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Symposium
Mammary carcinoma and tumormarkers

State of the art

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The third symposium, organised by the Tumormarkers Work Group, was devoted to mammary carcinoma. The strategy of the earlier symposia was applied again: clinical presentations in the morning and support by the laboratory for the diagnostic proceedings and follow-up in the afternoon. First, the epidemiology was discussed, including risk factors, early detection and screening. Integration of the anatomical pathology, where the vessel structures are scored, with the measurement of a tumormarker with low (TPS) or high (CA 15-3) molecular weight may provide better understanding of the release of the markers. Nowadays, early detection results in more cases of pre-invasive ductal carcinoma in situ (DCIS) and demands a different surgical regime. The morning session was closed with the adjuvant therapy for metastatic carcinoma. High doses of cytostatics are combined with bone marrow replacement or peripheral stem cell transplantation. Despite promising results in a selected high-risk population, this approach should be applied only in the setting of clinical studies, because of morbidity and costs.

The role of episialin (CA 15-3) in the adhesion of tumor cells was elucidated in the afternoon, and currently certain patterns of episialin expression on primary mammary carcinoma can be found that correlate with metastasis to the axillary lymph nodes. Measurement of serum levels of tumormarkers has no value for screening or detection, but is useful during follow-up and monitoring of the patient. The many different assays with monoclonals against different epitopes of episialin were reviewed, which is important for understanding the discrepancies in results obtained with these diagnostic products. The diagnostic and prognostic tools of molecular biological origin enable us to define patient groups who are in need of specific therapeutic intervention. The DNA amplification technique has to be integrated in the laboratories for clinical chemistry as soon as possible.

More than a hundred participants took part in the lively discussions and made a fruitful contribution to this symposium which was sponsored by Byk-Netherlands.

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Breast cancer epidemiology and screening in the Netherlands

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Four subjects will be dealt with in this paper. First, some breast cancer statistics will be presented. Secondly, it will be described how the occurrence of breast cancer is related to risk factors. Subsequently, it will be shown that early diagnosis is the current way to improve prognosis, and finally, the early outcomes of the national screening programme in the Netherlands will be presented.

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Statistics

Breast cancer remains the most common cancer and the most frequent cause of cancer death among women in Holland. At present, the lifetime probability of developing breast cancer is about 10% and the probability of dying of the disease is 4%. This means that there is a 40% chance of dying of breast cancer after having a primary breast cancer diagnosed. These rates of occurrence are the highest in North America and northern Europe. In absolute numbers, 3,500 women die of breast cancer in the Netherlands annually. The current incidence is 9,000 cases of breast cancer each year. The incidence is highest in women aged 50 to 70 years, i.e. 45%. Above age 70 it is 35%, 15% in the age-group 40-49 years, and 5% in the under age 40 group (1).

Risk factors

It is postulated that premenopausal and postmenopausal breast cancer have different etiologies (2). The former is believed to be associated with reproductive characteristics, which in turn are closely related to the function of the ovaries. The latter seems to be more associated with exogenous factors, like nutrition and life-style. Many epidemiologic studies have been conducted in this field. These have established that early age at first birth (<18) is a protective factor. The first full-term delivery after age 35 is a risk factor for breast cancer. Early age at menarche (<12) and late age at menopause (>55) increase breast cancer risk, while removal of the ovaries earlier than age 35 reduces the risk to about one-third. A combining role in all these factors is ascribed to the endogenous hormones, in particular to estrogens. However, special case-control studies covering biochemical analyses of plasma, urine and saliva failed to demonstrate significant differences in estrogen concentrations. On the other hand, these results do not preclude the possibility that estrogens stimulate cancer growth. The estrogen levels at a younger age may be more important for the development of breast cancer. The role of endogenous hormones in breast cancer etiology has raised concern about the possibly harmful effect of two widely used exogenous hormones containing estrogens: oral contraceptives and estrogen replacement medicines for perimenopausal complaints. As far as the cancer-promoting or inducing properties of estrogen replacement therapy are concerned, it is to be noted that many studies have methodological limitations and do not show consistent results. The provisional conclusion is that there is no clear-cut effect.

It has been suggested for many years that nutrition plays a role in breast cancer etiology. In countries where relevant data are available, there is a fairly strong correlation between the per capita consumption of fats and oils and breast cancer mortality rates. The increase in breast cancer death rates among offspring of Japanese immigrants in the United States can be correlated with changes in their dietary habits. An upward trend in breast cancer incidence in Iceland and England is correlated with an increased dietary fat intake. Because of the influence of many other factors, it is difficult to detect causal relations. Several case-control studies that analysed nutrition and reproductive factors simultaneously could only demonstrate a weak association between high fat intake and breast cancer. It should be noted that a retrospective study can hardly determine the dietary habits of years back. Other studies among postmenopausal women show an association between obesity and breast cancer. In addition, age at menarche is influenced by nutrition. Fat children become "mature" at an earlier age, and early menarche has already been mentioned as a risk factor.

For the sake of completeness, high socioeconomic status and family history of breast cancer have to be designated as risk factors too. It is still unknown to what extent environmental or genetic factors play a role. Many studies, however, indicate that women who have a first-degree relative with breast cancer have a risk of twice or three times the risk in the general population. If mother and sister are diagnosed for breast cancer, the relative risk ratio even increases to 8-10.

The associations are weak and causal to an unknown degree only. The possibility of prevention is therefore restricted, all the more because too few women are exposed to these risk factors. Consider e.g. obesity as a causal factor. Women with a Quételet-index of at least 29 (i.e. more than 15 kg above the ideal body weight) have a risk ratio of 1.5, compared with less obese women. Given the prevalence of women with such a high Quetélet-index, it can be estimated that the incidence of breast cancer could be reduced by 10% at most, provided dietary treatment were successful in all these women. It can be concluded that primary prevention will hardly contribute to breast cancer incidence reduction.

Breast cancer screening trials

Methods of preventing breast cancer have not yet been established, and scientific efforts have concentrated on developing new and improved ways to treat the cancer once it occurs. In addition, efforts have focused on early detection of breast cancer in women through screening, so that ensuing treatment can be more effective and save more lives.

Studies of breast cancer screening - including mammography, clinical breast examination, and breast self-examination - have been conducted for at least 30 years. In addition to several case-control and cohort studies including the ones in Nijmegen and Utrecht, eight major randomized controlled trials of breast cancer screening were conducted during this period: an unparalleled accomplishment in research on cancer detection (3). The randomized trials alone included about 500,000 women. After the early results of several trials had been reported, organizations and expert groups around the world began making recommendations for breast cancer screening at the population level. In general, these groups have agreed that scientific evidence supports breast cancer screening with mammography alone or mammography and clinical breast examination in women aged 50 years or older. On the other hand, recommendations regarding breast cancer screening for women 40-49 years old have varied, with some groups recommending screening and others not recommending screening. Most groups did not make specific recommendations about women over 70. With the appearance of breast cancer screening recommendations, screening practices have become increasingly common in several countries.

National screening programme in the Netherlands

After extensive consultations of several advisory boards, a completely new organization was set up with specialized screening units, a training programme for radiologists, radiographers and pathologists (4,5). At present (1995), almost 90% of the country, i.e. the age-group 50 to 70, have received their first invitation. For this screening programme, the Netherlands has been divided by the Ministry of

Health into 9 regions, e.g. north Holland, west, south-west, etc. Each of these 9 regions has its own joint management board consisting of regional health authorities who are responsible for inviting the women and for collecting data. Every region has several central units and each central unit consists of 2-3 specialized screening units. These screening units may be stationary, mobile or semi-mobile. The screening units accommodate the most modern mammography apparatus. Two-view mammography is performed in the initial screening examination. One-view mammography is performed at the subsequent examinations. Films are developed immediately so as to enable the radiographer to decide whether an additional view is required, for instance because of technical faults or difficulty in interpretation. Each region has 1 to 3 central units, where the mammograms coming from the screenings units are evaluated. The mammograms are assessed independently by 2 radiologists who have to reach consensus about advising referral. After full implementation of the programme in Holland, which will be at the end of 1995, a total number of 54 screening units will be operative, with more than 500,000 screening examinations annually.
After 2 years, women receive a personal letter of invitation with fixed data. Those women who do not respond receive a reminder. The screening examination itself may result in a negative outcome or in a positive one in case of suspicion of cancer. In that situation the woman is referred to her general practitioner who is responsible for further referral to an outpatient clinic for assessment. There is no self-referral system in the Dutch screening programme.

Early screening outcomes

The total female population in Holland comprises 7.5 million women. The annual target population, i.e. the age-group 50 to 70 is 725,000. From 1990 to 1992, 426,000 women were invited for their first screening; 315,000 of them participated in the programme, i.e. an attendence rate of 75%. Of the woman actually screened, 4,300 were referred for abnormalities suggestive of cancer. Almost 3,200 of these women underwent biopsy. In 2,100 women breast cancer was detected by screening.
If these numbers are transformed into some statistical data, the following results are obtained for newly screened women. See table 1. Of 315,000 women, 1.4% were referred because of suspicion of cancer.

Table 1. Results first screening round covering 1990-92.

Screen positives (% of screened women)	1.4 %
Biopsy (% of referred women)	74 %
Breast cancer detection rate	6.8 ‰
Predictive value screening	50 %
Biopsies with malignant diagnosis	67 %
Lymph node metastases (inv.)	32 %

N = 315,537

Table 2. Screenings outcomes first and second examination.

Results	screening examination	
	First N=315,537	subsequent N=112,113
Screen positives (% of screened women)	1.4 %	0.75 %
Biopsy (% of referred women)	74 %	62 %
Breast cancer detection rate	6.8 ‰	3.3 ‰
Predictive value screening	50 %	45 %
Biopsies with malignant diagnosis	67 %	72 %
Lymph node metastases (inv.)	32 %	32 %

Table 3. Tumour size distribution within and outside the screening programme.

DCIS & tumour size	screening carcinoma		clinically diagnosed
	first examination	second examination	
DCIS	13 %	14 %	4 %
T1a (≤ 5 mm)	4 %	26 %	1.4 %
T1b (6-10 mm)	22 %	28 %	6.1 %
T1c (11-20 mm)	39 %	32 %	30.5 %
$T2^+$ (> 20 mm)	17 %	19 %	50.1 %
Tx/not yet clasified	5 %	7 %	7.9 %

74% of them underwent biopsy. The breast cancer detection rate in the screened population was 6.8 cancers per one thousand screenees. The last line of table 1 shows that 32% of the invasive screen-detected cancers showed up with axillary lymph-node metastasis. Finally, the predictive value of a positive screening mammography, which is the number of screen-detected cases per 1 hundred referrals, was 50%. The predictive value of biopsy was 67%.
More than 112,000 women were screened for their subsequent examination 2 years later. Table 2 subdivides the results into first screenings and subsequent screenings. As already shown in table 1, the results for newly screened women are good: only 1.4% of women are referred for assessment without negatively influencing the detection rate of 6.8 per 1 thousand. In contrast, the referral and detection rates in subsequent screenings are lower: 75% and 3.3 per thousand. To be clear, these are also good screening outcomes. The proportion of lymph node positivity remains the same. The same goes for the predictive value of a positive screening test and the relative proportion of biopsies showing malignant lesions.
Screening significantly advances the diagnosis. The extreme right column of table 3 shows that clinically diagnosed cases of breast cancer reveal 4% of ductal

carcinoma in situ, and 1.4% plus 6.1% of very small tumours, totalling 12% of early cancers. In the screening situation, however, the histology and size distribution is quite different. Among the screen-detected cancers of the first examination, 13% were of the intraductal type, which is comparable with the 2nd screening examination (based on 370 cases). The non-invasive and small invasive cancers up to 10 millimetres now amount to 39% and 42%, whereas in the clinical setting the latter was just 12%. Finally, the percentage of large tumours, i.e. more than 20 mm, declined from 50% outside screening to less than 20% in the screening programme.
In summary, the early outcomes of the Dutch screening programme are satisfying for several reasons. The invitation system is based on a 100 per cent covered population registry with high participation rates. The low referral rates, combined with high predictive values show that the number of false positive screening test results can be minimized. The data further show that the routine application of mammographic screening can attain high quality levels. This means that the 2-yearly screening programme for women aged 50 to 70 will yield the predicted 20% breast cancer mortality reduction.

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Summary

Breast cancer epidemiology and screening in the Netherlands. Verbeek ALM. Ned Tijdschr Klin Chem 1995; 20: 282-285.
Breast cancer is the most common cancer in Holland, with the highest incidence in women aged 50 to 70 years. Premenopausal cancer is related to the ovarian function, whereas postmenopausal cancer is related to exogenous factors. Screening trials including mammography, clinical breast examination and self-examination led to the set-up of specialized screening units and almost 90% of the women aged 50 to 70 years have meanwhile had their first invitation. From 1990 to 1992, 315,000 women were examined and breast cancer was found in 2100 women. The predictive value of the mammography was 50%, and 67% for the following biopsy. Screening significantly advances the diagnosis, while the prognosis for the early cancers forms a far bigger group in the screened population than in the group of clinically diagnosed breast cancer. It is predicted that 2-yearly screening of women between 50 and 70 years will reduce mortality by 20%.
Key-words: breast cancer, epidemiology, screening, mortality reduction, mammography, biopsy.

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Surgical management in operable breast cancer: DCIS, breast conservation and approach of the axilla; state of the art 1995

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In the past decade, there have been some important changes in the surgical approach of early breast cancer. Screening and adjuvant therapy have greatly contributed to the improvement of survival rates, and a shift towards earlier presentation by the screening efforts has resulted in a much more frequent feasibility of a breast-conserving approach. Several items in the technique and indication for breast conservation are still subject to discussion. The pre-invasive ductal carcinoma in situ (DCIS) is now a frequently diagnosed entity. Important research on DCIS is in progress.

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Treatment of the axilla is still a controversial subject with staging and treatment aspects; new techniques of selecting patients for surgery are now being studied.
Some remarks on these important subjects will be given below.

DCIS

Improvements of mammography and the broad introduction of screening in countries with a high breast cancer incidence have raised the number of cases of in situ breast cancer to 15% of all detected breast cancers. Finding the right treatment for this disease is a major challenge in our daily medical practice. A good understanding of the biology is needed to find the optimal therapeutic measures; as for DCIS, there are still many uncertainties (1,2,3). It is difficult to estimate the risk of change to invasive disease, and also the time frame for this to happen is difficult to