Commentary

Recent translational research: computational studies of breast cancer

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Abstract

The combination of mathematics – queen of sciences – and the general utility of computers has been used to make important inroads into insight-providing breast cancer research and clinical aids. These developments are in two broad areas. First, they provide useful prognostic guidelines for individual patients based on historic evidence. Second, by suggesting numeric tumor growth laws that are correlated to clinical parameters, they permit development of biologically relevant theories and comparison with patient data to help us understand complex biologic processes. These latter studies have produced many new ideas that are testable in clinical trials. In this review we discuss these developments from a clinical perspective, and ask whether and how they translate into useful tools for patient treatment.

Keywords: breast cancer, computer models, dormancy, early detection, exponential growth, Gompertzian growth, risk

Introduction

We selectively and briefly review the recent literature describing mathematical modeling and computer simulation of breast cancer biology, as well as how this work might ultimately aid patient care. The first group of papers provide a basis for measuring prognosis among individual patients after therapy, employing neural network or statistical regression tools. The second set of papers use simulations of the growth and/or spread of tumors and, on this basis, predict clinically relevant results.

Prognostic assessment by neural net or regression analysis

In a report published in 1989, Gail and coworkers [1] discussed the risk for developing breast cancer using family history. The proposed model was validated and variously modified by other researchers, who incorporated genetic risks but not hormonal factors. Tyrer and coworkers [2] attempted to include most known predictive factors and proposed a model for calculating the risk for breast cancer based on a knowledge of individual genetic markers such as *BRCA*, family factors, and personal history data. It requires verification, however.

The need to take into account multiple clinical and prognostic factors, the limitations of traditional mathematical models, and the effort needed to apply inferences to individuals rather than to populations has fueled the development of artificial neural network (ANN) methods. An ANN is an information-processing paradigm that is inspired by the way in which biologic nervous systems, such as the brain, process information. The structure consists of a large number of highly interconnected processing elements working in unison to recognize patterns. ANNs, like people, learn by example. Learning in biologic systems and ANNs involves successive adjustments to the synaptic connections [3] using a training set. ANNs may be used in the process of therapeutic decision making and as exploratory tools for studies of disease dynamics. Although all ANNs require

ANN = artificial neural network.

both a training set and a validation set of data, their true performance should be tested on a separate verification set.

The most important of the ANN programs is that developed by Ravdin [4], termed 'Adjuvant!' (www.adjuvantonline.com), which is used to provide prognosis of early stage breast cancer patients after various modes of standard adjuvant therapy. This program is available online and has recently been independently verified to predict recurrence and survival to within 2% of actual observed outcomes. It will probably be widely used by clinicians to make treatment decisions in concert with patients, and it may eventually supplant TNM as a staging system. Like all neural network methods, however, it is not useful for new therapies, such as the forthcoming adjuvant antiangiogenic and targeted pathway modalities, because it depends on mature clinical data. That is the one drawback to Adjuvant! that we can identify.

Other tools are under development that are based on ANN, fuzzy logic, linear regression, and partial logistic ANN [5–10]. These have important potential for clinical applications because there are many clear needs. However, none of these mathematical tools are at the mature level or as valuable as Adjuvant!

Mathematical and computer models of breast cancer growth

Before publication of a report by Collins and coworkers in 1956 [11], tumors were said to grow fast or slow. Those investigators introduced tumor volume doubling time to quantitatively describe the rate at which a tumor grew and assumed that the doubling time was constant (exponential growth) and that tumors grew continually. The spontaneous mutation model of acquired drug resistance based on exponential kinetics by Coldman and Goldie [12] was an important theoretical development in our understanding of adjuvant chemotherapy.

It was observed, however, that exponential growth could only fit data for some particular conditions, such as multipassaged animal models [13] and when a limited life span of the tumor was studied. These difficulties prompted the next step in the evolution of mathematical models, which is the use of Gompertzian or damped exponential kinetics, in which growth is approximately exponential in its early stages before gradually slowing and asymptotically approaching zero.

Laird [14], who first proposed that Gompertzian growth (formerly used for population kinetics) applies to tumors, measured the growth of '19 examples of 12 different tumors of the rat, mouse, and rabbit' and concluded that 'The pattern of growth defined by the Gompertz equation appears to be a general biological characteristic of tumor growth.' That is a far-reaching statement based on only 18 rodents and one rabbit. The Gompertzian model proved better than the exponential model in describing tumor growth and became widely used. These early models are 'continuous growth' models and, for breast cancer in particular, they are unable to account for the long-lasting recurrence risk (metastasis appearance even more than 30 years after curative primary tumor removal) and many observations of temporary dormancy [15–26]. This major discrepancy between theory and observation leads us to reject the continuous growth assumption of Collins and coworkers.

In addition to temporary dormancy, there are other striking aspects of breast cancer that must be addressed. A double-peaked hazard of relapse with menopausal status dependent features has been reported for early stage breast cancer patients undergoing resection of the primary tumor. Distinct peaks at 1–2 years and at 5–6 years appear in several large and mature databases [7,27–34]. Moreover, a screening paradox has resulted for women aged 40–49 years. As reported by eight randomized trials of breast cancer screening, women aged 50–59 years who are invited to screening have a 20–30% mortality advantage as compared with control women. However, when women aged 40–49 years are screened, there is either no advantage or a slight disadvantage for the first 6–8 years in individual trials, meta-analyses, and overviews of all trials. After that, an advantage begins to appear [35–42]. Clearly, models incorporating more biology and possessing more general growth patterns than exponential or Gompertz dynamics are required to explain such phenomena.

The Norton–Simon [43] model assumes Gompertzian growth kinetics and has played an important 'cultural' role [44–47], although it suffers from the continuous growth flaw. It has nonetheless aided the recent development of dose-dense adjuvant chemotherapy and significant survival gains for certain patient subsets.

A paper by Guiot and coworkers [48] proposed application to tumors of the general model of ontogenic growth proposed by West – that is, a scaled variation of Gompertz growth derived from basic principles for the allocation of metabolic energy between maintenance of existing tissue and production of new biomass. It does not address points in the continuous growth crisis, and the conclusions should therefore be used with caution to help design therapies for clinical evaluation [49].

Plevritis [50] presented a growth model incorporating exponential growth to analyze screening data. Interestingly, despite the use of exponential growth, that author calculated a histogram of primary tumor doubling time distribution that agrees remarkably with stochastic dormancy model results.

The biology-based model for breast cancer growth and metastases development by Retsky, Demicheli and co-workers [51–53] incorporates tumor dormancy, transitions between micrometastatic phases, and metastasis acceleration by surgery. The computer simulation proposed an explanation of the various peaks in relapse hazard and predicted that more than half of all relapses in breast cancer are accelerated. The model quantitatively describes tumor dormancy, the mammography paradox and the bimodal relapse pattern, and it gives clues as to why adjuvant chemotherapy works best in premenopausal node-positive patients [53]. It suggests that an antiangiogenic drug given before surgery or timing surgery to the menstrual cycle for young women will reduce growth stimulation from surgery. This model has spawned a few clinical trials and logically could lead to metronomic therapy protocols [54–60]. The fundamental difference in this approach is that it specifies and quantifies the inherently intermittent or saltatory nature of tumor growth. Consideration of the duration, timing, and frequency of dormant spans is a unique attribute of this model. The dynamics of the dormancy–growth pattern are determined, over time, by the balance between tumor-based and host-based factors.

Objectively speaking, the weakness in this model is that it is based on only one database and is the product of one group. Although it is perhaps unlikely that the computer simulation will be duplicated by others, independent verification of the bimodal relapse pattern plus supportive reactions from breast cancer clinicians and researchers in the inevitable debate is needed before acceptance should be considered.

Conclusion

Medical science has long relied on empirical methods to learn how to successfully treat disease. However, that strategy does not work well with a disease like breast cancer with over 10 years between application of treatment and ultimate determination of outcome. It is primarily for this reason that computational methods have played an important historical role in the very long struggle to understand breast cancer – a still elusive goal. Perhaps recent computational efforts are making some progress in that direction. We are also reminded by this study (the mammography paradox in particular) that according to the scientific method when theory and experiment disagree, we are compelled to revisit the theory.

Competing interests

The author(s) declare that they have no competing interests.

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