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Breast Carcinoma and Skeletal Formation

Roberto Mondina, Giovanni Borsellino, Silvano Poma, Mario Baroni, Brunella Di Nubila and Paola Sacchi

We have studied skeletal structure in 67 women with breast carcinoma and in 59 women without breast carcinoma, looking for differences of development that might be correlated with hormonal, metabolic or genetic abnormalities. We have measured the lengths of the limbs and of their segments (upper arm, forearm, thigh, leg), of the bisacromial and bitrochanteric transverse diameters and total height and height divided into the parts from vertex to pubis and from pubis to the ground. The analysis showed statistically significant coefficients of regression with presence of mammary carcinoma for height (0.0904262, S.D. 0.0461), length of thigh (0.12989, S.D. 0.03981) and length of lower leg (−0.68475, S.D. 0.1390). This skeletal type might be the expression of a genetic condition that is associated with the existence of mechanisms that permit development of mammary cancer.
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INTRODUCTION

THE MECHANISMS for origination of most mammary carcinomas are still essentially unknown, as they are for most carcinomas. Many different hypotheses for the origins of these tumours have been presented, especially in relation to the so-called 'risk factors' or to associated diseases. These include, among others, metabolic abnormalities, either single ones, such as serum cholesterol levels [1], or more general ones, such as type of diet [2–4], body weight [5–10] or general development of the skeleton [7, 11, 12]. Other things that have been looked for are genetic or racial factors [13, 14].

Since the breast is a typical hormone-dependent organ, it has also been hypothesised that the same endocrine stimuli that induce its normal development and function might also promote origin of carcinoma. This theory is supported by the favourable effects on mammary carcinoma of anti-oestrogen treatment. However, no endocrine genesis of the tumour has as yet been supported by the levels of hormones found in the biological fluids of these patients [15], and it has been suggested to explain this that there might have been abnormal activity of the gonads in some definite period of life [16, 17].

In recent years there have been reports in the literature indicating a correlation between skeletal development, especially in terms of height, and mammary carcinoma [7, 11], but not all investigators agree with this [6, 10]. In addition, data about height are difficult to use to interpret the aetiopathogenesis since differences in height can result from many different factors, environmental, dietary, genetic, racial or others.

We have studied skeletal structure in its several parts, looking for differences of development that might be correlated with hormonal, metabolic or genetic abnormalities. We have measured the lengths of the limbs and of their segments (upper arm, forearm, thigh, leg), of the bisacromial and bitrochanteric transverse diameters and total height and height divided into the parts from vertex to pubis and from pubis to the ground, for women with and without mammary carcinoma, the latter both normal women and women with mammary dysplasia.

Correspondence to R. Mondina.
R. Mondina is at the Consiglio Nazionale delle Ricerche, Clinica Ostetrica Ginecologica della Università, via Commenda 12; 20122 Milano; G. Borsellino and S. Poma are at the IV Clinica Chirurgica della Università, Ospedale Maggiore, via Francesco Sforza 35, 20122 Milano; and M. Baroni, B. Di Nubila and P. Sacchi are at the Divisione di Medicina Generale degli Istituti Clinici di Perfezionamento, via S. Barnaba 8, 20122 Milano, Italy.
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PATIENTS AND METHODS

The patients were 126 women who came to our hospital's Outpatient Centre for Prevention of Mammary Cancer for their first breast checks (mean age 49.3, S.D. 12; range 23–79), with no endocrine, metabolic or systemic disease. Their medical histories did not include any osteoarticular abnormalities nor abnormalities of somatic development. 67 of these women had mammary carcinoma (20 premenopausal stages I–III, 47 postmenopausal stages I–III). The diagnosis was based on physical, thermographic, ultrasound and mammographic examinations and the cytology of a needle aspiration biopsy sample, and was then confirmed by the histology of the surgical specimen.

There were 59 women in the control group, 46 premenopausal and 13 postmenopausal, randomly chosen from women coming to the same outpatient clinic in the same period, without mammary cancer on the basis of clinical, thermographic, ultrasound and mammographic examinations and comparable for age, weight, medical and general histories with the neoplastic women. 21 of these women were considered to have 'normal' breasts and 37 had more or less obvious cysts associated with thickening of the stroma (benign breast dysplasia). A fibroadenoma was found in 1 woman.

Total height (top of head to bottom of the feet) was measured anthropometrically, and measurements were also made of the upper portion (top of head to upper margin of pubic symphysis) and lower portion (upper pubic margin to the sole). Lengths of the limbs were measured with a metric measuring tape: upper arm, from the upper edge of the humerus to the tip of the elbow, forearm from the tip of the elbow to the end of the styloid process of the ulna; thigh from the upper edge of the great trochanter to the head of the fibula; the lower leg from that point to the lower edge of the external malleolus. A caliper was used to measure the transverse diameters, for the bisacromial between the two points sticking out farthest laterally from the acromions, for the bitrochanteric between the two points sticking out farthest from the two great trochanters. These measurements were done under the same conditions for both cancer patients

Table 1. Anthropometrical measurements for women with and without mammary carcinoma, in cm

	Carcinoma	Controls
Height	159.8 (6.3)	159.1 (6.8)
Top of the head to pubis	81.5 (4.9)	80.7 (5.2)
Pubis to ground	78.0 (5.8)	78.4 (6.0)
Bisacromial	40.4 (3.9)	38.5 (3.8)
Bitrocantheric	33.0 (4.0)	33.3 (3.2)
Upper arm	33.0 (2.8)	30.4 (3.1)
Forearm	25.7 (1.6)	21.6 (7.9)
Thigh	48.3 (5.2)	53.2 (6.5)
Leg	39.9 (3.1)	35.9 (2.8)

Mean (S.D.).

and controls and verified by cross-over of the people making the measurements.

The anthropometric measurements of each patient were evaluated by a logistic regression analysis [18] in which the dependent variable was the presence or absence of mammary cancer and the independent variables were the anthropometric values for the two groups.

We also did discriminant analysis, with the grouping criterion being either presence or absence of mammary carcinoma and the variables being the anthropometric values, with a tolerance limit for admission to the classification function of $F = 1$.

RESULTS

Table 1 contains the anthropometric values for the two groups (carcinoma patients and controls). Total height and the distances from top of the head to top of pubic symphysis or pubic symphysis to bottom of feet did not differ for the two groups. The most interesting difference was in the development of the limbs, especially the lower limbs, which measurements were found to be of special importance for the purposes of this study. In fact, the analysis showed that the height of the individual, the length of the thigh and the length of the lower leg have statistically significant coefficients of regression with presence of mammary carcinoma. For height the coefficient is 0.090426, S.D. 0.0461; for the thigh 0.12989, S.D. 0.03981 and for the lower leg −0.68475, S.D. 0.1390.

With these three variables we can calculate the probability for a subject to have mammary carcinoma, using:

$$1 - \frac{e^{-a}}{1 + e^{-a}}$$

in which $a = 4.8742 + 0.90426\,H + 0.12989\,T - 0.68475\,L$, with H = height, T = length of the thigh and L = length of the lower leg (in cm).

With this equation, we could construct for each height a nomogram to be used for reading off directly the probability that a woman would develop mammary cancer from the lengths of her thighs and of her legs.

Fig. 1 contains the results of a discriminant analysis between the groups of patients with mammary carcinoma and healthy controls (histogram of canonical variable, $F_{4,121} = 26.10$, $P < 0.01$).

DISCUSSION

Our results show that the carcinoma group and the controls did not differ in either total height or height divided into the sections top of the head to top of pubic symphysis or top of pubic symphysis to bottom of the feet, nor did they differ in transverse measurements (bisacromial or bitrochanteric). They differ only in the values for the segments of the limbs, especially the lower limbs, which at equal total lengths were more developed distally or peripherally in the carcinoma patients, which is to say that the length of the leg was longer and the length of the thigh shorter in the patients than in the healthy controls: shorter thighs and relatively longer lower legs in relation to the total height.

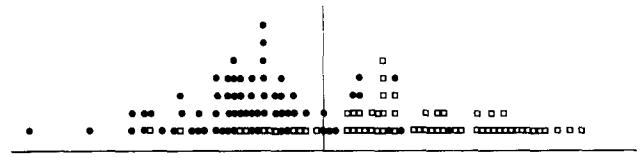

Fig. 1. Histogram of canonical variable. ● = Carcinoma, □ = controls.

In fact our study indicates statistically significant correlations between height, length of the leg and carcinoma of the breast, but using only height, whether total or those of the upper and lower halves of the body, did not differentiate patients from controls, nor did the transverse diameters.

In recent years there have been only a few studies of correlations between skeletal measurements, mostly total height, and in some of these studies correlations were found [7, 11] and in others not [6, 10]. For Japanese women, but not for white women, Kolonel *et al.* [12] found a correlation between presence of mammary carcinoma and foot length (based on shoe size reported in a questionnaire) [12].

This study appears to agree with our results because their patients also had greater development of the distal parts [foot] of the lower limb. It is not easy to interpret the data about anomalies of skeletal development because we know so little about the mechanisms of regulation of growth of different segments of the limbs. All we can do is make some suggestions.

Korenman's suggestion [16] that there is some abnormality of gonadal activity in some definite period of the life span is not very useful for explaining our data, since the difference in our patients is not in the development of the long bones but in the relative lengths of the segments of the lower limb, which are profoundly different relative to height.

Another suggested hypothesis [4] was that the greater height of carcinoma patients might be caused by some dietary factor and that weight increases might also trigger the tumour. This hypothesis does not fit our patients, in which there is not an overall hyperdevelopment of the skeleton but a disequilibrium of growth, as compared with the controls, between the different segments of the lower limbs (the thigh is shorter, the leg longer).

The hypothesis that is most convincing at this time is that this skeletal type might be the expression of a genetic condition that we might hypothesise to be associated with the existence of mechanisms that permit development of mammary cancer (derepression of oncogenes?).

From a practical point of view, if our data will be confirmed by other groups of investigators who study populations and ethnic strains different in both genetics and life habits, they might be used with the other methods used currently to screen populations for risk of developing mammary cancer; the method is certainly very simple and costs very little. The measurements could be started at a young age, in which skeletal development is finalised: much earlier, that is, than development of mammary

carcinoma. For this reason, we intend to extend this study, to many more patients of different ages, including younger patients.

Additional data might also provide information useful for theoretical study of the pathogenetic mechanisms for mammary carcinoma, also for evaluating better the genetic hypothesis of the origin of mammary carcinoma, which appears to be consistent with our data obtained in this study.

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Increased Myelosuppression during Cytostatic Treatment and Pleural Effusion in Patients with Small Cell Lung Cancer

Jørn Herrstedt, Paul Clementsen and Ole Paaske Hansen

30 patients with small cell lung cancer (SCLC) and malignant pleural effusion were compared with 30 matched patients with SCLC but without pleural effusion. In the 30 with pleural effusion, white blood cell and platelet counts fell significantly after initial chemotherapy, necessitating dose reduction. Of the patients with pleural effusion, 16 developed severe (WHO grade IV) leukopenia, 7 had severe thrombocytopenia, and 2 patients died of infection. Accordingly, exhaustive aspiration of radiologically verified pleural effusion before starting chemotherapy in patients with SCLC is recommended.
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INTRODUCTION

MYELOTOXICITY IS the dose-limiting factor for the majority of cytostatics. It is well known that during methotrexate treatment pleural effusion may act as reservoirs, resulting in a prolonged presence of methotrexate in the plasma compartment [1]. The plasma concentration and especially the time of exposure of methotrexate correlate well with the myelotoxicity [2]. Such relationships make it important that the physician is aware of the existence of an extra non-physiological compartment. Other cytostatics, e.g. doxorubicin [3], have also been detected in malignant effusions during therapy. Unfortunately, the clinical importance of pleural effusion for the metabolism and toxicity, especially the myelotoxicity, of cytostatics is largely unknown.

The aim of the present study was to compare the toxicity of