

Synopsis

Breast cancer (BC) has emerged as public health issue in India in last two decades surpassing cervix cancer. Mortality from breast cancer is 30-40% higher than maternal causes. Breast cancer 5 year survival rates are abysmally low (near 50%). Aforementioned facts singularly trace back to lack of awareness and clinical detection in advanced stage (around 75% cases in stage III). This thesis presents BC epidemiology modelling using two stage deterministic clonal expansion model with time varying parameters. The time varying parameters enable inferences about age specific aggressive cellular growth and mutation rate. However, the model studies only age as the risk factor while other factors stay confounded. We also demonstrate the utility of the parameters towards formulating optimal and feasible screening using Clinical Breast Examination (CBE) as the modality for improved mortality reduction for BC in India. The combined approach use carcinogenesis and disease progression models in conjunction. Using carcinogenesis model, a deterministic clonal expansion model, we derive age specific growth rates for initiated cells, which subsequently progress to fully transformed malignant cells. Scaled up growth rates for initiated cells, when used as proxy to malignant cell growth, provide an estimate of age specific time scales for emergence of screen detectable tumors, which we incorporate to formulate adaptive screening policies. The adaptive screening policies are assessed for potential mortality reduction using Markov transition model, i.e. a disease progression approach.

In later half of the twentieth century, carcinogenesis, modeled deterministically or stochastically as accumulation of sequential genetic mutations had been demonstrated as successful approach for the description of cancer epidemiology as well experimental data. Knudson's two hit hypothesis and it's application to retinoblastoma incidence in children turned out as landmark for validity of the multistage models. The most popular of these models is the Two Stage Clonal Expansion (TSCE) model that posits, carcinogenesis as a result of two successive hits or events. A first hit initiates the stem cells, transforming it into an intermediate cell. The step is called initiation. The intermediate cell can undergo clonal expansion, and would eventually with a second hit generate a

malignant cell, called promotion. The malignant cell could grow up into a full blown tumor or even go extinct. The parameter estimates viz, net growth and mutation rates from these models provide insight into cancer incidence dynamics.

We adapted deterministic clonal expansion model to describe breast cancer incidence from different countries using the data from International Agency for Research on Cancer (IARC). The aim was twofold. To estimate time varying cellular kinetics that could provide qualitative insight on biological features of the underlying population. The non-linear optimization, we propose, seeks to minimize the sum of squared errors (SSRs) for the observed and predicted incidence of breast cancer in piecewise. The model results were tested for the following two cases.

1. Risk factor specific mutation rates. We used risk factor dataset for breast cancer to estimate the ratio of mutation rate with and without the given risk factor. We considered early menarche, parity/age at first birth and presence of first degree relative with breast cancer.
2. Estimation of age specific sojourn time to assess the effect of screening frequency for early detection of breast cancer. We infer an optimal window for annual screening at 38-43 age group.

A Markov transition model was with 6 different health states, such as detected and undetected early and advanced stages, and death was formulated for assessment of adaptive screening using CBE at population level. The cost effectiveness of the policies for improved mortality reduction was reported.

The thesis is organized into 6 chapters.

Chapter 1 presents the prevailing cancer burden, the cancer control measures, cancer registries, and incidence and mortality trends in India and worldwide using the International Agency for Research on Cancer publications. An assessment of early detection for breast cancer, survival rates, and suitable screening modality reveals urgent need for population level early detection programs.

Chapter 2 presents the details of the data source used. Major was the IARC's Cancer in Five Continents (CI5) volumes I-X for three cities in India, Mumbai, Bangalore, Chennai and USA, Finland, and Shanghai. GLOBOCAN 2012 estimates are also discussed and worldwide cancer incidence is compared to draw attention on differences in incidence trends. The Breast Cancer Surveillance Consortium (BCSC) datasets were presented with the risk factor features for BC cases recorded between 2000-2009. The

formalism of multistage models, an essential part of the proposed model was presented in brief.

Chapter 3 details the proposed Deterministic Clonal Expansion/Two Stage Clonal Expansion model for breast cancer. The assumption and mathematical details are presented. The IARC's datasets were used for model validation. Since it was known beforehand that all the parameters of the model are not identifiable from the incidence data, we verified the time varying growth rates of stem and initiated cell were correlated. This was expected as these rates are expected to be under influence of growth hormones, especially estrogen. The robustness of the parameter estimation is demonstrated across breast cancer incidence in different countries.

Chapter 4 presents the adoption of the validated model for assessment of relative mutational rates among different risk factors.

Chapter 5 describes a Markov model for natural history of breast cancer to demonstrate the optimal screening policies for the Indian cities. The policies are based on age specific sojourn time estimated from TSCE model, and evaluate the adaptive screening in younger age group (<50 years) in India.

Chapter 6 summarizes the conclusion of the thesis work and scope of future work.