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Determinants of Compliance in a Cluster Randomised Controlled Trial on Screening of Breast and Cervix Cancer in Mumbai, India

2. Compliance to Referral and Treatment

Ketayun Dinshaw Gauravi Mishra Surendra Shastri Rajendra Badwe
Rajendra Kerkar Subhash Ramani Meenakshi Thakur Pallavi Uplap
Anagha Kakade Subhadra Gupta Balasubramanian Ganesh

Tata Memorial Hospital, Mumbai, India

Key Words
Screening · Compliance · Randomised controlled trial · Breast cancer · Cervix cancer

Abstract
Objectives: The study aims to investigate the efficacy of screening by low-cost technology in down-staging and reduction of mortality due to breast and cervix cancer. ***Methods:*** The present trial is a community-based, cluster randomised controlled cohort study on screening for breast and cervix cancers (clinical breast examination and visual inspection of the cervix after application of 4% acetic acid). Univariate and multivariate logistic regression analyses are conducted to identify the predictors of compliance to referral among screen-positive women and to treatment among cancer cases. ***Results:*** The compliance to diagnostic investigations is 73% among screen-positive women referred for breast cancer and 79% among women referred for cervix cancer. Younger women, women working in service or being self-employed, school level-educated women, mother tongue Marathi, participation in screening in all 3 rounds and women referred as screen positive for cervix cancer had higher compliance to diagnostic investigations. The compliance to treatment completion is higher in women diagnosed with breast cancer, at 95%, compared to 86% for cervix cancers and 81% for cervix pre-cancers. ***Conclusions:*** Good compliance rates along with a proper system of referral, further investigations, confirmation of diagnosis and treatment as demonstrated in this trial are crucial for successful screening programmes.

Introduction

Cervix and breast cancers account for 50% of cancers among Indian women. In many regions of developing countries, cervix cancer is responsible for 80% of cancer cases and is reported to be the commonest cancer among women [1, 2]. The age-standardised rate for cervix cancer ranges from 11 to 30 per 100,000 women in different regions of India [3]. Nearly 70% of cervix cancer patients present at stages III and IV [4]. The 5-year relative survival rate is 50%, and 20% of women who develop cervix cancer die within the first year of diagnosis [5]. Breast cancer is the second most common cancer among women and its incidence is rapidly rising, which is more evident

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Mishra Gauravi, MD, DPH, DHA
Department of Preventive Oncology, 5th Floor, Annexe Bldg., R. No. 8
Tata Memorial Hospital, E. Borges Marg, Parel
Mumbai 400 012, Maharashtra (India)
Tel. +91 22 2415 7532, Fax +91 22 2410 1656, E-Mail gauravi2005@yahoo.co.in

in urban areas like Mumbai (age-adjusted rate per 100,000: 33.1) [6, 7]. According to the data from the Tata Memorial Hospital Cancer Registry, 50% of breast cancers are detected in stages III and IV at the time of diagnosis when chances of cure are poor [4]. As many as 21% of women who develop breast cancer in Mumbai die within the first year of diagnosis, suggesting that they already have metastatic disease when the cancer is detected [8]. Nearly 550,000 cancer patients die each year in India. This large-scale morbidity and mortality associated with cancer continues unabated due to the single most important fact that cancer prevention and early detection services are almost non-existent. This situation could be easily reversed if we had well-planned cancer education and organised screening and early detection programmes.

Organising a good screening programme will result in mortality reduction only if the community participates in the programme entirely at all stages. Good compliance is required not only for the initial screening activity but also at the level of confirmatory diagnostic investigations among the screen positives and for treatment completion among the diagnosed cancer cases. The Philippines trial was designed as a randomised controlled trial to study the efficacy of 5 annual clinical breast examinations (CBE) carried out by trained nurses/midwives in reducing mortality from breast cancer. Though the trial had good participation for screening (92%), the compliance to diagnostic investigations was only 37%. The active intervention in the trial had to be discontinued after completion of the first screening round because of poor compliance to follow-up of screen-positive women [9].

The present study is a randomised controlled trial initiated in 1997 by investigators from the Tata Memorial Hospital with the primary aim to investigate the efficacy of well-planned health education programmes (HEP) along with low-cost screening methods, such as CBE and visual inspection of the cervix after application of 4% acetic acid (VIA), performed by trained primary health workers (PHW), in down-staging breast and cervix cancers. The long-term endpoint is to evaluate reduction in mortality due to breast and cervix cancer in the intervention arm compared to the control arm. The trial was approved by the Institutional Review Board of the Tata Memorial Hospital. The present paper discusses the determinants of compliance to diagnostic investigations among the screen-positive women and to treatment completion among the cancer cases.

Methodology

Study Design

The study design is shown in the previous paper [see fig. 1 in Dinshaw et al., this issue, pp 145–153. This is a cluster randomised study involving 151,538 women between the ages of 35 and 64 years from the slums of Mumbai, India, staying in 20 geographically defined clusters that were randomly allocated into an intervention arm (10 clusters, n = 75,360) to receive 4 rounds of the intervention, that is well-planned HEP, VIA and CBE at 24-month intervals and a control arm (10 clusters, n = 76,178). Trained female PHW conduct these examinations. The occurrence of significant down-staging is assessed by the end of 8 years, that is, after completion of 4 rounds of screening. To assess reduction in mortality, these clusters will be monitored for a further period of 8 years and incidence and mortality due to cervix and breast cancers of the enrolled women belonging to these clusters will be recorded. The control group receives the same HEP in the first round. Thereafter, the control group women are monitored every 2 years by active surveillance for the next 7 rounds to record the incidence and mortality due to breast and cervix cancers (1 round of HEP and 7 rounds of active surveillance). A total of 86 salaried project staff members are involved in the study, including medical social workers (MSW), PHW, project assistants and the data management team. The investigators and the project co-ordinator from the Tata Memorial Hospital plan and guide the project team.

Inclusion Criteria for Women in the Study

Women between the ages of 35 and 64 years, living in the selected clusters for more than 1 year, without any previous history of breast or cervix cancer or any other form of malignancy, were included in the study.

Cluster Randomisation and Field Work Strategy

The procedures of community rapport building, baseline survey, preparation of road maps, cluster randomisation, informed consent, training of staff, community-based group health education in both arms, procedures for screening and quality control in the intervention arm are all described in the earlier paper. During the screening, the PHW identified women as screen positives if any suspicious lesion as described in the pre-defined referral criteria was detected during screening. The screened positive women were referred to the Preventive Oncology Clinic at the Tata Memorial Hospital. Here, the cervix-screened positive women underwent diagnostic tests like colposcopy and Pap smear testing, as well as cervix biopsy and ultrasonography when necessary. The women underwent mammography, fine needle aspiration cytology or biopsy when referred as screen positive for breast cancer.

The eligible women in both arms are provided with colour-coded project identity cards and information about the availability of services at the Tata Memorial Hospital and other centres in Mumbai. Screened positive women or self-referred women who approach Tata Memorial Hospital seeking diagnostic or treatment services for breast or cervix cancer from either arm are provided the standard treatment according to the evidence-based medicine protocols of the Tata Memorial Hospital [10] free of cost. No differentiation whatsoever is made in the type of treatment instituted to women from either arm, as the treating physician is

Table 1. Compliance to screening and referral in the intervention arm

Screening round	Site	Eligible women	Compliance to screening[1]	Screening positive[2]	Compliance to referral[3]	Histologically confirmed cancers
First round (IC 1–10)	breast	75,360	56,985 (75.62)	350 (0.61)	238 (68)	32
	cervix	71,561[7]	51,145 (71.47)	672 (1.31)	505 (75.15)	20
Second round (IC 1–10)	breast	71,500[6]	49,012 (68.55)	551 (1.12)	389 (70.60)	24+24[4]+3[5]
	cervix	66,219[7]	41,354 (62.45)	791 (1.91)	621 (78.51)	12+11[4]+3[5]
Third round (IC 1–10)	breast	67,530[6]	47,133 (69.80)	638 (1.35)	498 (78.06)	25+15[4]+2[5]
	cervix	61,108[7]	36,643 (59.96)	642 (1.75)	536 (83.49)	17+18[4]+5[5]

IC = Intervention cluster.
[1] Figures in parentheses are percentages of eligibles.
[2] Figures in parentheses are percentages of screened.
[3] Figures in parentheses are percentages of screen positives.
[4] Interval cancers.
[5] Among non-compliers for screening.
[6] There is 5.12% attrition between rounds 1 and 2 and 5.55% attrition between rounds 2 and 3 because of expired and shifted women who could not be traced.
[7] The numbers of eligible women are lower for cervix screening than for breast screening because 3,799 women (5.04%) in round 1, 5,281 (7.01%) in round 2 and 6,422 (8.52%) in round 3 underwent hysterectomy.

blinded to the patient group. The details of diagnosis, stage of the disease, treatment undertaken and so on are obtained from the treating physician for women getting treatment from other hospitals either from the intervention or control arm. In this paper, the compliance is evaluated at the following levels: level 4 = compliance to diagnostic confirmation among screen-positive cases; level 5 = compliance to treatment initiation among the diagnosed cases; level 6 = compliance to treatment completion among women diagnosed with cancer.

Compliance at levels 1, 2 and 3 is described in the earlier paper. Compliance at level 5 is calculated as percentage. The characteristics of compliant and non-compliant women are compared using the χ^2 test. The effects of various sociodemographic and reproductive characteristics of women on compliance to diagnostic confirmation among screen-positive women and for treatment completion among the cancer cases, that is, at levels 4 and 6, respectively, are evaluated by estimating odds ratios and their 95% confidence intervals using Stata software and analysed by univariate and multivariate logistic regression analyses. All variables considered for the univariate analysis were included in the logistic regression model for the multivariate analysis using the stepwise method. Hence, only the results of significant variables that remained in the model are presented in the multivariate analysis.

Results

The PHW conducted the screening in the community by CBE for breast and VIA for cervix cancer and referred the screened positive women to the Tata Memorial Hospital. A total of 1,539 women were referred for breast cancer (screening positivity rate of 1.01%) and 2,105 for cervix cancer (screening positivity rate of 1.63%) to the nodal hospital for undergoing further investigations for a confirmation of the diagnosis. The referral in each round for breast and cervix screening is documented in table 1. The screening positivity rate for both breast and cervix cancer is lower (0.61 and 1.31%, respectively) in the first screening round. These low rates of referrals can be attributed to the learning curve in the screening test providers. Thereafter, the screening positivity rate for breast cancer remains in the range of 1.12–1.35%. The screening positivity rate for cervix cancer also remains constant in the range 1.75–1.91%. Each screen-positive woman was counselled at the screening camp by the PHW and MSW. The importance of complying to further diagnostic investigations was emphasised. Every effort was made to attain a balance during counselling to avert unnecessary fear and anxiety, while at the same time achieving good compliance to the diagnostic confirmatory procedures. A home visit was made in the second week for women who did not comply within a week of referral by the senior PHW and senior MSW. A trained counsellor and/or a doctor counselled the persistent non-compliers in the third week, in order to relieve their anxiety, motivate them and further understand the reasons for non-compliance. The compliance achieved after all these repeated counselling sessions in various screening rounds for breast and cervix cancer is presented in table 1. An average compliance of 73.1% was achieved when women were referred for breast cancer and 78.95% when women were referred for cervix cancer at the end of 3 screens. Age, occupation, education, language, compliance to screening in 3 screening rounds and the site for

Table 2. Distribution of compliers and non-compliers to referral in the intervention arm by important sociodemographic variables and the results of univariate and multivariate logistic regression analyses identifying predictors of compliance to referral diagnostic test

Variables	Total screen positives	Compliers %	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Age groups								
35–39 years	1,268	77.44	1		0.000	1		0.000
40–44 years	796	81.41	1.275	1.021–1.592	0.032	1.446	1.145–1.826	0.002
45–49 years	622	77.17	0.984	0.783–1.238	0.893	1.189	0.930–1.520	0.167
50–54 years	417	73.38	0.803	0.623–1.035	0.090	1.104	0.834–1.462	0.487
55–59 years	237	73.42	0.804	0.586–1.104	0.178	1.068	0.758–1.506	0.706
60–64 years	191	64.92	0.539	0.389–0.746	0.000	0.842	0.589–1.202	0.343
≥65 years	8	50.00	0.291	0.072–1.172	0.082	0.358	0.086–1.492	0.159
Community								
Hindu	2,827	77.43	1		0.000			
Muslim	410	70.73	0.704	0.559–0.887	0.003			
Others	298	80.20	1.181	0.876–1.591	0.275			
Occupation								
Housewife	3,134	76.77	1		0.000	1		0.000
Service	157	84.08	1.598	1.034–2.469	0.035	1.642	1.039–2.594	0.034
Manual labour	246	73.17	0.825	0.615–1.107	0.200	0.817	0.594–1.123	0.213
Education								
Illiterate	1,295	71.51	1		0.000	1		0.000
School level	2,212	79.97	1.591	1.357–1.866	0.000	1.439	1.208–1.714	0.000
Graduates	30	76.67	1.309	0.557–3.077	0.537	1.231	0.503–3.015	0.649
Monthly per capita income								
≤500 rupees	1,700	75.71	1		0.000			
>500 rupees	1,835	77.87	1.129	0.966–1.321	0.127			
Language								
Marathi	2,213	79.62	1		0.000	1		0.000
Hindi	522	74.33	0.741	0.594–0.925	0.008	0.807	0.635–1.026	0.081
Others	802	70.82	0.621	0.517–0.747	0.000	0.701	0.577–0.852	0.000
Marital status								
Single	22	59.09	1		0.000			
Married	2,984	77.58	2.396	1.020–5.629	0.045			
Widowed/divorced	530	73.58	1.929	0.807–4.611	0.140			
Previous consultation for breast or gynaecologic complaints								
No	3,114	76.56	1		0.000			
Yes	425	78.59	1.113	0.870–1.423	0.396			
Family history of breast cancer								
Yes	33	75.76	1		0.000			
No	3,498	76.93	0.937	0.421–2.086	0.874			
No. of times women complied to screening								
Once	470	53.19	1		0.000	1		0.000
Twice	1,103	72.98	2.377	1.899–2.976	0.000	2.308	1.832–2.909	0.000
Thrice	1,966	84.59	4.830	3.881–6.010	0.000	4.659	3.717–5.839	0.000
Site referred for								
Breast	1,434	73.64	1		0.000	1		0.000
Cervix	2,000	79.65	1.401	1.194–1.644	0.000	1.375	1.148–1.646	0.001
Both	105	65.71	0.686	0.451–1.044	0.079	0.769	0.492–1.201	0.248

The odds ratio (OR) for trend for age when considered continuous is 0.995, at a 95% confidence interval (CI) of 0.983–1.007; for income, the OR is 1.000 at a 95% CI of 0.9999–1.0004.

referral (breast, cervix or both) emerged as independent predictors for compliance to diagnostic investigations from the multivariate logistic regression analysis. Women with the following characteristics showed higher compliance: younger women, women working in service or being self-employed, school level-educated women, mother tongue Marathi, women who complied to screening in all 3 rounds and women referred as screen positive for cervix cancer (table 2).

Among the women who complied to the diagnostic test, 81 cancers of the breast and 49 cancers of the cervix were diagnosed (screen-detected cancers). In addition, there were 5 cancers of the breast and 8 of the cervix among the non-compliers to screening (cancers occurring among non-participants to screening in all previous rounds) and 39 interval cancers (diagnosed after a negative screening test among those screened at least once) of the breast and 29 of the cervix from the intervention arm. In the control arm, 87 cancers of the breast and 51 of the cervix occurred during the same period. The project women enrolled from the intervention as well as the control arm were given project identity cards. They could benefit from the diagnostic and treatment facilities at the nodal hospital for breast or cervix cancer with this card during the project period. The compliance to treatment initiation after diagnosis of cancer was 95.3% for breast cancer cases and 88.24% for cervix cancer cases from the intervention arm. In the control arm, the compliance to initiation of treatment was 95.4% for breast cancer cases and 88.0% for cervix cancer cases. The information regarding treatment details could not be collected from 5 breast cancer patients from the intervention arm and 4 from the control arm. Similarly, complete information was not available for 6 cervix cancer patients from the intervention arm and 4 from the control arm. Treatment details could not be retrieved because these patients were undertaking treatment at other hospitals where the medical reports were not preserved, the papers were washed away in floods which took place in Mumbai in July 2005 or the patient had expired and the family had disposed of the papers. Among 173 pre-cancer cases of the cervix from the intervention arm, 19 women refused treatment, while among 8 pre-cancer cases from the control arm, none refused. The compliance to treatment completion was 95.06% among women screen diagnosed for breast cancer, 66.67% among cancers detected in women who did not comply to screening and 95.12% among interval cancers of the breast, in the intervention arm. The compliance was 79.59% among women screen diagnosed for cervix cancer, 100% for cases diagnosed among the non-compliers for screening and 92.86% among interval cancers of the cervix for treatment completion from the intervention arm. The overall compliance to treatment completion in the intervention arm is 94.4% for breast cancers and 85.88% for cervical cancers. In the control arm the compliance to treatment completion after positive diagnosis was 95.4% for breast and 86.0% for cervix cancer.

As shown in table 3, only site of cancer (breast or cervix) emerged as independent predictor for compliance to treatment among all cancer cases diagnosed in both arms, according to the multivariate logistic regression analysis. Women diagnosed with breast cancer are more likely to comply to treatment, compared to women diagnosed with cervix cancer. Finally, 32 women died of breast cancer, 22 of whom were from the intervention arm and 10 from the control arm, with overall case fatality rates of 17.6 and 11.49%, respectively. Until the completion of the third screen, 33 women died of cervix cancer, 18 of whom were from the intervention arm and 15 from the control arm, giving case fatality rates of 21.18 and 30%, respectively.

Discussion

In a community-based screening trial aimed at investigating reduction in mortality, good compliance at various levels, that is, participation in screening, compliance for further diagnostic work-up, initiation and completion of treatment, is equally important. The best screening tests will not succeed in reducing mortality in the absence of adherence to the screening protocol and good compliance at all levels.

In the present trial, the screening participation is lower for cervix than for breast examinations. However, the compliance to referral is higher among women screened positive for cervix cancer compared to breast cancer. This may probably be due to the presence of some symptoms like irregular menstrual bleeding, postcoital or postmenopausal bleeding or copious vaginal discharge among women screened positive for cervix cancer, which they could correlate with the referral. Whereas for women screened positive for breast cancer, it is usually an immobile lump, which is generally painless and does not cause any discomfort, and hence the women are not convinced about the necessity for undergoing further investigations. Overall, the compliance to diagnostic investigations is 73% among women referred for breast and 79% among women referred for cervix cancer. Diagnostic in-

Table 3. Distribution of compliers and non-compliers to treatment in the intervention arm by important sociodemographic variables and the results of univariate and multivariate logistic regression analyses identifying predictors of compliance to treatment

Variables	Total cancer cases	Compliers for treatment, %	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Age groups								
35–39 years	47	97.87	0.961	0.891–1.037	0.303			
40–44 years	82	97.56						
45–49 years	74	98.65						
50–54 years	57	94.74						
55–59 years	32	87.5						
60–64 years	35	100						
≥65 years	1	100						
Community								
Hindu	255	96.86	1		0.000			
Others	73	95.89	0.756	0.195–2.924	0.685			
Occupation								
Housewife	294	97.28	1					
Service	16	93.75	0.420	0.049–3.576	0.427			
Manual labour	18	88.89	0.224	0.044–1.141	0.072			
Education								
Illiterate	131	92.37	1					
School level	194	99.48	15.950	2.016–126.171	0.009			
Graduates	3	100						
Monthly per capita income								
≤500 rupees	156	96.15	1					
>500 rupees	172	97.09	1.336	0.400–4.467	0.638			
Language								
Marathi	199	96.48	1		0.000			
Hindi	56	96.43	0.984	0.199–4.877	0.985			
Others	73	97.26	1.294	0.263–6.378	0.751			
Marital status								
Single/divorced/ widowed	83	95.18	1					
Married	244	97.13	1.714	0.489–6.011	0.4			
Previous consultation for breast or gynaecologic complaints								
No	252	96.83	1					
Yes	76	96.05	0.828	0.214–3.204	0.785			
Site referred for								
Breast	203	99.01	1			1		0.000
Cervix	125	92.8	0.128	0.027–0.604	0.009	0.127	0.027–0.598	0.009
Cancer group								
Screening positive	123	94.31	1					
Interval	76	98.68	4.526	0.546–37.529	0.162			
Control	129	97.67	2.534	0.640–10.032	0.185			

OR = Odds ratio; CI = confidence interval.

vestigations were carried out at the screening site in one of the cervical cancer screening trials in India in order to increase compliance [11]. Among the screen positives, nearly two thirds complied to referral in the oral cancer screening trial [12]. Women living in high-poverty and low-education areas were most likely to have their cancer diagnosis ascribed to failure to follow-up after positive screening result [13]. The Philippines trial on CBE had to be discontinued because of very low compliance to diagnostic confirmation among women screened positive for breast cancer [9]. In our study, increasing age, women working as manual labourers, illiterate women, women

speaking languages other than Hindi and Marathi, women who participated in screening only once and women referred for both breast and cervix cancer were identified as predictors of non-compliance to diagnostic tests among women screened positive. During the repeated counselling sessions with the non-complier screen-positive women, opinion of the spouse was identified as an important factor in determining compliance to the referral hospital. Hence, the spouses of the referred women were counselled. Some women consulted their family physicians for his/her opinion on the necessity of attending the nodal hospital. Understanding the local doctor's role, special sessions about the trial were conducted for doctors from the community. Anecdotal evidence suggested family obligations as the main reason for non-compliance, as the women did not wish to devote their extra time and effort to attend the hospital. In order to overcome this, mop-up camps were organised at the completion of each screening round in each cluster for carrying out diagnostic investigations among the non-complier screen-positive women. During the mop-up camps, colposcopy, cytology and biopsy were performed for cervix screen positives and CBE, fine needle aspiration cytology for breast screen positives. This led to an increase in compliance of about 10% as the women now received the services in proximity to their residence.

The compliance to treatment completion is 94.81% for breast cancer, 85.93% for cervix cancers and 80.67% for cervix pre-cancers in our study. Only site of cancer was identified as an independent predictor of compliance to treatment. Women diagnosed with cervix cancer had poor compliance to treatment compared to women diagnosed with breast cancer in our trial. This may probably be due to the long duration of radiotherapy being advised to many cervical cancer patients. Treatment compliance was only 45% among the women not treated at the first visit in a cervical screening trial in South India [14]. In a previous cross-sectional study conducted at our institution in Mumbai, only 23% of women with low-grade squamous intraepithelial lesion accepted immediate treatment, whereas 25% of the women diagnosed with high-grade squamous intraepithelial lesion and 39% of women with frank cancers refused treatment [15]. The compliance to treatment among women diagnosed with high-grade squamous intraepithelial lesion was over 85% in the Osmanabad district study [16]. In order to maximise the compliance to treatment, the see and treat strategy is adopted for treatment of cervical pre-cancers in some trials in developing countries [11].

Good compliance rates at all levels have been demonstrated in the present trial. This study indicates that a proper system of referral, investigations, confirmation of diagnosis and treatment needs to be established and appropriately designed to achieve good compliance to diagnostic tests, treatment and follow-up, which will further translate into a successful screening programme. This trial has done extremely well so far and is expected to influence the future policies on cancer control programmes in India and other resource-poor countries.

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