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Modeling breast cancer and its optimal control

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Abstract: Breast cancer is the most common cancer among womenfolk, impacting above 1.5 million women every year, and correspondingly roots the utmost number of cancer-related deaths among women. In 2015, 570,000 women died from the disease that is about 15% of all cancer deaths amongst womenfolk. Although the disease rates are higher amongst womenfolk in more industrialized regions, rates are increasing in nearly every region globally. In this paper, a model of the disease is developed. Conditions are derived for the existence of disease free equilibrium. Stability analysis of the model shows that that disease free equilibrium is both locally asymptotically stable and globally asymptotically stable. Optimal control theory is applied to the model and Pontrygain's Maximum Principle is applied for analysis of the control. To this end, three control strategies were incorporated into disease transmission model. The impact of using possible combinations of the three control strategies was investigated.

Keywords: Breast cancer; Optimal control; Modeling

Introduction

Cancer is a comprehensive term for a class of infections branded by irregular cells that develop and attack healthy cells in the body. It is a genomic disease (Michor et al., 2004), which encompasses dynamic abnormalities in the genome (Bardelli et al., 2001). Though environmental and other non-genetic dynamics have parts in various phases of tumor genesis. It is generally acknowledged that the infectivity arises because of mutations in the disease susceptibility genes. The genes are in each cell's nucleus, which acts as the control room of every cell (Feng et al., 2018). Its occurrence has been on the upsurge due to an aging and rising global population, as well as the choices of cancer-causing lifestyle and behaviour such as alcohol, smoking, hormone replacement therapy (HRT) (Oke et al., 2018a). The disease of epithelial tissues is typically believed to progress gradually over several years (Loeb et al., 2003).

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Breast cancer starts in the cells of the breast as a group of cancer cells that can then invade surrounding tissues or spread (metastasize) to other areas of the body. The ailment affects both genders (Lukong, 2017). It arises once malignant tumors grow in the breast. These cells can spread by breaking away from the original tumor and entering blood vessels or lymph vessels, which branch into tissues throughout the body. When cancer cells travel to other parts of the body and begin damaging other tissues and organs, the process is called metastasis (Lukong, 2017). It is the utmost common cancer type disturbing womenfolk, representing 29% of entirely fresh cancer cases in United States womenfolk. Also common in womenfolk in western world in general (Jong et al., 2002). In its growth, hereditary and environmental dynamics also play a part with family history being the utmost vital factor for influential breast cancer threat. This threat is a function of the number of kinsfolks affected with the disease, the degree of affiliation to these relatives, and their age at diagnosis of the disease (Claus, 1995).

Breast cancer that are inherited accounts for 5-9% of all its cases (Ford & Easton, 1995). It was projected that the combination of The Breast Cancer Gene type 1 (BRCA1) and The Breast Cancer Gene type 2 (BRCA2) gene mutations was responsible for approximately 80% of the families with hereditary breast cancer (Jong et al., 2002). These estimates, however, may be too high owing to the way patients are selected, namely on the basis of a pronounced family history of the disease. However, another estimates put this risk at about 30% (Easton, 1997). Mutations of the BRCA1 and BRCA2 genes do not explain the occurrence of breast cancer in every breast cancer prone family.8 At least one other major breast cancer susceptibility gene is proposed to exist (Jong et al., 2002). In addition, a number of rare genetic syndromes are associated with high breast cancer risk. Together, these rare syndromes account for less than 1% of all hereditary breast cancers. Many literatures investigated the causes, problems and other factors associated with the disease (Easton, 1997; Oke et al., 2018; Oke at al., 2018). In the present work, the innovations with respect to the existing literature are modeling the disease considering the stages of the disease and population-based.

Method

The model formulation

The total human population at time t, denoted by $N(t)$, is sub divided into the following sub-populations of susceptible individuals $S(t)$, those exposed to the disease as a result avoidable risk factors $E_1(t)$, those exposed to the disease as a result non-avoidable risk factors $E_2(t)$, and those exposed to the disease as a result both avoidable and non-avoidable risk factors $E_{12}(t)$. Others includes the stages those individuals at stage 1 of the disease $I_1(t)$, those in stage 2 $I_2(t)$, those individuals in stage 3 $I_2(t)$, and those in stage 4 $I_4(t)$. So that $N(t)=S(t)+E_1(t)+E_2(t)+E_{12}(t)+I_1(t)+I_2(t)+I_3(t)+I_4(t)$.

The susceptible population $S(t)$is increased by a steady inflow into the population at rate Λ. Susceptible individuals are exposed either through avoidable risk factors $E_1(t)$ which includes: a sedentary lifestyle, lack of physical activity, poor diet, being overweight or obese: drinking alcohol, radiation to the chest and combined hormone replacement therapy (HRT) at a rate τ_1. Susceptible individuals are also through non-avoidable risk factors $E_2(t)$ which include: Gender, age, race, family history and genetic factors, personal health history, menstrual and reproductive history, dense breast tissue at a rate τ_2. The third exposed class $E_{12}(t)$is due the combination of avoidable and non-avoidable risk factors at a rate τ_3. The exposed classes $E_1(t), E_2(t)$ *and* $E_{12}(t)$ progress to the stage 1 $I_1(t)$of the infectivity at a rate β_1, β_2 *and* β_3 respectively. And the classes decreases due natural death at a rate μ. The stage 1 $I_1(t)$ decreases due to natural death at a rate

μ and progresses to stage 2 of the infectivity at a rate α_1. The stage 2 $I_2(t)$ decreases due to natural death at a rate μ and progresses to stage 3 of the infectivity at a rate α_2. The stage 3 $I_3(t)$ decreases due to natural death at a rate μ and progresses to stage 4 of the infectivity at a rate α_3. The stage 4 $I_4(t)$ decreases due to natural death at a rate μ and death due to infectivity at a rate μ_0. The above mentioned assumptions and description above give rise to the following

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - (\tau_1 E_1(t) + \tau_2 E_2(t) + \tau_3 E_{12}(t) + \mu)S(t) \\
\frac{dE_1(t)}{dt} &= \tau_1 E_1(t)S(t) - (\beta_1 + \mu)E_1(t) \\
\frac{dE_2(t)}{dt} &= \tau_2 E_2(t)S(t) - (\beta_2 + \mu)E_2(t) \\
\frac{dE_{12}(t)}{dt} &= \tau_3 E_{12}(t)S(t) - (\beta_3 + \mu)E_{12}(t) \\
\frac{dI_1(t)}{dt} &= \beta_1 E_1(t) + \beta_2 E_2(t) + \beta_3 E_{12}(t) - (\mu + \alpha_1)I_1(t) \\
\frac{dI_2(t)}{dt} &= \alpha_1 I_1(t) - (\mu + \alpha_2)I_2(t) \\
\frac{dI_3(t)}{dt} &= \alpha_2 I_2(t) - (\mu + \alpha_3)I_3(t) \\
\frac{dI_4(t)}{dt} &= \alpha_3 I_3(t) - (\mu + \mu_0)I_4(t)
\end{aligned} \tag{1}$$

The associated model variables and parameters are described in Table 1 and 2.

Model basic properties

In this section, we study the basic results of solutions of model system (1), which are vital in the proofs of stability results.

Lemma 1 The closed set

$$\Omega = \left\{ (S, E_1, E_2, E_{12}, I_1, I_2, I_3, I_4) \in \Re^8 : S + E_1 + E_2 + E_{12} + I_1 + I_2 + I_3 + I_4 \leq \frac{\Lambda}{\mu} \right\}$$

is positively-invariant and attracting with respect to the basic model (1) (Abdullahi et al., 2017).

Proof: Adding the model equations (1) yields:

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \mu_0 I_4(t) \tag{2}$$

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \mu_0 I_4(t) \leq \Lambda - \mu N(t) \tag{3}$$

Applying the theorem on differential inequality and separating the variables of equation (3) this yields:

$$\frac{dN(t)}{\Lambda - \mu N(t)} \leq dt \tag{4}$$

Integrating both sides of equation (4) gives

$$\int \frac{dN(t)}{\Lambda - \mu N(t)} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu} In(\Lambda - \mu N(t)) \leq t + c$$

$$\Rightarrow In(\Lambda - \mu N(t)) \leq -\mu(t + c)$$

Therefore,

$$(\Lambda - \mu N(t)) \leq Ae^{-\mu(t+c)} \tag{5}$$

Where A is constant. Using the initial condition

$$N(t) = N(0)$$

Yields,

$$A = \Lambda - \mu N(0) \tag{6}$$

Substituting equation (5) into (6) gives

$$(\Lambda - \mu N(t)) \leq (\Lambda - \mu N(0))e^{-\mu(t+c)} \tag{7}$$

Making $N(t)$ the subject in (7) gives

$$N(t) \leq \frac{\Lambda}{\mu} - \left[\frac{\Lambda - \mu N(0)}{\mu}\right] e^{-\mu t} \tag{8}$$

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}\left[1 - e^{-\mu t}\right] \tag{9}$$

Sine $\frac{dN}{dt} \leq \Lambda - \mu N(t)$

Since $\frac{dN}{dt} \leq \Lambda - \mu N(t)$t follows that $\frac{dN}{dt} < 0$ if $N > \frac{\Lambda}{\mu}$

Thus, using the standard comparison theorem (Abdullahi et al., 2015) it has been shown that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}\left[1 - e^{-\mu t}\right].$$

In particular, $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$. Thus, Ω is positively-invariant. Moreover, if and $N(t) > \frac{\Lambda}{\mu}$ and then either the solution enter Ω in finite time, or $N(t)$ approaches $\frac{\Lambda}{\mu}$, and the exposed and infected variables $E_1, E_2, E_{12}, I_1, I_2, I_3$ *and* I_4 approached zero. Hence Ω is attracting (that is, all solutions in $\Re_+^8$ eventually enter Ω).

Thus, in Ω, the model is well-posed epidemiologically and mathematically. Hence it is sufficient to study the dynamics of the model in Ω (Abdullahi et al., 2015).

Disease Free Equilibrium (DFE)

The *breast cancer* model (1) has a DFE, obtained by setting the right-hand sides of the equations in the model (1) equal to zero, given by the following;

$$E_0 = (S^*, E_1^*, E_2^*, E_{12}^*, I_1^*, I_2^*, I_3^*, I_4^*) = \left(\frac{\Lambda}{\mu}, 0,0,0,0,0,0,0\right)$$

This represents the state where there exist no infectivity in a community and it is acknowledged as the disease-free equilibrium point (*DFE*).

The linear stability of the disease can be established using the next generation operator method (Abdullahi et al., 2015) on the model equation (1), the matrix *F* and *V*, for the new infection terms and the remaining transfer terms, are respectively given by;

$$F=\begin{bmatrix} \frac{\tau_1\Lambda}{\mu} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\tau_2\Lambda}{\mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\tau_3\Lambda}{\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V=\begin{bmatrix} \beta_1+\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_2+\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_3+\mu & 0 & 0 & 0 & 0 \\ -\beta_1 & -\beta_2 & -\beta_3 & \mu+\alpha_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_1 & \mu+\alpha_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_2 & \mu+\alpha_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\alpha_3 & \mu+\mu_0 \end{bmatrix}$$

the basic reproduction number of the model equation (1) denoted by $\Re_0$, is given by

$$\Re_0=\frac{\tau_1\Lambda}{\mu(\beta_1+\mu)}+\frac{\tau_2\Lambda}{\mu(\beta_2+\mu)}+\frac{\tau_3\Lambda}{\mu(\beta_3+\mu)}$$

It follows that the exposed class to avoidable risk factor basic reproduction number of the model equation (1) denoted by $\Re_{0E_1}$, is given by

$$\Re_{0E_1}=\frac{\tau_1\Lambda}{\mu(\beta_1+\mu)},$$

the exposed class to non-avoidable risk factor basic reproduction number denoted by $\Re_{0E_2}$ is;

$$\Re_{0E_2}=\frac{\tau_2\Lambda}{\mu(\beta_2+\mu)}$$

and exposed class to both avoidable and non-avoidable risk factor basic reproduction number denoted by $\Re_{0E_{12}}$ is;

$$\Re_{0E_2}=\frac{\tau_3\Lambda}{\mu(\beta_3+\mu)}$$

Furthermore, using Theorem 2 of (Abdullahi et al., 2015) the following result is established.

Theorem: DFE of the model (1), given by $\Re_0$ is locally asymptotically stable (LAS) if $\Re_0<1$ and unstable if $\Re_0>1$.

Existence of endemic equilibrium point (EEP)

Next, conditions for the existence of endemic equilibria for the model (1) are explored. Let

$$\varepsilon_1=\left(S^{**},E_1^{**},E_2^{**},E_{12}^{**},I_1^{**},I_2^{**},I_3^{**},I_4^{**}\right)$$

be the arbitrary endemic equilibrium of model (1), in which at least one of the infected components of the model is non-zero. Setting the right-hand sides of the equations in (1) to zero gives the following expressions

Model system (1) has two possible endemic equilibria: those exposed to non-avoidable risk factors endemic equilibrium and the equilibrium where avoidable and non-avoidable risk factors co-exist, herein referred to as the interior equilibrium point.

$$S^{**} = \frac{\beta_2 + \mu}{\tau_2},$$

$$E_1^{**} = 0$$

$$E_2^{**} = \frac{\Lambda\tau_2 - \beta_2\mu - \mu^2}{\tau_2(\beta_2 + \mu)},$$

$$E_{12}^{**} = 0,$$

$$I_1^{**} = -\frac{\beta_2\left(-\Lambda\tau_2 + \beta_2\mu + \mu^2\right)}{\tau_2(\mu + \alpha_1)(\beta_2 + \mu)},$$

$$I_2^{**} = -\frac{\beta_2\alpha_1\left(-\Lambda\tau_2 + \beta_2\mu + \mu^2\right)}{\tau_2(\mu + \alpha_1)(\beta_2 + \mu)(\mu + \alpha_2)},$$

$$I_3^{**} = -\frac{\beta_2\alpha_1\alpha_2\left(-\Lambda\tau_2 + \beta_2\mu + \mu^2\right)}{\tau_2(\mu + \alpha_1)(\beta_2 + \mu)(\mu + \alpha_2)(\mu + \alpha_3)},$$

$$I_4^{**} = -\frac{\beta_2\alpha_1\alpha_2\alpha_3\left(-\Lambda\tau_2 + \beta_2\mu + \mu^2\right)}{\tau_2(\mu + \alpha_1)(\beta_2 + \mu)(\mu + \alpha_2)(\mu + \alpha_3)(\mu + \mu_0)}$$

And

$$S^{**} = \frac{\beta_3 + \mu}{\tau_3},$$

$$E_1^{**} = 0$$

$$E_2^{**} = 0,$$

$$E_{12}^{**} = \frac{\Lambda\tau_3 - \beta_3\mu - \mu^2}{\tau_3(\beta_3 + \mu)},$$

$$I_1^{**} = -\frac{\beta_3\left(-\Lambda\tau_3 + \beta_3\mu + \mu^2\right)}{\tau_3(\mu + \alpha_1)(\beta_3 + \mu)},$$

$$I_2^{**} = -\frac{\beta_3\alpha_1\left(-\Lambda\tau_2 + \beta_2\mu + \mu^2\right)}{\tau_3(\mu + \alpha_1)(\beta_3 + \mu)(\mu + \alpha_2)},$$

$$I_3^{**} = -\frac{\beta_3\alpha_1\alpha_2\left(-\Lambda\tau_3 + \beta_3\mu + \mu^2\right)}{\tau_3(\mu + \alpha_1)(\beta_3 + \mu)(\mu + \alpha_2)(\mu + \alpha_3)},$$

$$I_4^{**} = -\frac{\beta_3\alpha_1\alpha_2\alpha_3\left(-\Lambda\tau_3 + \beta_3\mu + \mu^2\right)}{\tau_3(\mu + \alpha_1)(\beta_3 + \mu)(\mu + \alpha_2)(\mu + \alpha_3)(\mu + \mu_0)}$$

Furthermore, using Theorem 2 of the following result is established (Abdullahi et al., 2014).

Theorem 1 the DFE of the model (1), given by $\Re_0$ is locally asymptotically stable (LAS) if $\Re_0 < 1$ and unstable if $\Re_0 > 1$ (Abdullahi et al., 2015)

Modified breast cancer Model

In this section, the breast cancer model (1) is modified to include medication such that there will be recovered individuals. Where γ_1, γ_2 *and* γ_3 are the recoveries form state 1, 2 and 3 respectively and ϑ is the medication. So that total human population is denoted by $N(t) = S + E_1 + E_2 + E_{12} + I_1 + I_2 + I_3 + I_4 + R$. The following model is obtained:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - (\tau_1 E_1(t) + \tau_2 E_2(t) + \tau_3 E_{12}(t) + \mu) S(t) \\
\frac{dE_1(t)}{dt} &= \tau_1 E_1(t) S(t) - (\beta_1 + \mu) E_1(t) \\
\frac{dE_2(t)}{dt} &= \tau_2 E_2(t) S(t) - (\beta_2 + \mu) E_2(t) \\
\frac{dE_{12}(t)}{dt} &= \tau_3 E_{12}(t) S(t) - (\beta_3 + \mu) E_{12}(t) \\
\frac{dI_1(t)}{dt} &= \beta_1 E_1(t) + \beta_2 E_2(t) + \beta_3 E_3(t) - (\mu + \alpha_1 + \vartheta + \gamma_1) I_1(t) \\
\frac{dI_2(t)}{dt} &= \alpha_1 I_1(t) - (\mu + \alpha_2 + \vartheta + \gamma_2) I_2(t) \\
\frac{dI_3(t)}{dt} &= \alpha_2 I_2(t) - (\mu + \alpha_3 + \vartheta + \gamma_3) I_3(t) \\
\frac{dI_4(t)}{dt} &= \alpha_3 I_3(t) - (\mu + \mu_0 + \vartheta) I_2(t) \\
\frac{dR(t)}{dt} &= \gamma_1 I_1 + \gamma_2 I_2 + \gamma_3 I_3 - \mu R
\end{aligned} \tag{20}$$

Table 1: Description of variables for Breast cancer model

Parameter	Description
S	Susceptible human
E_l	Exposed human to avoidable risk
E_2	Exposed human to non-avoidable risk
E_{12}	Exposed human to both avoidable and non-avoidable risk
I_1	Breast cancer stage 1
I_2	Breast cancer stage 2
I_3	Breast cancer stage 3
I_4	Breast cancer stage 4
R_l	Recovered human

Table 2: Description of parameters for breast cancer model

Par.	Description
Λ_l	Recruitment rate of human
τ_1	Avoidable risk factors
τ_2	Non-avoidable risk factors
τ_3	Avoidable and non-avoidable risk factors
μ	Natural death

Par.	Description
μ_0	Death due to infectivity
β_1	Progression of exposed human due to avoidable risk factors to stage 1
β_2	Progression of exposed human due to non-avoidable risk factors to stage 1
β_3	Progression of exposed human due to both avoidable and non- avoidable risk factors to stage 1
α_1	Progression of stage 1 to stage 2
α_2	Progression of stage 2 to stage 3
α_3	Progression of stage 3 to stage 4
γ_1	Recovery rate of stage 1
γ_2	Recovery rate of stage 2
γ_3	Recovery rate of stage 3
ϑ	Medication

Optimal control model

Public health education, breast cancer screening (u_1, u_2) and medication (u_3) efforts as controls were introduce into the model (20), to curtail the spread of the disease. The breast cancer model

(20) Yields

$$\frac{dS(t)}{dt} = \Lambda(1-u_1) - (\tau_1 E_1(t)(1-u_2) + \tau_2 E_2(t)(1-u_2) + \tau_3 E_{12}(t)(1-u_2) + \mu)S(t)$$
$$\frac{dE_1(t)}{dt} = \tau_1 E_1(t)S(t)(1-u_2) - (\beta_1 + \mu)E_1(t)$$
$$\frac{dE_2(t)}{dt} = \tau_2 E_2(t)S(t)(1-u_2) - (\beta_2 + \mu)E_2(t)$$
$$\frac{dE_{12}(t)}{dt} = \tau_3 E_{12}(t)S(t)(1-u_2) - (\beta_3 + \mu)E_{12}(t)$$
$$\frac{dI_1(t)}{dt} = \beta_1 E_1(t) + \beta_2 E_2(t) + \beta_3 E_{12}(t) - (\mu + \alpha_1 + u_3 + \gamma_1)I_1(t)$$
$$\frac{dI_2(t)}{dt} = \alpha_1 I_1(t) - (\mu + \alpha_2 + u_3 + \gamma_2)I_2(t)$$
$$\frac{dI_3(t)}{dt} = \alpha_2 I_2(t) - (\mu + \alpha_3 + u_3 + \gamma_3)I_3(t)$$
$$\frac{dI_4(t)}{dt} = \alpha_3 I_3(t) - (\mu + \mu_0 + u_3)I_4(t)$$
$$\frac{dR(t)}{dt} = \gamma_1 I_1 + \gamma_2 I_2 + \gamma_3 I_3 - \mu R \quad (22)$$

In order to examine the best control efforts that would be desired to manage the disease, it is necessary to consider the best control problem with the objective (cost) functional given by;

$$J = \min_{u_1,u_2,u_3} \int_0^T (A_1 E_1(t) + A_2 E_2(t) + A_3 E_{12}(t) + A_4 I_1(t) + A_5 I_2(t) + A_6 I_3(t) + A_7 I_4(t) + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2))dt \quad (23)$$

where T the final time and the coefficients is $A_1, A_2, A_3, A_4, A_5, A_6, A_7, B_1, B_2, B_3$ are positive weights to balance the factors. With the given objective functional J (U♆), it is aimed at

minimizing the number of exposed and infected humans, while minimizing the cost of control $u_1(t), u_2(t), u_3(t)$. Therefore, an optimal control u_1^*, u_2^*, u_3^* is obtained such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{u_1,u_2,u_3} \{J(u_1, u_2, u_3) | u_1, u_2, u_3 \in \Upsilon\}$$

where the control set

$$\Upsilon = \left\{(u_1^*, u_2^*, u_3^*) | u_i : [0,T] \to [0,1] \text{ Lebesgue measurable } i = 1,2,3\right\}$$

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle (Abdullahi et al., 2015). This principle converts (22)-(23) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u_1, u_2, u_3)

$$\begin{aligned}
H = {} & A_1E_1(t) + A_2E_2(t) + A_3E_{12}(t) + A_4I_1(t) + A_5I_2(t) + A_6I_3(t) + A_7I_4(t) + B_1u_1^2 + B_2u_2^2 + B_3u_3^2 \\
& + \lambda_1\{\Lambda(1-u_1) - (\tau_1E_1(t)(1-u_2) + \tau_2E_2(t)(1-u_2) + \tau_3E_{12}(t)(1-u_2) + \mu)S(t)\} \\
& + \lambda_2\{\tau_1E_1(t)S(t)(1-u_2) - (\beta_1 + \mu)E_1(t)\} \\
& + \lambda_3\{\tau_2E_2(t)S(t)(1-u_2) - (\beta_2 + \mu)E_2(t)\} \\
& + \lambda_4\{\tau_3E_{12}(t)S(t)(1-u_2) - (\beta_3 + \mu)E_{12}(t)\} \\
& + \lambda_5\{\beta_1E_1(t) + \beta_2E_2(t) + \beta_3E_3(t) - (\mu + \alpha_1 + u_3 + \gamma_1)I_1(t)\} \\
& + \lambda_6\{\alpha_1I_1(t) - (\mu + \alpha_2 + u_3 + \gamma_2)I_2(t)\} \\
& + \lambda_7\{\alpha_2I_2(t) - (\mu + \alpha_3 + u_3 + \gamma_3)I_3(t)\} \\
& + \lambda_8\{\alpha_3I_3(t) - (\mu + \mu_0 + u_3)I_2(t)\} \\
& + \lambda_9\{\gamma_1I_1 + \gamma_2I_2 + \gamma_3I_3 - \mu R\}
\end{aligned}$$

where λ_i $for\ i = 1,\ldots,9$ are adjoint variables or co-state variables

Theorem: Given an optimal control u_1, u_2, u_3 and solutions $S, E_1, E_2, E_{12}, I_1, I_2, I_3, I_4, R$ of the corresponding state system (22) that minimizes $J(u)$ over U. Then there exists adjoint variables λ_i $for\ i = 1,\ldots,9$ satisfying

$$\begin{aligned}
-\frac{d\lambda_1}{dt} &= ((-\tau_1E_1 - \tau_2E_2 - \tau_3E_{12})u_2 + \tau_1E_1 + \tau_2E_2 + \tau_2E_{12} + \mu)\lambda_1 + (-1 + u_2) \\
-\frac{d\lambda_2}{dt} &= -A_1 + \lambda_1\tau_1(1-u_2)S - \lambda_2(\tau_1(1-u_2)S - \beta_1 - \mu) - \lambda_5\beta_1 \\
-\frac{d\lambda_3}{dt} &= -A_2 + \lambda_1\tau_2(1-u_2)S - \lambda_3(\tau_2(1-u_2)S - \beta_2 - \mu) - \lambda_5\beta_2 \\
-\frac{d\lambda_4}{dt} &= -A_3 + \lambda_1\tau_3(1-u_2)S - \lambda_4(\tau_3(1-u_2)S - \beta_3 - \mu) - \lambda_5\beta_3 \\
-\frac{d\lambda_5}{dt} &= -A_4 - \lambda_5(-\mu - \alpha_1 - u_3 - \gamma_1) - \lambda_6\alpha_1 - \lambda_9\gamma_1 \\
-\frac{d\lambda_6}{dt} &= -A_5 - \lambda_6(-\mu - \alpha_2 - u_3 - \gamma_3) - \lambda_7\alpha_2 - \lambda_9\gamma_2 \\
-\frac{d\lambda_7}{dt} &= -A_6 - \lambda_7(-\mu - \alpha_5 - u_3 - \gamma_3) - \lambda_8\alpha_3 - \lambda_9\gamma_3 \\
-\frac{d\lambda_8}{dt} &= -A_7 - \lambda_8(-\mu - \mu_0 - u_3) \\
-\frac{d\lambda_9}{dt} &= \lambda_9\mu
\end{aligned}$$

and with transversality conditions

$\lambda_i = 0,\ for\ i = 1,\ldots,9$

and the controls u_1^*, u_2^* *and* u_3^* *satisfy the optimality conditions*

$$u_1^* = \max\left\{0, \min\left(1, \frac{\lambda_1 \Lambda}{2B_1}\right)\right\},$$

$$u_2^* = \max\left\{0, \min\left(1, \frac{S\left(\lambda_4 \tau_3 E_{12} - \lambda_1 \tau_1 E_1 - \lambda_1 \tau_2 E_2 - \lambda_1 \tau_3 E_{12} + \lambda_2 \tau_1 E_1 + \lambda_3 \tau_2 E_{12}\right)}{2B_2}\right)\right\}$$

$$u_3^* = \max\left\{0, \min\left(1, \frac{\lambda_8 I_4 + \lambda_5 I_1 + \lambda_6 I_2 + \lambda_7 I_3}{2B_3}\right)\right\}$$

Proof The governing equations of the adjoints variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as

$$-\frac{d\lambda_1}{dt} = \frac{\partial S}{\partial t} = \left(\left(-\tau_1 E_1 - \tau_2 E_2 - \tau_3 E_{12}\right)u_2 + \tau_1 E_1 + \tau_2 E_2 + \tau_2 E_{12} + \mu\right)\lambda_1 + \left(-1 + u_2\right)$$

$$-\frac{d\lambda_2}{dt} = \frac{\partial E_1}{\partial t} = -A_1 + \lambda_1 \tau_1 (1-u_2)S - \lambda_2\left(\tau_1(1-u_2)S - \beta_1 - \mu\right) - \lambda_5 \beta_1$$

$$-\frac{d\lambda_3}{dt} = \frac{\partial E_2}{\partial t} = -A_2 + \lambda_1 \tau_2 (1-u_2)S - \lambda_3\left(\tau_2(1-u_2)S - \beta_2 - \mu\right) - \lambda_5 \beta_2$$

$$-\frac{d\lambda_4}{dt} = \frac{\partial E_{12}}{\partial t} = -A_3 + \lambda_1 \tau_3 (1-u_2)S - \lambda_4\left(\tau_3(1-u_2)S - \beta_3 - \mu\right) - \lambda_5 \beta_3$$

$$-\frac{d\lambda_5}{dt} = \frac{\partial I_1}{\partial t} = -A_4 - \lambda_5\left(-\mu - \alpha_1 - u_3 - \gamma_1\right) - \lambda_6 \alpha_1 - \lambda_9 \gamma_1$$

$$-\frac{d\lambda_6}{dt} = \frac{\partial I_2}{\partial t} = -A_5 - \lambda_6\left(-\mu - \alpha_2 - u_3 - \gamma_3\right) - \lambda_7 \alpha_2 - \lambda_9 \gamma_2$$

$$-\frac{d\lambda_7}{dt} = \frac{\partial I_3}{\partial t} = -A_6 - \lambda_7\left(-\mu - \alpha_5 - u_3 - \gamma_3\right) - \lambda_8 \alpha_3 - \lambda_9 \gamma_3$$

$$-\frac{d\lambda_8}{dt} = \frac{\partial I_4}{\partial t} = -A_7 - \lambda_8\left(-\mu - \mu_0 - u_3\right)$$

$$-\frac{d\lambda_9}{dt} = \frac{\partial R}{\partial t} = \lambda_9 \mu$$

and with transversality conditions;

$$\lambda_i = 0, \quad for\, i = 1,\ldots,9$$

On the interior of the control set, where $0 \le u_i < 1$, for $i = 1,..3$ yields

$$0 = \frac{\partial H}{u_1} = 2B_1 u_1 - \lambda_1 \Lambda$$

$$0 = \frac{\partial H}{u_2} = 2B_2 u_2 - \left(\lambda_4 \tau_3 E_{12} - \lambda_1 \tau_1 E_1 - \lambda_1 \tau_2 E_2 - \lambda_1 \tau_3 E_{12} + \lambda_2 \tau_1 E_1 + \lambda_3 \tau_2 E_3\right)$$

$$0 = \frac{\partial H}{u_3} = 2B_3 u_3 - \left(\lambda_8 I_4 + \lambda_5 I_1 + \lambda_6 I_2 + \lambda_7 I_3\right)$$

Thus, it obtained that

$$u_1^* = \frac{\lambda_1 \Lambda}{2B_1},$$

$$u_2^* = \frac{S\left(\lambda_4\tau_3 E_{12} - \lambda_1\tau_1 E_1 - \lambda_1\tau_2 E_2 - \lambda_1\tau_3 E_{12} + \lambda_2\tau_1 E_1 + \lambda_3\tau_2 E_3\right)}{2B_2}$$

$$u_3^* = \frac{\lambda_8 I_4 + \lambda_5 I_1 + \lambda_6 I_2 + \lambda_7 I_3}{2B_3}$$

By standard control arguments involving the bounds on the controls, it can be concluded that

$$u_1^* = \begin{cases} 0 \ \ if\ \xi_1^* \le 0 \\ \xi_1^* \ if\ 0 < \xi_1^* < 1 \\ 1 \ \ if\ \ \xi_1^* \ge 1 \end{cases}$$

$$u_2^* = \begin{cases} 0 \ \ if\ \xi_2^* \le 0 \\ \xi_2^* \ if\ 0 < \xi_2^* < 1 \\ 1 \ \ if\ \ \xi_2^* \ge 1 \end{cases}$$

$$u_3^* = \begin{cases} 0 \ \ if\ \xi_3^* \le 0 \\ \xi_3^* \ if\ 0 < \xi_3^* < 1 \\ 1 \ \ if\ \ \xi_3^* \ge 1 \end{cases}$$

Where

$$\xi_1^* = \frac{\lambda_1 \Lambda}{2B_1},$$

$$\xi_2^* = \frac{S\left(\lambda_4\tau_3 E_{12} - \lambda_1\tau_1 E_1 - \lambda_1\tau_2 E_2 - \lambda_1\tau_3 E_{12} + \lambda_2\tau_1 E_1 + \lambda_3\tau_2 E_3\right)}{2B_2}$$

$$\xi_3^* = \frac{\lambda_8 I_4 + \lambda_5 I_1 + \lambda_6 I_2 + \lambda_7 I_3}{2B_3}$$

This implies that the optimal problem goes minimization at u^*

Result and Discussion

In this section, the results of analysis is verified with numerical simulations. Numerical simulations are carried out using parameter values $\Lambda = 0.93$, $\tau_1 = 0.3, \tau_2 = 0.3,\ \tau_3 = 0.4$, $\mu = 0.4, \mu_0 = 0.5,$ $\beta_1 = 0.56, \beta_2 = 0.63,\ \beta_3 = 0.62,\ \alpha_1 = 0.5, \alpha_2 = 0.2,\ \alpha_3 = 0.11, \gamma_1 = 0.6, \gamma_2 = 0.5,\ \gamma_3 = 0.3,\ \vartheta = 1.$ With this control strategy, public health education (u_1) is used to optimize the objective functional J , while the breast cancer screening (u_2) and medication (u_3) are set to zero. In figure 1, the result shows a significant difference in the susceptible human S with optimal control strategy compared to S without control. It was observed in figure 1(a) that the susceptible humans S decrease as a result of control strategies against the increase in the uncontrolled case.

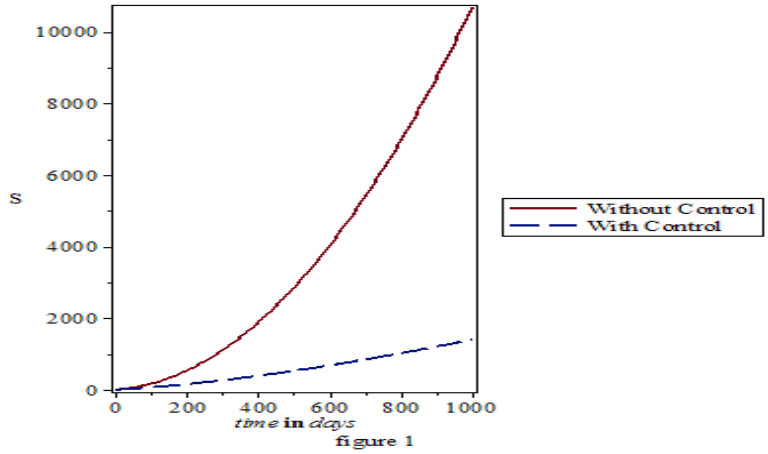
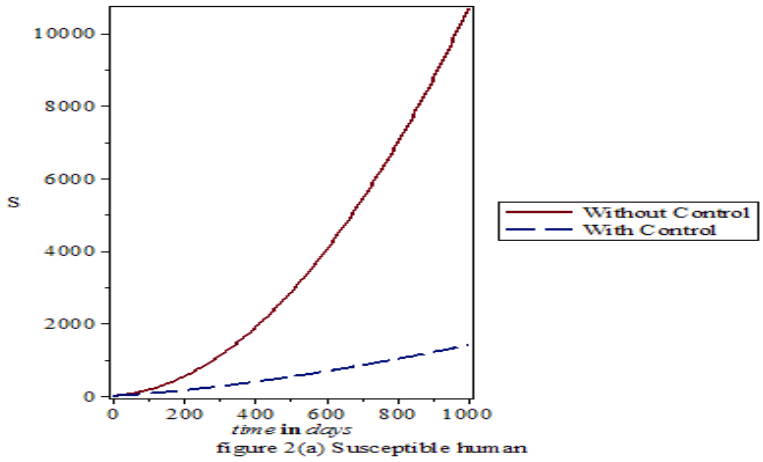
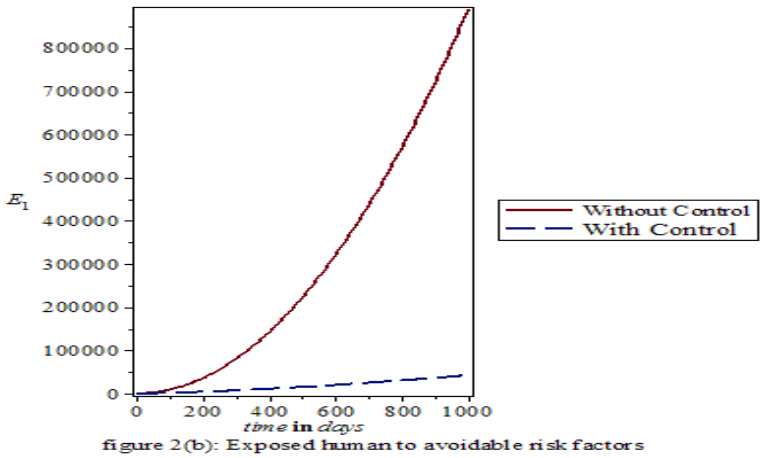


Figure 1: Simulations showing the effect of optimal public health education to control on the spread of breast cancer.

Optimal use of breast cancer screening (u_2)

In this control strategy, optimal breast cancer screening (u_2) is used to optimize the objective functional J, while the control public health education (u_1) and medication $(u_3)$are set to zero. In figure 2, the result shows a significant difference in the $S, E_1, E_2 and\ E_{12}$, with optimal control strategy compared to $S, E_1, E_2 and\ E_{12}$, without control. It was observed in figure 2 that the exposed and infected livestock and humans $S, E_1, E_2 and\ E_{12}$, decrease as a result of control strategies against the increase in the uncontrolled case.





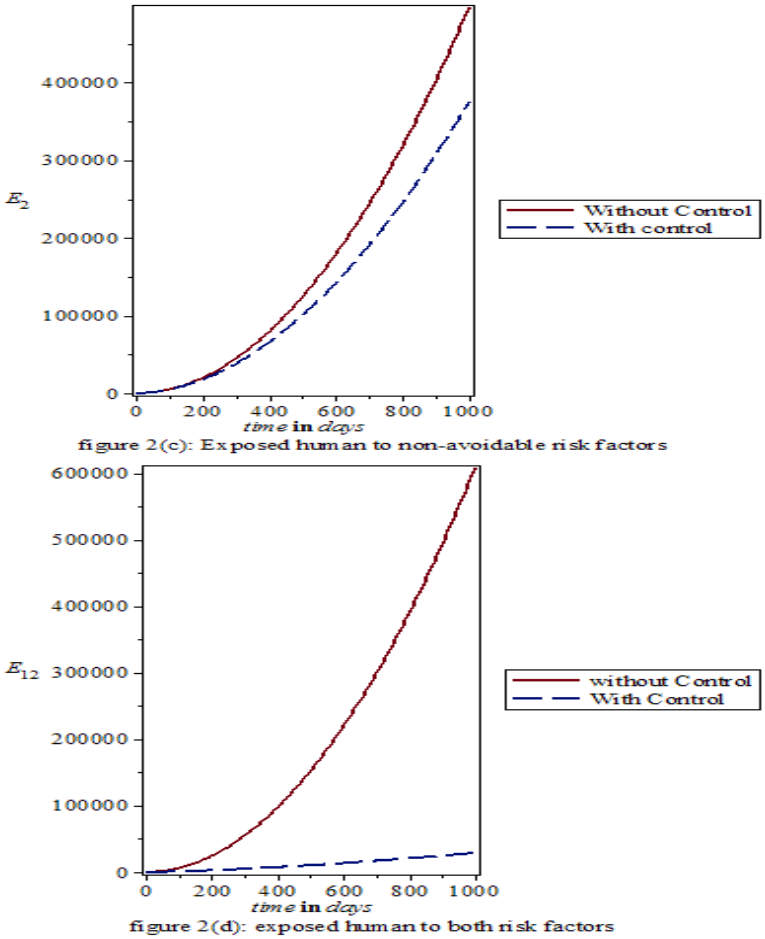
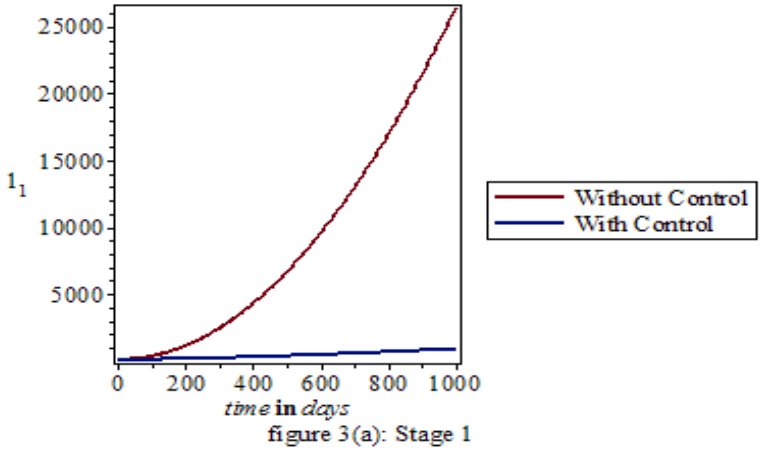


Figure 2. Simulations of breast cancer model showing effect of optimal use of breast cancer screening on the spread of the disease in human.

Optimal Use Medication (u_3)

In this control strategy, use of medication (u_3) is used to optimize the objective functional J, while the public health education (u_1) and breast cancer screening (u_2) are set to zero. In figure 3, the result shows a significant difference in the I_1, I_2, I_3 *and* I_4 with optimal control strategy compared to I_1, I_2, I_3 *and* I_4 without control. It was observed in figure 3 that the all the stages I_1, I_2, I_3 *and* I_4 decrease as a result of control strategies against the increase in the uncontrolled case.



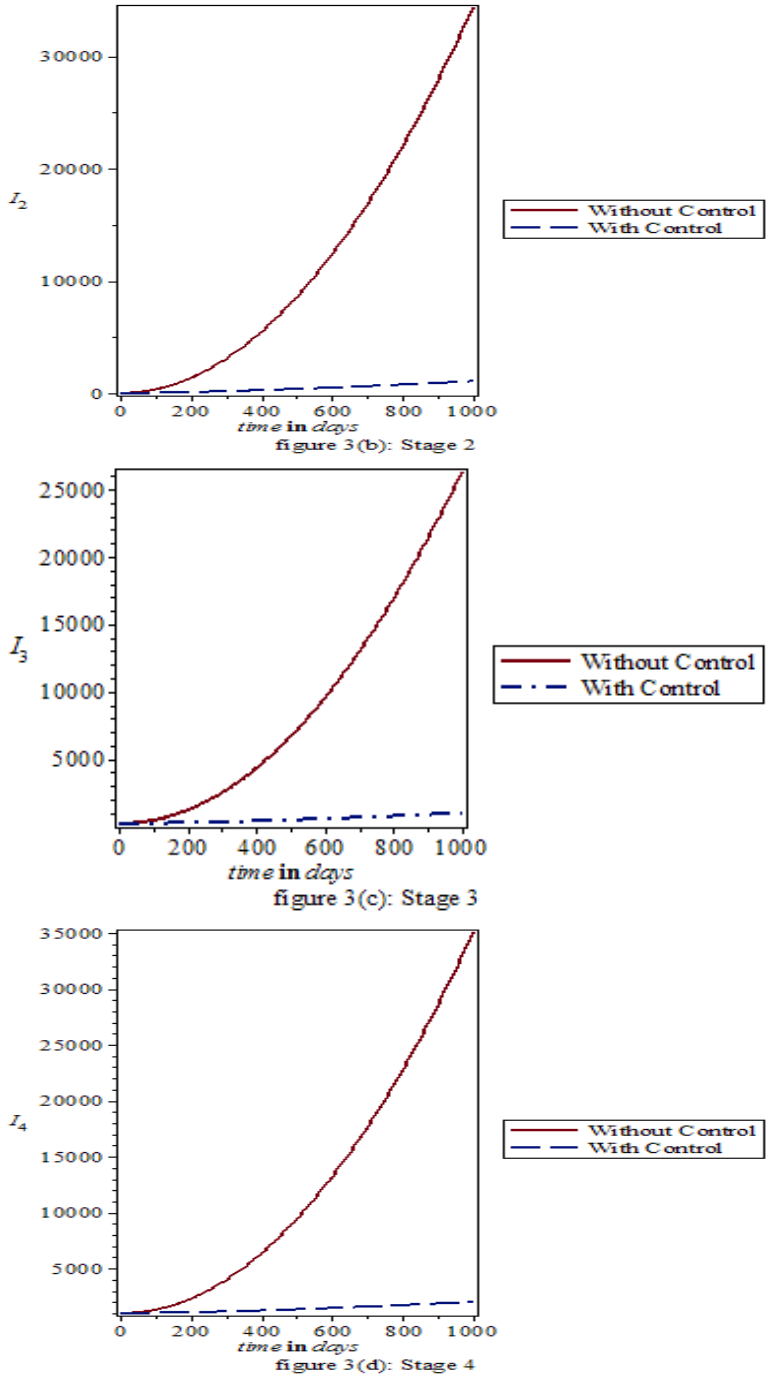


Figure 3. Simulations of the breast cancer model showing effect of optimal use medication on the spread of the disease.

Conclusion

In this paper, a mathematical model for breast cancer optimal controls is developed. The model investigated the stages in infectivity of the disease. And, it is established that the model is locally asymptotically stable when $\Re_0 < 1$ and unstable for $\Re_0 > 1$. The numerical simulation results have shown that the best control strategies for control of the disease combination of the three control strategies. However, the implication of using all the controls is that additional cost will be incurred. This is because; strategy B has a significant effect on this control of the disease. It

can be concluded therefore, to control the breast cancer, the most cost-effective all of the strategies is the use of breast cancer screening (strategy B).

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