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Study of the Role of Breast Self-examination in the Reduction of Mortality from Breast Cancer

The Russian Federation/World Health Organization Study.
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The protocol of a study, sponsored by the World Health Organization, of the role of breast self-examination (BSE) in reduction of mortality from breast cancer is presented. The major objective of the study is to determine the effect of a BSE programme on mortality from breast cancer. A population of over 193 000 women aged 40 to 64 has been defined in Moscow and St Petersburg and randomised to study and control groups. In Moscow the education programme is based on a two-way communication principle allowing efficient person-to-person education in groups of up to 20 individuals and feedback information through specially designed personal calendars. In St Petersburg, class and individual instruction is carried out. After a 1-year feasibility study the project is planned to last for 15 years. It consists of an aggressive education programme, during and following which, all newly diagnosed breast cancers will be registered and treated, and followed up for 3 to 15 years. A key issue of the study is compliance of the population with BSE. The frequency and competence of BSE practice has been defined in subsamples of 400 randomly selected women by means of surveys at 6 months, 1, 2 and 3 years after the start of the project. The study is expected to result in the accrual of more than 1470 new breast cancer cases and 778 deaths from breast cancer. The power of the study is expected to permit detection of a 30% reduction in cumulative breast cancer mortality, assuming that 50–70% of the women in the study group practise BSE.
Eur J Cancer, Vol. 29A, No. 14, pp. 2039–2046, 1993.

INTRODUCTION

Background

SINCE THERE is no practical method of primary prevention of breast cancer immediately available at present, screening, resulting in the diagnosis and treatment of breast cancer at an early stage, seems to be a rational approach to reducing mortality from this common tumour. Poor prognosis has been repeatedly associated with an advanced stage of the disease. Thus, screening that detects cancer at an early stage when treatment may be more effective, is likely to become a major contributor to strategies for control of breast cancer.

Screening of limited groups of the population (on an experimental basis), health demonstration programmes to promote early breast cancer detection, and—more recently—national policies for breast cancer screening have been established in a number of countries during the last two decades. Different technologies to meet this goal have been developed: mammography, thermography, diaphanography, ultrasound, physical examination by health professionals and self-examination by women. The reported results indicate that screening by mammography with or without breast physical examination can reduce mortality from breast cancer in woman age 50–69 [1, 2]. However, breast cancer screening programmes involving imaging technologies can be expensive and for this reason cannot be adopted in many countries as a routine public health approach [2].

Justification of the study

Available statistics show that despite current efforts to encourage earlier detection of breast cancer, as many as 70–80% of all cases of breast cancer are accidentally detected by women themselves. In many developing countries, without public education programmes on breast cancer, such detection often occurs at a late stage. In this respect, breast self-examination (BSE) has been suggested as a possible means of improving breast cancer control. BSE may be particularly suitable for countries which cannot afford the development of sophisticated screening services to reach the whole female population at risk. BSE is believed to be simple, inexpensive, non-invasive and non-hazardous. In addition, it implies the transfer of partial responsibility for cancer detection to women themselves, in line with current approaches designed to establish interrelations between healthy populations and health-care services.

The concept of BSE has been enthusiastically proclaimed in several countries for many years. On the other hand, the value of BSE has been questioned by a number of investigators because it may increase costs in identifying benign lesions and little evidence is available to confirm that its use will reduce breast cancer mortality. Thus, it is not appropriate to advocate BSE just because of its apparent simplicity without adequate evidence of its efficacy.

For several years attempts have been made to evaluate the effectiveness of BSE, and most have demonstrated a positive impact on the extent of the disease at diagnosis. However, because of different end-points and lack of measures to control possible biases these studies have failed to prove the value of BSE on the overall prognosis of the disease [3]. To date there has only been one population-based quasi-experimental study that utilised classes to teach BSE and evaluated mortality from breast cancer [4, 5]. There was no significant reduction in mortality from breast cancer over a 10-year period [5], though compliance with invitations to attend BSE classes was poor. There have also been two case–control studies reported [6, 7] of programmes which did not associate BSE with reduced risk of developing advanced breast cancer, although in one [6] the authors noted a possible effect of BSE in reducing the prevalence of advanced breast cancer in the small number of women who appeared to be BSE compliers.

As a whole, these studies support the view that BSE could be useful for early detection of breast cancer and have shown that its practice has few adverse consequences. Women practising BSE are more likely to consult their physicians and to utilise more sensitive detection modalities such as mammography, which may enhance the overall impact of breast cancer early detection programmes. However, the major question of the influence of BSE-containing programs on mortality from breast cancer remains to be answered. This can only be achieved through prospective studies with careful attention to research design and methodology.

This issue was raised at the WHO International Meeting for Formulation of Prevention Strategies in Cancer in 1981. It was also considered in greater detail by a group of experts convened by the WHO in 1983. It was agreed that it was warranted to further test the effectiveness of BSE as a potential means of reduction in mortality from breast cancer [3].

AIM OF THE STUDY

The aim of the study was to determine the magnitude of the effect of a BSE-containing programme on reduction in mortality from breast cancer.

In addition, as a result of the findings from the study, it is planned:

— to evaluate whether BSE can be considered as an integral part of the public health care approach to control the problem of breast cancer;

— to determine the behavioural, cultural and psychological problems which can occur when healthy women are invited to participate in a breast cancer early detection programme, with BSE as the screening component;

— to provide the data for an estimation of the cost and resource needs of a programme of early breast cancer detection including the use of BSE in relation to its effectiveness.

DESIGN AND METHODOLOGY OF THE STUDY

Recruitment of the population

To ensure results representative of those achievable in the general population, groups from the healthy female population (units) were randomly identified both for BSE education and for control. A number of city polyclinics (health care centres) serving an identified population represented such units in St Petersburg. In Moscow, factories and other establishments served this purpose.

Groups, rather than individuals, were chosen as the unit for randomisation for a number of reasons. First, the teaching of BSE and its subsequent reinforcement is facilitated when groups are involved. Secondly, the possibility of contamination of the control group is reduced. Thirdly, as the teaching of BSE is simplified, the study was expected to be easier to run and, therefore, less costly.

Method of randomisation

In the process of identification of the female population for the study in Moscow, factories with known occupational hazards were excluded. From the remainder, more than 200 factories were selected for participation in the study, a number deliberately taken in excess to guard against possible refusal of some.

Randomisation of factories to study and control groups was carried out in two phases:

For the first 99 factories, using the telephone directory, telephone numbers of all listed factories were written down. The first three figures of the numbers were ignored as they reflected the location of a factory in a certain area of Moscow. The fourth figure has nothing to do with the location and, therefore, it was chosen as a discriminator. Depending on its character, even or odd, (zero was considered as an even number), two groups of factories were formed containing 53 "even" and 46 "odd" factories, respectively. By means of casting lots, the second group was allocated for the BSE intervention group, the first for control.

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For the remaining 138 factories included in the study in Moscow, randomisation was performed in the WHO Cancer and Palliative Care Unit in Geneva by Dr K Stanley, using tables of random sampling numbers. The Moscow investigators were then informed of the allocations.

In St Petersburg the study was implemented through 18 district polyclinics and 10 large enterprises with well developed health care services. When selecting the above facilities only two factors were considered: absence of both occupational hazards and previously conducted BSE education programs. In view of the different organisational structure between the 18 district polyclinics and the 10 enterprise polyclinics, randomisation was stratified according to these two groups: nine district polyclinics were assigned to BSE education and nine were assigned to control; five enterprise polyclinics were assigned to BSE education and five were assigned to control. The random assignment was conducted at WHO, Geneva, using a table of random sampling numbers.

Criteria of eligibility

The study population consists of women aged 40–64 years at risk of developing breast cancer but who have not had it before. Informed consent to participate in the study was not required. However, women in the intervention groups were informed about the nature of the study and asked to fill in a questionnaire giving identifying information and core data on their major risk factors for breast cancer. That day was considered for them as day one of the study. All of them, no matter whether they start and continue to practice BSE or not, compose the population for comparison with the controls. In parallel, approximately the same number of records over the same time span were made for the controls. Data for the controls were made available from medical records in district polyclinics or factories (allocated randomly as indicated above). For the sake of completeness of registration of females at their working places, lists of entries were checked by the relevant personnel departments. The women in the control groups did not have any different care than usual and, therefore, they were not required to complete consent forms.

As indicated above, women with previously diagnosed breast cancer are ineligible for the study. Such women were not initially identified in the control groups. They are identified through the routine follow-up procedures in the study (see below), and will be excluded from the analysis of the study findings as initially ineligible.

Details of the program and logistic support in St Petersburg

Information and education programs. In the polyclinics allocated to the BSE intervention, prior to the initiation of the education of women, an information campaign was carried out. A message aimed at medical personnel was delivered by project officers who explained the objectives of the study, its design and logistics. District doctors and nurses in contact with the population were provided with standard information for educating women attending the polyclinics and were trained in teaching BSE and in keeping records of trainees.

Enrollment into the main study commenced in January 1985. An education programme for unselected women, who attended the polyclinics during the course of enrollment in the study, was run by the abovementioned trained nurses and/or doctors and delivered either individually (see below) or to groups of women (5–10–20 individuals), based on the Mama program developed by Gastrin [8]. These education sessions served as the primary vehicle for promotion of health awareness and program implementation. Utmost efforts to establish two-way dialogue were made and improvements of individual self-surveillance promoted by the use of personal calendars.

Different options of further motivation and reinforcement were tested during the pilot stage of the project. These included the broadcasting of messages within the polyclinics, and postcard reminders to individual women. In practice, broadcast messages through enterprise polyclinics proved feasible, while each woman included in the study in a polyclinic allocated BSE receives a personal calendar for reinforcement of BSE practice each year by mail.

Where feasible, individual instruction was given to women who attended for a routine health check (encouraged in the polyclinics on an annual basis). Women attending for such checks in polyclinics allocated to BSE received a physical examination of the breasts, were instructed in BSE and given a calendar. Reinforcement occurs on an annual basis when they return as instructed. In control polyclinics, such women receive physical examination of the breasts but no BSE instruction. The absence of BSE instruction of controls in polyclinics is assured as BSE instruction is not part of standard medical care in Russia.

For women attending for routine health checks, therefore, the effect of BSE over and above physical examination of the breasts is being assessed.

Registration. To attain the goal of the study, a complete enumeration of these populations is essential. To this end every woman invited to participate in the study, including those who do not attend teaching sessions, has been registered by designated medical staff. Corresponding information on the controls was compiled in the selected polyclinics by medical students under supervision of trained nurses. In order to avoid the possibility of double registration, for example, into an intervention group at the factory and control group in the district polyclinic, computer-aided control was conducted. Although the possibility of double registration was slight, the enterprise registration was given priority. Identification was carried out with the help of such discriminators as the name, year of birth and record number at the polyclinic or health care centre. This information is filed and updated in the study management office. It can be retrieved on demand when reinforcement of BSE practice or selective control of BSE performance, for example, is carried out or for calendar exchange to women of the target group at the end of each year. Updated information on women who find signs of a disease, consult a breast specialist and are referred to the Oncological Institute is recorded on each group. For those cases examined at the institute and/or treated there from both study and control polyclinics, follow-up during the whole period of the study will be assured. For these cases, additional registration cards are filled in, which contain information on the disease condition (benign or malignant), the mode of detection (self-examination, physician examination, mammography), cytological or histopathological classification, staging of the disease and treatment applied.

Examination and referral system. Examination and referral of women having detected symptoms of breast disease for establishing the diagnosis and further treatment if necessary is carried out in a standard manner making use of the existing health care structure and specialised services. A three-level referral system which has already been tested for several years has been adapted for the study (see Fig. 1). Women having

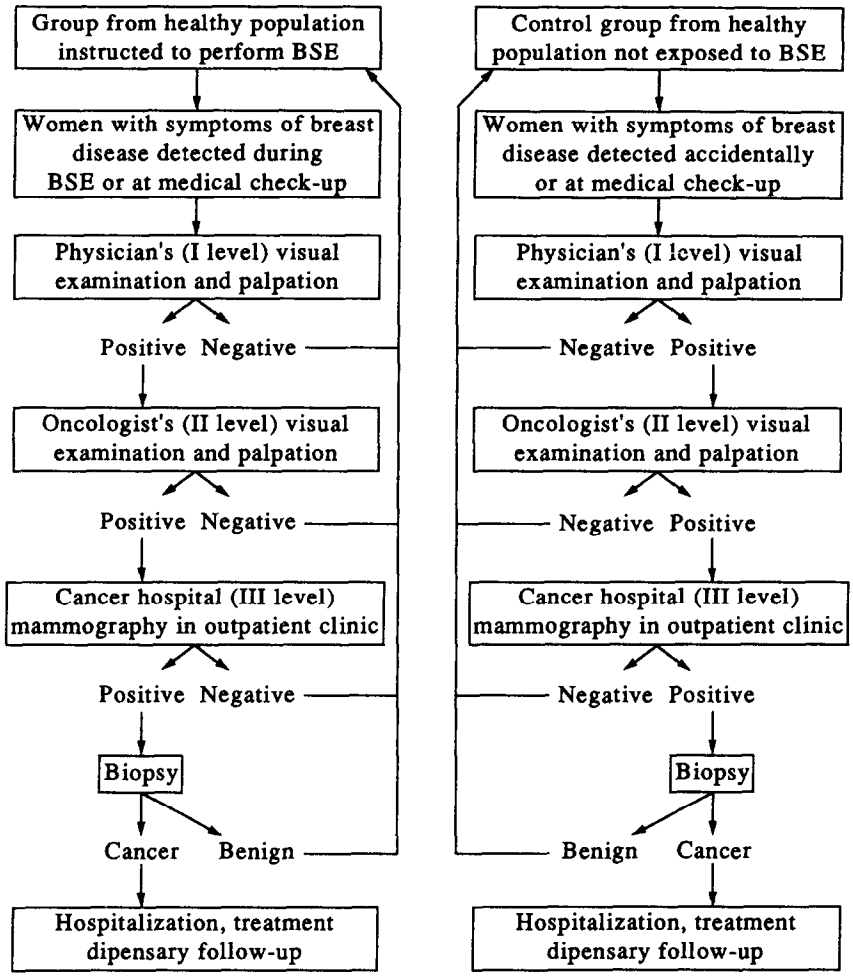

Fig. 1. Steps for referral and medical examination of women in the intervention and control groups.

detected symptoms have free access to a doctor, indicated on their BSE calendar, who refers all suspected and obvious cancer cases to a regional breast specialist (oncologist). Oncologists, on the basis of physical examination, sort out both obvious and suspect cases for referral to the Oncological Institute, where the necessary diagnostic (mammography, aspiration biopsy, excision biopsy) procedures and therapy are performed. The same referral system is in operation for women in the control group in the event that abnormalities in the breasts are noted either accidentally or at medical check-ups.

Treatment. All breast cancer patients (cases and controls) undergo standardised uniform treatment at the same cancer hospital, i.e. the Professor N.N. Petrov Research Institute of Oncology. Choice of the treatment is standardised depending on the extent of the tumour spread, clinically and pathologically staged according to the International Union Against Cancer (UICC) TNM (tumours, nodes, metastases) classification of breast cancer [9], age and menstrual status.

Follow-up. All cancer cases are routinely followed by the tumour registry of the Professor N.N. Petrov Research Institute of Oncology. The data are derived from the City Oncology Clinic and district oncologists. The study files are routinely linked to the tumour registry to capture the data for study purposes. Copies of death certificates are procured for those breast cancer cases that die. Women who migrate from St Petersburg will be lost from the study. However, the numbers who migrate are believed to be negligible and unbiased as to allocation.

Details of the programme in Moscow

The objective, aims and procedures of the study to be performed in Moscow are similar to those described above for St Petersburg in terms of major organizational implications and the content of information and education programs. The differences from the St Petersburg part of the study start with the approach to the female population. It has been decided to introduce an education programme of BSE at places of work and this has led to some other differences including:

— a greater number of units approached (237 factories);

— the only reliable option to implement the education programme is through trained project staff, though of limited numbers;

— provision of necessary treatment to self-referred women is not in one institution, as in the case of St Petersburg, but in a network of oncological dispensaries (hospitals).

Information and education programmes and registration. Factories and other establishments randomly allocated for intervention or control differ greatly in size and in their own health care facilities (number of health care workers, level of education and training, kind of duties imposed on them, etc.). This modified

the extent of help obtained from local health workers and the prior information disseminated. As mentioned above, the content of an education programme for both parts of the project was uniform, however, the means of delivering it was different.

For this purpose full-time staff were employed in the Russian Cancer Research Centre, which is running the project, and four teams of three people each were trained. The first three teams ran BSE instruction sessions and registered participating women at factories allocated to the intervention group, the fourth compiled lists of females for the control group.

As the basic information on controls was obtained from records which did not have risk factor information, data on risk factors for breast cancer for the Moscow control group are not available. In order to permit confirmation of comparability of study and control groups (and adjustment in the analysis should this prove necessary), a 10% random sample of controls within each unit of randomisation of the control group was drawn and administered the same questionnaire on risk factors for breast cancer as the study group.

Referral system and treatment. The referral system in Moscow consists of three conventional levels. Since methods of treatment of cancer patients in oncological dispensaries and institutions in Russia are rather uniform, special conditions for cancer cases from the study setting are not required. Women in the study are, therefore, referred along the channels of the existing cancer service and information retrieved for follow-up as described below. Women who develop breast cancer, after treatment in one of the city cancer hospitals, are given regular medical check-ups by district oncologists according to a routine (at least annual) procedure adopted for all Moscow residents with cancer.

Follow-up. All breast cancer patients from this population are being identified through the retrieval and checking of information of newly diagnosed breast cancer cases in the Moscow cancer registry (approximately 3000 cases yearly). The study files are linked to the registry files by computer on an annual basis. The procedure is time-consuming but reliable and unbiased due to the system of registration of cancer patients in the Russian Federation, which in Moscow for breast cancer is believed to be 98% complete. Women who migrate from Moscow will be lost from the study. However, the numbers who migrate are believed to be negligible and unbiased as to allocation.

A follow-up form is filled in annually for each cancer patient in the study and control groups by the staff of the project in the Russian Cancer Research Centre. This form is compiled from the data collected by the district oncologists. In this form data on therapy and health status of a woman for each year of follow-up are recorded.

Summary of information programme and training of the medical staff

Acquaintance of the medical staff (nurses, doctors' assistants, doctors) and paramedical personnel with the aim of the study and their training is made.

A 3-h program of teaching covers the following items: breast cancer problems; anatomy of the breast; physiology, evolution, involution of the breast; dyshormonal, benign and malignant lesions of the breast; present status of the problem of breast cancer detection and treatment; current concepts of BSE in the light of the problems of breast cancer control; the techniques of BSE.

Forty-five to sixty minutes are reserved for discussion and practice of the BSE technique.

The tasks of the "primary" team of medical and paramedical workers involved in the study

— Dissemination and collection of questionnaires at the beginning of the study. Registration of women invited to participate in the study and compilation of lists of controls.

— Teaching of women (groups 5–10–20 persons) on breast cancer problems, BSE value, its positive aspects, reasons for non-acceptance, BSE technique, symptoms of benign lesions and cancer of the breast (with the use of slides, figures, films, model). Duration of the lecture is 20–25 min and 15–20 min is left for discussion and practice.

— Twice a year motivation of enrolled women on the necessity to regularly practise BSE every month. Delivery of additional information and visual aids about BSE techniques and symptoms of cancer and pretumour lesions of the breast, when deemed necessary. Annual exchange of calendars.

Study documentation

Each women participating in the study who attended special lectures and practical teaching sessions in BSE under the guidance of a breast self-examination instructor, or personal instruction during the course of a physical examination, received a calendar and instructions on breast self-examination. This calendar is almost identical (except it is translated into Russian) to that developed by Gastrin [8].

The purpose of the calendar is 4-fold:

— To remind the woman of the technique of BSE and the necessity to practice it regularly once a month.

— To facilitate registration of any changes in the breasts detected during BSE.

— To provide information on how to act when abnormalities are detected including the name of a doctor to be consulted first.

— To serve as a means of feedback.

A special individual form is the main scientific document for women enrolled in the study and control groups. The form was filled in during BSE instruction sessions or when composing the control group and it will be kept in the file of the project office until the study is over. Data on BSE performance, i.e. frequency and competence, reports on symptoms of breast diseases to a physician, the way in which the tumour was discovered, the mode of treatment for breast cancer and subsequent medical checkups of a patient are recorded on the form during the course of the study.

Duration of the study

The duration of the study is dependent upon the rate of breast cancer incidence and deaths within the target populations. The exact time when an impact of BSE practice on mortality from breast cancer can be expected is unknown, yet if previous studies of breast cancer screening are a guide [1], a benefit after 5 years of initiating a BSE program might be seen in women aged 50 or more, but a delay of up to 10 years for women aged 40–49. As recruitment of the study population took over 4 years (see below), up to 12 years are planned for identifying breast cancer cases and 3 more years for further follow-up. As the initial participants were enrolled in 1985, the follow-up is planned to last until the year 2000, with reports on the findings appearing early in the 21st century.

STATISTICAL CONSIDERATIONS

Enrollment of intervention (BSE) and control groups of women

Women in the intervention group were invited to teaching sessions in successive waves. Until a women was invited to a

Table 1. Expected age distribution of participants and incidence of breast cancer

Age group	Age distribution in Moscow (%)	Age distribution in St Petersburg (%)	Estonian Republic incidence 1980 (100 000/year)
40–49	61	40	67.9
50–59	35	40	104.1
60–64	2	20	91.5

Table 3.

Compliance with BSE	Difference in breast cancer mortality	
	20%	30%
100%	93%	99%
70%	62%	94%
50%	42%	72%

teaching session, or registered at the time of a polyclinic attendance in St Petersburg, she was not considered to be a member of the intervention group—only a candidate for that group.

Women in the control group were also enrolled in the study in successive waves. Each time a group of women in the intervention group was invited to a BSE teaching session, the same number of women in the control group were enrolled into the study. The women in the control group were enrolled in an unbiased manner similarly to the enrollment of the intervention group.

If a woman on the list of candidates is found to have had a previously diagnosed breast cancer before she was enrolled in the study, her cancer will be registered in the study files, but women with previously diagnosed breast cancers are considered to be ineligible for the study.

It is thus important that the date of diagnosis of all breast cancers be carefully established. For the purpose of this study the date of diagnosis will be considered to be the date of biopsy that establishes the histological diagnosis, or for those without histological confirmation, the date the clinical diagnosis was made.

Incidence of breast cancer

Table 1 shows the expected age distribution in the Moscow factories, the age distribution expected in St Petersburg and the 1980 age-specific breast cancer incidence rates in Estonia. Using these numbers, we would expect among women of 40–64 years old a breast cancer incidence of 82/100 000/year in Moscow and 87/100 000/year in St Petersburg. Although incidence rates are rising in Russia and the women will get older during the study (and hence many will move from the 40–49 age group to the 50–59 age group) we will not assume a slightly higher incidence, to compensate for the loss of women from death or migration during the course of the study.

Mortality from breast cancer

The two centres have together enrolled over 193 000 women over 6 years. Table 2 shows how many patients have been entered each year, the expected incidence for each year and the cumulative incidence. Newly diagnosed cases will be identified for 10 years after day one of the study in St Petersburg and 12 years in Moscow and follow-up of all cases will continue for another 5 years in St Petersburg and 3 years in Moscow. Table 2 also shows the expected number of deaths. This is based on an assumption of exponential survival. About 40% of breast cancer patients in Russia die from their cancer by 5 years after diagnosis and about 64% die by 10 years after diagnosis. Thus, the exponential distribution fits very well.

We would like to be able to detect a decrease of deaths by 20–30% in the study group. However, the power of the study to detect such a mortality reduction will be attenuated if compliance with BSE is low. Using estimates of the number of deaths expected during the total 15-year period of the study, a one-sided α of 0.05, the power of the study for different effect and compliance levels is shown in Table 3. The study will, therefore, have good power to detect a 30% mortality reduction overall, and moderate to low power for a 20% reduction, depending on the BSE compliance.

Table 2. Recruitment of participants, expected number of cases of breast cancer and expected number of deaths from breast cancer

Year of study	Population entered	Expected number of cases	Follow-up (years)	Expected percent deaths	Expected number of deaths*
1	74 787	32	14.5	73	23.4
2	39 984	81	13.5	70	56.7
3	41 700	110	12.5	67	73.7
4	29 859	146	11.5	64	93.4
5	6 477	161	10.5	61	98.2
6	532	164	9.5	57	93.5
7	0	164	8.5	53	86.9
8	0	164	7.5	49	80.4
9	0	164	6.5	44	72.2
10	0	164	5.5	39	64.0
11	0	60	4.5	33	19.8
12	0	60	3.5	27	16.2
Total	193 339	1470			778.4

* Over the whole 15-year period of follow-up.

Table 4. Relative efficiency of a cluster randomised design

No. of factories randomised	Coefficient of variation 0.1	0.2	0.3	0.4	0.5
10	1.28	2.12	3.52	5.49	8.02
50	1.06	1.22	1.50	1.90	2.40
100	1.03	1.11	1.25	1.45	1.70

Effect of group randomisation

Since we used cluster randomisation with the units of randomisation being enterprises in Moscow and polyclinics in St Petersburg, the analysis has to reflect this design. We will, therefore, analyse the data using generalised linear models with extra variation to correspond to the cluster variation. The methods to be used have been described in detail [10].

Cluster variation may lead to loss of power. We have, therefore, computed the "relative efficiency" as a function of the cluster variation and the number of clusters that are randomised. Cluster variation is measured as a "coefficient of variation" defined as the standard deviation divided by the mean. Relative efficiency measures that proportional increase in sample size which is necessary to obtain the same power. In Table 4 we present the relative efficiency of a cluster randomised design as a function of the coefficient of variation and the number of units.

Based on some preliminary data on the incidence of breast cancer in the different enterprises in Moscow, we estimate that the factory-to-factory coefficient of variation is no greater than 30%. Although the calculations above are based on the coefficient of variation of breast cancer mortality rates, the data on incidence plus the fact that over 200 enterprises were randomised in Moscow suggest that the loss of efficiency due to cluster randomisation will be slight. Although similar data from St Petersburg are not yet available, we suspect that the polyclinics will be even more homogeneous (i.e. smaller between polyclinic coefficient of variation) than that seen in Moscow. Therefore, the use of cluster randomisation is unlikely to present difficulties in either the analysis or the precision of the results.

Contamination

The foregoing calculations assume that BSE will not be practised by members of the control group or only practised very inefficiently. The use of randomisation by groups ensures that contamination of the control group by the study procedures is very unlikely. Further, BSE has not been promoted in the Russian Federation, and there are no plans to introduce programs of promotion until the results of the study are available. Thus, contamination of the control group is far less likely than if the study had been conducted in another developed country.

IMPLEMENTATION OF THE STUDY

Assessment of compliance

During the first year (1984), a feasibility study was undertaken for developing and testing all components of the study and assessing compliance of the population. The overall compliance rate was 64%, i.e. over 85% in the target groups were taught BSE and over 75% of these practised it at 1 year. To assess the frequency and quality of BSE performance among women of the intervention group, randomly selected subsamples of enrolled women were approached at the end of 6 months, 1 year and 2 years. A randomly selected group of 400 women were interviewed at these times. (The questionnaire is available on request from the authors.) Since the efficacy of the training and degree of motivation of women may vary at different places, a stratified sampling scheme was used to assess compliance. In Moscow, 10 factories in the study group were chosen at random and a random sample of 40 women chosen at each of these factories. In St Petersburg, the sample was divided among all the institutions which received the intervention.

At the end of the first, second and third years, 400 women in each study and control group were questioned about their use of the health care system for consultation about breast cancer symptoms or for routine breast examinations by physicians. For both the study and control group sample there were also questions about the frequency of biopsies for breast disease. If a women had a biopsy, her medical record was checked for clinical and morphological findings relating to the biopsy.

More than one survey was conducted in two different communities of St Petersburg and several places of work in Moscow. This permits assessment as to whether the performance of BSE and the use of the health care system was the same in different factories or regions.

Re-education of study group women in BSE

In view of the length of the study, and the possibility that women taught BSE will cease to practice the technique, from year 5 of the study, re-education of women in the group is being attempted. In Moscow, this consists of a study team visiting enterprises previously involved in the study, and repeating the BSE instruction to relevant groups of women. In St Petersburg, women who re-attend the study polyclinics on a routine basis have BSE instruction repeated by the polyclinic nurse.

EVALUATION OF THE STUDY RESULTS

Main end-point

The main end-point of the study will be the comparison of rates of breast cancer deaths between study and control groups. In the evaluation of the study results, the data obtained in Moscow and St Petersburg will initially be considered independently but will then be combined.

Secondary end-points

Secondary evaluation will be made by:

(a) comparing the extent of the disease at diagnosis (tumour dimension, presence and number of metastatically involved regional lymph nodes in the study population compared with the controls).
(b) Duration of the time between self-detection (by BSE or accidentally) or detection by doctor of the signs of the disease and the start of treatment will be compared between the two groups.
(c) The mode of tumour discovery and diagnosis for the breast cancer patients will be analysed to determine the potential impact of the BSE program.
(d) The rate of BSE practice will be assessed among women invited to participate in the study at the beginning and at the end of the intervention on a subsample basis.
(e) The cost and workload for each case of cancer and other lesions of the breast will be assessed.
(f) The frequency of unwanted biopsies and the related cost will also be assessed (only possible in St Petersburg).

Coordinating offices of the project

In the Russian Federation, the coordinating offices are in the N.N. Petrov Research Oncological Institute for St Petersburg

and in the Russian Cancer Research Centre for Moscow. All information about the progress of the project is collected for the relevant area. The central coordinating office is the Cancer Unit at the World Heath Organization Headquarters in Geneva, assisted by the WHO Collaborating Center for Cancer Biostatistics Evaluation, Boston, U.S.A. and the WHO Collaborating Centre for Evaluation of Screening for Cancer, Toronto, Canada.

WHO SPONSORSHIP OF THE PROJECT

The study was designed and has been implemented under the sponsorship and with the direct help of the WHO. The Cancer and Palliative Care Unit at the headquarters, Geneva is responsible for the overall coordination of activities on the implementation, management and evaluation of the study. For the 15 years of study activities, collecting cases of breast cancer and their follow-up, regular meetings for evaluation of the progress of the study are organised in Geneva and Russia.

WHO, through its Collaborating Centres for Cancer Biostatistics in Boston, U.S.A. and for Evaluation of Screening for Cancer in Toronto, Canada will ensure consultations on statistical analysis of data and final presentation of the results. All paper records will be preserved in order to facilitate a review of the data when the study is completed.

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Feature Articles

Retinoid Receptors and Acute Promyelocytic Leukaemia

Ian D. Trayner and Farzin Farzaneh

INTRODUCTION

ACUTE PROMYELOCYTIC leukaemia (APL, M3 by FAB classification) represents a deregulated clonal expansion of haemopoietic progenitor cells arrested at the promyelocyte stage of differentiation. It is recognised clinically by a preponderance of granular promyelocytes in the bone marrow, and sometimes in the peripheral blood, together with a haemorrhagic syndrome.

APL cells carry a balanced t(15;17)(q22;q11.2-q12) chromosomal translocation which has become diagnostic for the disease [1]. The breakpoint on chromosome 17 lies within the retinoic acid receptor-α (RAR-α) gene locus [2–6] and results in the splicing of RAR-α to a novel gene of as yet unknown function, termed PML (promyelocytic leukaemia), on chromosome 15 [7–11]. Characteristically, promyelocytic cells with the t(15;17) translocation can be induced to differentiate into granulocytes by treatment with all-*trans* retinoic acid (RA), either *in vitro* or *in vivo*. This provides a very effective differentiation therapy for APL patients (for reviews see [12, 13]).

RA INDUCES DIFFERENTIATION OF APL CELLS

Several isomers of RA are produced from retinol (vitamin A) which occurs naturally in the diet as β-carotene and acyl retinol esters. Different retinoids display subsets of the physiological effects of vitamin A (for reviews see [14, 15]). RA is a powerful morphogen and teratogen which is thought to play a role in the development of the embryonic limb bud [16] and central nervous system [17]. These properties may be related to the ability of RA to regulate the sequential expression of homeobox genes [18]

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