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BREAST CANCER DIAGNOSIS UNDER THE AGE OF FORTY YEARS

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The authors report on a multicentric consecutive series of 382 cases of primary breast cancer detected before the age of 40 years. Physical examination (PE) was always performed, whereas other diagnostic tests were performed in selected cases, namely mammography (M) in 334, fine needle aspiration cytology (CYT) in 188 and thermography (TH) in 123 cases. Single tests showed a high rate of false-negative/benign cases (PE, 0.23; M, 0.26; CYT, 0.37 and TH, 0.50), especially when the T1 subgroup was considered (PE, 0.34; M, 0.38; CYT, 0.42 and TH, 0.78). The poor results recorded for TH make its current diagnostic use highly questionable. The policy of extensive biopsy of all « dubious » benign lesions on PE allowed for the detection of 41 of 382 cancers and reduced the PE false-negative/benign rate to 0.12 for the total or 0.15 for T1 cancers, although about 80 unnecessary biopsies for each cancer detected were performed in this way. The association of PE to one or more tests resulted in even lower false-negative rates (0.06 for the total, 0.10 for T1 cancers). The authors criticize the aggressive policy of extensive biopsy recommendation based only on a dubious report on PE alone and stress the opportunity of the routine association of M and CYT to PE, since this combination seems to achieve a higher breast cancer detection rate even in this age group.

The detection of breast cancer (BC) before the age of 40 is a relatively infrequent event, accounting for less than 7 % of all incident cancers of the breast (6.98 % in a retrospective survey of BC incidence in the District of Florence in the years 1977-1982) (2). The low incidence of breast cancer and the well-known reduction in sensitivity of mammography (M) at younger ages (3) are the main reasons for the exclusion of women aged less than 40 from almost all population-based mammographic screening programs in the world (6). The recommendations for BC diagnosis under 40 years of age, as suggested by most national guidelines, are limited to breast self examination and to clinical investigation of symptomatic cases. Unfortunately, even in clinical practice, diagnostic errors are not infrequent in this age group. Age does not affect only the accuracy of M; the physical examination (PE), even if to a lesser extent, also shows a reduction in sensitivity at younger ages (3, 7). The use of additional diagnostic tests, such as thermography (TH) or ultrasound mammography (US), has been suggested to improve the overall diagnostic accuracy.

In 1984, following a previous multicentric national review (5), the Italian National Task Force for Breast Cancer (FONCaM) promoted a multicentric study on detection modalities of BC in women aged under 40. The present report concerns the evaluation of a large series of BC

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cases collected from 6 institutions adhering to the study which was essentially aimed to assess the sensitivity of single or combined tests currently employed in BC diagnosis.

Material and methods

The study evaluated a consecutive multicentric series of 382 BC cases detected in women aged 39 or less. Study cases were retrospectively collected from 6 Italian institutions in the towns of Florence, Padua, Bari, Turin and Albano Laziale. The period considered for the retrospective review was not the same in all centers, and was as long as 15 years. The presence of BC was assessed on a histologic basis. The histologic type was in situ ductal in 14, in situ lobular in 6 and infiltrating in 362 cases. Of the latter group 258 were ductal NOS, 22 were lobular, 24 were ductal + lobular, 26 were ductal + other than lobular, 6 were mucinous, 5 were tubular, 4 were medullary and 17 were undetermined.

Tumor category, according to the UICC-TNM system, was TIS in 20, T1 in 116, T2 in 169, T3 in 52 and T4 in 25 cases. Pathologic nodal status was unknown in 42, negative in 171, and positive in 169 cases. Case distribution varied according to age, which was under 30 in 26 cases, between 30 and 34 in 93 cases and over 34 in 263 cases.

The present series was drawn from a population self-referred to a breast clinic for consultation, usually on a symptomatic basis. In fact, 355 (93%) patients referred with subjective symptoms, 320 (84 %) with a lump, 92 (24 %) with pain, 30 (8 %) with skin alterations and 8 (2 %) with nipple discharge. Only 27 (7 %) cases in this study had no subjective complaint at presentation.

PE and M were available in all study centers, whereas fine needle aspiration cytology (CYT) and TH where available in 5, US in 3, and diaphanoscopy (DIA) in 2 centers. PE was always performed, whereas the other tests were performed in selected cases in the absence of a fixed diagnostic protocol. Consequently, M was performed in 334 cases (87 %), CYT in 188 (49 % of cases when the test was available), TH in 123 (33 % when available), DIA in 57, and US in 19. Due to the low number of studied cases, DIA and US were excluded from evaluation, which was thus limited only to PE, X-ray (RX), TH and CYT. Also the combination of diagnostic tests varied between centers: 27 cases were examined by PE alone, 78 by PE+RX, 15 by PE+CYT, 5 by PE+TH, 84 by PE+RX+TH, 139 by PE+RX+CYT, 1 by PE+TH+CYT and 33 by all four tests.

For all cases the diagnostic outcome of each test was recorded. For PE, M, and CYT the diagnostic report was coded as negative, benign (no biopsy suggestion), dubious (evidence consistent with a benign lesion although sufficiently questionable to suggest histologic confirmation), and suspect/positive (evidence consistent with cancer). TH diagnostic report was coded as negative/benign (TH1-3 according to Amalric et al. (1)) or suspect/positive (TH4-5).

For each test the ratio of suspect/positive (detection rate = DR) or dubious + suspect/positive (biopsy detection rate = BDR) to total cases undergoing the test was determined. BDR indicates the rate of cases histologically confirmed as a consequence of recommended biopsies.

The correct identification of all false-negative cases was guaranteed only by one center (contributing to the whole series with 271 cases). The center included in the study all cancer cases clinically detected and recorded in a BC histologic registry, operating for the whole study period, within 6 months from test performance.

Data about the number of benign lesions biopsied on the basis of a dubious diagnostic report in women aged under 40 in the study period were available only from 2 centers, and the benign to malignant biopsy ratio (B/M) was then determined.

The DR and BDR of each test was determined on the whole series and according to different age groups or T categories.

Results

Table 1 reports the DR and the BDR of each single test. The DR was 0.77 for PE, 0.74 for M, 0.63 for CYT and 0.50 for TH. The BDR was 0.88 for PE, 0.77 for M and 0.72 for CYT.

Table 2 reports the DR of single tests in T1 cases. The DR was lower for all the studied tests than for the overall series (0.66 for PE, 0.62 for M, 0.58 for CYT and 0.22 for TH).

As regards CYT, the sampling technique probably played a major role in DR determination, since the rate of inconclusive smears was as high as 0.13 in the overall and 0.12 in the T1 series. When inconclusive smears were excluded from evaluation, the DR increased to 0.74 in the overall or to 0.65 in the T1 series. Similarly, the BDR increased to 0.85 in the overall or to 0.84 in the T1 series.

No significant correlation was observed between age and PE, M or CYT DR when the total series was divided into two age groups according to an arbitrary cutoff of 35 years of age, as shown in Table 3. TH showed a higher DR (0.67 vs. 0.42) in the younger group.

Table 4 reports the DR and BDR of PE alone compared to the DR of the various test combinations for 355 overall and 100 T1 cases. The DR of combined tests was higher than the BDR or the DR of PE alone, i.e. 0.94 vs. 0.90 or 0.83 for the whole series and 0.90 vs. 0.85 or 0.71 in the T1 series.

The M report was suspect/positive in 42 of 68 (62 %) cases recorded as negative/benign/dubious on PE or in 27 of 41 (66 %) cases recorded as negative/benign on PE. The corresponding figures were 17 of 33 (51 %) or 10 of 18 (55 %) for CYT, and 8 of 27 (30 %) or 3 of 12 (25 %) for TH.

Only 6 of the 382 cases in the study were completely unapparent at PE and were occasional findings at M, which had been recommended in the presence of clinical abnormalities in the contralateral or in other quadrants of the ipsilateral breast.

Data about the B/M ratio were available only from 3 centers. During the study period, 2827 biopsies of benign lesions recorded as dubious on PE were performed, and 302 malignancies were detected, for a B/M ratio of 9.4: 1.

Discussion

A correct estimate of the sensitivity of the studied tests was not possible for the biases which may have affected the present series. First, a correct identification of false-negative cases was guaranteeed through a histologic BC registry only by one center, whereas data from the remaining centers only allowed for the identification of false-benign cases in which a biopsy was recommended. Second, as in any multicentric study, the accuracy of single tests may vary between centers. The average figures thus obtained would be more reliable if used to support recommendations for clinical practice on a national basis. Third, the period considered for the retrospective study was relatively long, with a maximum of 15 years.

Table 1 - Detection (DR) and bioptic detection rate (BDR) estimates for each diagnostic test considered.

Test	Examined cases	Suspect/ positive	DR	Dubious+ suspect/ positive	BDR
PE	382	295	0.77	336	0.88
M	334	247	0.74	257	0.77
CYT	188	118	0.63	136	0.72
TH	123	62	0.50	—	—

Table 2 - Detection rate (DR) of single tests in T1 cases and total cancer cases.

Test	T1			Total	
	No. of cases	Suspect/ positive	DR	No. of cases	DR
PE	116	77	0.66	382	0.77
M	90	56	0.62	334	0.74
CYT	66	38	0.58	188	0.63
TH	27	6	0.22	123	0.50

Table 3 - Detection rate of the studied tests according to age: < 35 and 35-39 age groups are considered.

Test	Age < 35		Age 35-39	
	No. of cases	DR	No. of cases	DR
PE	119	0.79	263	0.79
M	97	0.72	237	0.74
CYT	61	0.65	127	0.68
TH	40	0.67	83	0.42

Table 4 - Detection (DR) and bioptic detection rate (BDR) of PE and DR of PE+associated tests (one or more) for total and T1 cancers (cases undergoing PE alone are excluded).

	PE suspect/ positive	PE dubious/ suspect/ positive	PE+ assoc. tests suspect/ positive
Total cases (N = 355)	0.83	0.90	0.94
T1 cases (N = 100)	0.71	0.85	0.90

Significant changes in the operators skill and improvements in imaging techniques (e.g., for M in the last 10 years) are most likely to have occurred. Unfortunately, due to the low age specific incidence, the period to be considered for the collection of a sufficient number of cases had to be long.

Owing to the above mentioned biases, the sensitivity of the studied tests was not considered, and we limited the estimate of diagnostic accuracy to the DR, i.e., to the proportion of cases correctly identified by the test in a given series of cancer cases observed in the study period.

The comparison of the DR of different tests might also be biased, since the diagnostic report of tests performed at the end of the diagnostic sequence could have been influenced by the knowledge of a cancer being previously suspected and the DR could thus have been overestimated. Anyhow, the relevance of such a bias, which is always present in retrospective reviews of diagnostic series drawn from everyday practice, is probably not very high in the present series, since the DR of M, TH and CYT was always lower than PE in spite of the fact that PE was always the first test performed.

The aim of the study was thus only to assess the diagnostic accuracy of PE in breast cancer diagnosis in women aged under 40 and to define whether the best method to improve such accuracy is an aggressive use of biopsy in the presence of minimal doubts on PE or the association of other diagnostic tests. Unfortunately, the present series was not sufficiently homogeneous to allow for the evaluation of the optimal test combination to be associated with PE. In any case, on the basis of the present series, some critical considerations may be made.

PE was confirmed to be the test of choice since it achieved the highest DR in this series. Nevertheless, it did not reveal 23 % of the total or 34 % of T1 cancers. Such a high false-negative/benign rate could be improved by a more aggressive diagnostic approach of PE, i.e., suggesting a biopsy in all dubious cases. According to this policy, PE would have missed only 12 % of the total or 15 % of T1 cancers, although an excess of unnecessary biopsies would therefore have been recommended. Such a biopsy cost may be evaluated for the subset of cases observed in the two centers providing data on the B/M biopsy ratio. In the study period a biopsy was suggested and performed on the basis of a dubious report on PE in 2827 benign lesions and in 33 cancers, with an average cost of 85.6 unnecessary biopsies performed for each cancer case detected owing to a dubious report on PE.

Another possibility to improve the DR of PE alone is the association of other diagnostic tests. In the present report, when one or more tests were associated with PE the cumulative DR was higher than the DR or the BDR of PE alone. The present study did not define the best test combination to be associated with PE, although TH could probably be ruled out for its extremely poor results. Moreover, although M and CYT are currently reported to have a relatively high specificity, the present study did not allow for an estimate of the number of unnecessary biopsies due to false-positive cases of these tests. A comparison of the B/M ratio of PE alone (with extensive biopsy recommendation) with that of the combination of PE+M+CYT is thus not possible.

In conclusion, we believe that PE is fundamental for the diagnosis of BC under the age of 40, but it cannot be used alone. An aggressive use of PE based on the extensive biopsy suggestion in the presence of even a minimal doubt has a high cost in terms of unnecessary biopsies and increases the cancer DR to a lesser extent than does the association of other diagnostic tests, such as M and CYT.

La diagnosi del carcinoma mammario in età inferiore ai 40 anni

Gli autori considerano una serie consecutiva di 382 carcinomi mammari diagnosticati in età inferiore ai 40 anni. Tutti i casi erano studiati con esame clinico (PE), 334 con mammografia (M), 188 con citologia su agoaspirato (CYT) e 123 con termografia (TH). Il tasso di falsi negativi/benigni dei singoli tests è elevato (PE: 23 %, M: 26 %, CYT, 37 % e TH: 50 %), specie nei casi T1 (PE: 34 %, M: 38 %, CYT: 42 % e TH: 78 %). Sulla base dei modesti risultati l'uso corrente della TH come test diagnostico è assai discutibile. La politica di ricorrere alla biopsia in tutti i casi di reperto « dubbio » benigno alla PE ha consentito di identificare 41 cancri su 382 in questa serie e di ridurre il tasso di falsi negativi/benigni di PE a 0.12 per i ca. totali e 0.15 per i T1 ma il costo è stato in media di 80 biopsie inutili per ogni cancro diagnosticato in tal modo. L'associazione di PE ad altri tests, invece, ha consentito tassi di false negatività ancora inferiori (0.06 per i ca. totali, 0.10 per i T1). Gli autori criticano la politica aggressiva basata sul ricorso estensivo alla biopsia di tutti i reperti dubbi benigni alla PE e ribadiscono l'opportunità di associare alla PE la M e la CYT in quanto questa combinazione sembra consentire una maggiore accuratezza diagnostica.

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