patterns of the contralateral breast were classified according to one of the four groups described by Wolfe [8, 9]. According to Wolfe, the risk of developing breast cancer depends only on mammographic parenchymal patterns. He identified four features, called N1, P1, P2 and DY.

N1 indicates a breast which is considered 'normal' according to the age of the patient. In young women, the breast is mainly composed of fat or connective tissue of trabeculated appearance. In older women, N1 refers to a breast composed almost exclusively of fat. P1 is a breast composed mainly of fat but with a beaded linear pattern representing prominent ducts in the subareolar area, or in the upper axillary quadrant, or in other portions of the breast. P2 indicates a more severe involvement of the breast with a prominent duct pattern that often has a triangular design in the central portion of the breast and involves half of the parenchymal volume or possibly nearly all of it. DY indicates primarily a general increase in density of the parenchyma of the breast with a variable degree of prominent ducts. Radiographically, one observes a general increase in density, either homogeneous or not.

Table 1. Clinical data of 149 4-HPR patients

Age (years)	
Median	49
Range	36–65
Menopausal status	
Premenopausal (*n*)	89 (60%)
Postmenopausal (*n*)	60 (40%)
Parity	
Nulliparous (*n*)	42 (28%)
Median age at first childbirth (years)	27 (range 22–35)

Wolfe identified different risks for developing breast cancer in these four patterns and considered P2 and DY as the highest risk groups. Indeed, these two groups had a breast cancer incidence 18 times higher than the N1 and P1 groups, which are considered as the lowest risk groups.

All mammographic examinations were performed at the Istituto Nazionale Tumori, using a Siemens MAMMOMAT B and a Siemens MAMMOMAT 2 with a moving grid and a focal spot of 0.3 mm. All mammograms were carried out with automatic exposure to allow for comparison.

RESULTS

To test whether 4-HPR induced visible changes in mammographic parenchymal patterns, as seen in subgross mammary slices of experimental animals, we reviewed the mammographies of 149 consecutive patients who received 4-HPR for more than 4 years. Each patient had at least five mammographies of the contralateral breast, classified according to Wolfe's grades. The median age of this group of patients was 49 years (range 36–65), about 60% of them being premenopausal when entering this prospective study. There were approximately 28% nulliparous women and the median age at first childbirth was 27 years (Table 1).

Primary breast cancer occurred in the right breast in 83 cases (56%) and in the left breast in 66 cases (44%).

Ductal carcinoma was the main histological diagnosis (112 cases, 75%), while lobular carcinoma occurred in 28 cases (19%), and other less common histotypes in 9 cases (6%) (Table 2).

The contralateral baseline mammographies were divided according to Wolfe's classification, as shown in Table 3.

The review of all mammographies after 4 years of follow-up showed no evidence of substantial changes in breast patterns, except in 1 patient in which P2 turned into P1.

Table 2. Histological data of the 149 HPR patients

	No. of cases (%)
Site of the first tumour	
Right breast	83 (56%)
Left breast	66 (44%)
Size of the first tumour	
T1/N0	149 (100%)
Histological diagnosis	
Ductal carcinoma	112 (75%)
Lobular carcinoma	28 (19%)
Other histotypes	9 (6%)

Table 3. Wolfe's classification of baseline mammographies of 149 patients

Group	Number of cases	%
N1	9	6.0
P1	51	34.2
P2	59	39.6
DY	30	20.2

DISCUSSION

Wolfe's conclusions about the increased risk for P2 and DY patterns are controversial [10, 11]. This controversy can be explained by the different associations of patterns with other main risk factors (age, parity, menopausal status, weight, age at birth of the first child), and by the different methods used by the authors when gathering their series of patients [12, 13].

A recent meta-analysis on the risk of breast cancer associated with mammographic parenchymal patterns found different summary odds ratios depending on the study design, ranging from 0.54 (prevalence surveys) to 5.19 (cohort studies), suggesting a higher risk for P2 and DY patterns in relation to other main risk factors [14].

The present paper does not discuss the validity of Wolfe's conclusions, but the authors used his classification as reference.

Some studies were performed to evaluate potential mammographic parenchymal pattern changes during or after non-contraceptive oestrogen treatment, or with different kinds of diet [15, 16]. In particular, Brisson analysed the association of breast tissue morphology seen on mammograms with diet, especially with the intake of fat and vitamin A. He concluded that a high carotenoid and fiber intake was associated with a reduction in the extent of densities on mammograms, but retinol intake seemed to have little or no effect on mammographic features.

In the 149 patients who received 200 mg of 4-HPR per day for more than 4 years, only 1 case showed a modification in the parenchymal pattern: P2 at baseline mammography turned into P1 at the fourth radiological examination.

A physiological change in parenchymal patterns usually occurs during a lifetime, and is often correlated with hormonal status. A modification due to the drug could, therefore, only take place in a short time.

In our series no substantial changes in parenchymal patterns were observed. This may be due to the dose used (200 mg/day). Changes occurred in female rats fed with a much higher dose (782 mg/kg of diet): the reduction of the end-bud proliferation and ductal branching noted in experimental animals might result from higher doses which are not visible for chronic small dosages.

Another interpretation might be that structural modifications in the breast are only visible in subgross slices but not in the mammographic parenchymal pattern. However, we have not performed such a biopsy of the contralateral breast for that purpose.

Finally, the anti-proliferative and differentiative effects of 4-HPR occur on single epithelial cells with modulation of the oncogene expression or changes of the cell membrane [17].

According to Arthur [18], Wolfe's patterns express the distribution of connective and fat tissues in the breast; as a result,

ultrastructural modifications in epithelial cells might not influence mammographic features.

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Feature Articles

Familial and Genetic Aspects of Colorectal Carcinogenesis

Rodney J. Scott and Hansjakob Müller

There is abundant clinical and pathological evidence which suggests that colorectal cancer arises in a sequential manner through a series of events that can be followed during the progression of the disease from early adenoma through to metastatic disease. The molecular events that are associated with the initiation and progression of the disease are gradually being unravelled. As the molecular characterisation of colorectal cancer continues, new mechanisms by which the disease progresses are becoming evident. In this short review, a brief description of current knowledge of colorectal cancer development is presented.
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INTRODUCTION

COLORECTAL CANCER (CRC) is the second most common malignancy in European countries, with similar incidence rates for both men and women. Epidemiological studies imply that environmental factors play a significant role in the aetiology of the disease [1]. For example, the incidence of CRC is very much higher in countries where the diet is rich in fat and low in fibre [2,3]. In addition, there exist a number of distinct genetic syndromes which predispose people to the development of CRC, these are listed in Table 1. From this table, there are two genetic entities, familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC) which predispose persons to an extremely high risk of developing CRC at a young age. In addition to CRC, other neoplasia and symptoms tend to aggregate in these families, implying that the effects of the predisposition are not restricted to the colon alone. However, not all

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