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Global Dynamics of a Breast Cancer Competition Model

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Abstract

In this paper, we present a system of five ordinary differential equations which consider population dynamics among cancer stem cells, tumor cells, and healthy cells. Additionally, we consider the effects of excess estrogen and the body's natural immune response on the aforementioned cell populations. Employing a variety of analytical methods, we study the global dynamics of the full system, along with various submodels. We find sufficient conditions on parameter values to ensure cancer persistence in the absence of immune cells, and cancer eradication when an immune response is included. We conclude with a discussion on the biological implications of the resulting global dynamics.

Keywords

Breast cancer; Ordinary differential equations; Tumor-immune dynamics; Estrogen; Global dynamics

1 Introduction

Breast cancer is the most common invasive cancer in females worldwide. The production of malignant tumors begins in the cells of the breast, known as epithelial cells, and can invade surrounding tissues or metastasize to other areas of the body. The formation of breast cancer can occur in the inner lining of the milk ducts, known as ductal carcinoma, or in the lobules of the breast, known as lobular carcinoma [15]. Throughout the study of breast cancer, several mathematical models have been developed to gain further knowledge about its development and possible treatment. The aim of our paper is to develop a system of nonlinear ordinary differential equations which describes the role of excess estrogen in the development of breast cancer and its impact on the body's natural immune response. We

also model the interactions among cancer stem cells, non-proliferative tumor cells, and healthy epithelial cells in the breast tissue.

One key feature of our model is the cancer stem cell hypothesis which states that malignant tumor cell populations are developed and maintained by a population of tumor cells which act similarly to adult stem cells. These specialized cancer cells, known as cancer stem cells (CSCs), are believed to repopulate tumor cell populations. The population of CSCs is generally small which makes it harder to detect and therefore, harder to eradicate. Because the tumor cell population may be repopulated by CSCs, it is important to eliminate both tumor cells and CSCs to prevent cancer recurrence [1].

In addition to CSCs, increased estrogen levels assist the growth of the tumor cell population. A mitogen is a chemical substance that encourages cells to undergo mitosis. Estrogen can act as a mitogen by triggering cell division by breast tissue. Estrogen can also act as a carcinogen by directly damaging DNA, causing healthy epithelial cells to have a higher likelihood of malignant conversion [14]. Our model considers these properties of estrogen as a factor in the persistence of breast cancer.

The biological implications of mathematical models concerning tumor-immune competition and breast cancer dynamics have been previously studied by a number of authors [3,7,13,17]. Most notably, Mufudza, Sorola, and Chiyaka [14] examined the effects of excess estrogen on breast cancer dynamics with the inclusion of an immune cell population to model the body's natural response to tumor growth. This study was able to establish equilibrium points, as well as conditions for local and global stability of models with and without excess estrogen. Our current work expands upon the previously studied dynamics to include the cancer stem cell hypothesis, limited rates of estrogen-induced proliferation and mutation, and estrogen absorption rates for each of our cell populations.

We begin in Section 2 by outlining the development of our model and presenting our list of parameters and preliminary results. In Sections 3–4 we analyze the stability of a basic competition submodel and an immune-free submodel to better understand the dynamics among cell populations and the role of estrogen. Global attractivity of a cancer persistence state can be determined in each case. We then analyze the full system in Section 5 and establish conditions for a globally attractive cure state. Section 6 provides numerical simulations to support our mathematical findings, and we conclude with a discussion of our results in Section 7.

2 Presentation of the Model

We begin to develop our model by assuming logistic growth of cell populations and basic competition between tumor cells and healthy cells. With the inclusion of the CSC hypothesis, the tumor cell population depends on cancer stem cell growth. We consider the immune cell population to consist of NK cells and CD8⁺T cells as in [14] and we use the same equation to model the immune dynamics. The estrogen equation has been built off of a model presented by Pinho, Freedman, and Nani [16]. In their paper, a chemotherapy agent is continuously infused into the body, absorbed by various cell populations, and is washed out

naturally. We treat excess estrogen in a similar fashion and assume it is infused daily through birth control. The equation will include a constant source rate of estrogen, a washout term, and Holling Type-II terms which represent the absorption of estrogen by various cell types. Similarly to [9, 14, 23] our system ignores any spatial dependence of the dynamics. In total, the developed system is composed of five ordinary differential equations including cancer stem cells (C), tumor cells (T), healthy cells (H), immune cells (I), and excess estrogen (E):

$$\begin{aligned}\frac{dC}{dt} &= k_1 C \left(1 - \frac{C}{M_1}\right) - \gamma_1 IC + \frac{p_1 CE}{a_1 + C} \\ \frac{dT}{dt} &= k_2 C \left(\frac{C}{M_1}\right) \left(1 - \frac{T}{M_2}\right) - n_1 T - \gamma_2 IT + \frac{p_2 TE}{a_2 + T} \\ \frac{dH}{dt} &= qH \left(1 - \frac{H}{M_3}\right) - \delta HT - \frac{p_3 HE}{a_3 + H} \\ \frac{dI}{dt} &= s + \frac{\rho IT}{\omega + T} - \gamma_3 IT - n_2 I - \frac{uIE}{v + E} \\ \frac{dE}{dt} &= r - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H}\right)E.\end{aligned}\tag{1}$$

We shall further examine each term in more detail, beginning with the equation for cancer stem cells:

$$\frac{dC}{dt} = k_1 C \left(1 - \frac{C}{M_1}\right) - \gamma_1 IC + \frac{p_1 CE}{a_1 + C}.$$

The first term represents the natural increase in cancer stem cells with a division rate k_1 and a carrying capacity of M_1 . This is recognized as a logistic growth term of the cancer stem cell population. The second term shows the induced death of cancer stem cells by immune cells at a rate of γ_1 [14]. The final term is a Holling Type-II term which represents the rate of increased cancer stem cell proliferation due to excess estrogen where p_1 is the maximum rate and a_1 is the number of cells for which the rate is at half of its maximum [16]. The equation for tumor cells is similar:

$$\frac{dT}{dt} = k_2 C \left(\frac{C}{M_1}\right) \left(1 - \frac{T}{M_2}\right) - n_1 T - \gamma_2 IT + \frac{p_2 TE}{a_2 + T}.$$

The first term of the equation is a limited growth term for tumor cells which depends on the population of cancer stem cells. Even if tumor cells are eradicated, any existing CSCs will repopulate tumor cells. The additional $\frac{C}{M_1}$ factor slows the production of tumor cells in favor of the CSCs repopulating themselves. The natural death rate of tumor cells is represented by n_1 . Additionally, tumor cells are also removed by the immune system at a rate of γ_2 . We assume that the immune response is more effective against the tumor cell population than against the CSC population, leading to the inequality $\gamma_2 > \gamma_1$ [25]. As in the CSC equation, the final term describes the increased rate of tumor cell division due to excess estrogen. We assume tumor cells divide a limited number of times and have low proliferative potential [2],

therefore estrogen's impact on tumor cell division will be negligible. Thus, we assume $p_2 \ll p_1$. Next we consider:

$$\frac{dH}{dt} = qH \left(1 - \frac{H}{M_3} \right) - \delta HT - \frac{p_3 HE}{a_3 + H}.$$

Similar to the previous equations, the first term represents the logistic growth of healthy cells at a rate of q and a carrying capacity of M_3 . The second term represents the competition between healthy cells and tumor cells over space and resources at a rate of δ [14]. The final term describes the decrease in healthy cells due to DNA mutation caused by the presence of excess estrogen. We assume $p_3 < p_1$ as a majority of cancer cells are estrogen-receptor positive and only a small proportion of epithelial cells are estrogen-receptor positive [8]. The immune cell population is represented by the equation:

$$\frac{dI}{dt} = s + \frac{\rho IT}{\omega + T} - \gamma_3 IT - n_2 I - \frac{uIE}{v + E}.$$

The constant variable s represents the source rate of immune cells replenished in the body daily. The next term is a nonlinear recruitment term for immune cells where ρ is the immune response rate and ω is the immune cell threshold [3]. We assume that immune cells are inactivated upon interacting with tumor cells at a rate of γ_3 . The natural death rate of immune cells is represented by n_2 . The final term describes a limited rate at which estrogen suppresses immune cell activation where u is the rate of immune suppression and v is the estrogen threshold [14]. Lastly we consider our equation for estrogen:

$$\frac{dE}{dt} = r - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E.$$

The constant infusion of excess estrogen is denoted by r . The rate at which estrogen is being washed out of the body is denoted by μ . The remaining terms describe the absorption of excess estrogen by CSCs, tumor cells, and healthy cells where d_i is the estrogen absorption rate and a_i is the number of cells at which the absorption is at half of its maximum [16].

Assuming (1) is subject to non-negative initial conditions, we note that the system is invariant in the non-negative orthant. Additionally, because the associated vector field is continuously differentiable, there exists a unique solution to our system by the Picard–Lindelöf Theorem.

Our parameters are listed in Table 1. Notationally, cells_C, cells_T, cells_H, and cells_I represent CSC, tumor cell, healthy cell, and immune cell populations respectively. While some parameter values have been taken from literature, as noted below, others have been estimated (marked with est.) in order to showcase the possible dynamics of our system. Because the focus of our work is to examine the mathematical implications of the model, we acknowledge that some of our parameters are not associated with experimental data [4].

3 Basic Competition Submodel

We begin by analyzing the basic dynamics of cancer stem cells, tumor cells, and healthy cells in the absence of immune cells and excess estrogen ($I=0$ and $E=0$):

$$\begin{aligned}\frac{dC}{dt} &= k_1 C \left(1 - \frac{C}{M_1}\right) \\ \frac{dT}{dt} &= k_2 C \left(\frac{C}{M_1}\right) \left(1 - \frac{T}{M_2}\right) - n_1 T \\ \frac{dH}{dt} &= qH \left(1 - \frac{H}{M_3}\right) - \delta HT.\end{aligned}\tag{2}$$

Without the dynamics of the immune system and excess estrogen, the equation governing the dynamics for the CSC population is simply logistic. For this reason, it is clear that the CSC population will approach its carrying capacity, M_1 , given a positive initial population. Substituting $C = M_1$ into the tumor cell population reveals that tumor cells will approach an equilibrium population of

$$T^* = \frac{k_2 M_1 M_2}{k_2 M_1 + M_2 n_1}.$$

Once the tumor cell population is determined, we can substitute $T = T^*$ into the differential equation for healthy cells to study their dynamics. We see that $H' = 0$ when $H = 0$ or

$$H = M_3 - \frac{\delta M_3 T^*}{q} =: H^*.$$

If $\delta < \frac{q}{T^*}$, then the internal coexistence state (M_1, T^*, H^*) exists

and is globally asymptotically stable. On the other hand, if $\delta \geq \frac{q}{T^*}$, then there is no

coexistence state and the cancer persistence state $(M_1, T^*, 0)$ is globally asymptotically stable. Biologically, we can interpret this as follows. For $\delta < \frac{q}{T^*}$, the detrimental effect

interactions with tumor cells have on the healthy cell population is sufficiently low compared to the growth rate of healthy cells. In this case, healthy cells will coexist with the CSC and tumor cell populations. If this inequality is not met, the healthy and tumor cell interactions will cause the healthy cells to be eradicated, leaving only CSC and tumor cells. In either case, it is clear that for the above basic population dynamics, cancer will persist without an additional immune response. Before we consider the dynamics of the full model with an immune response, we shall next explore the role of excess estrogen on the basic competition submodel.

4 Immune-Free Submodel

We now include a constant infusion of excess estrogen in order to analyze how estrogen specifically impacts the cancer and healthy cell dynamics. With the exclusion of an immune response, the submodel we now consider is as follows:

$$\begin{aligned}
\frac{dC}{dt} &= k_1 C \left(1 - \frac{C}{M_1}\right) + \frac{p_1 C E}{a_1 + C} \\
\frac{dT}{dt} &= k_2 C \left(\frac{C}{M_1}\right) \left(1 - \frac{T}{M_2}\right) - n_1 T + \frac{p_2 T E}{q_2 + T} \\
\frac{dH}{dt} &= q H \left(1 - \frac{H}{M_3}\right) - \delta H T - \frac{p_3 H E}{a_3 + H} \\
\frac{dE}{dt} &= r - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E.
\end{aligned} \tag{3}$$

Attempting to solve for equilibria of (3) proves intractable. Biologically, given the dynamics of the basic competition submodel, incorporating excess estrogen without an immune response should lead to cancer persistence. To study the dynamics of the cancer persistence state, we use the method of the Localization of Compact Invariant Sets as developed in [10,11] along with standard comparison theory to derive conditions on parameters to guarantee a globally attractive cancer persistence state. The method of Localization of Compact Invariant Sets has been used as a tool to study cancer dynamics in [12,18–24,26]. Before we examine the global dynamics of this submodel, we present some preliminary results that can be found in the aforementioned references and are included here for the benefit of the reader.

Consider a nonlinear system of the form

$$\dot{\mathbf{x}} = f(\mathbf{x}), \tag{4}$$

where f is a smooth vector field and $\mathbf{x}$ is a state variable that in this analysis represents cell populations. Let h a continuously differentiable scalar function that is not a first integral of (4). Further, let $S(h) = \{\mathbf{x} | \nabla h \cdot f = 0\}$ and denote $h_{\inf} = \inf S(h)$ and $h_{\sup} = \sup S(h)$. We then define the localizing set of h to be $K(h) = \{\mathbf{x} | h_{\inf} \leq h(\mathbf{x}) \leq h_{\sup}\}$, and we call h a localizing function of the system (4). The following theorem in [26] will be utilized throughout the remainder of the paper.

Theorem 1

Given a localizing function h of the system (4), the localizing set $K(h)$ contains all compact invariant sets of (4).

Note that such compact invariant sets will include possible equilibrium points, limit cycles, homoclinic and heteroclinic orbits, and so on. Thus the identification of localizing sets provides insight into the possible long-term dynamics of the model. We next explore the global dynamics of (3) using the above machinery. More specifically, we establish sufficient conditions under which CSC and tumor cell populations will persist and healthy cell populations will tend to 0.

Theorem 2

Under the following hypotheses, (3) has a globally attractive cancer persistence state:

$$(H1) \ k_1 > k_2$$

$$(H2) \ r > \frac{q(\mu + d_1 + d_2 + d_3)(a_3 + M_3)}{p_3}$$

Proof—We begin by developing a localizing set for (3). Consider the localizing function $h_4 = E$. This gives

$$S(h_4) = \left\{ r - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E = 0 \right\}.$$

The directional derivative of h_4 along trajectories of (3) is zero when

$$E = \frac{r}{\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H}}.$$

Notice that

$$\frac{r}{\mu + d_1 + d_2 + d_3} \leq \frac{r}{\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H}} \leq \frac{r}{\mu},$$

which allows us to define

$$K(h_4) = \left\{ \frac{r}{\mu + d_1 + d_2 + d_3} \leq E \leq \frac{r}{\mu} \right\}.$$

We continue with another localizing function $h_1 = C$. We have

$$S(h_1) = \left\{ k_1 C \left(1 - \frac{C}{M_1} \right) + \frac{p_1 C E}{a_1 + C} = 0 \right\}.$$

The directional derivative of h_1 along trajectories of (3) is 0 when $C = 0$ or

$C = M_1 + \frac{M_1 p_1 E}{k_1(a_1 + C)}$. Using the upper bound derived above for E and a lower bound of 0 for

C , we see that the set $S(h_1) \cap K(h_4)$ is contained in the set defined by the following inequality:

$$M_1 + \frac{M_1 p_1 E}{k_1(a_1 + C)} \leq M_1 + \frac{M_1 p_1 r}{k_1 \mu a_1}.$$

Thus, we define

$$K(h_1) = \left\{ 0 \leq C \leq C^* := M_1 + \frac{M_1 p_1 r}{k_1 \mu a_1} \right\}.$$

In a similar fashion, letting $h_2 = T$ and $h_3 = H$, we find

$$S(h_2) = \left\{ k_2 C \left(\frac{C}{M_1} \right) \left(1 - \frac{T}{M_2} \right) - n_1 T + \frac{p_2 T E}{a_2 + T} = 0 \right\}$$

and

$$S(h_3) = \left\{ q H \left(1 - \frac{H}{M_3} \right) - \delta H T - \frac{p_3 H E}{a_3 + H} = 0 \right\}.$$

The directional derivatives of h_2 and h_3 along trajectories of (3) vanish when $n_1 T = k_2 C \left(\frac{C}{M_1} \right) \left(1 - \frac{T}{M_2} \right) + \frac{p_2 T E}{a_2 + T}$, and $H = 0$ or $H = \frac{M_3}{q} \left(q - \delta T - \frac{p_3 E}{a_3 + H} \right)$, respectively. Thus, the set $S(h_2) \cap K(h_1) \cap K(h_4)$ is contained in the set defined by the inequality:

$$\frac{k_2 C}{n_1} \left(\frac{C}{M_1} \right) \left(1 - \frac{T}{M_2} \right) + \frac{p_2 T E}{n_1 (a_2 + T)} \leq \frac{k_2 (C^*)^2}{M_1 n_1} + \frac{p_2 r}{n_1 \mu}.$$

This gives

$$K(h_2) = \left\{ 0 \leq T \leq T^* := \frac{k_2 (C^*)^2}{M_1 n_1} + \frac{p_2 r}{n_1 \mu} \right\}.$$

Lastly, by neglecting negative terms on the right side of $H = \frac{M_3}{q} \left(q - \delta T - \frac{p_3 E}{a_3 + H} \right)$, we obtain

$$K(h_3) = \{0 \leq H \leq M_3\}.$$

Thus, all compact invariant sets of (3) are contained within our localizing set $K_1 := K(h_1) \cap K(h_2) \cap K(h_3) \cap K(h_4)$.

Before arguing that K_1 is absorbing, we note that

$$\frac{dE}{dt} = r - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E \leq r - \mu E.$$

This comparison gives that trajectories of (3) will enter the following set in finite time:

$\{E \leq \chi \frac{r}{\mu}\}$, where $\chi > 1$. Utilizing this new bound on E , we now argue that K_1 is absorbing by considering the candidate Lyapunov function $V_1 = C + T + H + E$. Letting f represent the vector field associated with (3), we have

$$\begin{aligned} \nabla V_1 \cdot f \leq & -\frac{(k_1 - k_2)}{M_1} \left(C - \frac{k_1 M_1}{2(k_1 - k_2)} \right)^2 - \frac{k_2 C^2 T}{M_1 M_2} - n_1 T - \frac{q}{M_3} \left(H - \frac{M_3}{2} \right)^2 \\ & - \delta H T - \frac{p_3 H E}{a_3 + H} - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E + \sigma_1, \end{aligned}$$

where $\sigma_1 = \frac{k_1^2 M_1}{4(k_1 - k_2)} + \frac{M_3 q}{4} + \frac{p_1 \chi r}{\mu} + \frac{p_2 \chi r}{\mu} + r$. With the assumption (H_1) , for sufficiently large (C, T, H, E) , we have $\nabla V_1 \cdot f < 0$. Thus, all trajectories of (3) are bounded and will enter K_1 in finite time.

The next step in showing the existence of a globally attractive cancer persistence state is to argue that the plane $H = 0$ is attractive. Consider

$$\begin{aligned} \nabla h_3 \cdot f &= H \left(q - \frac{qH}{M_3} - \delta T - \frac{p_3 E}{a_3 + H} \right) \\ &\leq H \left(q - \frac{p_3 r}{(\mu + d_1 + d_2 + d_3)(a_3 + M_3)} \right). \end{aligned}$$

Under assumption (H_2) , $\nabla h_3 \cdot f < 0$ and thus $H = 0$ is attractive.

We conclude our argument for cancer persistence by ensuring that C and T stay bounded away from 0. Note that

$$\frac{dC}{dt} \geq k_1 C \left(1 - \frac{C}{M_1} \right).$$

Thus solution trajectories will enter the set $\{M_1 - C - C^*\}$ in finite time. Likewise, we can compare the population dynamics of T as follows:

$$\frac{dT}{dt} \geq k_2 M_1 \left(1 - \frac{T}{M_2} \right) - n_1 T.$$

We similarly see that trajectories of the system will enter the set $\left\{ \frac{k_2 M_1 M_2}{k_2 M_1 + n_1 M_2} \leq T \leq T^* \right\}$ in finite time.

Hence, for (3), under assumptions $(H_1) - (H_2)$, we have shown that the localizing set K_1 is absorbing. Moreover, we know that healthy cell populations tend to zero, while CSC and tumor cell populations stay bounded away from zero. Thus, we conclude that trajectories approach a globally attractive cancer persistence state.

5 Full Model

We now turn our attention to the study of the full model (1) and seek the possibility of a tumor clearance state with the inclusion of the immune response. As with the immune-free

submodel, a complete local stability analysis is infeasible. However, the methods presented in Theorem 2 will also prove useful in establishing the following main theorem of our paper:

Theorem 3

Assume (H1). Then under the following additional hypotheses, system (1) has a globally attractive cure state:

$$(F1) \ n_2 > \rho,$$

$$(F2) \ s > \left(\frac{p_1 r}{a_1 u} + k_1 \right) \left(\frac{n_2 + \gamma_3 T^* + u}{\gamma_1} \right),$$

$$(F3) \ s > \left(\frac{p_2 r}{a_2 u} - n_1 \right) \left(\frac{n_2 + \gamma_3 T^* + u}{\gamma_2} \right),$$

$$(F4) \ a_3 q \mu > p_3 r,$$

where T^* is defined as in the proof of Theorem 2.

Proof—Consider the localizing functions $h_1 = C$, $h_2 = T$, $h_3 = H$, $h_4 = E$, and $h_5 = I$. We first note that the same localizing sets used in Theorem 2 also bound the compact invariant sets of system (1), and we thus take $K(h_1), K(h_2), K(h_3)$, and $K(h_4)$ as above. Continuing with $h_5 = I$, we have

$$S(h_5) = \left\{ s + \frac{\rho IT}{\omega + T} - \gamma_3 IT - n_2 I - \frac{uIE}{v + E} = 0 \right\}.$$

The directional derivative of h_5 along trajectories of (1) is 0 when

$s = n_2 I - \frac{\rho IT}{\omega + T} + \gamma_3 IT + \frac{uIE}{v + E}$. Thus, the set $S(h_5) \cap K(h_1) \cap K(h_2) \cap K(h_4)$ is contained in the set defined by the inequality:

$$n_2 I - \frac{\rho IT}{\omega + T} + \gamma_3 IT + \frac{uIE}{v + E} \leq I(n_2 + \gamma_3 T^* + u).$$

Moreover, we see that

$$n_2 I - \frac{\rho IT}{\omega + T} + \gamma_3 IT + \frac{uIE}{v + E} \geq I(n_2 - \rho).$$

From this, we obtain

$$K(h_5) = \left\{ I^* : \frac{s}{n_2 + \gamma_3 T^* + u} \leq I \leq \frac{s}{n_2 - \rho} \right\}.$$

Notice this set is well-defined due to assumption (F1). Thus, in the case of the full model, we take our localizing set to be $K_2 = K(h_1) \cap K(h_2) \cap K(h_3) \cap K(h_4) \cap K(h_5)$.

As in the proof of Theorem 2, we now argue that K_2 is absorbing by considering the candidate Lyapunov function $V_2 = C + T + H + I + E$. Using the same comparison on the dynamics of E as in the proof of Theorem 2, we have trajectories of (1) entering in finite time the set $\{E \leq \chi \frac{r}{\mu}\}$, where $\chi > 1$. Letting f represent the vector field associated with (1), we have

$$\begin{aligned} \nabla V_2 \cdot f = & -\frac{(k_1 - k_2)}{M_1} \left(C - \frac{k_1 M_1}{2(k_1 - k_2)} \right)^2 - \gamma_1 IC - \frac{k_2 C^2 T}{M_1 M_2} - n_1 T - \gamma_2 IT \\ & - \frac{q}{M_3} \left(H - \frac{M_3}{2} \right)^2 - \delta HT - \frac{p_3 HE}{a_3 + H} - (n_2 - \rho) I - \frac{\rho \omega I}{\omega + T} - \gamma_3 IT \\ & - \frac{uIE}{v + E} - \left(\mu + \frac{d_1 C}{a_1 + C} + \frac{d_2 T}{a_2 + T} + \frac{d_3 H}{a_3 + H} \right) E + \sigma_2, \end{aligned}$$

where $\sigma_2 = \frac{k_1^2 M_1}{4(k_1 - k_2)} + \frac{M_3 q}{4} + r + \frac{p_1 \chi r}{\mu} + \frac{p_2 \chi r}{\mu} + s$. With assumptions (H1) and (F1), for sufficiently large (C, T, H, I, E) , we have $\nabla V_2 \cdot f < 0$. Thus, all trajectories of (1) are bounded and will enter K_2 in finite time.

The next step in showing the existence of a globally attractive cure state is to argue that the plane $C = 0$ is attractive. Consider

$$\begin{aligned} \nabla h_1 \cdot f &= C \left(k_1 - \frac{k_1 C}{M_1} - \gamma_1 I + \frac{p_1 E}{a_1 + C} \right) \\ &\leq C \left(k_1 - \gamma_1 I^* + \frac{p_1 r}{a_1 \mu} \right). \end{aligned}$$

Under assumption (F2), $\nabla h_1 \cdot f < 0$ and thus $C = 0$ is attractive.

In order to conclude tumor clearance, it remains to show that the tumor cell populations are also decaying to zero and the healthy cell populations are bounded away from zero. To achieve this, we next show that $T = 0$ is attractive. Since $C = 0$ is attractive, we substitute $C = 0$ into (1), examine $\nabla h_2 \cdot f$, and note that under assumption (F3) we have

$$\begin{aligned} \nabla h_2 \cdot f &= T \left(-n_1 - \gamma_2 I + \frac{p_2 E}{a_2 + T} \right) \\ &\leq T \left(-n_1 - \gamma_2 I^* + \frac{p_2 r}{a_2 \mu} \right) \\ &< 0. \end{aligned}$$

To conclude our proof, we begin by noting that under assumption (F4), the equilibrium point of (1)

$$\left(0, 0, 0, \frac{s(r + \mu v)}{n_2 r + r u + n_2 \mu v}, \frac{r}{\mu} \right)$$

is locally unstable due to a positive eigenvalue of the Jacobian matrix obtained by linearizing system (1). Moreover, substituting $T = 0$, we have the following comparison:

$$\begin{aligned}\frac{dH}{dt} &= qH\left(1 - \frac{H}{M_3}\right) - \frac{p_3 H E}{a_3 + H} \\ &\geq qH\left(1 - \frac{H}{M_3}\right) - \frac{p_3 r H}{\mu(a_3 + H)}.\end{aligned}$$

To study the behavior of the above differential inequality, we consider the dynamics of the associated differential equation

$$\frac{dH}{dt} = qH\left(1 - \frac{H}{M_3}\right) - \frac{p_3 r H}{\mu(a_3 + H)}. \quad (5)$$

Rewriting (5) as

$$\frac{dH}{dt} = \frac{H}{M_3 \mu(a_3 + H)} \left(-q\mu H^2 + (M_3 - a_3)q\mu H + M_3(q\mu a_3 - p_3 r) \right),$$

we see that (5) has a globally stable positive equilibrium solution under (F4). Using standard comparison theory, we conclude that healthy cell populations of (1) are bounded away from zero.

In summary, for (1) we show the existence of a globally compact attracting region in which the CSC and tumor cell populations are approaching zero and the healthy cell populations are bounded away from zero. Thus we conclude that under assumptions (H1) – (H2) and (F1) – (F4), (1) has a globally attractive cure state.

Note: Similar stability analysis as in the full model can be conducted for an estrogenfree submodel in which $E \equiv 0$. We find a globally attractive cure state depending on the parameter s satisfying the condition:

$$s > \frac{k_1(n_2 + \gamma_3 \hat{T})}{\gamma_1},$$

where $\hat{T} = \frac{k_2 M_1 M_2}{M_2 n_1 + k_2 M_1}$. Recall that s is the source rate of immune cells, given in immune cells per day. If we compare this s condition to condition (F2) for the full system, it can be shown through simple algebraic manipulation that $\hat{T} \leq T^*$, which implies that the necessary value for s in the estrogen-free submodel is significantly lower than the condition on s in the full model. This supports the claim that estrogen assists the development of breast cancer and hinders the effectiveness of the immune system [14].

We next provide numerical simulations below to further illustrate the differences between the estrogen-free submodel and full model.

6 Numerical Simulations

Figure 1 compares the behavior of the estrogen-free submodel and the full model over time with cancer stem cells and tumor cells starting at one-third of their carrying capacities. Healthy cells begin at their carrying capacity. Estrogen, when included, begins at 2000 pg/mL. The first row of simulations is carried out with $s = 1.3 \times 10^4$, which is the natural replenishing rate of immune cells. The second row of simulations is carried out with $s = 1.3 \times 10^6$, which can be thought of as the infusion of immune cells through immunotherapy. All other parameter values are taken from Table 1.

As demonstrated in the top row of Figure 1, the natural source rate of immune cells is not sufficient to eradicate cancer in either the estrogen-free or full models. However, we can observe that the full system reaches a cancer persistence state at a quicker rate than the estrogen-free submodel. On the other hand, when a sufficient amount of immunotherapy is introduced in the second row, the estrogen-free submodel is able to completely eradicate cancer stem cells. In contrast, cancer stem cells are still present in the full system with the same amount of immunotherapy. These numerical simulations support the assumption that excess estrogen increases the likelihood of cancer persistence.

The bifurcation diagram in Figure 2 further demonstrates the relationship between the source rate of immune cells, s , and the steady-state population of cancer stem cells in both the full system and the estrogen-free submodel. As shown, the steady-state population of cancer stem cells approaches zero in the estrogen-free submodel at an s value of about one-third that of the value necessary for cancer clearance in the full system. This implies that excess estrogen increases the difficulty of eradicating cancer, but a sufficiently high immune response s will allow for a stable cure state to be achieved in both the estrogen-free submodel and the full model.

7 Discussion

Our model extends previous models of breast cancer development and immune- cancer competition dynamics to include the cancer stem cell hypothesis and the effects of excess estrogen. We explore the global dynamics of basic competition and immune-free submodels, as well as the full system. Analysis of the basic competition submodel confirms the existence of a globally attracting cancer persistence state when ignoring the body's natural immune response. Furthermore, when the effects of excess estrogen are included in the immune-free submodel, a threshold estrogen infusion rate is established beyond which healthy epithelial cells cannot survive longterm. The existence of a globally attractive cancer persistence state in this case is to be expected when the body's immune response is suppressed.

The analysis of the full system highlights the significance of the natural source rate of immune cells, s , produced daily by the body. In contrast to [14], we determine that the full system possesses a globally attractive cure state given a sufficiently large immune response. The biologically feasible value of s chosen from the literature does not meet this condition, implying the necessity of immune assistance through the introduction of immunotherapy. It

is interesting to note that the required threshold on s (source rate of immune cells) depends on both r and p_1 (excess estrogen infusion rate and the rate at which estrogen encourages CSC proliferation, respectively). Thus, our model supports the notion that high levels of excess estrogen along with the tendency of estrogen to increase cancer stem cell proliferation require significantly enhanced immune responses to achieve tumor clearance. While the conditions on s presented here are sufficient, future work should include finding necessary bounds for s to determine minimal immune responses required to achieve a cure state. These bounds may be further improved by determining more biologically realistic parameters as more conclusive studies on the effects of estrogen on breast cancer become available.

We also note the analysis of the immune-free submodel and full model conducted above showcases the flexibility and usefulness of the method of localization of compact invariant sets developed in [10,11]. In previous studies, Starkov and coauthors [20, 23, 24, 26] have employed this method on simpler nonlinear systems of cancer dynamics for which a thorough study of equilibrium states was feasible. Here, the complexity of systems (3) and (1) prohibits the identification of specific globally asymptotically stable equilibrium solutions, yet the method still allows for the creation of sufficient conditions on model parameters to guarantee the existence of general cancer persistence and cure states, respectively. We are furthermore able to establish bounds for compact global attractors of these systems, and we leave open the resolution of the dynamics on the remaining subsystems (3) with $H=0$ and (1) with $C=T=0$. We are hopeful that the method presented here could be employed on other biologically complex models which have not previously admitted sufficient global analysis.

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References

1. Abernathy, Kristen; Burke, Jeremy. Modeling the Treatment of Glioblastoma Multiforme And Cancer Stem Cells with Ordinary Differential Equations. Computational and Mathematical Methods in Medicine. 2016; doi: 10.1155/2016/1239861
2. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective Identification of Tumorigenic Breast Cancer Cells. Proceedings of the National Academy of Sciences of the United States of America. 100(7):3983–3988.2003; [PubMed: 12629218]
3. De Pillis LG, Radanskaya A. A Mathematical Tumor Model with Immune Resistance and Drug Therapy: An Optimal Control Approach. Journal of Theoretical Medicine. 3:2–100. 79–100.2001;
4. De Pillis LG, Gu W, Fister Kr, Head T, Maples K, Murugan A, Neal T, Yoshida K. Chemotherapy for Tumors: An Analysis of the Dynamics and a Study of Quadratic and Linear Optimal Controls. Mathematical Biosciences. 209:1–315. 292–315.2006;
5. DePillis FG, Gu W, Radanskaya AE. Mixed Immunotherapy and Chemotherapy of Tumors: Modeling, Applications and Biological Implications. Journal of Theoretical Biology. 238:4–862. 841–862.2006;

6. De Pillis, Lisette; Radunskaya, Ami; Wiseman, Charles. A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth. *Cancer Research*. 65:17–7958. 7950–7958.2005;
7. Enderling, Heiko; Chaplain, Mark AJ; Anderson, Alexander RA; Vaidya, Jayant S. A mathematical model of breast cancer development, local treatment and recurrence. *Journal of Theoretical Biology*. 246:2–259. 245–259.2007;
8. Kang, Kyung-Sun; Morita, Ikue; Cruz, Angela; Jeon, Young Jin; Trosko, James E; Chang, Chi-Cheng. Expression of Estrogen Receptors in a Normal Human Breast Epithelial Cell Type with Luminal and Stem Cell Characteristics and its Neoplastically Transformed Cell Lines. *Carcinogenesis*. 18:2–257. 251–257.1997;
9. Kareva, Irina; Berezovskaya, Faina. Cancer Immunoediting: A Process Driven by Metabolic Competition as a Predator-Prey-Shared Resource Type Model. *Journal of Theoretical Biology*. 380:463–472.2015; [PubMed: 26116366]
10. Krishchenko AP. Localization of invariant compact sets of dynamical systems. *Differential Equations*. 41:1669–1676.2005;
11. Krishchenko AP, Starkov KE. Localization of compact invariant sets of the Lorenz system. *Physics Letters A*. 353:383–388.2006;
12. Krishchenko AP, Starkov KE. On the global dynamics of a chronic myelogenous leukemia model. *Communications in Nonlinear Science and Numerical Simulation*. 33:174–183.2016;
13. McDuffie, Michelle. A Hormone Therapy Model For Breast Cancer Using Linear Cancer Networks. *Rose-Hulman Undergraduate Mathematics Journal*. 15(1):142–156.2014;
14. Mufudza, Chipo; Sorofa, Walter; Chiyaka, Edward. Assessing the Effects of Estrogen on the Dynamics of Breast Cancer. *Computational and Mathematical Methods in Medicine*. 2012; doi: 10.1155/2012/473572
15. Nordqvist, Christian. Breast Cancer: Causes, Symptoms and Treatments. *Medical News Today*. 2016
16. Pinho STR, Freedman HI, Nani F. A Chemotherapy Model for the Treatment of Cancer with Metastasis. *Mathematical and Computer Modelling*. 36:773–803.2002;
17. Robertson-Tessi, Mark; El-Kareh, Ardith; Gorielly, Alain. A mathematical model of tumor-immune interactions. *Journal of Theoretical Biology*. 294:56–73.2012; [PubMed: 22051568]
18. Starkov KE, Bunimovich-Mendrazitsky S. Dynamical properties and tumor clearance conditions for a nine-dimensional model of bladder cancer immunotherapy. *Mathematical Biosciences and Engineering*. 13:1059–1075.2016; [PubMed: 27775397]
19. Starkov KE, Coria LN. Global dynamics of the Kirschner-Panetta model for the tumor immunotherapy. *Journal of Nonlinear Analysis Series B: Real World Applications*. 14:1425–1433.2013;
20. Starkov, Konstantin E; Krishchenko, Alexander P. On the Global Dynamics of One Cancer Tumour Growth Model. *Communications in Nonlinear Science and Numerical Simulations*. 19:1486–1495.2014;
21. Starkov KE, Plata-Ante C. On the global dynamics of the cancer AIDS-related mathematical model. *Kybernetika*. 50:563–579.2014;
22. Starkov KE, Pogromsky AY. On the global dynamics of the Owen-Sherratt model describing the tumor-macrophage interactions. *International Journal of Bifurcation and Chaos*. 23:1350020.2013;
23. Starkov, Konstantin E; Villegas, Antonio. On Some Dynamical Properties of a Seven-Dimensional Cancer Model with Immunotherapy. *International Journal of Bifurcation and Chaos in Applied Sciences and Engineering*. 2014; doi: 10.1142/S0218127414500205
24. Starkov, Konstantin E; Gomboa, Diana. Localization of Compact Invariant Sets and Global Stability in Analysis of One Tumor Growth Model. *Mathematical Methods in Applied Sciences*. 37:2854–2863.2014;
25. Valentine, Bruttel; Wischhusen, Jörg. Cancer Stem Cell Immunology: Key to Understanding Tumorigenesis and Tumor Immune Escape? *Frontiers in Immunology*. 5:1–13.2014; [PubMed: 24474949]
26. Valle, Paul A; Starkov, Konstantin E; Coria, Luis N. Global Stability and Tumor Clearance Conditions for a Cancer Chemotherapy System. *Communications in Nonlinear Science and Numerical Simulation*. 40:206–215.2016;

27. Villasana, Minaya; Radunskaya, Ami. A Delay Differential Equation Model for Tumor Growth. *Journal of Mathematical Biology*. 47:3–294. 270–294.2003;
28. Wu, Chung-Hsiu; Motohashi, Toru; Abdel-Rahman, Hany; Flickinger, George; Mikhail, George. Free and Protein-Bound Plasma Estradiol-17 β During the Menstrual Cycle. *The Journal of Clinical Endocrinology*. 43(2):436–445.2009;

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Fig. 1.
The Role of Excess Estrogen in Cancer Persistence

Fig. 2.
Bifurcation Diagram

Table 1

Parameter List

Parameter	Symbol	Value	Units	Ref.
Normal rate of division for C cells	k_1	.75	day ⁻¹	[17]
Normal rate of division for T cells	k_2	.514	day ⁻¹	[6]
Normal rate of division for H cells	q	.70	day ⁻¹	[14]
Carrying capacity of C cells	M_1	2.27×10^6	cells _{C}	[6]
Carrying capacity of T cells	M_2	2.27×10^7	cells _{T}	[6]
Carrying capacity of H cells	M_3	2.5×10^7	cells _{H}	[6]
Cancer stem cell death rate due to immune cell response	γ_1	3×10^{-7}	cell _{I} ⁻¹ day ⁻¹	[est]
Tumor cell death rate due to immune cell response	γ_2	3×10^{-6}	cell _{I} ⁻¹ day ⁻¹	[est]
Immune cell death rate due to tumor cell response	γ_3	1×10^{-7}	cell _{I} ⁻¹ day ⁻¹	[5]
Rate at which estrogen helps to proliferate cancer stem cells	p_1	600	cell _{C} day ⁻¹ (pg/mL) ⁻¹	[est]
Rate at which estrogen helps to proliferate tumor cells	p_2	0	cell _{T} day ⁻¹ (pg/mL) ⁻¹	[est]
Rate at which healthy cells are lost to DNA mutation by estrogen presence	p_3	100	cell _{H} day ⁻¹ (pg/mL) ⁻¹	[est]
Number of C cells at which the rate of absorption is at half its maximum	a_1	$\frac{1}{2} M_1$	cells _{C}	[est]
Number of T cells at which the rate of absorption is at half its maximum	a_2	$\frac{1}{2} M_2$	cells _{T}	[est]
Number of H cells at which the rate of absorption is at half its maximum	a_3	$\frac{1}{2} M_3$	cells _{H}	[est]
Normal death rate of tumor cells	n_1	.01	day ⁻¹	[9]
Normal death rate of immune cells	n_2	.29	day ⁻¹	[14]
Healthy cell death rate due to competition with tumor cells	δ	6×10^{-8}	day ⁻¹ cell _{T} ⁻¹	[est]
Source rate of immune cells	s	1.3×10^4	cell _{I} day ⁻¹	[27]
Immune cell response rate	ρ	.20	day ⁻¹	[27]
Immune cell threshold	ω	3×10^5	cells _{T}	[3]
Rate of immune suppression by estrogen	u	.20	day ⁻¹	[est]
Estrogen threshold	v	400	pg mL ⁻¹	*
Continuous infusion of estrogen	r	2000	pg mL ⁻¹ day ⁻¹	*
Washout rate of estrogen by the body	μ	.97	day ⁻¹	[28]
Absorption rate of estrogen by cancer stem cells	d_1	.01	day ⁻¹	[est]
Absorption rate of estrogen by tumor cells	d_2	.01	day ⁻¹	[est]
Absorption rate of estrogen by healthy cells	d_3	.01	day ⁻¹	[est]

* These values have been approximated from accepted birth control dosages.