RESEARCH ARTICLE

Assessment of Adaptive Breast Cancer Screening Policies for Improved Mortality Reduction in Low to Middle Income Countries

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Abstract

Objective: To investigate adaptive breast cancer screening policies using clinical breast examination for early detection and mortality reduction in low to middle income countries like India. **Methods:** Using published data from the Mumbai randomized cluster control trial (1998-2006), we first estimated the mean sojourn time at 5.9 years (95% Confidence Interval: 5.3-6.5) assuming 52% sensitivity of the test. The estimated mean sojourn time was used as a "silent interval" in time varying cellular kinetics with the two stage deterministic clonal expansion model, and we found age specific sojourn times in years as follows: 35-39. 0.8; 40-44, 1.0; 45-49, 1.8; 50-54, 3.2; and 55+, 5.9. Equipped with age specific sojourn times and sensitivity, we investigate adaptive screening policies for various year age groups using different screening intervals, maintaining a constant screen count of 10 and a 6 state Markov transition model. The rationale for using a fixed number of screens was to benchmark the effect of the screening interval. **Result:** We found that annual screening at ages 35-39 and biennial from 41-49 would achieve a mortality reduction of 27.9%, while annual screening from 38-42 and triennial from 43-58 would achieve a mortality reduction of 25.5%. Biennial screening from 40-60 years of age showed a mortality reduction of 23.6%, indicating inclusion of annual screening might be effective. We demonstrated a modelling framework that could be applied to the final data of randomized controlled trials, such as the ongoing Mumbai and Trivandrum trials in India, for assessing efficacy of annual screening in younger women. **Conclusion:** The framework could be useful to decide age groups that would yield maximal effectiveness in screening trials with selected screening intervals. Further, the framework could be adapted in other low to middle income countries for designing either screening trials or adaptive screening policies.

Keywords: Adaptive screening- clinical breast examination- sojourn time- multistage models

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Introduction

Clinical Breast Examination (CBE), followed by diagnostic ultrasound has been leveraged as cost effective, feasible and affordable modality for mass screening of breast cancer (BC) in low to middle income countries (LMIC) (Sankaranarayanan and Boffetta, 2010; Dey, 2014; Sankaranarayanan, 2014; Anderson et al., 2015; Tsu et al., 2015). Mammography is infeasible and unaffordable in these countries; however, regional programs had been organized, such as the BC screening drive to reach 2,30,000 women in rural India by Tata Trusts using mobile vans equipped with mammography and mobile colonoscopy equipment. But mass screening campaign to reach out larger number of population is required, as 883,000 new cases of BC were reported in less developed countries according to GLOBOCAN 2012 (Ferlay et al., 2015). Low CBE sensitivity is an impediment for its serious consideration as modality for mass screening programs for significant mortality reduction. A comparative sensitivity of 88% in Asian women compared to 35% in white women, on the other hand, supports the recommendation (Oestreicher et al., 2002). Estimates of CBE performance had been obtained indirectly, because most of randomized controlled trials (RCTs) assessed mammography efficacy in resourceful countries (Chiarelli et al., 2009). An important program among them, the Canadian National Breast Screening Study-2 that examined effectiveness of mammography over and above that of CBE found that there was no significant difference in mortality reduction between screening and control groups (Rijnsburger et al., 2004). But it couldn't establish the mortality reduction benefits due to CBE alone. Therefore, RCTs using CBE in LMIC settings are required for direct evaluation of cost effectiveness and potential mortality reduction. Of such prospective projects initiated, two RCTs are ongoing in India. The Mumbai Trial (Mittra et al., 2010) which was initiated by Tata Memorial Hospital with a grant from National Cancer Institute in May, 1998, and the Trivandrum Trial (Sankaranarayanan et al., 2011) that was

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initiated by International Agency for Research (IARC) on Cancer, Lyon, France in January, 2006. The interim data and results from both these trials are published recently (Mittra et al., 2010). The screen and interval BC incidence in these trials could be used for estimation of mean sojourn time (MST), and other parameters for screening decisions. Markov chain models had been extensively used for this purpose (Day and Walter, 1984; Chen et al., 1996; Olsen et al., 2006; Ventura et al., 2013). Further, optimization of cancer management in LMICs has been investigated, but the issue of dynamic screening policies using CBE had not been addressed (Anderson et al., 2011). On the other hand, various aspects such as static or adaptive screenings, start age, screening interval effect, over diagnosis for mammography performance had been studied across different mammography screening data. Age specific sensitivity of CBE is quite low in young age groups (~ 26% in 40-49 year age), and it exhibits an inverted U shape (8 and it's effective in detecting tumors of size ≥2 cm with a reasonable sensitivity of 58% but still very low compared to mammography (75.6%, for 5-6 mm size tumor)) (Kavanagh et al., 2000). Since the sensitivity and estimated lead time gained from CBE, are dismal, optimization of screening intervals is an important problem that could shed light on feasibility of screening policies.

We study the problem of optimal age specific screening intervals for Indian women and its effect on mortality reduction, using the Mumbai BC incidence and RCT data. Since the Mumbai is ongoing, our approach could be expanded or refined to include the final screening data, but presently both are provisional.

Materials and Methods

IARC CI5 volume IX and X was accessed for breast cancer incidence in Mumbai, Chennai, Bangalore, and Delhi from 1998-2007. GLOBOCAN (2012) estimates for BC incidence and mortality for India were obtained from IARC. Mumbai breast and cervix cancer RCT interim results were obtained from its publication (Mittra et al., 2010) . It is the most reliable and extensive data available till date, since the IARC initiated trial in Trivandrum has not been completed and published it's data. However the accepted MST of 5-6 years is standard in BC screening literature, which is also used in the study, hence results are not affected significantly. Stage specific survival rates for breast cancer for Mumbai were obtained from SurvCan, IARC. Mortality rates for other causes were obtained from Life table from 2001 Census of India, Government of India. The 2001 census was used to match up with the screening trial period from 1998-2006, however sensitivity analysis of Markov transition rates indicate the estimated parameters do not change significantly.

Modeling Approach

To evaluate adaptive screening policies, estimates of age specific sojourn time are required, and mathematical model is the only feasible way to do it. We use integrated results from three different modules (Figure 1), which comprise the proposed modeling framework. First module estimated MST using BC incidence at three biennial screens and interval incidence from Mumbai RCT. Various Markov Chain approaches had been reported for MST estimation in BC screening. We, however, adopted a two stage Markov model, demonstrated by Ventura et al., (2014) (Ventura et al., 2013) (Table 1). A MATLAB script was used for the maximum likelihood estimation. We used Poisson distribution for interval cancer cases and a Binomial distribution for the cases detected at screens (Ventura et al., 2013). Since the Mumbai trial is ongoing, age specific CBE sensitivity was not reported or available, and we had to resort to published information, which led to formulation of reasonable assumptions. For example, age specific CBE sensitivity of 26% in age 40-49 year, 48% in age 50-59, and 36% in age 60-69 is indicative that the MST estimate is more representative of women in age 50-59 year. The preliminary results from Trivandrum trial report a CBE sensitivity of 52% in the first round of screening (Sankaranarayanan et al., 2011). We use this assumption to estimate age specific sojourn times in second module. Second module, used the MST estimate, as "silent interval" in multistage modeling literature, for computing age specific clonal expansion rates for the initiated cells in breast tissue from a nonlinear optimization of Two Stage Clonal Expansion model (see Figure 1). The model is similar to Zhang and Simon (Zhang and Simon, 2005), but we limit the number of stages to two, and make the clonal expansion and mutation rates time dependent.

The deterministic TSCE model equations are:

$$\frac{dY_S}{dt} = \gamma_S(t)Y_S(t)\left(1 - \frac{Y_S(t)+Y_i(t)}{N_0}\right) - \mu_S(t)Y_s(t) \quad (1.1)$$

$$\frac{dY_i}{dt} = \mu_s(t)Y_s(t) + \gamma_i(t)Y_i(t) - \mu_i(t)Y_i(t) \quad (1.2)$$

$$\frac{dY_M}{dt} = \mu_i(t)Y_i(t) \quad (1.3)$$

where Y_s (t),Y_i (t), Y_M (t) are stem/progenitor cell, intermediate cell and malignant cell population (number, #) at time t, γ_1 (t),γ_2 (t) are the net growth rates of stem/progenitor and intermediate cell at time t, respectively.

μ_1 (t),μ_2 (t) are the mutational rates of stem/progenitor and intermediate cell at time t, respectively. N_0 is the carrying capacity of stem cell population. When a single stem cell transit into initiated cell and the initiated cell transform into malignant cell, it develops into a malignant tumor.

The incidence was induced by hazard rate h(t), defined as,

$$h(t) = \lim_{\Delta t \to 0} \frac{Prob\{t \le T < t+\Delta t \,|T > t\}}{\Delta t} \quad (2)$$

The hazard rate, in TSCE model is given by

$$h(t) = \mu_i(t)E\{Y_i|Y_M = 0\}$$
$$h(t) \approx \mu_i(t)E\{Y_i\} \approx \mu_i(t)Y_i(t) \quad (3)$$

Finally the incidence per 100000 females for a given age group is given by,

$$I_{est}(t) = 2 \times 100000 \times h(t) \quad (4)$$

A nonlinear optimization problem was set as follows,

$$\min_{\gamma(t),\mu(t)} \sum (I_{obs} - I_{est})^2$$

where the constraints are equation (1.1) and (1.2) to obtain an estimate of h(t) in equation (3).

The optimization generated time varying parameters, γ(t)' s and μ(t)'s for progenitor and initiated cells. Using the estimated net growth rates we estimate the age specific sojourn time.

The assumptions in the estimation of age specific sojourn rates are:

The age specific net growth or clonal expansion rates of initiated cells reflect the corresponding growth rates of malignant clones in that age group. Since the clonal expansion rates are under the influence of estrogen levels, therefore, the malignant cells are too. This hypothesis is tested by Zhang et al., (2014).

The MST obtained from screening trials for CBE is representative of older ages such as >50 years because the sensitivity of the test is greater in these age groups.

The higher the clonal expansion rate lower the time required to attain the tumor size of 2 cm starting from a single malignant cell. The clonal expansion rates of initiated cells may not be direct representatives of malignant tumor growths, which are expected to be more aggressive. However, the rates compared to rates at older ages (>50 years), capture the relative influence of estrogen levels, and likely to be nearly same for malignant tumor growths.

Using the relative rates, the MST can be weighted to find sojourn times at younger ages

Consider the age specific incidence generates a clonal expansion rates i.e. Y_i (t), where t is age in years. Then age specific sojourn time can be estimated, given MST for 55-59 years of age, denoted as T. Note that a slightly less value of T can also be used, and depends upon the age distribution at screening, as well as modal age at detection in screening. The calculations are illustrated in table 2.

Using optimized parameter TSCE model fit to Mumbai BC incidence for identical time period as of two screens in Mumbai RCT, viz. 1998-2002, we normalized the best fit clonal expansion rates at a given age group to that of age 50-59 year. The normalization provided age specific weights, for finding age specific sojourn times.

Third module, evaluated adaptive screening policies based on these age specific sojourn times and sensitivity of CBE, using a 6 state Markov transition model. The estimation method was Maximum Likelihood.

Table 1. MST for Selected CBE Sensitivity from Mumbai RCT and Markov Chain Model

CBE Sensitivity	Mean Sojourn time (MST), years	Comments
40%	6.2 (95% Confidence Interval: 5.5-6.8)	Table 7 from Mitra et al., (2009) was used for Mumbai RCT results in screening arm, while method of Olsen et al. (2006) and Ventura et al (2014) was used MST estimation.
52%	5.9 (95% CI: 5.3-6.5)	
55%	5.2 (95% CI: 4.9-5.5)	

Results

Table 1 shows the estimates of mean sojourn time from healthy to early (0-IIA) stages from preliminary results of Mumbai RCT. Figure 1 shows the Markov transition model where states were identified as healthy, early stage BC (0-II) and advanced stage BC (III-IV), consistent with staging reported in Mumbai RCT while Table 3 shows the maximum likelihood estimated as well as sourced model

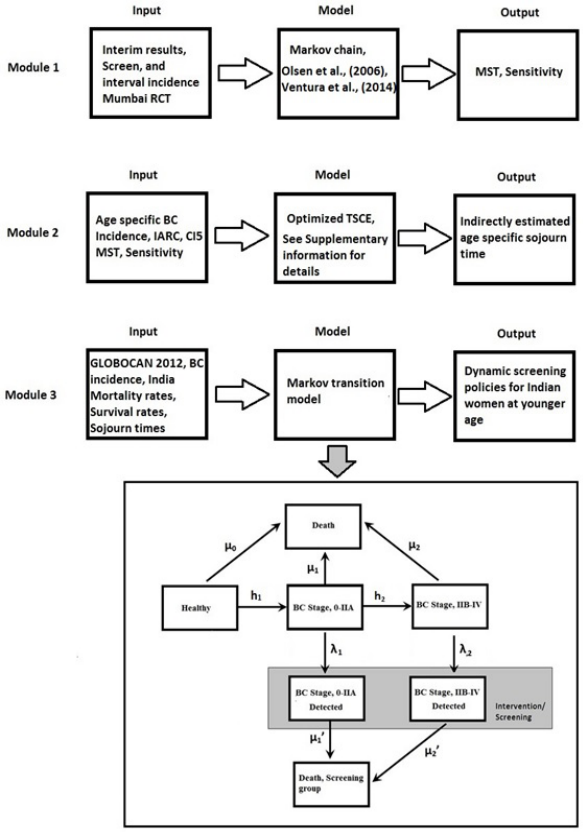

Figure 1. Modeling Approach, All Modules of Markov Models, for Values and Descriptions of Transition Parameters in Module 3, See Table 2.

Table 2. Age Specific Sojourn Time Calculations. for Notation, See Explanation in Text

Age, years	Averaged rates	Normalized rates or weights.	Sojourn time, years
35-39	$R_1 = \overline{Y_i(35-39)}$	$w_1 = \frac{R_1}{R_5}$	$\frac{T}{w_1}$
40-44	$\overline{R_2 = Y_i(40-44)}$	$w_2 = \frac{R_2}{R_5}$	$\frac{T}{w_2}$
45-49	$\overline{R_3 = Y_i(45-49)}$	$w_3 = \frac{R_3}{R_5}$	$\frac{T}{w_3}$
50-54	$\overline{R_4 = Y_i(50-54)}$	$w_4 = \frac{R_4}{R_5}$	$\frac{T}{w_4}$
55-59	$R_5 = \overline{Y_i(55-59)}$	$w_5 = \frac{R_5}{R_5} = 1$	T

Table 3. Parameters of the Screening Model

Transition,	Parameter Value	Source/Remarks
Healthy → Early stage (0-II), h_1	0.0-0.000577	GLOBOCAN 2012
Early stage (0-II) → Advanced stage (III-IV), h_2	1-0.16	From estimated age specific sojourn time
Healthy → Death, μ_0	0.175	Life Tables, Indian census 2000
Early stage (0-II) →Death, μ_1	0.21	1.5 times μ'_1, assumed
Advanced stage (III-IV) → Death, μ_2	0.85	1.4 times μ'_2, assumed
Early stage (0-II) →Early stage (0-II) detected, $\lambda_1=\lambda_{Sc}+\lambda_{CL,1}$	0.5	From screening rate, ML estimation.
Advanced stage (III-IV) →Advanced stage (III-IV) detected, $\lambda_2=\lambda_{Sc}+\lambda_{CL,2}$	0.78	Advanced stage cancers are always detected
Early stage (0-II) detected → Death, μ'_1	0.145	SurvCan, IARC See Ref 21
Advanced stage (III-IV) detected → Death, μ'_2	0.6	SurvCan, IARC, See Ref 21
Stage distribution, screening, early stage	0.7	Mumbai RCT, Trivandrum RCT
Stage distribution, screening, advanced stage	0.3	Mumbai RCT, Trivandrum RCT
Stage distribution, clinical, early	0.538	Mumbai RCT
Stage distribution, clinical, advanced	0.462	Mumbai RCT
Screening rate	0.30-40	Assumed

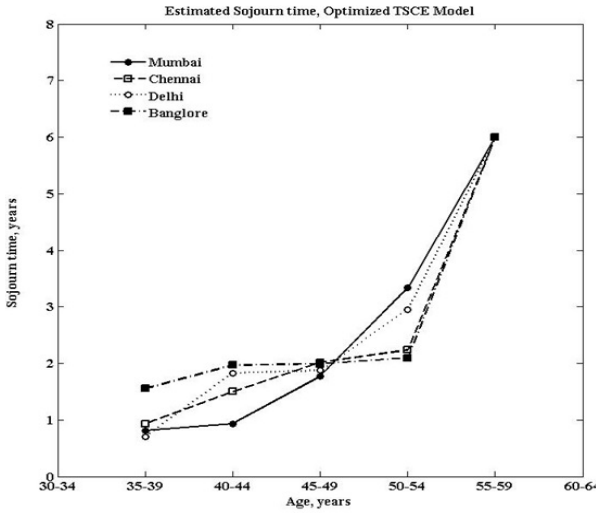

Figure 2. Age specific Sojourn Times from Optimized Parameter Estimation from TSCE Model

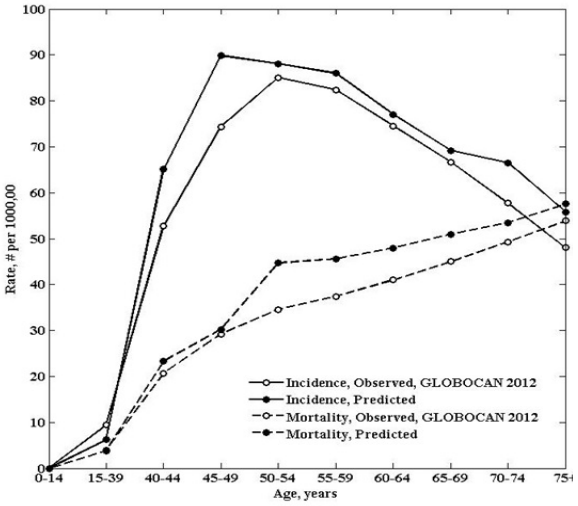

Figure 3. Observed and Markov Model Predicted Incidence and Mortality for BC in India

parameters. Figure 2 shows the age specific sojourn times as projected from clonal expansion rates of initiated cells from model fitting to BC incidence in Mumbai, Chennai, Bangalore and Delhi and corresponding Table 2 shows the calculation scheme for estimating age specific sojourn times. Figure 3 shows the estimated incidence and mortality comparison with GLOBOCAN (2012). Table 4 shows the assessment of screening policies with different screening frequencies.

Table 4. Dynamic Screening Policy Assessment

Parameter	Policy 1	Policy 2	Policy 3	Policy 4
Initiating age	35	30	38	40
Terminating age,	50	50	58	60
Annual screens?	Yes, 35-39	No	Yes, 38-42	No
Biennial screens?	Yes, 41-49	Yes	No	Yes
Triennial screens?	No	No	Yes, 43-58	
Total number of screens	10	10	10	10
Mortality reduction.	27.90%	20.40%	25.50%	23.60%
Number of life year gained	13340	8709	11840	8895

Discussion

On average, a MST of 5.9 years with confidence intervals of 5.3-6.5 year was found. The estimate compares well with Okonkwo et. al., (2008) (Okonkwo et al., 2008) study of screening policies for India. Table 1 from Okonkwo et al., (2008) (Okonkwo et al., 2008), report a MST of 5.22 years for transition from healthy to Ductal Carcinoma In Situ stage (DCIS). Adding the time required to reach a stage IIA where tumors are of size 2 cm, the effective MST is 7.33 years. Our estimates are small from 5.2 to 6.2 year, because we used limited data of screening trial for estimation, and these estimates would be better compared once the full data is available. However, a slight variation in MST won't affect the analysis of screening policies as decisions require identification of age groups

suitable for a given screening frequency. We assumed the estimated MST as representative for women of age >55 years, and calculated sojourn time for other age groups using the weights obtained in net growth rates of initiated cells. Assessing the estimated age specific sojourn time, Chennai and Bangalore estimates show a steady sojourn time of 1.0 - 2.1 years from 35-39 to 50-54 years. This indicates a peak in BC incidence around 50 years of age that was confirmed in the IARC data. In contrary, Mumbai and Delhi populations show a sojourn time of around 3 years at 50-54 years of age. A remarkable feature across all cities is the sojourn time of 2 years at age of 45-49. Testable predictions could be made from Figure 2. For example, Mumbai RCT is using 4 rounds of biennial screening, and age >45 year has sojourn time >2 year. This suggests a modal incidence age of BC should be > 45 year in the screening data. The interim results report a mean age of 49.80 years as age of BC diagnosis in screening group, and 47.07 year for interval incidence (Mittra et al., 2010). These match well with the prediction. A lower age at diagnosis of interval BC cases could be accounted for by "actual sojourn time" being slightly less than 2 years, among other confounding factors such as test sensitivity. Figure 2 helps to identify, age groups suitable for a given screening interval. For example, annual screening might be effective in 35-49 age group, and biennial might be suitable from 40-50 age group in Bangalore and Chennai. But in Mumbai biennial might be effective after 45 year of age, and triennial after 50 years of age. However, when the age specific cancer incidence especially for interval cases will be accessible, the estimates of age specific sojourn time could be directly verified and improved. To evaluate, the effect of these dynamic screening policies on mortality reduction, we used a Markov transition model with 6 different stages of disease progression (Figure 1). The states were identified as healthy, early stage BC (0-II) and advanced stage BC (III-IV), early stage detected BC, advanced stage detected BC and death from various states. BC staging system of American Cancer Society was used consistent with staging reported in Mumbai RCT. The transition parameters of the model are presented in Table 3, informed on the sources or methods used to obtain the values. 100,000 women were transited from healthy state, where they started off at age 30 years, into subsequent stages year by year. The theoretical natural history of BC is simulated till they reach an age of 85 years. The BC incidence and mortality rates were used from GLOBOCAN (2012) estimates. Women from healthy state to early stage (0-II) were transited according to age specific incidence and sojourn time. The transition rate from early to advanced stage (h_2) were inverse of age specific sojourn times. The transition rates from undetected to detected early and advanced stages consisted of two components - the screening and clinical detection. While the screening rate was varied from 30-40%, the clinical detection rate was assumed constant and estimated using maximum likelihood. The estimation procedure maximized the likelihood till the stage distribution in simulations converged to values reported for screening and clinical presentation in Mumbai trial. The model replicated the BC incidence and mortality in India as per GLOBOCAN (2012) numbers (Figure 3).

We evaluated the effect of varying screening frequencies for a total screen count of 10 (Table 3). To compare our results with earlier modeling framework/s of cost effective analysis, we used the biennial screening policy from 40 to 60 years of age and using CBE, reported by Okonkow et al., (2008) (Okonkwo et al., 2008). The choice of biennial policy was motivated by the predicted 16.3% mortality reduction and the nearly same effectiveness of CBE as of biennial mammography (Okonkwo et al., 2008). Our simulations predict 23.6% mortality for this case – Policy 4, Table 4. The higher mortality reduction is confounded by different modeling approaches as well as use of age specific sojourn times in our model. Figure 2 indicates annual screening might be effective in catching the progressive cases of cancer till age 44 years for Mumbai, while Delhi and Bangalore, biennial screening from age 40 years onwards would be suitable. Accounting for these dynamics, we formulate three different policies with inclusion of annual, biennial and triennial intervals and estimate the mortality reduction in each case (Table 4). Inclusion of annual screening during 35-42 years of age would improve mortality reduction by additional 3.5-4%. The effect of using Mumbai trial data or for that matter any new screening trial using CBE such as ongoing Trivandrum trial, would not affect the results of the study significantly, as because the CBE sensitivity shall be close to 50% or even less for younger populations. We, therefore, emphasize the extension of the model to include the entire RCT data for more accurate estimates.

In conclusion, we demonstrated a modeling framework, for estimating age specific sojourn time, as well as MST from screening trial data, which in turn is utilized for selection of dynamic screening interval for BC using CBE. The framework consisted variants of Markov transition models. Although, we used interim data from Mumbai RCT, and our results are, therefore, provisional, we showed inclusion of annual screening in specific age groups such as 35-39, 38-42 year, and biennial or triennial screening for rest of the eligible age groups, improved the mortality reduction compared to biennial policy alone. The estimates of MST and age specific sojourn time match well with estimates from other sources in similar studies. The framework can also be extended to investigation of adaptive screening for other LMIC settings. As more reliable data become available, the framework could be extended to include Multistage Clonal Expansion model, and different stages of diseases progression such as node status in parallel with tumor size. Alternately the framework could be used to obtain initial estimates of age groups in which annual or biennial screening might be suitable, and use them in the design of RCTs for LMICs.

Limitations of the Study

Two important limitation of the study can be pointed out. First, the study uses Mumbai screening trial data, as well as incidence in Mumbai and South India for estimating the age specific sojourn times in approximate way. Therefore, the results are applicable and valid mostly for the South Indian women. Registries in other Eastern and Northern part of India, do not have extensive

data as that of South Indian registries, compelling us to use the most reliable data of oldest registries - Mumbai and Chennai. The model, however, could be adapted to other regions where BC incidence is known extensively and is comparatively reliable. Second, we used clubbed stages I-IIA into early while rest into advanced stage (III-IV) rather than using 4 different stages in Markov model. We had to resort to such an approximation since the stage distribution is known reliably for early and advanced stages and accordingly reported in Mumbai and Trivandrum screening trials. Using four stages shall introduce more free parameters viz. the transition rates, which is avoided by using only two states - early and advanced.

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Conflict of Interest

The authors have no conflict of interest.

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