# Bio-clinical problems in the screening of breast cancer

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**Summary.** Screening programs for breast cancer show particular bio-clinical aspects which should be taken into consideration and evaluated before the screening is performed. The Authors report the diagnostic accuracy of contact thermography (C.T.) performed on 780 patients referred to the I.S.T. Gynaecological Out-patients Clinic. Possible correlations are considered between CT. result and biological parameters, such as hystologic grading and hormone receptors. Finally the possible prognostic role of C.T. in a breast cancer screening program is evaluated.

**Key words** breast cancer; screening, biological markers, contact thermography.

## A) INTRODUCTION

**1.** Breast cancer is the **most frequent tumour** in females, and the second cause of death after the cardio-vascular diseases in women between 35 and 54 yrs of age. Every yr, about 14,000 new cases are diagnosed in Italy and about 8,000 women die of it yearly. A woman diagnosed as having breast cancer has a 5 yrs survival rate of about 65%, but the prognosis is closely related to the stage of the cancer, when detected. About 47% of the cases are diagnosed while still in the local stage, giving an 85% 5 yrs survival rate, while lymph node involvement is observed in 53% of the cases, resulting in a 35% chance of surviving 5 yrs.[2] The only presently available system to reduce the mortality rate of this disease, seems to be an early diagnosis.

2. Breast cancer is the only tumour for which randomized controlled trials have been performed demonstrating the efficiency of **mass screening** in the early diagnosis of the disease.[6] In 1964 the Health Insurance Plan of Greater New York (H.I.P.) study compared the effect of physical examination (P.E.) and mammography (M.) in women ranging in age from 40 to 60 yrs, with a non-screened control population. After 10 yrs a significant difference in mortality was seen between the screened and the control groups. The group followed-up showed 93 deaths due to breast cancer while 133 deaths were recorded in the control group. The greatest increase in the survival rate was seen in women over the age of 50. Despite the numerous biases involved (lead time bias, patient self-selection bias, length bias and over-diagnosis bias) a screening utilizing P.E. and M. is effective in reducing by l/3 the mortality rate of breast cancer, and is especially effective in women over 50 yrs of age. The risks involved in such a screening program are due to M. Two major risks exist: the carcinogenic effect of radiation and suspicious test findings, resulting in biopsies in patients who have not breast cancer. Costs can range widely depending on the organization of the program and the training of the personnel involved. For example, a M. examination can cost 5-25 $ (USA) depending on the efficiency of the program. The cost also varies greatly depending upon whether it is done in a private physician's Office or in a paramedic-staffed public Clinic.[4] The same is true for the P.E. examination. The planning of any practical screening program must take into account the population involved and the funds available.

3. The problems affecting the accuracy of the diagnosis of breast cancers are largely due to the **particular biology** of the tumour itself. Breast cancers show different degrees of malignancy, generally considered as the tumour's ability to metastasize. This ability is closely linked to the tumour's growth characteristics and the time required for the tumour

to double in size. Doubling times can vary from a few days to more than one yr depending on the type of tumour. Rapidly growing breast tumours are more likely to have metastatized at the time of diagnosis and result in a lower survival after mastectomy. Markers other than the growth rate exist; they can better define the degree of malignancy (hormone receptors, histological grading, etc.). Significant differences in survival rates have not been demonstrated between patients who have undergone mastectomies and untreated patients.[3] This apparent paradox could be due to 2 different factors influencing the survival rate. First, the natural history of breast tumours is a long process which may involve relapses -occurring over periods as long as 20 yrs; so long term studies are necessary to accurately evaluate the overall survival rate. Secondly, the 2 groups examined were not comparable. The untreated women probably refused treatment because of the slow growth rate of the tumour, whereas the treated group probably showed more agressive cancers. Thus the 2 groups studied probably presented 2 different non-comparable types of tumours.

## 6) BREAST CANCER SCREENING

Problems affecting the accuracy of the screening itself are numerous and generally defined as specific biases which can lead to misleading interpretation of the efficiency of the screening program.' Four major biases are generally considered: the ***lead time bias;*** patient ***self-selection bias; length bias*** and the ***over-diagnosis bias.***

**1.** The **lead time bias** is based on the time between the early detection of cancer and the moment when cancer would have otherwise been detected (by the patient noting signs and symptoms). To be effective, early detection must increase this «lead time» and will do so by automatically moving up the time of diagnosis. Early detection may only increase the period the patient is aware of the disease but has no effect on her overall survival rate.

2. The patient's **self-selection bias** deals mainly with the type of patient who choosed to undergo periodic breast screening. It is very probable that patients who agree to take part in the study are more health-conscious than the population and this could be reflected in their life-style, diet and their tendency to be more aware of the presence of symptoms and signs and more reliable in following treatment. This bias can be adjusted for by tracking the survival of patients who were offered but refused screening.

3. A 3rd bias inherent in screening programs is the **length bias,** and deals with the interval between the time a screening test could detect a cancer and the time a patient would seek care due to the appearance of signs or symptoms. The interval is related to the growth rate and other biological parameters of the tumour and is also affected by the awareness of the patient to cancer signs and symptoms. Cancer detected in a periodic early detection program tend to have longer preclinic intervals than average. Thus, tumours detected in a screening program may have a slower growth rate and may be less malignat, affecting the interpretation of results derived only from a screened population.

4. Another bias in the interpretation of early detection programs is due to possible errors of **over-diagnosis** in the actual diagnosis of the lesions. Early detection is based on the premise of diagnosing a tumour when it is very small and it is quite possible to over-diagnose a lesion that is not and will not become a cancer. This could inflate the number of ((early cancers)) detected and give falsely increased survival statistics. In summary, the abovementioned biases can affect the overall evaluation of the accuracy of a screening program. These biases are eliminated by randomized controlled trials in which the mortality of all patients offered the screening is compared to the screened group. Unfortunately, this is not always possible and non-randomized trials can provide a great deal of information if interpreted carefully, recognizing the problems and adjusting for them whenever possible.

## C) PROPOSALS

Due to the high cost of extensive screening,

a pre-screening through the evaluation of risk factors (age, family history of breast cancer, fertility after 30 yrs of age, age of menarcha and age of menopause) offers an effective method for reducing cost without greatly affecting the accuracy of the screening.[6,7]. Limiting the screening to a segment of the population presenting a greater probability of developing breast cancers is especially desirable when dealing with asymptomatic women less than 50 yrs of age. This pre-screening should be performed in conjunction with the utilization of less damaging techniques such as contact thermography (CT.), especially in a sub-population in which the other methods have some risk.[5] The aim of this study was to evaluate the validity of the use of risk factors as pre-screening determinants and to investigate the diagnostic accuracy of C.T. in 780 randomly-selected women from the Breast Screening Centre of I.S.T.

## D) METHODS

P.E. and C.T. examinations were performed; further examinations were utilized when necessary. All women were submitted to an interview in order to evaluate the risk factors. C.T. was performed in frontal and lateral views, following a previous cooling.

## E) RESULTS

The personal experience is based on 780 patients examined by C.T., 84/780 being breast cancers. The determination of cumulative relative risk provided a discriminating basis between positive and negative cases. As previously demonstrated,[8] the pre-selection of the screened women, based on a cumulative risk factor lower than 60, reduces to 50% the population to screen but identifies the 76% of the breast cancers present in the whole population. In the personal series, a good predictive value of 40% by C.T. was obtained. The correlation between C.T. features and both histological grading and hormone receptors levels in breast cancers was also evaluated. Since the number of cases examined was too small for statistical analysis no correlation was found.

## F) CONCLUSION

**1.** Controlled clinical trials of breast cancer diagnosis should be done on **large groups of women,** comparing traditional diagnostic methods with a screen based on cumulative risk factors. Screening frequency should depend upon the examined sub-population.

2. The harmlessness and low cost of C.T. let it to be be applied to a sub-population of **young high risk women** who require repeated check-ups.

3. The not complete knowledge about the biological events causing the characteristic C.T. pattern requires extensive basic research on the **thermogenetic turnout-al power** and its correlations with C.T. pattern, in order to uniform the interpretation of C.T. images.

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# The role of self-examination and of contact thermography in breast cancer screening

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FREE COMMUNICATION

## A) INTRODUCTION

The improvement of the results in the treatment of breast cancer depends from its early diagnosis. It is well known that a correct screening is followed by an increasing rate of T1 NO in the whole amount of -detected breast cancers, and by a decrease of total mortality rate. Nevertheless, a correct screening approach needs some conditions, as follows.

## B) STEPS IN BREAST SCREENING

**1.** The first step in a correct screening program is represented by **complete information** on its aim and modalities. These information have to be furnished both to the female population undergoing the screening and to the practitioners operating in the screening area. In absence of this necessary' collaboration the screening program will not get any success.

2. Second step is the identification of the **«high risk»** group of women, in order to reduce the total amount of women to be screened.

3. The third step is represented by the **physical examination** associated with **diaphanoscopy.** The contact thermography examination (C.T.) is placed in this step, taking in account its low cost, non invasivity and easy handling.

## C) SELF-EXAMINATION AND SELF-CONTACT THERMOGRAPHY

These procedures are placed as a support to a screening program.

**1.** The **self-examination** did not provide encouraging results; this, in spite of a large advertising campaign. The personal experience, referred to 600 women sensitized to self-examination, reveals that only 21% (126/600) performed monthly the self-examination, while this was made occasionally by 32% (192/600) and finally never by 47% (282/600) of the screened women. Taking into account the age distribution, the very important different behaviour between the younger and other women must be stressed. In the younger group (20 yrs-40 yrs), 106/196 (53%) performed the self-examination monthly; 59/196 (29%) made it occasionally and 31/196 (18%) did never performed it. In the older group (over 40 yrs), only 20/404 (3.5%) performed the self-examination monthly, 133/404 (44%) occasionally and finally 251/404 (52.5%) did never perform self-examination.

**2.** The **self-contact thermography** unit consists of a plastic corset in which are enclosed 2 plates of two layers of micro-incapsulated cholesteric liquid crystals. A range of temperature between 30°C-35°C is warranted. This unit ought to allow the self-C.T. examination at home. The personal experience is referred to 200 women sensitized to self-C.T. examination aged between 20-40 yrs (78%) and more than 40 yrs (22%). From the operating point of view, the self-CT. examinations might cover the time interval between 2 senologic controls. In spite of the theoretical interest of these new procedures, it must be remembered that also the self-C.T. examination presents the same above mentioned drawbacks, i.e. the scarce availability to self-examination of the women, particulary in the older group, with higher risk. Furthermore, being the sensibility of the conventional C.T. plates and of the self-C.T. plates different, it is not easy to compare the obtained results. The best solution should be to provide also the

Practitioner with 2 or 3 C.T.-corsets at different sensibility, in order to make the results comparison more reliable.

In conclusion, C.T. examination may play a definite role in a screening program for breast cancer, probably also the self-C.T. examination could be utilized for this purpose, though needing further clinical surveys.

# Accuracy of combined physical examination, contact thermography, mammography and cytology in breast cancer diagnosis

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Summary. In one progress in a breast cancer screening program 52 biopsy-proved cancers were detected in 1 ,197 women (4.3%). In these physical examination (P.E.) was positive or suspicious in 27 (51.9%); contact thermography (C.T.) in 37 (71.1%); mammography (M.) in 47 (90.3%); cytology (C.) in 48 (92.3%). These accuracy in detection of cancers was similar to that reported in the preceding 2 yrs activity of the same screening program. In this period of time 2,440 women were screened with detection of 112 biopsy-proved breast cancers. The accuracy in diagnosis increased with the increase of lesion size, except for C.T., the association of the 4 diagnostic methods carried out positive diagnosis in 96.8% of the cumulative cases.

**Key** words: breast cancer screening; contact thermography; cytology.

## A) INTRODUCTION

The association of several diagnostic methods may reduce the false negative rate in detection of breast cancer. A breast cancer screening program was established in the Tumour Centre at the University of Pavia in January 1978, using physical examination (P.E.), contact thermography (C.T.), mammography (M.) and cytology (C.) sequentially. The 2 yrs results of this screening program have been previously reported,' demonstrating the value of the methodological association in order to identify 112 biopsy-proved breast cancers in 2,440 screened women. Aim of this paper is to take into consideration a further series of 1197 screened women in which 52 breast cancers were identified.

## B) MATERIAL AND METHODS

From January 1980 to December 1980, at the Tumour Centre of the «Delmati» Hospital in Sant'Angelo and at the Departments of Radiology and General Pathology of the University of Pavia, 1197 women aged 20-75 yrs, were screened, both on self admission or referred by different Medical Centers. All women were evaluated by P.E. according to the **HAAGENSEN** technique[4] and C.T., using a Cawo-Bayer apparatus.

The criteria of evaluation of C.T. pattern were based on the anomalies both of the vascular breast network and of the thermal background, according to the **TRICOIRE** method.'* M. was performed when P.E. or C.T. or both were positive or suspicious for breast cancer.

M. was also performed in the high risk women, even if negative at P.E. and C.T. Finally,[4] C. was performed both in nipple secretion not associated with lactation and in all palpable masses, independently from the diagnostic judgement of P.E., C.T. and M. The fine needle biopsy was performed according to the ZAJICEK technique.[14] The therapeutic approach in the patients with some breast disease, either benign or malignant was personalized according to the several data obtained from each diagnostic method. Conservative surgery is recommended when a palpable mass appears not indicative for libro-adenoma at M. examination demonstrating also cellular aspirates at C. examination, since well differenciated breast cancers or other proliferative conditions[8, 15] can support these remarks. Conservative surgery is also recommended when the palpable mass appears of benign type at M. examination; on the contrary mastectomy is required when the M. patterns are typical of malignancy, possibly associated with axillary lymphadenectomy; an histological diagnosis, obtained from frozen sections is taken in consideration. Finally, if the breast lesion appears to be malignant or suspicious at the diagnostic examination, being negative the C. examination, surgery is also suggested. In all cases the surgical specimens were examined to identify the histological type of the tumour. The size of the tumoural nodule was established in the surgical specimen when the M. examination failed to detect it.

**1. Accuracy,** in the personal series of 1197 women 52 (4.3%) breast cancers hystologically confirmed were detected. AtP.E., 27152 breast cancers were detected (51.9%), 37152 (71.6%) at C.T. examination, 47152 (90.3%) at M. examination, and finally 48/52 (92.3%) at C. examination. The methods association lead to an accuracy of 96.1% (50/52) (Tab. I).

The accuracy of each method arose in proportion to the tumour size, except for the C.T. examination, whose accuracy was quite the same in the middle sized tumours and in the small ones. The largest tumours (size>3 cm in diameter) were costantly identified with whatever method used.

2. In particular, as regards **contact thermography,** the specific diagnosis of malignancy was reached in 71.1% (37/52 breast cancers), in 10/52 (19.2%) the findings were equivocal, in 5/52 (9.6%) the C.T. findings were false negative. The highest incidence of false negativity (3/5) was releaved in scirrhous carcinoma, depending upon the low thermogenie power of fibrous tissues. Equivocal C.T. findings (lo/52 breast cancers), were based both on vascular anomalies (6/10) and thermal background anomalies (4/10). Although inadeguate for the specific diagnosis of breast cancer, these equivocal findings, however, were useful in order to adress to other examinations.

The false positive rate of C.T. was evaluated in 1145 of the screened women which were demonstrated free of tumour at screening (Tab. II). The total amount of C.T. false positive rate was 10% (114/1145). No C.T. false positives at all, were observed in normal breasts being the false positive cases detected in breasts affected by some benign disease, with greater prevalence of dysplasia (72/114: 63.2%).

Tab. I. **Accuracy of single diagnostic methods and their association in breast cancer.** (52 detected cancers in 1197 screened women).

| Lesion size (cm) | 0.5 - 1 | 1 - 2 | 2 - 3 | > 3 | Total |
|---|---|---|---|---|---|
| No cases | 10 | 33 | 7 | 2 | 52 |
| Physical examination | 2 (20.0%) | 17 (51.5%) | 6 (85.7%) | 2 (100%) | 27 (51.9%) |
| Contact thermography | 7 (70.0%) | 24 (72.7%) | 4 (71.4%) | 2 (100%) | 37 (71.1%) |
| Mammography | 8 (80.0%) | 30 (90.9%) | 7 (100%) | 2 (100%) | 47 (90.3%) |
| Cytology | 8 (80.0%) | 31 (93.9%) | 7 (100%) | 2 (100%) | 48 (92.3%) |
| Association | 9 (90.0%) | 32 (96.9%) | 7 (1 00%) | 2 (1 00%) | 50 (96.1%) |

Tab. II. **Contact thermography false positive rate in no cancerous screened women.** (1145 obs.).

| Benign lesion | Mean age | C.T. false positive rate |
|---|---|---|
| Total | 32 | 114/1145 (10.0%) |
| Dysplasia | 34 | 72/114 (63.2%) |
| Adenosis | 43 | 17/114 (14.9%) |
| Fibro-adenoma | 22 | 21/114 (18.4%) |
| Inflammatory conditions | 28 | 4/114 (3.5%) |

## D) DISCUSSION

The above reported data are generally in agreement with those of Literature.[1, 3, 4, 5, 7, 10, 13] The usefulness of C.T. in association to P.E. in detecting early cancer was demonstrated. It is a very simple and harmless method and therefore largely applicable. M. examination was the most efficient non invasive method. This method has to be performed in dubious cases.

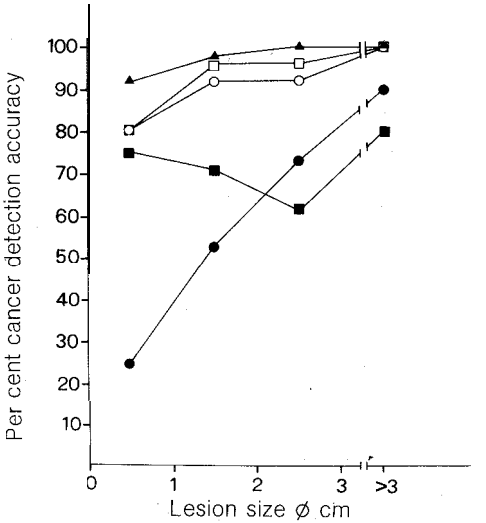
The real meaning of C.T. false positivity must be considered thoroughly. Without doubt, when other diagnostic methods (P.E., M. and C.) are negative, the surgery may be avoided. Nevertheless, it could not be excluded that the « present » C.T. false positivity will become a C.T. « true » positive in the future. In this evenience, C.T. positivity might realize a new category of risk factors, like hormonal, pharmacological, genetic factors and so on. For this purpose a further careful follow-up of C.T. false positivity in order to evaluate the real significance of this eventual risk factor seems to be necessary.

Afterwards, the previous personal results' were added to those of the present series. No important difference in the global results (Tab. III) was observed; particularl'y, P.E. alone demonstrated itself inadequate in detecting about 50% of the breast cancers, but this figure was even worse in the smaller ones (75% of false negatives). Consequently, C.T. examination improved the P.E. results. The M. examination confirms to be the best non invasive method, not much inferior to C. by fine needle biopsy. The results of the combined use of the several methods (Graph 1) gave the same results in the larger series (96.9%) and in the smaller (96.1%). This means that a false negative rate of 3%-4% must be accepted, at this moment.

The fine needle C. examination requires some considerations. Some people think[4, 16] that the breast punction might be charged by a risk of tumoural spread. On this purpose the survival rate after mastectomy was compared in 2 series of women,[2, 16] the first of which submitted before mastectomy to fine needle biop-

Tab. III. **Accuracy of single diagnostic methods and their association in breast cancer.** (164 detected cancers in 3537 screened women).

| Lesion size (cm) | 0.5 - 1 | 1 - 2 | 2 - 3 | > 3 | Total |
|---|---|---|---|---|---|
| No cases | 36 | 92 | 26 | 10 | 164 |
| Physical examination | 9 (25.0%) | 49 (53.2%) | 19 (73.0%) | 9 (90.0%) | 86 (52.4%) |
| Contact thermography | 27 (75.0%) | 65 (70.6%) | 16 (61.5%) | 8 (80.0%) | 116 (70.7%) |
| Mammography | 29 (80.5%) | 85 (92.3%) | 24 (92.3%) | 10 (100%) | 148 (90.2%) |
| Cytology | 29 (80.5%) | 88 (95.6%) | 25 (96.1%) | 10 (100%) | 152 (92.6%) |
| Association | 33 (91.6%) | 90 (97.8%) | 26 (100%) | 10 (100%) | 159 (96.9%) |




Graph. 1. Diagnostic accuracy of the single methods and their combined evaluation in 164 cancers during the screening of 3.637 cases (1978-1980) (●)Physical examination; (■) Thermography; (○) Mammography; (□) Cytology; (A) Combined evaluation.

sy, the second ones directly mastectomized. There was no difference in the 10 yrs survival rate between the 2 groups of patients. Nevertheless, the implantation of tumoural cells in the needle tract is possible and has been observed but it must be reminded that the needle tract with the implanted cells is removed during mastectomy.[6] At the present time, the available pathological data overwhelmingly support the great interest of breast fine needle and also exfoliative C. Nevertheless, there are 2 types of breast masses in which the fine needle C. may not bring about the true diagnosis, even if carefully performed, namely the very firm scirrhous carcinoma and fibro-adenoma with very indurated connective tissue components. But such cases are relatively easy and fairly reliable on M. examination.

When fine needle C. in the diagnosis of mammary lesions is positive for breast cancer, radical mastectomy must be performed without pre-operative histologic confirmation of the fine needle C. diagnosis.[15] In personal opinion, the most satisfactory success of the fine needle C. seems to be due to the fact that breast cancers never arise from inflammatory dysplasias; thus, false positive C. evaluations due to flogistic processes do not occur in breast cancer, unlike, for example, in the cases of vaginal and urotelium smears. The case of breast aspirational smears with malignant cells intermingled with predominant lymphocytes can be referred to a cancer histotype, namely breast medullary carcinoma. Further, the differential diagnosis between mastitis and inflammatory carcinoma is relatively easy on fine needle C.

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