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
comprise the proposed modeling framework. First module results from three different modules (Figure 1), which is also used in the study, hence results are accepted MST of 5-6 years is standard in BC screening policies. We use integrated age specific sojourn time are required, and mathematical analysis of Markov transition rates indicate the estimated sensitivity and estimated lead time gained from CBE, are not affected significantly. Stage specific survival rates for breast cancer for Mumbai were obtained from SurvCan, Delhi from 1998-2007. GLOBOCAN (2012) estimates breast cancer incidence in Mumbai, Chennai, Bangalore, and Bangalore from 1998-2006, however sensitivity of India. The 2001 census was used to match up with the 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:

\[
\frac{dY_s}{dt} = \gamma_s(t)Y_s(t) \left(1 - \frac{Y_s(t)+Y_i(t)}{N_0}\right) - \mu_s(t)Y_s(t) \tag{1.1}
\]

\[
\frac{dY_i}{dt} = \mu_s(t)Y_s(t) + \gamma_i(t)Y_i(t) - \mu_i(t)Y_i(t) \tag{1.2}
\]

\[
\frac{dY_m}{dt} = \mu_i(t)Y_i(t) \tag{1.3}
\]

where \(Y_s(t), Y_i(t), Y_m(t)\) are stem/progenitor cell, intermediate cell and malignant cell population (number, ##) at time t. \(\gamma_s(t), \gamma_i(t), \gamma_m(t)\) are the net growth rates of stem/progenitor and intermediate cell at time t, respectively. \(\mu_s(t), \mu_i(t)\) 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,

\[
h(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}[t \leq T < t + \Delta t | T > t]}{\Delta t} \tag{2}
\]

The hazard rate, in TSCE model is given by

\[
h(t) = \mu_i(t) E[Y_i | Y_m = 0] \tag{3}
\]

Finally the incidence per 10000 females for a given age group is given by,

\[
I_{est}(t) = 2 \times 100000 \times h(t) \tag{4}
\]
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, $\gamma(t)$'s and $\mu(t)$'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.

**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.
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.

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

Table 3. Parameters of the Screening Model

| Transition | Parameter Value | Source/Remarks |
|------------|-----------------|----------------|
| Healthy → Early stage (0-II), \( h_i \) | 0.0-0.000577 | GLOBOCAN 2012 |
| Early stage (0-II) → Advanced stage (III-IV), \( h_j \) | 1-0.16 | From estimated age specific sojourn time |
| Healthy → Death, \( \mu_i \) | 0.175 | Life Tables, Indian census 2000 |
| Early stage (0-II) → Death, \( \mu_j \) | 0.21 | 1.5 times \( \mu_i \)_m, assumed |
| Advanced stage (III-IV) → Death, \( \mu_j \) | 0.85 | 1.4 times \( \mu_i \)_m, assumed |
| Early stage (0-II) → Early stage (0-II) detected, \( \lambda_1 = h_{01} + h_{CL,1} \) | 0.5 | From screening rate, ML estimation. |
| Advanced stage (III-IV) → Advanced stage (III-IV) detected, \( \lambda_2 = h_{02} + h_{CL,2} \) | 0.78 | Advanced stage cancers are always detected |
| Early stage (0-II) detected → Death, \( \mu_1 \) | 0.145 | SurvCan, IARC See Ref 21 |
| Advanced stage (III-IV) detected → Death, \( \mu_2 \) | 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 |

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 | No | Yes | No |
| Biennial screens? | Yes | 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 |
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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