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The same could be used for testing conventional treatment protocols and assess the reasons for failure of a particular strategy. Leads from the analysis can be utilized for proposing improvisations for the treatment protocol such as combinatorial strategies, which enables better suppression of tumor despite the resistant cells.

This commentary describes relevant concepts associated with simulation modeling of tumor growth and tumor-host interactions, and summarizes some of the prominent approaches.

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Simulation model for breast cancer management in India

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Abstract- The natural history of cancer in a patient can be simulated in a flexible broad-based disease model. Such models describe events and outcomes at the person level, the results of which can be aggregated to estimate the population morbidity. With minimal assumptions regarding the natural history of disease, models could project outcomes of interventions for cancer screening and treatment.

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I. Introduction

Mathematical models could potentially simulate the dynamic nature of biological processes. These models are the product of research in the interface between mathematics and biology. Such quantitative approaches benefit research in the field of cancer. Computational techniques should be applied to various aspects of tumor growth with an intent to understand the response of cancer cells to therapeutic interventions. Models could tally outcomes across individuals and gain insight into the underlying dynamics in risk factors and cancer interventions.

The life history of an individual might include events such as his current age, accumulation of risk factors for cancer since birth, age at which preclinical cancer develops, age's at which cancer landmarks progress and their metastatic spread, diagnosis of cancer (through screening or symptomatic presentation), treatment of cancer and death from cancer or other co-incident causes. The onset and progression rates of adenomas could be modified by risk factors, screening could detect pre-cancerous lesions and pre-clinical cancer, and treatment can alter post-diagnosis survival rates.

Models use indirect evidence for making assumptions about the process of carcinogenesis based on data from biopsy studies, prevention, screening and treatment trials, research studies, cancer registries and other types of studies. Such models account that tumor progression is a statistically distributed characteristic of cells influencing their global behavior. The parameters of the model are estimated using empirical data inputs initially and later through statistical algorithms. Such parameters will be predicted initially using observed data on cancer outcomes, and subsequently the impact of interventions could be studied. Outputs can include the full range of benefits and costs of the interventions.

In-silico trials will facilitate optimization of patient care by predicting patient-specific responses to various treatment combinations or dosage schedules.

The National Cancer Institute's (NCI) Cancer Intervention and Surveillance modeling network (CISNET)[1] model relies on assumptions regarding the natural history of the disease and is utilized for recommending mammography as a screening method in the USA. The research concept in this short report is to model the adenoma-carcinoma natural history sequence of breast cancer (BC) suitable to the Indian context.

II. Content

65% of BC related deaths are estimated to occur in low and middle income (LMIC) countries, by 2025[1]. Simulation models of BC progression, detection, and outcome usually include the natural history of the disease. Few other transparent models focus on observable events in disease progression, thus requiring fewer inputs from users and rendering portability across applications.

CISNET[2] Breast working group conducts collaborative modeling research to address critical early detection and clinical management issues in breast cancer. The aim is to evaluate improvised screening strategies such as using polygenic risk and emerging imaging technologies for their impact on the population. It also evaluates clinical management strategies with targeted treatment paradigms in the adjuvant setting and at recurrence. Such modeling leads to synthesizing research information for estimating future mortality trends in the United States. The common inputs are from observational studies from sources such as: National health interview survey (NHIS), Surveillance, Epidemiology and End Results (SEER), Breast cancer surveillance consortium (BCSC) and National center for health statistics (NCHS).

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Guidelines should enable good practices in modeling, which includes designing the approach, selecting a technique, implementing and validating the model, parameterizing the inputs and assessing uncertainty, and using the resulting tool to enable decision making[3].

We can summarize the six components of a model[3] as:

1. Conceptualization of model,
2. Estimation of model parameters and handling uncertainty,
3. Validation of models and concerns for transparency,
4. State transition modeling,
5. Discrete event simulation,
6. Dynamic transmission model,

We can consider several types of models[3] for problems with decision making:

i. If the conceptualization involves representing the disease or treatment process as a series of health states, 'the State transition model' could be appropriate.
ii. When disease or treatment process includes interaction between individuals, the modeling methods should evaluate those interactions ('Dynamic transmission models'; 'Discrete event simulations'; 'Agent-based models'),
iii. When individual pathways through the model are influenced by multiple characteristics of the entity, a 'Discrete event simulation' is recommended,
iv. 'Dynamic transmission model' could evaluate an infectious disease intervention which can impact disease transmission in the population, and the frequency distribution of agent strains is altered (e.g. genotypes or serotypes),
v. Uncertainty estimation can be either deterministic or probabilistic. The link to the underlying evidence should be clear whether employing deterministic sensitivity analysis methods (point estimate and range) or probabilistic sensitivity analysis (parametrized distribution),
vi. Documentation of the model will enable evaluation and potential reproduction. Such process includes terms such as type of model and intended applications, funding sources, the structure of model, inputs, outputs, other components that determine model's function and their relationships, data sources, validation methods, results and limitations.

We can capture the dynamics of sub-cellular interaction of a tumor in the model. We need to develop simulation tools for visualizing the same, with the possibility of interventions to control the action of tumor cells. Treatment as an outcome is defined either as induction of cell death among proliferating cancer cells or reduction of tumor support such as by decreasing the carrying capacity. We can define the strategies for tumor treatment in a differential equation model (DEM)[4], which captures the tumor cell differentiation (proliferation/death) based on the considered time difference.

The total number of cancer cells in the patient's body is not the only determinant of the health outcome. Among cancer patients, the local invasion of tissues and metastasis to distant sites of the body are the main causes of death as an outcome. The DEM does not capture such spatial processes, which however can be simulated in a partial differential equation model[4] (PEM).

PEM models could also examine the interplay between cancer cells, degrading enzymes, and the tissue, thus further improvising equations towards a reaction-diffusion-taxis model. Such models explain 'haptotaxis'; which describes determinants of cancer cell migration, such as extracellular matrix density and gradients of adhesive molecules in the matrix[4].

The Surgeons tend to visualize the visible margin of the cancerous tissue, however individual cancer cells have the potential to migrate beyond the same. Discrete models of tumor growth could explore the context of stochastic events and their probability of invasion[4].

The immune system recognizes the tumor cells, and tries to compete and deplete them. When the tumor cells win, they start condensing into a solid form. Such tumor cells diffuse signals to the outer environment, which in-turn are the means of communication for cellular interaction. The sequential evolution of steps in such a system could be summarized as[5]:

a) changes in the genetic make-up, cell cycle distortions and lack of apoptosis,
b) regulation of cell activities (both immune and environmental) through the emission of cytokine signals,
c) tumor cell condensation into solid forms, angiogenesis, and diffusion of macroscopes,
d) dissemination of metastatic cells,

In order to develop a valid model in India, we need to utilize the existing data which represents the epidemiology of BC. Contextually, clinical breast examination (CBE) has the potential to improve the stage at diagnosis as the same is delayed to Stage 3 & 4[6] in India.

The Microsimulation Screening ANalysis (MISCAN) model used in Koning[6] et al.'s study estimates the effectiveness and cost-effectiveness of CBE and mammography in India. This model simulates and compares individual life histories in a population, whether a cancer screening program is present or absent. The model incorporates demographic and epidemiological characteristics of the population to provide reliable predictions of BC morbidity.

In Western countries, the preferred method of screening is mammography. However, such facilities

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may not be cost-effective, and its availability in rural India is a concern. The peak incidence of BC in India is among pre-menopausal women who are relatively young for using mammography as a screening tool. Hence, the analysis in the model[5] includes screening with CBE among varying eligible age groups and screening intervals.

The differences in natural history of breast cancer in India when compared with other developed countries, includes the fact that beneficiaries are not subjected to effective screening procedures regularly, and access to care is delayed due to late presentation of symptoms. The assumption of the model[5] is that when an early stage is detected, it leads to improved survival of the patient.

This Model[6] finds that given the young demographics of the Indian population, it is cost-effective to screen the 40 to 60 years age group, when compared with 50 to 70 years group. The younger age group strata chosen for screening in this model, is influenced by determinants such as low life expectancy (62 years) and peak incidence among younger ages. The frequency of screening could be either every-5 year intervals or biennial or annual CBEs, all of which considerably reduce the mortality and increase the gain in the number of life years.

The concept that screening service is a privilege that needs to be sought, is reinforced by the estimates of the screening costs for CBE and mammography in the model[6]. These were 10% and 28% respectively, of the routine BC management strategies. The model[6] shows that the cost-effectiveness ratio gained is Int $1341 per life-year, which is 50% of the GNI per capita. Thus screening with CBE is a very cost-effective measure in India, as the WHO commission on Macroeconomics and health proposes a guideline of cost-effectiveness ratio being less than the per-capita GDP[6].

The microenvironment of a tumor comprises of the immune cells and cytokines, which act as the 'soil' nourishing the development of the tumor. The formation of tumor triggers the production of cytokines from the immune system. The core of tumor comprises of the following cells[7],

a) Cancer stem cells (S),
b) Cancer cells (C),
c) Resistant stem cells (SR),
d) Resistant cancer cells (CR),

Differentiation of S leads to the evolution of heterogenous sub-population of tumor cells, which is the 'seed' component. The interactions between the soil and seed determine the development of drug resistance and treatment failure in cancers.

The model can virtually depict the seed-soil interaction in the development of a tumor. 'S' numbers are low in the initial stages of tumor and due to their slow replication rate are resistant to radiotherapy and are partially sensitive to chemotherapy. The models can thus analyze treatment failures due to conventional chemotherapy and radiotherapy, which probably could be due to SR and CR within the tumor. Since S have an immunosuppressive effect on the soil, treatment protocols should additionally include immunotherapy. Models could simulate the temporal evolution dynamics of such tumor-immune interaction.

The efficacy of the treatment protocol is an outcome measure in this model[7]. This concept should be defined in terms of reduction in tumor size, and recovery from immune-suppression induced by the tumor. The parameters which should be included are the fold change of tumor mass and the TH1/TH2 (T helper cells) ratio. Mathematical strategies could be combined in the model to encompass the effect of molecular events (viz.. angiogenesis), chemokines and exosomes as mediators of cellular interactions, and the influence of miRNA in the pathways. Such models could enable optimizing drug dosage and advanced protocols for cancer treatment.

Advanced models could further shed light on cancer prognosis through studying the role of M2 macrophages in regulating tumor proliferation through feedback loops, differentiation of S from symmetric to asymmetric pattern rendering refractoriness for treatment, IL10 (Interleukin) feedback influence on TH1/TH2 ratio, and TH1 derived IFN-v (Interferon) differential elimination of S.

It is imperative to develop modeling tools because the impact of indicators on benefits (eg.: mortality reduction) and harm (e.g.: over-diagnosis) cannot be observed directly. It is not possible to immediately measure the outcomes among population, who either did or did not undergo screening procedures. Changes in screening programs are inevitable, and they tend to accumulate over time. The impact of one change can be entangled with another, and it is difficult to assess them discretely.

Randomized controlled trials (RCT) usually provide the required data to build the models. The results of RCT are from diverse centers, and usually depict post-hoc meta-analysis of the research studies. However, comparative modeling could facilitate the synthesis of evidence and relevant comparisons.

III. Conclusion

This commentary builds on existing evidence regarding the development of quantitative models and their comparison with experimental data. Models combine clinical and epidemiologic risk factors with new biologic and genetic data for accurately assessing the risk of cancer. They can function as virtual laboratories conducting synthetic experiments such as comparison of various interventions (in varied conditions) and

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estimating their population-level impact. Valid models enable inference on the natural history of cancer from partially observed processes, including the impact of interventions (prevention, screening, treatment). Such models find utility as risk assessment tools during screening activities, which in-turn could enable devising either targeted high risk or population-based interventions. Novel models which focus on complex biological processes such as tumor-immune interactions and the effect of microenvironment, will enable improvising cancer treatment protocols. Model simplicity ensures transparency, description, and ease of validation. Simultaneously, models should preserve face validity for clinical experts. Such models provide a framework to support evidence-based policy decisions in India.

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