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Mathematical Models of Breast and Ovarian Cancers

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Abstract

Women constitute the majority of the aging United States (US) population, and this has substantial implications on cancer population patterns and management practices. Breast cancer is the most common women's malignancy, while ovarian cancer is the most fatal gynecological malignancy in the US. In this review we focus on these subsets of women's cancers, seen more commonly in postmenopausal and elderly women.

In order to systematically investigate the complexity of cancer progression and response to treatment in breast and ovarian malignancies, we assert that integrated mathematical modeling frameworks viewed from a systems biology perspective are needed. Such integrated frameworks could offer innovative contributions to the clinical women's cancers community, since answers to clinical questions cannot always be reached with contemporary clinical and experimental tools.

Here, we recapitulate clinically known data regarding the progression and treatment of the breast and ovarian cancers. We compare and contrast the two malignancies whenever possible, in order to emphasize areas where substantial contributions could be made by clinically inspired and validated mathematical modeling. We show how current paradigms in the mathematical oncology community focusing on the two malignancies do not make comprehensive use of, nor substantially reflect existing clinical data, and we highlight the modeling areas in most critical need of clinical data integration. We emphasize that the primary goal of any mathematical study of women's cancers should be to address clinically relevant questions.

Keywords

ovarian cancer; breast cancer; mathematical modeling; systems biology

INTRODUCTION

Women constitute the majority of the aging United States (US) population, as, on average, they outlive men by 5 years[1]. According to the US Bureau of the Census in 2010, the life

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expectancy of a female at birth was 81.1 years versus 76.2 years for a male. In this latest census, women accounted for about 60% of the population aged 70 years or older. Moreover, based on these demographic data, the computed ratio of number of postmenopausal women to women of reproductive age was 2:3. This has substantial implications on existing clinical practices, as an increased proportion of aging women is associated with new disease patterns, such as differential incidence or prevalence rates.

In this review we focus on two subsets of women's cancers, specifically breast and ovarian cancers, which are diseases seen more commonly in postmenopausal and elderly women[2]. Herein, we assume that the transition to menopause represents the defining threshold between pre- and postmenopausal stage, or between reproductive and non-reproductive age. For a definition of menopause and subsequent terminology used throughout the review, we refer to the attached Sidebars 1, and 2. We seek to emphasize the complex degrees of heterogeneity of breast and ovarian cancers from a clinical perspective, and subsequently highlight the pressing need for developing mathematical models that accurately reflect emerging clinical data.

Breast cancer is the most common cancer type affecting women, representing 29% of all new cancer cases in US women[2]. Nonetheless, it has a good prognosis, with an approximately 89% five-year overall survival rate[3]. Breast cancer is most frequently diagnosed among women aged 55-64, with a median age of 61 years[4]. Ovarian cancer is a relatively rare women's cancer, representing 2.6% of all new cancer cases in US women[2]. However, it is the most fatal gynecologic cancer type, with an approximately 45% five-year overall survival rate[5]. Ovarian cancer is most frequently diagnosed among women aged 55-64, with a median age of 63 years[2].

Herein, we provide a summary of the clinical progression, and current detection and therapeutic strategies for these two malignancies. We begin by reviewing the latest clinical information and statistics regarding the progression and treatment of breast and ovarian cancers. To this end, we focus our attention on various malignancy-specific aspects such as target organ biology, existing prevention and early detection strategies, current systemic and targeted therapies, and proposed drug resistance mechanisms. In doing so, we highlight the open clinical questions we believe a substantial contribution could be potentially made to by mathematical modeling. Next, we systematically review and comment upon the existing mathematical models aimed at describing various aspects of the malignancies' natural history and progression. We chose to compare and contrast disease etiologies whenever possible, in order to highlight areas of (di)similarity in view of developing relevant systems biology-oriented mathematical frameworks. In doing so, we note the scarcity of existing inferences aimed at modeling the spatiotemporal growth, progression, and therapeutic targeting of the breast and ovarian malignancies. We also comment on the limitations of the existing modeling frameworks in the context of the mathematical approaches utilized, and point out the areas where the modeling efforts could be further expended.

Our purpose here is two-fold. First, we show how current paradigms in the mathematical oncology community focusing on the two malignancies do not make comprehensive use nor substantially reflect existing clinical knowledge, and we highlight the modeling areas in

most critical need of clinical data integration. We seek to emphasize the pressing need for truly integrative mathematical-oncology collaborations that reflect and make use of the clinically known aspects of malignancy heterogeneity, progression, detection and therapeutic options. Second, we argue in favor of the potential of mathematical modeling to integrate clinically derived data and to suggest novel future directions for clinical research, given validated *in silico* mathematical models of the breast and ovarian malignancies.

Lastly, we note that the focus of the present review is on mathematical models of cancer dynamics, and not on statistical modeling (such as absolute risk prediction models, or multiple regression analyses assessing epidemiologic risk factors), or specific algorithmic approaches (such as machine-learning approaches to specifying rules for genetic and molecular stratification of individual patients). Additionally, we differentiate between mathematical modeling of cancer dynamics or drug resistance and other related topics such as cancer imaging or detection algorithms, in which mathematics has historically played an instrumental role[6-10]. We consider the latter topics to be beyond the scope of the present review.

Human breast cancers

In 2016, it is estimated that 246,660 new cases of breast cancer with an estimated 40,450 deaths related to the disease will occur in the US, for a calculated 4:25 death to incidence ratio[11]. The high 5-year survival rate following diagnosis has been attributed to the higher rates of screening for breast cancer in the general risk population, patient presentation during early stages when prognosis is good, and to the effectiveness of surgery, radiation and systemic therapies, such as chemo- or hormonal therapies. Women with localized disease may have no symptoms and be identified by screening or they may present with specific disease symptoms such as a breast mass, skin changes or irritations, nipple discharge other than breast milk, or lumps in the underarm area[12]. These symptoms however, are not exclusively indicative of a malignant disease, and can also be signs of less serious conditions, such as infection, cysts or other benign masses in the breast.

The target organ—Breast cancers represent a collection of malignancies that arise in the epithelial cells of the breast (Figure 1). Histologic subtypes include the ductal (70-80% of diagnosed cases), lobular (10-15% of diagnosed cases), or medular[13] (3-5% of diagnosed cases). About 65% of breast cancers are either estrogen receptor (ER) or progesterone receptor (PR) positive[14]; these hormone receptor-positive cancers tend to have a higher 5-year survival rate compared to other subtypes[15]. Other subtypes include HER2-positive breast cancer, characterized by HER2 protein overexpression or *HER2* gene amplification, and triple negative breast cancer (TNBC), which lacks ER/PR expression and HER2 amplification or overexpression.

Morphomolecular analyses have revealed further novel ways of classifying breast cancers[16,17]. Based on comprehensive genomic classifications[17], breast cancers have been divided into four groups: i) the luminal A subtype, which is ER and/or PR positive and HER2-negative, and has a low Ki67 proliferative index; ii) the luminal B subtype, which is ER and/or PR positive and may be HER2 positive, has a high Ki67 index and has a poorer

prognosis than the luminal A subtype[18]; iii) the HER2-enriched subtype, which displays extra copies of the *HER2* gene and lacks ER or PR expression, and is more aggressive than the luminal subtypes; and iv) the basal-like subtype, which is largely comprised of TNBC. The latter is a high-grade cancer that grows quickly and has the worst prognosis compared to all other subtypes[15]. The triple-negative subtype tends to occur more often in younger, premenopausal women[19], and is thought to be more prevalent in some high-genetic risk patients (as defined by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[20]), specifically in germline *BRCA1* mutation carriers[21]. These high-genetic risk patients also have an increased risk of developing ovarian cancer at some point in their life[22].

Prophylactic and early detection strategies—The goal of any screening test for breast cancer is early detection and decrease in cancer-related mortality. So far, existing non-invasive tools for screening and detecting early stage breast cancers of all subtypes in general risk women include imaging procedures, such as mammograms and magnetic resonance imaging (MRI), and clinical breast and self-breast examinations. Screening imaging procedures can be used to view and evaluate breast tissue changes, but do not always demonstrate adequate sensitivity or specificity[23].

In 2016, the US Preventive Services Task Force (USPSTF) updated their recommendations for mammography screening[24]. Their most recent recommendation stratifies screening by age, recommending against routine screening in general risk women aged 40-49 years and for biannual screening mammography in asymptomatic women without known genetic mutations aged 50-74 years. In the case of high-risk women, USPSTF recommends that these women be considered for an annual MRI in addition to an annual screening mammogram. Additionally, some high-genetic risk women voluntarily choose to undergo prophylactic mastectomies, which have been proven to reduce breast cancer incidence in this subset of women by approximately 90%[25].

For the time being, there is evidence that screening for breast cancer with mammography and MRI reduces breast cancer mortality, with the greatest benefit of screening occurring in women aged 60-69 years[24]. However, debate surrounding the issues of frequency of screening (i.e. annual versus biannual), low specificity of screening methods and overdiagnosing of non-invasive ductal carcinoma in situ in younger, reproductive age women remains[26-29].

Current treatment strategies and targeted therapy—Standard treatments for breast cancer subtypes include surgery (usually a mastectomy or lumpectomy with either sentinel node biopsies or axillary lymph node dissection), adjuvant systemic hormonal and/or chemotherapy, and localized radiation therapy (externally targeted post-surgery, or administered internally during surgery). To exploit the synergistic effects of using multiple drugs, systemic combination therapies are used, through combinations of anthracyclines such as doxorubicin, alkylating agents such as cyclophosphamide, platinum compounds such as cisplatin or carboplatin, or taxanes such as paclitaxel or docetaxel. For example, dose-dense doxorubicin and cyclophosphamide followed by paclitaxel is used in treating early stage breast cancers in the adjuvant or neoadjuvant setting[30]. Depending on the hormone-

receptor status of the cancer upon diagnosis, subtypes of early, localized or metastatic breast cancers may also be treated with hormone-based therapies, such as tamoxifen, which blocks the estrogen receptor, or aromatase inhibitors, which prevent the production of estrogen in post-menopausal women[31].

In addition to systemic chemo- or hormone-based therapies, targeted therapies blocking breast cancer cell growth in subtype-specific ways are also used. For example, monoclonal antibodies, such as trastuzumab and pertuzumab, are used in early stage and metastatic HER2 positive cases; lapatinib, a tyrosine kinase inhibitor, is used in metastatic HER2 positive cases, and palbociclib, a cyclin-dependent tyrosine kinase 4/6 inhibitor, is used in treating metastatic ER positive, HER2 negative cases[32].

Development of drug resistance: implications for predicting recurrence—Initial response rates to current standard treatments for breast cancer patients are very high (more than 90% of primary breast tumors respond to the first-line therapy[5]). Yet, with current treatments, more than 20% of the HER2 positive or ER/PR positive cases, and about 40% of the TNBC cases are expected to recur by 10 years after primary tumor diagnosis[33]. Recurrent breast cancer is often associated with drug resistance, and most patients die with progressive resistant metastatic disease[34]. Factors that mediate clinical breast cancer recurrence and the timing of drug resistance remain largely unknown, but may be strongly influenced by the presence of dormant breast cancer cells[35].

Several mechanisms of cellular resistance to existing breast cancer therapies have been proposed. One possible mechanism of drug resistance is the overexpression of the multi-drug resistance protein 1[36] (MDR1) , or the breast cancer resistance protein[37] (BCRP). Other proposed mechanisms include the overexpression of β1-integrin levels in ER positive metastatic breast cancer patients[38], or the acquisition of activating mutations in the ER in hormone resistant metastatic ER positive patients, previously treated with anti-estrogens and estrogen deprivation therapies[39].

A further, more recently proposed drug resistance mechanism is the emergence of secondary mutations restoring BRCA function in BRCA1 or BRCA2-deficient patients and enabling cells to survive subsequent drug-induced cellular apoptosis and genomic aberrations[40,41]. *BRCA1* and *BRCA2* are tumor suppressor genes considered instrumental in repairing damaged DNA via homologous recombination repair mechanisms[42]. It is estimated that about 31% of diagnosed TNBCs and 50% of diagnosed high-grade serous ovarian cancers (HGSOCs) initially have some abnormality in their DNA repair mechanisms[43]. *BRCA1* or *BRCA2*-deficient carcinomas have decreased capacity to repair DNA, and show high responsiveness to platinum agents[44]. They are also found to be susceptible to synthetic lethality via poly ADP-ribose polymerase inhibitors (PARPis) monotherapy. However, after the emergence of secondary mutations restoring BRCA function, some of the BRCA1 and BRCA2-deficient breast and ovarian cancers are no longer sensitive to PARPi-induced synthetic lethality[45-47]. The subsequent proliferation of these cells is thought to lead to the lack of response to subsequent treatment and disease recurrence[41].

We note that despite the recent advances in early detection and understanding of the molecular bases of breast cancer biology, the precise biological pathways implicated in the development of breast cancer resistance and recurrence remain largely unknown. Great interest in elucidating the molecular mechanisms contributing to clinical drug resistance in breast cancers exists. Exploring and classifying these mechanisms through joint basic, mathematical, and translational research efforts is clinically relevant and crucial for advancing therapeutics.

Human ovarian cancers

In 2016, it is estimated that 22,280 new cases of ovarian cancer with an estimated 14,240 deaths related to this disease will occur in the US, for a computed 2:3 death to incidence ratio[11]. The high mortality rate following diagnosis has been partly attributed to the approximately two thirds of patients presenting with advanced stage, when recurrence is common, and leads to the incurable disease. Several studies suggest the usefulness of a symptom index tool to identify women who may have ovarian cancer; this includes new (within 1 year) and persistent (more than 12x/month) pelvic/abdominal pain, abdominal size/bloating, difficulty eating/feeling full, and urinary urgency/frequency[48,49], which should trigger evaluation by a gynecologic oncologist. The extent and quality of surgical debulking has important prognostic value and is an integral part of the upfront management of ovarian cancer patients. In addition, the absence of accurate early detection screening methods poses additional difficulties in reducing ovarian cancer mortality levels[50].

The target organ(s)—It is becoming increasingly recognized that ovarian cancers do not constitute a single disease, but rather a family of non-uterine tubo-ovarian cancers[51-53] (Figure 2). Ovarian tumors may develop from epithelial, stromal or germ cells[54]. About 10-15% of all ovarian malignant tumors are nonepithelial in origin, are often found at an early stage, and generally have a good prognosis[55]. Epithelial ovarian cancers constitute about 85-90% of all ovarian cancer cases, with a subset of these epithelial ovarian cancers, HGSOCs, representing nearly 70% of all ovarian cancer cases[56]. HGSOC is considered to be an aggressive histological subgroup of the ovarian malignancies[53]. Although the 5-year survival rate for stage I ovarian cancer is greater than 80%, stage I diagnoses represent the exception rather than the rule[11]. Most patients present with stage III/IV tumors, for which the 5- year survival rate is less than 30%[2].

One of the obstacles to the detection of early-stage HGSOC, has been the poor understanding of its histopathogenesis. It was initially thought that epithelial ovarian tumors originate from the ovarian surface epithelium, a single cell layer covering the ovaries, coming from the coelomic epithelium[57,58]. Recent data suggest secretory cells inside the distal fallopian tubes give rise to the earliest precursor lesions in a proportion of HGSOC cases[57-60]. This finding was first reported in women with germline *BRCA1* and *BRCA2* mutations undergoing a prophylactic bilateral risk-reducing salpingo-oophorectomy procedure[61-63]. For the general-risk population however, it remains unclear whether diagnosed ovarian tumors commonly arise with apparently fallopian tube involvement, or constitute truly ovarian-derived diseases.

Prophylactic and early detection strategies—Any proposed screening strategy should be highly sensitive and specific to detecting truly malignant ovarian cancer cases. Transvaginal ultrasound (TVU), serum biomarkers (CA125, HE4) testing, pelvic examinations or simultaneous TVU and CA125 testing have been examined as non-invasive tools for detecting early stage ovarian cancer in general risk women. However, mounting evidence suggests that annual screening with TVU and serum biomarkers, does not reduce mortality[64]. Furthermore, high false positive rates leading to intervention are associated with potential harm, such as unnecessary surgical intervention and related complications. The lack of utility of such screening tools is possibly due to the absence of adequate TVU sensitivity in detecting small increases in tumor volume and distinguishing between malignant and benign cases[65]. Furthermore, the addition of serum biomarkers testing (e.g. CA125 levels) does not improve early-stage detection levels either[50,66].

The largest ever ovarian cancer screening study of 202,638 general risk women demonstrated that multimodal screening including serial TVU and CA125 level testing yielded a 15% mortality reduction rate compared with a 0% no screening or 11% unimodal TVU-based screening cohort mortality reduction rate over 0-14 follow-up years[64,67]. However, this study also showed increased CA125 levels can be detected in benign conditions, rendering it inadequate for use in screening asymptomatic women for early-stage ovarian cancer. The lack of adequate early-detection tools might be explained by the fact that any epithelial ovarian cancers diagnosed in stage I might be fundamentally different from those diagnosed in advanced stages, which are preponderantly high and not low-grade cases[68].

USPSTF has recently reconfirmed their previous recommendation against screening in asymptomatic women without known genetic risk for ovarian cancer[69]; existing screening methods are either not recommended as uni- or multimodal prognostic markers for low HGSOC volume detection[28,70,71], or have not been shown to confer a mortality benefit in general risk women[72]. High-genetic risk women should be considered for genetic counseling and offered the option to undergo regular monitoring via a combination of TVU examinations and CA125 tests. Additionally, many high-genetic risk women voluntarily choose to undergo various risk-reducing gynecologic surgeries, such as prophylactic oophorectomies, bilateral salpingo-oophorectomies or hysterectomies[28,73-77], which have been proven to reduce mortality from both breast[78] and ovarian cancer[62,74,79]. Collectively, the question of whether ovarian cancer is a valid target for routine screening in general or high genetic-risk women still remains highly controversial[67,71,80,81].

Current treatment strategies and targeted therapy—Standard treatments for ovarian cancers include debulking surgery, (neo)adjuvant platinum-based combination chemotherapy, such as cisplatin or carboplatin, and a taxane such as paclitaxel or docetaxel. In addition to systemic chemotherapy, targeted therapies such as small molecule tyrosine kinase inhibitors are also used. For example, platinum-resistant recurrent ovarian cancers have been shown to respond to angiogenesis inhibitors (e.g. bevacizumab) in combination with chemotherapy, which restrict cancer growth by suppressing the development of blood vasculature to the tumor[82]. Additionally, PARPis have been used in clinical trial settings and the PARPi olaparib (Lynparza) was recently approved by the US Food and Drug

Administration (FDA) as a therapy for germline *BRCA*-mutations associated recurrent ovarian cancer[83].

Development of drug resistance: implications for predicting recurrence—Initial response rates to current standard treatments for ovarian cancer patients are high (70%-80%), but the majority of women with advanced disease relapse with within two years[5]. Recurrent ovarian cancer is not curable, and most women eventually develop platinum-resistant disease.

Several mechanisms of cellular resistance to platinum compounds or PARPis have been described, such as intracellular cisplatin inactivation via augmented glutathione synthesis[84-86], or reduced intracellular drug concentration via overexpression of MDR1 protein acting as a drug efflux transporter[87]. Another possible mechanism of platinum resistance is the development of secondary mutations restoring functions of BRCA and other proteins of homologous recombination repair in *BRCA*-mutation related ovarian cancers. However, BRCA restored functionality does not explain all cases of cisplatin resistance in these patients[40,41], since not all platinum-resistant recurrent ovarian carcinomas exhibit detectable secondary mutations. Norquist *et al.* showed only 12 of 26 (46%) platinum-resistant recurrent cases had detectable secondary mutations restoring BRCA function[45]. Further pre-clinical and clinical investigations of mechanisms of platinum or PARPi resistance are thus needed. Larger-scale prospective and retrospective cohort studies are warranted in order to better examine therapy response heterogeneity and adaptability of the ovarian cancer genome under the selective pressure of cytotoxic therapies[46,52,88].

MATHEMATICAL MODELS OF WOMEN'S MALIGNANCIES

While considerable mathematical modeling effort has been directed towards modeling carcinogenesis, cancer progression, and cancer treatment[6,89-91], relatively few mathematical investigations have been published specifically targeting the breast and ovarian cancers. After a comprehensive literature search, we note that, to best of our knowledge, the models presented below represent the majority of the published breast and ovarian cancer mathematical models. We thus chose to discuss these mathematical models in detail, and highlight areas where novel *in silico* modeling frameworks could be further developed.

Breast cancer

Modeling disease natural history and the tumor growth law controversy—The pattern of growth of human breast cancers is clinically important, specifically for estimating the duration of pre-diagnosis silent growth and for the design of an optimal post-surgery chemotherapeutic schedule. The theoretical study of breast cancer growth patterns has been the subject of considerable debates and controversy among mathematical oncologists for over two decades. For a more comprehensive recent review and theoretical comparison of the various mathematical formulations used to model tumor growth dynamics, we recommend the interested reader to consult Ribba *et al.*[92].

In 1984, Speer *et al.* proposed a stochastic numerical model of breast cancer growth wherein all individual tumors are assumed to grow with identical Gompertzian parameters but

subsequently develop kinetic heterogeneity by random time-dependent processes[93]. The basic growth model of Speer *et al.* is illustrated in Figure 3A. Speer *et al.* estimated that the average time for the tumor burden to increase from 1 cell to detection was on average 8 years. Their model also derived quantitative relationships between the likelihood of remission versus number of years after mastectomy, and the number of metastatic sites versus number of positive nodes in an *in silico* cancer-positive cohort. This approach to modeling breast cancer growth kinetics allows for the generation of individual growth curves, rather than averaged, population-based cancer growth dynamics. However, growth dynamics similar to the one quantitatively proposed by Speer *et al.* are yet to be confirmed *in vivo* or *in vitro*, and may involve unnecessary additional parameterization.

In contrast to the Speer *et al.* model, Norton *et al.* demonstrated in 1988 that the deterministic Gompertz equation provided the best fit when used to relate clinical breast cancer tumor sizes and rates of regression post-therapy[94]. Using a data set comprising of 250 women with untreated diagnosed breast cancer, during the years 1805 to 1933 in the UK[95], Norton generated a hypothetical survival curve fitting the classical Gompertzian growth model to the percentage of surviving patients per year after diagnosis (see Figure 3B). He estimated the probability distribution function of the growth decay parameter to be log-normal and dependent on the current number of tumor cells, in contrast to the stochastic nature of the equivalent parameter used by Speer *et al*[93,96]. While the model proposed by Norton fits clinical data on untreated breast cancer, it is unclear whether Gompertzian kinetics (or a variant of it) also applies to the disease progression during or post therapy.

Untreated breast cancer growth rates prior to diagnosis were also calculated by Spratt *et al.* in 1993[97]. They used data derived from mammographic breast cancer tumor measurements and conducted a least squares regression analysis to prove that a generalized logistic equation provided the best fit to the observed data. The mathematical analysis performed excluded data from patients whose tumors were clinically detected between two consecutive mammogram screenings, or whose tumors showed no change in size during the period of clinical observation. Using their growth model, Spratt *et al.* generated probability distributed functions of tumor doubling time at mammographic detection and untreated tumor size increase after 1 and 2 years after detection. While the model quantitatively underscores the significant natural variability in untreated human breast cancer growth rates, it is unclear from this approach how histological and morphomolecular characteristics influence modeling results. Moreover, the reported mathematical results might have been selectively biased towards reflecting the progression of slower growing tumors, as these tumors are more representative of clinical cases amenable to detection via regular mammographic screening.

In a different attempt at modeling breast cancer natural history, Koscielny *et al.* considered in 1985 two patterns of growth, exponential and Gompertzian, in order to assess the timing of initiation of distant metastases using observed data in breast cancer patients[98]. For both growth patterns, Koscielny *et al.* estimated that the median metastasis growth duration is about 3.8 years, and that a 30% reduction in metastases incidence is predicted if the primary tumors are treated 12 months earlier. In order to assess the time at which metastases are initiated, Koscielny *et al.* assume a linear relationship between doubling times of primary

breast tumors and of their metastases. However, the validity of such a limiting assumption is empirically questionable as, to best of our knowledge, a deterministic relationship between the two has not been established in any published *in vitro* or *in vivo* investigations.

We note that none of the models discussed above, specifically focuses on a breast cancer subtype. It is however empirically known that different subtypes exhibit differential growth rates and clinical progressions[99]. For example, luminal ER positive breast cancers are thought to have a slower growth progression than the TNBC subtypes; moreover, interval breast cancers, defined as cancers detected between two consecutive screening examinations, are more likely to be ER and/or PR negative than screen-detected breast cancers[100]. Additionally, distinct morphomolecular tumor subtypes can be concomitantly reported in the same breast cancer patient[101], underscoring the importance of prospectively assessing spatial intrapatient tumor heterogeneity prior to treatment initiation[102]. Arguably, considerable biological realism and any translational/clinical relevance of such modeling results are lost if existing mathematical models aggregate the various breast cancer subtypes into one singular disease. Moreover, the existing models use population-based cohort studies in order to predict aggregate clinical statistics of untreated breast cancer growth and model heterogeneous timing of cancer progression in the *in silico* cohorts. Yet, the extent to which such models contribute to understanding subsequent therapeutic outcomes remains unclear. We point out that hardly any clinically diagnosed breast cancer is nowadays left untreated and the impact of existing therapeutic strategies on growth rate dynamics remains an open clinical question that cannot be quantitatively determined using the existing mathematical models.

We thus argue the need for mathematical models that better integrate current clinical and morphomolecular data, and aim at modeling spatiotemporal breast cancer growth dynamics and heterogeneity.

Modeling sporadic and hereditary breast carcinogenesis—In a more recent attempt in modeling breast cancel natural history, De Vargas Roditi and Michor considered a mathematical model for the evolutionary dynamics of *BRCA1* mutations in order to explain the differential role of *BRCA1* mutations in sporadic and hereditary cancers[103]. Initially, the populations of cells within the breast tissue was assumed to be proliferating according to a stochastic Moran process. A linear ODE approximation of the stochastic process was then used to model the different evolutionary trajectories involving spontaneous or hereditary mutations in the *BRCA1* and a different tumor suppressor gene. Tumorigenesis was assumed to initiate once sufficiently many mutations in these genes accumulated. The model was calibrated based on published statistics regarding the role of *BRCA1* mutations in sporadic and hereditary breast cancers: sporadic *BRCA1* mutation incidence, the prevalence of germline *BRCA1* mutation carriers, and the differential probability of developing breast cancer in these two subsets of patients. The main results predict that the loss of one *BRCA1* allele in combination with the homozygous loss of a different tumor suppressor gene confers a fitness disadvantage compared to a single allele alteration in both genes. Moreover, a cell with two mutated BRCA1 alleles and one mutate tumor suppressor gene allele has a fitness advantage compared with a cell with alterations only in the *BRCA* gene.

We note that the total cancer population size considered susceptible to genetic alterations in the model was kept constant at very low levels. It would be useful to extend the mathematical framework to more realistic tumor growth models and population size, to validate whether the effect of the heterozygous *BRCA1* phenotype and its differential involvement in sporadic and hereditary tumorigenesis are maintained in human tumors.

Modeling therapeutic targeting and treatment—Mathematical models for the growth and invasion of breast cancer tumors into the surrounding tissue, together with modeling frameworks for surgery and radiotherapy were first developed by Anderson *et al.*[104,105]. To simulate breast cancer growth prior to diagnosis and quantify the effects of conventional fractionated radiotherapy versus more targeted irradiation, Anderson *et al.* initially developed a continuum model of ordinary (ODEs) and partial differential equations (PDEs)[106]. Numerical schemes were subsequently adapted to model the results of simulating radiotherapy treatment in the two scenarios[107]. A basic description of the ODE-PDE model incorporating the effects of radiotherapy is illustrated in Figure 4. Enderling *et al.* found that high doses of targeted internal radiotherapy administered immediately post-surgery are more likely to eliminate residual occult sources of cancer recurrence, rather than fractionated external radiotherapy doses. In the latter case, their model simulations showed that a fraction of the remaining tumor cells would be able to repair radiation-induced DNA damage and favor the development of a recurrent tumor.

It is important to note that like in many other mathematical models, some of the modeling assumptions could potentially influence the qualitative nature of the results. First, the radiotherapeutic doses were assumed to be uniformly administered throughout the simulation domains, which has not been validated in practice[108]. Second, tumors do not generally grow in a radially symmetric fashion, and thus spatial cellular heterogeneity could be an important factor when predicting disease progression or therapeutic outcomes. Third, a recently published phase III, randomized clinical trial performed on patients with early invasive and in-situ breast cancer showed no difference between intraoperative and external beam radiotherapy with respect to local recurrence, disease-free survival, and overall survival, in contrast to the predicted modeling results[109]. Lastly, it is well known that the heterogeneous nature of breast cancers mediates differential response outcomes among women treated with radiotherapy[110]. Hence, the models of Enderling *et al.* could be potentially improved by including the appropriate disease subtype, using corresponding experimental parameters and subsequently calibrating against the relevant clinical trial data.

In a different attempt to model breast cancer treatment, Roe-Dale *et al.* used an ODE model to incorporate cell cycle specificity and resistance to study why differential scheduling of CMF and doxorubicin doses used in breast cancer patients yield different clinical outcomes[111]. In their model, they simulated alternating and sequential regimens assumed to be delivered instantaneously to the tumor cell population and to kill a constant fraction of the cell each dose. Figure 5A illustrates the basic modeling framework used in this mathematical investigation. Roe-Dale *et al.* assumed cellular resistance induced by increased MDR1 expression, and modelled resistance following drug administration by instantaneously converting a specified fraction of the cells from the sensitive to the resistant compartments. To investigate differential treatment outcomes due to cellular resistance, Roe-

Dale *et al.* used parameters derived from *in silico* uniform distributions, and performed sensitivity analyses for specific parameter combinations to determine the parameter spaces that yielded the greatest regression (or alternatively the lowest progression) of the *in silico* tumor cell burdens. Their computational results indicated that the sequential CMF plus doxorubicin treatment results in a 62% survival rate, compared with a 50% survival rate for the alternating regimen. Roe-Dale *et al.* also found that the two regimens resulted in differential outcomes at a statistically significant level in their simulated *in silico* patient cohort, and concluded that the sequential treatment would be preferred to the alternating one.

It is important to note that the constant cellular survival fractions illustrated in Equations (3) and (4) of Figure 5A and cellular interactions are not substantiated by current pharmacodynamic and kinetic models of CMF and doxorubicin in breast cancer patients[112]. It thus remains difficult to quantitatively extrapolate from the proposed model whether MDR1 resistance or rather cell cycle specificity is responsible for the observed superiority of the sequential treatment regimen versus the alternative one in breast cancer patient cohorts[113]. In addition, the value of the combination therapy mathematically studied in Roe-Dale *et al.* (i.e. CMF plus doxorubicin) with respect to recurrence and mortality rates has only been clinically established in high-risk early stage cancer patients, but does not otherwise represent current standard therapy protocols for all breast cancer subtypes or stages[114]. Finally, choosing to model the dynamics as a system of linear ODEs enables Roe-Dale *et al.* to derive analytical, closed form solutions. We note that such an approach is somewhat limited and could be mathematically adjusted to reflect non-constant dynamics, since clinical transition rates between the modeled compartments are most likely temporally varying.

Another attempt at incorporating cell-cycle specific drug kinetics and interactions is represented by the two-compartment linear ODE model proposed by Panetta[115] and illustrated in Figure 5B. Panetta's model takes into account the proliferating cell population, which is assumed to be responsive to cell-cycle specific drug therapies, and the quiescent cell population, which is assumed to be non-responsive to paclitaxel treatment. Using published breast and ovarian cancer data[116,117], parameters such as cell-cycle length, proliferative fraction, doubling time, transfer rates between the two compartments, and time spent in either resting or cycling phase were estimated for both the formulated breast and ovarian cancer models. Using the framework exemplified in Figure 5B, Panetta derived analytic, closed form solutions for the proliferating and quiescent compartments. A parameter sensitivity analysis with respect to active drug phase and drug administration times was performed. Using the model, Panetta studied the numerical range of the associated characteristic multipliers for which the simulated total cancer cell mass at the end of treatment period is substantially reduced. Considering a treatment period of 21 days, and a dose strength of 3 units, Panetta observed that for active phases smaller than 8.5 days, the maximum characteristic multiplier was greater than 1, which would translate in a clinical context into breast/ovarian cancer cell growth. For values of the active phase greater than 8.5 days however, the maximum characteristic multiplier was less than 1, which implied that cancer cell decay was ongoing. In the context of the duration of the treatment period (e.g. every 21 days), Panetta was able to conclude that longer active drug phase times with respect

to the length of the treatment period lead to shrinking tumors, while shorter active phase times and fixed lengths of treatment periods lead to cancer growth in both the formulated breast and ovarian progression models.

While these modeling results correspond to current breast cancer clinical recommendations[118], several of the modeling constraints used in the Panetta model could be relaxed in future work, in order to better integrate the related clinical knowledge. For example, the constant modeling parameters used in the current model could be modified to reflect the action of the drug. A further extension of the model could include a study of non-constant or stochastic growth parameters calibrated against human breast tumor growth data. Moreover, different functional forms could be used to represent the drug action term, or expanded to reflect multi-drug based therapies under study in current clinical trials.

Modeling in vitro invasive cancer cell kinetics—To simulate carcinogenesis and account for the role of angiogenesis in tumor recurrences, Gatenby *et al.* developed an individual-based, hybrid cellular automaton model in which mutant cells are initially separated from the blood supply by an intact basement membrane[119]. Their working hypothesis was that a local variation in substrate and glucose metabolite concentrations in ductal carcinoma *in situ* cells would initiate cellular adaptations required for the emergence of invasive breast cancers[120]. To test this hypothesis, Gatenby *et al.* used a two-dimensional cellular automata model, with rules governing the cellular evolution of normal and tumor cells, oxygen, glucose, and H^+ fields satisfying reaction-diffusion equations. Each automaton was assumed to be representative of a single cell. The parameters were set to match quantitative data derived from experiments performed on MCF-7/HER2 breast cancer cells growing in spheroids. Simulations of the model demonstrate that malignant cells may evolve towards a phenotype that exhibits constitutive upregulation of glycolysis and resistance to acid-induced toxicity via increased H^+ concentrations. Gatenby *et al.* predicted that the distinctive pattern of nodular growth and cellular evolutionary sequence was representative of late carcinogenesis, in which malignant cells must breech the basement membrane in order to transition to an invasive cancer type.

We point out that it is unclear whether upregulation of the hypoxic and glycolytic metabolic pathways can be considered a universal, constitutive emergent cellular phenomena in the clinical evolution of human breast cancers. Further clinical investigations are warranted to elucidate the validity of these quantitative modeling results applied to patient cases.

Modeling in vivo invasive cancer cell kinetics in mouse xenografts—Marusyk *et al.*[121] developed a mathematical model of an initially heterogeneous tumor growth incorporating clonality interference. This model was developed to investigate the long-term impact of sub-clonal heterogeneity on tumor phenotypes and the possibility of competitive expansion of individual tumor sub-clones, formed after orthotopic transplantation into the mammary fat pads of immunodeficient mice. Two scenarios were considered: sub-clones either compete against parental cells (monoclonal primary tumors or compete against each other (polyclonal primary tumors). The paper concludes that an exponential growth pattern best explains the dynamics of the growth of the monoclonal tumors. In addition, nested ODE models of exponentially growing competing sub-clones were used to study the impact of

sub-clonal heterogeneity on polyclonal tumor growth. The modeling results of Marusyk *et al.* suggest that in the absence of treatment, tumor heterogeneity is predicted to eventually vanish, in the presence of sub-clones with high proliferation rates that outcompete the less fit competitors. However, after treatment with doxorubicin, differences in competitive fitness between sub-clones are amplified. Additional clinical investigations are warranted to extend these conclusions to pre- and post-treatment patient samples.

Modeling stem cell dynamics—Liu *et al.* developed a mathematical model to explore the growth kinetics of breast cancer stem cells both *in vitro* (using cell culture experiments of MCF-7/HER2 cells) and *in vivo*[122] (using tumor cells derived from primary *MMTV-Her2* transgenic mice tumors). A system of ODEs was used to describe the population dynamics of cancer stem, progenitor and terminally differentiated cells; the model also included a negative feedback regulation on the division probabilities to produce differentiated or stem daughter cells. The Liu *et al.* model is illustrated in Figure 6. Simulation of the model predicted that the majority of tumor spheres grown in their experiments were derived from progenitor cells. They also showed that the frequency of tumor sphere formation increased with time while the frequency of cancer stem cells decreased over time. According to Liu *et al.*, the proportion of cancer stem cells in any tumor sphere culture would be determined by the self-renewal frequency of stem cells during tumor sphere formation and the ratio of tumor sphere derived from the primary stem or progenitor cells. The results of Liu *et al.* also suggest that a therapy aimed at targeting the breast cancer stem cell population would be less effective in immediately shrinking tumor sizes, but more effective in the long-term suppression of tumor growth and prevention of tumor relapse.

We point out that the mathematical model proposed by Liu *et al.* does support the empirical observations derived from the adjacent *in vitro* and *in vivo MMTV-Her2* transgenic mouse experiments performed in this investigation. However, it is unclear whether the modeling inferences can be translated to human breast cancer recommendations, since the presence and effect of human breast cancer stem cells on therapeutic outcomes are highly debated in the literature[13,123,124].

Ovarian cancer

Modeling disease natural history and early detection strategies—Focusing exclusively on unimodal TVU screening, Danesh *et al.* developed a mathematical model to study the frequency at which ovarian cancer screening should be done in order to be effective[125]. To model ovarian cancer growth and progression, Danesh *et al.* developed a multi-type branching processes model, where the different types represent stages in the serous epithelial ovarian cancer progression, but without differentiating between the low and high-grade subtypes. In their model, *type 0 cells* are present in the primary tumor in the ovary or fallopian tube, *type 1 cells* are floating in the abdominal cavity, and *type 2 cells* are attached to the peritoneum. *Type 2 cells* are assumed to infiltrate the cellular matrix and eventually metastasize to distant organs, so that when they are present in significant (and clinically detectable) numbers, the cancer would be classified as stage III. In addition to giving birth to nonmutant offspring or dying, cells may transition from *type 0* to *type 1* and from *type 1* to *type 2* at differential rates. These rates were then used as transition rates in a

continuous time Markov chain. In the model, transitions between types are assumed to involve migration of cells rather than genetic mutations. Results for the multi-type branching process that enables Danesh *et al.* to quantitatively estimate the behavior of all three cell types are illustrated in Theorems 1-3[125].

In order to address their motivating question, Danesh *et al.* introduced the concept of a "window of opportunity" for screening, defined as the difference between the time when cells of *type 2* reach 10^9 cells (corresponding to a late-stage tumor) and cells of *type 0* reach 6.5×10^7 cells (corresponding to the detection threshold). Using data on tumor growth from Brown and Palmer[126], they concluded that the window of opportunity corresponds to 2.9 years, with most of the distribution concentrated between 2.5-3 years. According to their model, TVU-based ovarian cancer screening should occur biannually.

The underlying assumption in the Danesh *et al.* modeling framework is that metastatic ovarian cancer cells growth at a significantly higher rate than primary tumor cells. This assumption has yet to be validated clinically. In contrast to the dynamics portrayed in this work, it is generally believed that ovarian cancers that present clinically during early stages do not necessarily represent precursors to cancers that, if left undetected, would otherwise present at advanced stages[60,127]. Moreover, the theoretical results derived assume exponential stage residence times and an infinite time period when determining cancer growth and progression. Using non-exponential growth kinetics and a finite observation time (as done empirically) could alter the modeling outcomes. Finally, in contrast to the biannual TVU-based ovarian screening recommendation based on the Danesh *et al.* modeling inferences, latest data from ovarian cancer screening randomized controlled trials demonstrate the failure of annual, unimodal TVU examinations to improve ovarian cancer detectability and overall survival rates[64].

In another attempt to model the preclinical natural history of serous epithelial ovarian cancer as a function of tumor size, stage and its implications for TVU-based screening[126], Brown and Palmer identified and analyzed available reports on occult ovarian cancers, and used a comprehensive meta-analyzed of published data to model the growth, progression and TVU-based detection of ovarian cancer[62,74,79]. Data were collected from published studies of healthy germline *BRCA1* and *BRCA2* mutation carriers[25,63], who had their ovaries and fallopian tubes removed prophylactically. In some of these women, unsuspected ovarian cancers were discovered upon surgery[61]. Brown and Palmer performed a Monte Carlo simulation of tumor life histories to fit an exponential *in silico* model for tumor growth using parameters derived from their meta-analysis, with separate growth rate parameters for early and advanced stage cancers. A basic description of the theoretical tumor growth model proposed by Brown and Palmer is demonstrated in Figure 7. In this model, the "window of opportunity" was defined as the time duration for early detection, i.e., the time during which the tumor is expected to remain early stage (localized or regional). They estimated the window of opportunity for TVU detection of early stage cancers to be around 4.3 years, and predicted that most detected advanced stage serous cancers would have become advanced a median of 0.8 years prior to detection.

Similar to the Danesh *et al.* model, the underlying assumption in the Brown and Palmer quantitative analysis is that ovarian cancers that are clinically present during early stages are precursors to cancers that if left undetected, would otherwise present at an advanced stage. We point out that a timely detection of low volume ovarian cancer, which does not necessarily represent early stage disease, should be the goal of any screening studies as well as of any mathematical modeling framework aimed at exploring screening scheduling. Moreover, while prophylactic risk-reducing bilateral salpingo-oophorectomies or hysterectomies are predominantly performed in high-genetic risk women who exhibit an increased risk of developing HGSOC, the data used by Brown and Palmer to calibrate the estimated tumor growth rate were collected from studies where proper histological classification was not performed. Some of the reported clinical cases were non-HGSOC, and ovarian cancer subtypes were aggregated into one singular disease. Failing to recognize such confounding factors could potentially underestimate quantitative data generated by the mathematical model.

To assess dynamic plasma biomarker kinetics in relation to the genesis of cancer, Hori and Gambhir incorporated tumor growth into a linear one-compartment biomarker secretion model, beginning with a single parental tumor cell[128]. The model is shown in Figure 8. Hori and Gambhir aimed to quantify the time required for a growing malignant tumor cell population to reach a sufficient size so that its shed blood biomarker levels were high enough to be detectable by current clinical blood biomarker assays. The model was then used to calculate changes in the detection capability based on log-order perturbations in the parameters fundamental to biomarker shedding. Tumor cell growth was represented by either the exponential or Gompertzian model, while the healthy cell population was assumed constant. Hori and Gambhir aimed to identify the biomarker-related parameters that would most greatly impact blood-based early cancer detection, and quantify how far each baseline parameter value would need to change in order to achieve earlier, sub-millimeter tumor detection. It was found that tumors in the mm diameter range could only be detected under ideal conditions of extremely high rates of biomarker secretion by tumor-associated cells and zero background level from healthy cells.

Hori and Gambhir concluded that clinical implementation of a CA125 biomarker-based early serous epithelial ovarian cancer detection would be extremely difficult for the time being. Several limiting assumptions were made in the current model that could potentially be addressed by future mathematical framework modeling fluctuating biomarker levels in relationship with tumor progression. Specifically, Hori and Gambhir assumed that CA125 is shed only from malignant cells and not benign or healthy cells. The number of healthy cells considered in the model was assumed to be constant and all tumor cells were assumed to shed the biomarker. These modeling constraints could be relaxed in future models for a more realistic description of the dynamic biomarker blood levels and disease detection times. While the relationship between tumor sizes and CA125 biomarker levels is not entirely understood[72] and serial CA125 measurements are not common practice[64,129], further modeling efforts could potentially drive further cohort screening studies.

Modeling therapeutic targeting and treatment—A key question related to optimal sequencing and scheduling of chemotherapy and surgery is whether the optimal therapeutic

strategy would be to maximally debulk a cancerous tumor followed by chemotherapy or vice versa. Kohandel *et al.* considered[130] one population of tumor cells, a non-cell cycle phase specific drug, and various growth/cell-kill laws in order to compare two approaches for therapy: a) chemotherapy followed by surgery, or b) surgery followed by chemotherapy. Kohandel *et al.* combined Gompertzian and generalized logistic growth models with different cell-kill hypotheses, and assumed that surgery instantaneously kills a fraction of the tumor cells at the time of the treatment. The model is illustrated in Figure 9. For both the Gompertzian and generalized growth models, chemotherapy followed by surgery proved to be the optimal approach.

We note that the constant parameters and the functional forms proposed in the model of Kohandel *et al.* can be generalizable to any solid cancer, and bear no affinity to ovarian cancer specifically. The results presented are general and independent of a particular choice of parameters or drug administration protocols. Furthermore, in contrast to the mathematical modeling results, recently performed meta-analyses of randomized trials comparing chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer[131] as well as locally advanced breast cancer[132] showed no difference between the two clinical scenarios in terms of survival or overall disease progression. We note that a key assumption of the Kohandel *et al.* model is that chemotherapy administered prior to surgery solely alters primary tumor growth, rather than also affect the formation and growth of (micro)metastatic tumor foci, which could be clinically occult at the time of surgery. We point out, however, that the clinical rationale for adjuvant chemotherapy (i.e. after surgical resection) is to eliminate any systemic, distant microscopic disease that would most likely already be present pre- or post-surgical resection. A future mathematical investigation based on the Kohandel *et al.* model could, for example, address the open clinical question of how to reliably identify the subsets of patients without any microscopic, residual disease, who would not benefit from adjuvant chemotherapy. Lastly, while the choice of the appropriate tumor growth law for modeling disease kinetics is discussed at length[130] and its impact on therapeutic sequencing outcomes is theoretically derived through mathematical analysis, ovarian cancer primary tumor growth dynamics and clinical progression prior to or after therapy are most likely more complex than the basic growth and progression dynamics considered in this work.

In a different attempt to model combination therapy, Jain *et al.* developed a mathematical model of ovarian cancer xenograft growth to study the effect of carboplatin, and ABT-737, a small-molecule inhibitor of anti-apoptotic proteins Bcl-2 and Bcl-xL, on tumor growth inhibition[133]. Their model of ovarian cancer growth and treatment was based on a coupled system of ODEs and PDEs[134], representing the temporal dynamics of proliferating and arrested cancer cells, and concentrations of the two drugs inside the peritoneum, plasma and tissue. This combination therapy model carefully accounted for the pharmacodynamics and pharmacokinetics of both drugs, and was calibrated against *in vivo* experimental data collected from xenografted mice treated with carboplatin and/or ABT-737 on a fixed period schedule[135]. Their goal was to study dosage/timing combinations of the two drugs leading to the fastest time to minimal residual disease, or to the minimization of total drug lead in order to achieve a predetermined tumor growth inhibition. Simulations of the *Jain et al.* model suggest that when combined with ABT-737, the infusion time of carboplatin doses together

with the AUC of the drug were the most important predictors of the tumor long-term response to the combination therapy. While the model is validated by *in vitro* ovarian cancer cell lines xenografted from patient ascitic tumor cells, further clinical investigations are needed to explore and examine the synergy between carboplatin and Bcl-2 family inhibitors.

Lastly, the previously discussed two-compartment linear ODE model proposed by Panetta[115] attempted to mathematically derive optimal treatment strategies in the sense of promoting the biggest tumor cell burden reduction. Using clinical variables such as treatment period, drug-infusion time, and proliferative fraction of ovarian cancerous cells, Panetta quantitatively demonstrate that for short periods (i.e. close to the active phase time) more drug is required to notice a decay in the ovarian cancer cell population. The results were qualitatively similar to those obtained when simulating breast cancer cells. It is likely, however, that a careful calibration of the model may alter the results. For instance, the work of Panetta involved combining growth rates/doubling times from ovarian tumors xenografted in nude mice[116] with cell cycle kinetics derived from ovarian cancer cell lines[117].

Modeling in vitro invasive cancer cell kinetics—To simulate *in vitro* cancer-cell kinetics after cisplatin administration, Montalenti *et al.* developed a linear model of cell-cycle phase transitions based on experiments using IGROV-1 ovarian cancer cell line[136]. They used flow cytometry variables (derived experimentally) and implemented them as the input to a quantitative description of the action of cisplatin on the carcinoma cells. The aim was to specifically model the intermitotic time of cell-cycle phases, delays and block-effects, with consequent repair or cell mortality following the exit from the blocks. It was assumed that drug administration forces cells to leave asynchronous growth, with the main effects being a) cell death; b) cell-cycle phase delays; or c) cell-cycle blocks. At the end of each cell-cycle phase, cells were assumed to progress to the next phase only if they passed an internal molecular checkpoint. Montalenti *et al.* considered various levels of complexity in their cell-cycle simulation: (i) inter-cell differences in phase duration (modeled via a two-parameter probability distribution of the likelihood of a cell of a certain phase age leaving the specific phase); (ii) the probability that a cell can either bypass the quiescent phase or enter it for an indefinite period of time; and (iii) the probability that cells can be killed by cisplatin at a distinct rate in every phase, blocked but then repair damage and recycle, or frozen in a specific age compartment, inhibiting age maturation.

While a certain amount of information could be obtained by visual inspection of the raw experimental data performed and used, the task of the parameter-fitting simulation was to consider all experimental data together with a number of drug doses and recovery times, in order to derive a coherent kinetic scenario. Once the input baseline set of kinetic parameters was determined, the data were simulated on the cisplatin-treated IGROV-1 cells using a trial-and-error-procedure to find biologically appropriate estimates of the cisplatin-induced delays, block effects and cell mortality induced at every cell-cycle phase. The Montalenti *et al.* modeling results yielded a very detailed kinetic description of the IGROV-1 cell cycle dynamics treated with cisplatin. It remains unclear whether their modeling inferences can be easily translatable to human ovarian cancer tumor-drug interactions. No such description of *in vivo* cancer cell kinetics has been described to date, and the clinical relevance of ovarian cancer cell lines remains an issue subject to further exploration[137].

Modeling stem cell dynamics—To estimate stem cell self-renewal probabilities in serous epithelial ovarian carcinomas, Ciampi *et al.* proposed a method for estimating the probability of self-renewal of serous epithelial ovarian tumor stem cells starting from experimentally derived distributions of clonal colonies obtained in cell culture[138]. The model was based on tumor cell populations being composed of (i) tumor stem cells, capable of self-renewal and subsequent tumor self-regeneration; (ii) transitional cells, not capable of self-renewal but characterized by a limited potential for further proliferation (i.e. de-differentiation); and (iii) end-stage cells, incapable of further proliferation, and thus considered terminally differentiated. In this model, the proliferation of the cancer cell population was treated as a multi-type Galton-Watson process in which stochastic fluctuations lead to probability distributions in the number of each cell type, under the assumption that cell division does not necessarily occur at the same time for same-age cells. Using a Nelder-Mead algorithm and equating the theoretical moments of the distribution of cell types with the observed experimental colony size mean and variance, Ciampi *et al.* derived parameter estimates for the probability of self-renewal of a tumor stem cell, and the clonal expansion number expressed in the generations, i.e. the number of de-differentiated states.

We note that a key assumption of this model is that ovarian cell populations are organized in a hierarchy of decreasing proliferation potential and increasing degrees of cellular differentiation. However, it is unclear if stem cells are responsible for the initiation and progression of clinical ovarian cancers[139]. Moreover, the lack of unique markers that are able to identify stem cells in the context of ovarian cancers make it difficult to characterize the proliferative landscape of such cells *in vitro* or *in vivo*.

FUTURE PERSPECTIVES

In this review, we survey the existing mathematical oncology literature, focusing on two major subsets of women's cancers, specifically the breast and ovarian malignancies. First, we summarize the existing clinical data regarding malignancy progression and breast/ovarian cancer patients' specific therapy response. From a systems biology perspective, we demonstrate that few mathematical modeling inferences have been concerned with any of breast cancer subtypes, and even fewer with ovarian cancer subtypes. Whenever possible, we compare and contrast the known clinical information about the families of breast and ovarian cancers, and complement the existing clinical paradigms with a description and discussion of the corresponding mathematical modeling attempts. In doing so, we show how current mathematical models that focus on the two women's malignancies do not make comprehensive use nor substantially reflect existing clinical data. We then highlight the modeling areas in most critical need of clinical data integration. Lastly, we argue that the existing mathematical models reviewed and discussed in this paper are not adapted to reflect the complex, heterogeneous behaviors of women's malignancies.

With respect to main themes addressed by current breast and ovarian cancer mathematical modeling, the models discussed in this review generally address primary tumor growth, optimal biomarker characteristics, and therapy sequencing, omitting to varying degrees disease-specific characteristics, such as histological classification, or specific drug-body

pharmacodynamics and pharmacokinetics. We note, however, that considerable biological realism and any translational/clinical relevance of such modeling results are lost if the existing mathematical models aggregate the various women's cancers subtypes into one singular disease. Moreover, existing mathematical models tend to either completely ignore current standard therapeutic approaches and existing combination treatments, or model any multidrug therapeutic combinations as single drugs, without reflecting the differential pharmacodynamic and pharmacokinetic behavior of the various drugs.

From a mathematical point of view, the quantitative tools employed in these models range from probabilistic techniques (e.g. branching processes, bootstrap resampling, time-homogeneous Markov chains), through differential equation-based approaches (single or multiple compartment ODE, PDE or coupled ODE-PDE models). There are, however, several underlying, limiting assumptions with using such modeling approaches. Most such models rely on the “perfect mixing” assumption that cellular populations are spatially homogeneous, and are only able to quantify average cellular behavior, rather than heterogeneous genetic and phenotypic cellular profiles. In doing so, existing models are only able to generate aggregate statistics or outcomes similar to results derived from population-based cohort studies. The extent to which such modeling results would contribute to understanding patient-specific cancer progression or subsequent therapeutic outcomes is thus unclear. Mathematical modelers of women's cancers should also devote careful attention to parameterization details and model calibration against experimental data, as more often than not, parameter estimations for a singular model are derived from various cancer cell lines, mouse models, and/or xenografted tumor data. The applicability of such modeling attempts to clinical scenarios thus remains tenuous at its best.

Outlook for the future

Studying the natural history, growth, progression or dynamic response to treatment of breast and ovarian cancers in an integrated systems biology/mathematical framework offers an innovative contribution and a complementary tool at the disposal of the women's cancers clinical community. If accurately and realistically applied to existing clinical data, such frameworks could represent a substantial step forward, and can be performed in a relatively inexpensive manner, that relies only on computing power. Mathematical modeling can provide insights about the disease dynamics that reach beyond contemporary clinical and experimental tools and are impossible to obtain even in large-scale cohort studies. Dynamic spatiotemporal mathematical models of women's cancers and their evolution can provide a quantitative understanding of the *likelihood of occurrence* of specific clinical scenarios in response to detection, treatment and the *when* and the *why* of emergence of resistance.

This is precisely why we believe mathematical modeling could potentially make a substantial contribution to cancer research and therapy. To that end, current and future modeling attempts should be properly integrated with clinical data, and thus parameterized to reflect disease heterogeneity in progression and therapeutic responses. We point, however, that this issue is double-sided.

First, we believe that an adaptation of the modeling attempts discussed in the present review to current clinical data does not require any revolutionary or novel mathematical modeling

framework. Existing mathematical approaches and techniques utilized in modeling the progression and therapeutics of one malignancy can be similarly translated to another malignancy, despite the complex degrees of heterogeneity of different malignancies from a clinical perspective. Instead, we argue that all that is needed are an increased awareness of the mathematical modeling community to the limitations of current models in providing an accurate representation of the contemporary clinical knowledge, and more sustained efforts at understanding disease specifics before attempting any modeling implementation. To that end, we believe that mathematical oncologists focused on modeling the breast and ovarian malignancies would greatly benefit from extensive collaboration with specialists outside their primary domain of expertise, in order to refine the aims of their modeling efforts, calibrate and mechanistically validate their modeling results in the context of clinical applications. We stress that augmented and sustained efforts at bringing together researchers with complimentary expertise (e.g. mathematicians, cancer biologists, and clinicians/experimentalists) should be initiated to introduce *a new research paradigm* to women's cancers studies. There is a pressing urgency to bring in quantitative, truly integrated modeling to preclinical and clinical development of novel breast and ovarian cancer therapeutics.

Second, to successfully calibrate and validate modeling frameworks, it is crucial to point that more often than not, data collected by clinicians during therapeutic interventions or follow-up of patients in trials is not reported in a format that is suitable for mathematical modeling. This may severely limit the translational value of any mathematical model. Mathematical modeling could substantially benefit from a more comprehensive data collection and reporting. Single values (such as tumor size at diagnosis, categorical thresholds such surgical debulking cytoreduction values, tumor shrinkage response and related endpoints, or single serum biomarker measurements), should be replaced by reporting dynamical information, such as the levels of change. Longitudinally measured markers, molecular and imaging data performed and measured over the course of a patient's care would provide excellent discriminatory and predictive power to mathematical models.

Several recent randomized controlled trials have begun incorporating serial measurements of relevant clinical parameters, and the inclusion of such temporal data yielded substantially improved predictive power when analysis was performed within tumor subsets stratified by patient characteristics. Examples include the I-SPY 1 TRIAL - a cohort of 221 patients with histologically confirmed invasive breast cancer whose pathologic complete response to therapeutic care and recurrence-free survival rates were temporally evaluated[140], and the UK Collaborative Trial of Ovarian Cancer Screening that randomly allocated 202,638 post-menopausal UK women to different temporal multimodal screening algorithms in order to establish the effect early detection by screening on ovarian cancer mortality[64]. Herein, serial CA125 serum levels and TVU examinations were collected and used to inform their risk of ovarian cancer prediction algorithm.

Open challenges

More recently, the increasing availability of high throughput genomic datasets to identify the molecular basis of a number of cancers has heralded an emerging approach to cancer

treatment, specifically precision medicine. The long term goal of such an approach is to identify and subsequently use the observed changes and patterns in a patient's individual cancer to better inform therapeutic outcomes and yield treatment options tailored to an individual's specific clinical parameters.

A significant amount of clinically motivated efforts has been aimed in producing dynamic molecular datasets. High depth sequencing is used to study the functional role of genetic heterogeneity during a cancer's evolutionary progression and to better disseminate between individual tumors of different subtypes based on their molecular profiling. Novel clinical trial designs are attempting to identify the rules for the dissemination of individual patients according to a comprehensive set of clinical characteristics and match them to therapeutic outcomes[52,141-143]. Such designs play a key role in providing data for mathematical models, and the relatively few modeling efforts informed by such datasets have yielded promising results, leading to the inference of novel mechanistic relationships and possible links to therapeutic outcomes in chronic myelogenous[144] and chronic lymphocytic leukemias[145], Barrett's esophagus[146], or glioblastomas[147], to name a few.

With regards to breast and ovarian cancers, such high throughput dynamic molecular datasets are yet not widely available, and enhanced serial data collection is not routinely performed. As such, numerous open questions remain, many of which cannot be feasibly or exclusively addressed experimentally. A list summarizing questions presently of great interest to the clinical community, that could potentially be addressed using mathematical models, is given in Table 1.

Conclusions

In this review, we seek to emphasize the pressing need for truly integrative mathematical-oncology collaborations that reflect and make use of the clinically known aspects of malignancy heterogeneity, progression, detection and therapeutic options. We believe that the primary goal of any mathematical study of women's cancers should ultimately be to address current clinical open questions. In order to achieve this goal, the design of any future mathematical models will have to closely follow women's cancers biology, be driven by it, and be closely supported and informed by enhanced clinical and experimental data.

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SIDEBARS

Sidebar 1. Clinical terminology used throughout the review listed by order of reference.

Menopause is defined as occurring 12 months after a woman's last menstrual period and marks the end of menstrual cycles. It implies the permanent cessation of ovulation and menses without any obvious pathological cause.

Early detection refers to the discovery and diagnosis of a malignancy prior to the occurrence of any clinical symptoms.

Systemic cancer therapy refers to a type therapy that uses substances which travel throughout the body via the bloodstream, and affects cancer cells wherever they may be located.

Targeted therapy refers to a type of therapy that uses drugs or other substances to identify and attack specific pathways in cancer cells that are necessary for the cancer cell growth, with limited toxicity to normal cells.

General risk women are defined as asymptomatic women without any known genetic mutations or known family history of breast and/or ovarian cancer.

High-genetic risk women are defined as individuals from families with a known deleterious *BRCA1* or *BRCA2* mutation or women with a family history of breast or ovarian cancer, such as a first- or second-degree blood relative with a personal history of breast or invasive ovarian cancer.

Screening refers to monitoring of asymptomatic, apparently healthy patients with the intent of achieving an earlier diagnosis, if disease is found.

Tumor dormancy refers to clinically undetectable microscopic metastases that remain in a dormant state for prolonged periods of time, and that eventually progress to detectable cancer sometime during a patient's lifetime.

Sidebar 2. Mathematical modeling terminology used throughout the review listed by order of reference.

Temporal refers to the progression in time of a clinical variable, e.g. tumor size, biomarker levels, effects of a drug on the body.

In silico refers to a numerical simulation performed on a computer.

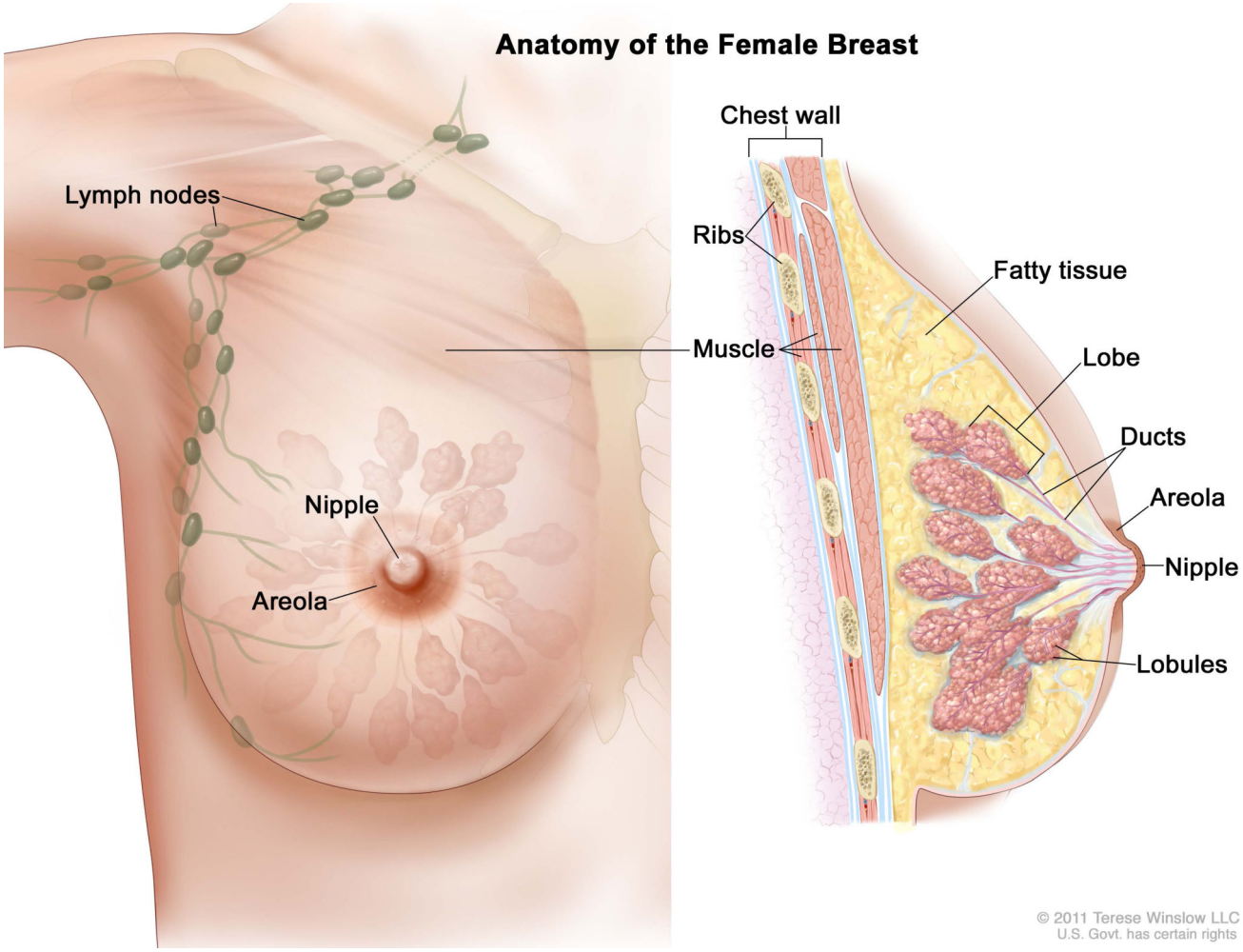

Figure 1.

"Breast Anatomy Female": For the National Cancer Institute © 2011 Terese Winslow LLC, U.S. Govt. has certain rights.

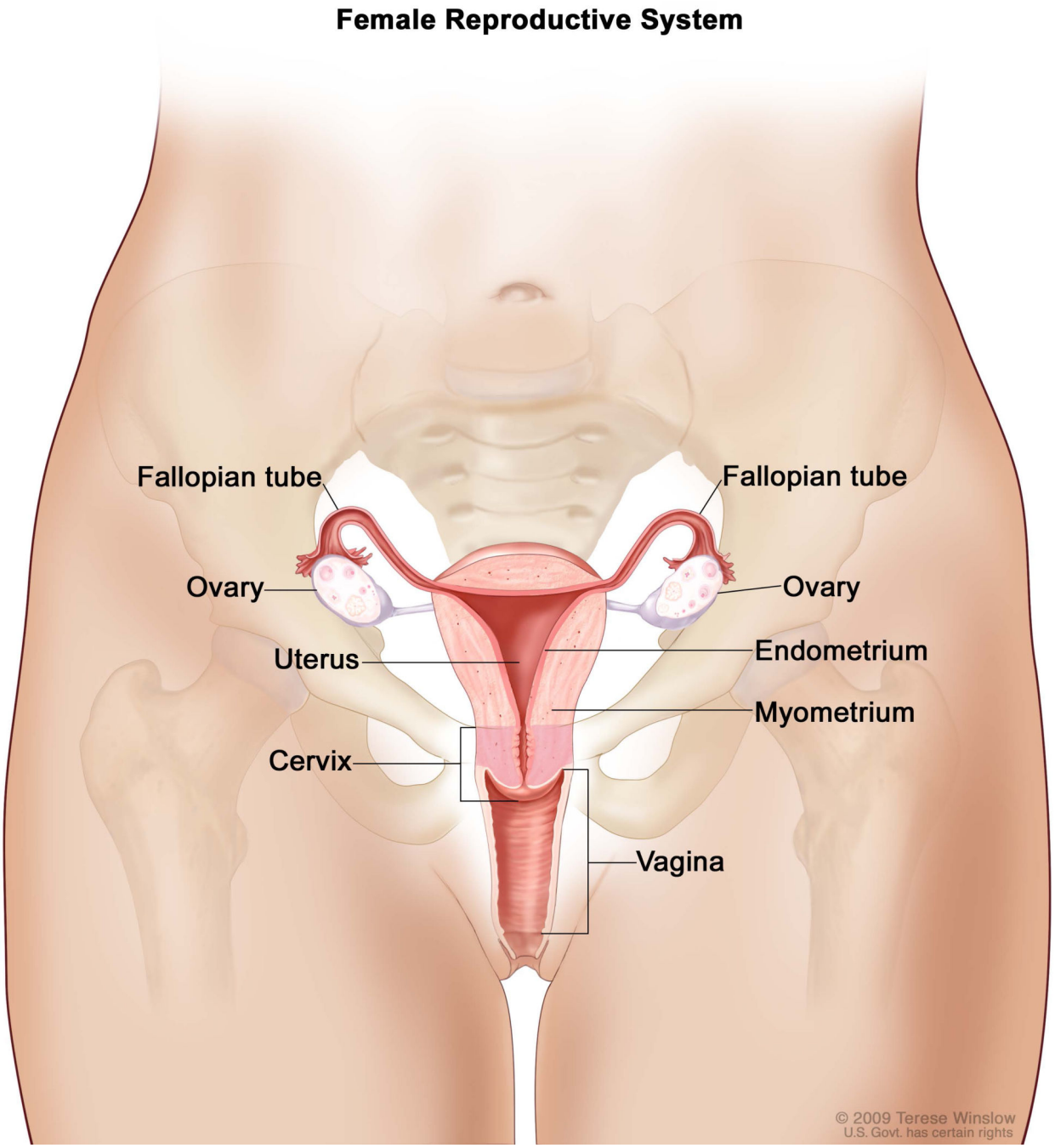

Figure 2.
"Female Reproductive System": For the National Cancer Institute © 2009 Terese Winslow LLC, U.S. Govt. has certain rights.

$$N(t) = \exp\left[\frac{A_0}{\alpha}\left(1 - e^{-\alpha t}\right)\right],$$

$$\alpha = \frac{\alpha}{1 + rA_3}.$$

Figure 0003

$$N(t) = N(0)\exp\left[k(1 - e^{-bt})\right], \quad k = \log\frac{N(\infty)}{N(0)}.$$

$$t_i = -\frac{1}{b_i}\log\left[1 - \frac{1}{k}\log\frac{N_L}{N(0)}\right].$$

Figure 0004

Figure 3. The breast cancer growth models proposed by (A) Speer *et al.*[93] and (B) Norton[94]

(A) The first equation corresponds to classical Gompertzian growth kinetics, where *N(t)* is the number of tumor cells measure at time *t* after the start of tumor growth, A_0 is the initial growth rate, and α is the rate of growth decay. In this model, time is incremented in intervals of 5 days. A random number, r_1, between 0 and 1 is generated at each time interval, and compared to a predetermined value A_4, defined as the probability that α undergoes a change in a 5-day period. If $r_1 > A_4$, the tumor continues growing at the previous rate. However if $r_1 < A_4$, α is reduced by an amount depending on A_4, r_2, another randomly generated number between 0 and 1, and A_3, the predefined determinant of the amount of change in α. This process is illustrated in the second equation. Computations of the simulated growth curves are performed until either simulation time runs out, set at 40 years elapsed since the beginning of tumor growth, or until a lethal *in silico* tumor burden threshold is reached, set at $N(t)=10^{12}$ cells. The Speer *et al.* model beings with 1 cell at time 0 and uses predefined values of A_0, α, A_4, A_3. A_0 and α are expressed in units of days^{-1}, and A_3 and A_4 are dimensionless. Simulation time is measured in days. Each computed growth curve is generated using the same baseline parameter set.

(B) The first equation corresponds to classical Gompertzian growth kinetics, where *N(t)* is the number of tumor cells measure at time *t* after the start of tumor growth set at t = 0, *N(0)*

is the tumor starting size, b is the rate of growth decay, and $N(\infty)$ is the limiting size. To generate the probability distribution function of b, the proportion, $P_L(t)$ of patients who have died by time t since the onset of symptoms after having reached the lethal tumor size, N_L, is generated from the 250 breast cancer survival curve data set in (Bloom *et al.*). Re-arranging the Gompertz, Equation (2) is obtained, where $P_L(t_i)$ represents the proportion of the 250 cancers with growth decay rate $b<b_i$. The model is initialized with a set of initial values for $N(0)$, N_L, and $N(\infty)$, and a least-squares based numerical algorithm is used to determine the mean and standard deviation of b. A randomly generated initial value for b_i is then chosen from the computed distribution to calculate t_i to ensure $N(t_i) = N_L$, and the process described in the second equation is repeated until the value of b_i that provides the best fit to $P_L(t_i)$ is found.

$$\frac{\partial n}{\partial t} = \lambda n(1-n-f) + d_n \nabla^2 n - \gamma \nabla \cdot (n \nabla f),$$

$$\frac{\partial f}{\partial t} = -\eta m f,$$

$$\frac{\partial m}{\partial t} = d_m \nabla^2 m + \alpha n(1-m) - \beta m,$$

$$BED = n(\alpha n + \beta d^2),$$

$$S = \exp\left[-nd\alpha\left(1 + \frac{d\beta}{\alpha}\right)\right].$$

Figure 4. The ODE-PDE framework used to model breast cancer development, treatment and recurrence[105], subsequently used to model radiotherapeutic strategies[107]

The system of equations describing the interactions of tumor cells (n), extracellular matrix (f), and matrix-degrading enzymes (m) is illustrated in the first equation. Therein, the terms in the first equation correspond to cellular proliferation, random motility and haptotaxis, defined in the model as the movement of tumor cells according to gradients of chemicals in the tumor environment. The second equation corresponds to the extracellular matrix degradation by existing tumor cells. Lastly, the terms in the third equation correspond to the diffusion of matrix-degrading enzymes secreted by the tumor cells, the production of new enzymes and natural decay.

The fourth equation represents the biologically effective dose [102], where n is the number of radiotherapeutic fractions administered, d is the dose delivered per fraction, α is the coefficient of single-hit DNA double-strand breaks, and β is the number of DNA single-strand break pairs that combine into forming double-strand breaks. d is measured in Gray. The surviving probability S, i.e. the proportion of cells that survive the radiation-induced damaged is modeled in the fifth equation.

$$\begin{aligned}\frac{dN_1}{dt} &= -\lambda_1 N_1 + 2\lambda_2 N_2,\\ \frac{dN_2}{dt} &= \lambda_1 N_1 - \lambda_2 N_2,\\ \frac{dN_3}{dt} &= -\lambda_1 N_3 + 2\lambda_2 N_4,\\ \frac{dN_4}{dt} &= \lambda_1 N_3 - \lambda_2 N_4.\end{aligned} \tag{1}$$

$$\mathbf{N}(\mathbf{m}\tau^+) = \mathbf{T_i}\mathbf{N}(\mathbf{m}\tau^-). \tag{2}$$

$$\mathbf{T_A} = \begin{bmatrix} (1-\kappa_A)(1-\mu_A^1) & 0 & 0 & 0\\ 0 & (1-\kappa_A)(1-\mu_A^2) & 0 & 0\\ \kappa_A(1-\mu_A^1) & 1 & 0 & 0\\ 0 & \kappa_A(1-\mu_A^2) & 0 & 1 \end{bmatrix}, \tag{3}$$

$$\mathbf{T_C} = \begin{bmatrix} (1-\kappa_C)(1-\mu_C^1) & 0 & 0 & 0\\ 0 & (1-\kappa_C)(1-\mu_C^2) & 0 & 0\\ \kappa_C(1-\mu_C^1) & 0 & (1-\mu_C^1) & 0\\ 0 & \kappa_C(1-\mu_C^2) & 0 & (1-\mu_C^1) \end{bmatrix}. \tag{4}$$

Figure 0006

$$\begin{bmatrix}\frac{dP}{dt} & \frac{dQ}{dt}\end{bmatrix} = \begin{bmatrix}\gamma-\alpha-\delta-sf(t) & \beta\\ \alpha & -\beta-\lambda\end{bmatrix}\begin{bmatrix}P\\Q\end{bmatrix} \tag{1}$$

$$f(t) = \begin{cases}\frac{T}{a}, & \text{if } nT \le t \le a+nT\\ 0, & \text{if } a+nT < t \le (n+1)T.\end{cases} \tag{2}$$

Figure 0007

Figure 5. (A) The four compartment cell cycle and resistance framework modeled by Roe-Dale *et al.*[111]. (B) The two compartment cell cycle framework modeled by Panetta[115]

(A) In the system of equations illustrated in (1), cells are separated by cell cycle status in two states, and drug sensitivity status in two other states, for a total of four possible states: either G1 or S sensitive (N_1) or resistant cells (N_3) and G2 or M sensitive (N_2) or resistant cells (N_4). In this model, resistant cells are defined as cells that express the activated *MDR1*

gene. The terms in each equation correspond to cell-specific constant transitions rates between the four compartments.

The treatment equation for the Roe-Dale *et al.* model is illustrated by (2), where $\boldsymbol{N}$ represents the matrix-vector notation for the four different compartments whose temporal dynamics is modeled by (1), T_i is the corresponding treatment matrix for drug i, and m is the number of administered treatments with drug i at time intervals of τ hours. The fraction of cells surviving treatment with doxorubicin ($\mathbf{T_A}$ in the model) and with CMF ($\mathbf{T_C}$ in the model) are described in Equations (3) and (4), respectively.

(B) In the system of equations illustrated in (1), P is the number of proliferating tumors cells, and Q is the number of quiescent tumor cells. Additional parameters include γ, the growth rate of proliferating cells, α, the transition rate from the proliferating to the quiescent compartment, δ, the natural proliferating cell death rate, β, the transition rate from the quiescent to the proliferating compartment, and λ, the natural quiescent cell death rate. All parameters in the model are assumed to be positive, and constant. Herein, the system outlined in (1) represents a linear system of ODEs modeling the dynamics of the proliferating and quiescent cell compartments. The function $f(t)$ described in Equation (2) represents a step function describing the effects of the chemotherapeutic treatment, e.g. paclitaxel. The periodic function modeling the paclitaxel effects is assumed to target only the proliferating cell compartment. In its functional representation, s is the strength of the drug, a is the active drug time, T is the period of paclitaxel administration and n stands for the n^{th} administered drug dose.

$$\frac{dx_0}{dt} = (p_0 - q_0)v_0x_0(t) - d_0x_0(t),$$
$$\frac{dx_1}{dt} = (1 - p_0 + q_0)v_0x_0(t) + (p_1 - q_1)v_1x_1(t) - d_1x_1(t),$$
$$\frac{dx_2}{dt} = (1 - p_1 + q_1)v_1x_1(t) - d_2x_2(t).$$

Figure 6. The Liu *el al*. breast cancer stem cell model[122]

The population dynamics of the cell types considered is illustrated in the above equations. Therein, $x_i(t)$ is the number of cells measured at time t of type i, where $i=0$ is the cancer stem cell phenotype, $i=1$ is the progenitor cell phenotype, and $i=2$ is the terminally differentiated cell phenotype. $p_0(p_1)$ is the probability that a cancer stem cell (progenitor cell) divides into 2 cancer stem cells (progenitor cells), $q_0(q_1)$ is the probability that a cancer stem cell (progenitor cell) divides into 2 progenitor cells (terminally differentiated cells), v_0 and v_1 are the synthesis rates representing the transition rates from the cancer stem to the progenitor cell compartment and respectively, from the progenitor cell to the terminally differentiated cell compartment. Lastly, d_i, where i = 0, 1 or 2, represents the death rates of cells of type i.

$$\log(\text{size}) = a + b\,t_1, \tag{1}$$

$$\log(\text{size}) = c + d\,t_2. \tag{2}$$

Figure 7. The tumor growth model proposed by Brown and Palmer[126]

Tumors in both early and advanced stages were assumed to grow exponentially. Specifically, the early stage tumor growth model is illustrated in Equation (1). Therein, *a* is the size at which a particular tumor is detectable by histopathology, *b* is the (exponential) growth rate constant and t_1 is the time since the tumor became detectable by histopathology. Detection thresholds for each individually simulated growth curve were set to match the corresponding value found in the collected tumor data set.

The advanced stage tumor growth model is illustrated in Equation (2). Therein, *c* is the log value of the tumor size at disease progression from early to advanced stage (estimated from the Monte Carlo simulation of tumor life histories), *d* is the difference between the log values of the tumor size at empirical diagnosis obtained from the collected tumor data set and the log value of the size at progression from the generated simulation, and t_2 is the *in silico* measured time since progression.

$$\frac{dq_{PL}(t)}{dt} = u_T(t) + u_H(t) - k_{EL}q_{EL}(t),$$

$$u_T(t) = f_{PL,T}R_T N_T(t),$$

$$u_H(t) = f_{PL,H}R_H N_H(t),$$

$$N_T(t) = N_{T,0}\exp\left[\frac{k_{GR}}{k_{\text{decay}}}\left(1 - e^{-k_{\text{decay}}t}\right)\right],$$

$$N_T(t) = N_{T,0}\exp[k_{GR}t].$$

Figure 8. The plasma biomarker temporal dynamics model of Hori and Gambhir[128]

The change in the mass of the plasma biomarker with respect to time is equal to the difference between the influx of plasma biomarker shed by the tumor cells, $u_T(t)$, healthy cells, $u_H(t)$ and the outflux of biomarker from the plasma, $q_{EL}(t)$, are as illustrated in the first equation. The rate of biomarker entry into the plasma is the sum of the input from tumor cells (as modeled in the second equation) and from healthy cells (as modeled in the third equation). Tumor cell growth is represented here by either the Gompertzian growth model (the fourth equation) or the exponential growth model (the fifth equation). The healthy cell population is assumed to remain constant throughout simulation time, and is set at $N_H(t) = N_{H,0}$.

$$\frac{dN}{dt} = f(N) - G(t,N) - k_s I(t = t_{surgery})N,$$

$$G(t,N) = \begin{cases} c(t)N, & \text{if log-kill model,} \\ c(t)f(N), & \text{if NS model,} \\ c(t)\frac{N}{N+\delta}, & \text{if } E_{max} \text{ model.} \end{cases}$$

Figure 9. The one-compartment ODE model of Kohandel *et al.*[130]. Modeled are tumor growth, and surgical and chemotherapeutic treatments

Kohandel *et al.* considered one population of tumor cells, a non-cell cycle specific drug and various growth and cell-kill laws formulated in the following manner. The dynamics of the number of tumor cells at time *t, N(t),* is described by differential functional forms for the growth law, where *f(N)* is the tumor cell growth dynamics (e.g. *f(N) = aN* for the exponential growth law, where *a* is the constant proliferation rate), *G(t,N)* describes the effects of the drug on the system , and $I(t = t_{surgery})$ is an indicator function (equal to 1, if $t = t_{surgery}$, and 0 otherwise). Differential functional forms chosen for *G(t,N)* are provided in the second equation. Surgery is assumed to be instantaneous, and to remove a fixed fraction of *exp(−k_s)* of tumor cells, where k_s is the fraction of removed cells during surgery.

Table 1

List of clinically relevant open questions regarding the breast and ovarian malignancies.

1. Cancer initiation	Can we predict whether subtypes arise from distinct lineages or from a common precursor in both malignancies? Can we predict who is more likely to get breast or ovarian cancer in high-genetic risk cases? Can we integrate the knowledge about causative disease factors to identify more effective prevention and treatments?
2. Cancer progression	Can we develop a quantitative metric to predict which ductal carcinomas in situ are more likely to progress to invasive cancer? Similarly, can we develop a quantitative metric to predict which in situ fallopian tube lesions would progress to invasive high-grade serous cancer? Can we predict which invasive breast/ovarian detected carcinomas are more likely to have become metastatic prior to diagnosis? Which specific women's cancer would be more likely to benefit from systemic therapy? Can we quantitatively stratify the risk of relapse and/or need for chemotherapy without being able to or having to conduct large scale prospective cohort studies?
3. Cancer dormancy	Can we quantitatively predict why dormant breast cancer tumor cells start to grow and invade, as observed anecdotally? How do dormant residual cells switch to a proliferating stage and regenerate tumors? Can we determine what the qualitative mechanism behind dormancy activation is? Specifically, are dormant cancer cells already present within the tumor or are they induce by therapy?
4. Treatment of metastatic and/or resistant disease	Is it feasible to develop mechanistic models of drug penetrability and/or biological function in order to better study drug sequencing and emergence of resistance? Can we use mathematical analysis to guide the selection of drugs to be used for each patient? Specifically, can we mathematically quantify the spatio-temporal propagation of resistance in order to better predict treatment outcomes? Can we use generated *in silico* cumulative distributions of disease-free survival times prior to recurrence to guide subsequent therapeutic scheduling?