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Mathematical model on prostate cancer growth and its control

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Abstract
In this work, we considered the general overview of the prostate cancer disease, and some of the factors influencing its growth, then presented a mathematical model describing the growth of the disease based on those factors. The model consists of a set of three ordinary differential equations, each describing the process of formation of prostate cancer. The solutions to the model equations have were obtained and ways of controlling or preventing the disease also presented. The equilibrium and stability conditions and the results of the model simulations are also discussed.

Keywords: equilibrium state equations, hormonal imbalance, mutation, prostate cancer, stability equations

Introduction

Prostate cancer is a malignant growth or tumor that is caused by uncontrolled or abnormal cell division in the tissues of the prostate gland. The prostate gland is an exocrine gland of the male reproductive system that is located in front of the rectum, just below the bladder. The prostate surrounds the urethra; the tube that carries urine from the bladder to outside of the body. The main function of the prostate gland is to produce a secretion known as the prostate fluid which makes up most of the liquid part of semen; the fluid that transports the sperm. The prostate gland helps to control urination by pressing directly against the part of the urethra that it surrounds. It also contains smooth muscles which help to expel semen during ejaculation. The normal prostate gland is of the size of a walnut. However, the gland tends to increase in size as men get older. This hormone related enlargement with aging is called benign prostatic hyperplasia (BPH), and this condition is not associated with prostate cancer. There are three types of disorders that can occur in the prostate gland: inflammation or infection (prostatitis), enlargement (benign prostatic hyperplasia- BPH), and cancer. However, the prostate cancer is the focus of this work.

Prostate cancer is mostly diagnosed in men older than 45 years. Generally, the tumor grows slowly and remains confined to the gland for many years. During this time, it produces little or no symptoms or outward signs. However, all prostate cancers do not behave similarly. Some aggressive types grow and spread more rapidly than others and can cause a significant shortening of life expectancy in men affected by them. As the cancer advances, it can spread beyond the prostate into the surrounding tissues (local spread). Moreover, the cancer also can metastasize (spread even farther) throughout other areas of the body, such as the bones, lungs, and liver. Symptoms and signs therefore are more often associated with advanced prostate cancer.

Prostate cancer is an increasingly common disease in western societies and in those emulating western lifestyles and diets. In the year 2001, there were estimated to be 198,100 new cases and almost 31,900 deaths attributable to this condition in the United States. Approximately one in seven American men will be diagnosed with prostate cancer during their lifetime, making it the most common solid tissue cancer in the United States (Greenlee, T. *et al*, 2009) [15].

In Africa, prostate cancer was previously perceived to be low but recent studies have shown that Africa has a high prevalence up to 300 per 100,000. It occurs in a younger age group in Africa, approximately a decade earlier than it does in western countries, and patients are diagnosed with advanced disease in over 70% of cases. This is probably as a result of insufficient screening programs in Africa because of the perceived low prevalence, and in addition PSA testing is expensive and widely unavailable. The diagnosis of prostate cancer is limited both by non-availability of ultrasound guided biopsy technique and inadequate pathology services (Bowa, 2010) [7].

In Nigeria, prostate cancer has been on the increase and recently it has become the number one cancer constituting about 11% of all male cancers (Ukoli, *et al*. 2003) [38].

For the general population, a man in his lifetime has about a 16% chance (1 in 6) of being diagnosed with prostate cancer and a 3% chance (1 in 33) of dying from prostate cancer. It is the second most common cancer in men and as the second leading cause of cancer in men over age 45, prostate cancer ranks fifth (Baade, *et al*. 2004) [5]. The older one is, the greater the risk for getting and being diagnosed with prostate cancer. While all men are at risk for prostate cancer, some factors increase risk.

Risk Factors for Prostate Cancer

A risk factor is anything that affects a person's chance of getting a disease. Some risk factors can be changed while others like one's age or family history cannot be changed. While the causes of prostate cancer are still precisely unknown as with many types of cancers, some risk factors that increase the chances for developing the disease have been identified.

Age

Advancing age is considered to be the strongest risk factor for prostate cancer. Prostate cancer is very rare in men younger than 40, but the chance of having it increases rapidly after the age of 50. Almost 2 out of 3 prostate cancers are found in men over

the age of 65 (Greenlee, *et al*. 2009) [15].

Family history
Prostate cancer seems to run in some families, which suggests that there may be an inherited or genetic factor. Men with fathers or brothers who have had prostate cancer are at a greater risk of developing it themselves. The risk is higher for men who have a brother with the disease than for those with an affected father. The risk is greater for men with more than one affected close relative, particularly if their relatives were young at the time the cancer was found. Research shows that approximately 10% of prostate cancer cases are hereditary (Badde, *et al*. 2004).

Ethnicity
Prostate cancer is more common in some racial and ethnic groups than in others. Different ethnic groups have different incidences of prostate cancer. It occurs more often in African American men than in men of other races. Compared with white men, African American men are twice as likely to develop prostate cancer in their early 50s and twice as likely to die of the disease. They are also more likely to be in an advanced stage of the disease when diagnosed. On the other hand, prostate cancer occurs less often in Asian-American and Hispanic/Latino men. It is less common in African, Asian, Hispanic, Pacific Islander, and Native American men than in white men (Spencer, G. 2009) [35].
Several reasons have been suggested as being responsible for these racial and ethnic differences, one of them is the over expression of androgen receptor proteins (the receptors for the hormones that regulate male traits like facial hair and baldness) on the prostates of black men; the levels of these proteins are 22% higher in the prostates of African Americans than in whites. And even more striking, they are 81% higher in the prostate cancers of African Americans (Achebe, C. 2005) [1]. So what this suggests is that the prostate of an African American is under much stimulation to grow and perhaps develop cancer because of greater simulation.
Differences in sex hormones including testosterone have also been suggested as an explanation for some of these differences.
More intensive screening in some developed countries probably accounts for at least part of this difference, but other factors such as lifestyle differences (diet, etc.) are likely to be important as well. For example, men of Asian descent living in the United States have a lower risk of prostate cancer than white Americans, but their risk is higher than that of men of similar backgrounds living in Asia (Muir, *et al*. 1991) [27].

Diets
Diets rich in animal fats such as red meat and high-fat dairy products have been associated with prostate cancer. They can elevate testosterone level which stimulates prostate cell growth and enlargement. Men who consume lots of red meat, a high-fat diet, and one that is low in fiber, fruits, vegetables, and whole grains, have a higher risk of developing prostate cancer than men who do not eat these foods. Some studies have suggested that men who consume a lot of calcium (through food or supplements) may have a higher risk of developing prostate cancer. (Though calcium is known to have some important health benefits, but very high calcium intake seems to increase risk). Dietary difference might explain why the disease is more common in African Americans than in the Chinese who do not have fatty foods as part of their general diet (Nomura, *et al*. 1991) [29].

Genetics
Scientists have found that genetics is responsible for about 5 to 10 percent of prostate cancer cases. Among the genes identified as being responsible is one called HPC1 (Hereditary Prostate Cancer Gene 1). Some inherited gene changes raise the risk for more than one type of cancer. For example, inherited mutations of the BRCA1 or BRCA2 gene changes are the reasons that breast and ovarian cancers are much more common in some families. Mutations in these genes may also increase prostate cancer risk in some men, but they account for a very small percentage of prostate cancer cases (Lorenzo, B. 2005) [26].

Environmental factors
Environmental factor such as workplace exposure to cadmium increases the chances of having prostate cancer. Studies show that men who work in certain occupations (e.g. tire plant workers, farmers, painters) are more likely to get prostate cancer. This is believed to be related to their exposure to chemicals. The contribution from environmental factors accounts for only a small percentage of prostate cancers.

Lifestyle and exercise
Men who are physically inactive are more likely to develop prostate cancer and other prostate disease. A study published in 2009 reported that men who regularly engaged in moderate exercise appeared to have a lower risk of developing prostate cancer (Spencer, G. 2009) [35].
Some other factors may include:

Inflammation
The presence of inflammation as a risk factor is a relatively new theory. Inflammation may contribute to the growth of prostate cancer by damaging cellular DNA and encouraging normal prostate cells to become cancerous. In fact, an increasing amount of research points to the major role inflammation plays not only in prostate cancer but other serious diseases as well.

Obesity
Most health experts agree that obesity is linked to prostate cancer and can have an impact in several areas. Some possible

reasons are that obese men tend to have lower testosterone levels, higher (or relatively so) estrogen levels, elevated levels of insulin-like growth factor-1 (IGF-1) which might spur the cancer on, and greater amounts of saturated fats in their diet (which can encourage prostate cancer growth).

Development of Prostate Cancer

Prostate cancer like other malignancies, arise when genetic alterations in the cells of the prostate gland cause uncontrolled division of abnormal cells. Other factors such as diet, hormones, and environmental influences promote the growth of the abnormal cells. The prostate cells can experience uncontrolled growth if there are damages or mutations to the DNA, and therefore damage to the genes involved in cell division. Four key types of genes are responsible for the cell division process:

- Oncogenes are genes which promote cell division and reproduction.
- Tumor suppressor genes are genes which inhibit cell division and survival.
- Suicide genes control apoptosis and tell the cell to kill itself if something goes wrong.
- DNA repair genes instruct a cell to repair damaged DNA.

Cancer occurs when a cell's gene mutation make the cell unable to correct DNA damage and unable to commit suicide. It is gene mutations that inhibit oncogene and tumor suppressor gene function, leading to uncontrollable cell growth and formation of tumors that may invade the surrounding healthy tissue, destroying it and spreading further.

Genetic Mutations

The genes which regulate cell growth and differentiation must be altered for a normal cell to transform into a cancerous cell. Malignant transformations can occur through the formation of novel oncogenes, or by the under expression or disabling of tumor suppressor genes. Changes in many genes are required to transform a normal cell into a cancer cell. Mutations are changes in the nucleotide sequence of genomic DNA (the DNA is a store for genetic information). Genetic changes can occur at different levels and by different mechanisms but there is a mechanism of error correction and prevention which is built into the process, and safeguards the cell against cancer. If significant error occurs, the damaged cell can self-destruct through programmed cell death, known as apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionizing radiations.

Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer. Tobacco, asbestos, arsenic, cadmium, radiation such as gamma and x-rays, the sun, and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to carcinogens, free radicals (organic ions with unpaired electrons) are formed that try to steal electrons from the DNA and other molecules in the body. These free radicals damage cells and affect their ability to function normally. DNA changes can either be inherited from a parent or acquired during a person's lifetime. There are two types of mutations;

- **Inherited DNA mutations**
- **Acquired DNA mutations**

Hormonal Imbalance

The development of prostate cancer may be linked to increased levels of certain hormones. High levels of androgens (male hormones, such as testosterone) promote prostate cell growth and may contribute to prostate cancer risk.

This also applies to another hormone known as IGF-1 (Insulin-like Growth Factor-1). IGF-1 is similar to insulin, but it affects cell growth, not sugar metabolism. Men with high levels of insulin-like growth factor-1 are more likely to get prostate cancer.

Elevated levels of male hormone; testosterone may be a risk factor, as this hormone is part of the process in encouraging prostate growth. However, while testosterone has a major role in prostate cancer growth, it is an imbalance of hormones (including testosterone) and not the hormone alone that is of the most concern in the development of prostate cancer. The main factors causing hormone imbalance is the increase of abdominal fat and shrinkage of muscle mass. Depression, stress, anxiety, excessive exercise, genetics, and performance enhancement chemicals (such as steroids) can also cause hormone imbalance which may lead to the enlargement of the prostate gland and formation of prostate cancer. There are two main explanations on why the prostate gland enlarges during multiple growth spurts, and both explanations indicate that hormonal changes over time are responsible.

Changes in the normal balance of sex hormones

With advancing age, the amount of the male hormone testosterone decreases relative to the amount of circulating estrogen, the main female hormone which also circulates in the male. This relative increase in circulating estrogen may strengthen the effect of the testosterone derivative DHT (dihydrotestosterone), which promotes cell growth in the prostate gland, and is formed when testosterone is acted upon by a specific enzyme known as 5α –reductase. As a consequence of estrogen and DHT acting together, cell growth and glandular enlargement are promoted.

Changes in the role of DHT

DHT, dihydrotestosterone is an androgen or male sex hormone. The enzyme 5α -reductase synthesizes DHT in the prostate, testes, hair follicles, and adrenal glands. DHT acts as the primary androgen in the prostate and hair follicles. The prostate gland development requires the conversion of testosterone into DHT, in the presence of the enzyme 5α -reductase. As aging occurs, the amount of DHT in the prostate gland remains high, even though the circulating estrogen level drops. This high level of

prostate DHT may by itself promote cell growth and lead to enlargement. In men, high levels of estrogen causes higher levels of testosterone to be converted to DHT which binds to the androgen receptors more strongly than testosterone, and severely increases susceptibility to prostate cancer.

Role of androgens in formation of fusion genes

Androgens promote the fusion of two specific genes which fuel the growth of prostate cancer. Genes that are not normally joined to each other can fuse if chromosomes break and rejoin in an abnormal way. Genes formed in this way are called "fusion genes", (and the process of formation is known as translocation) they can lead to uncontrolled cell division and contribute to tumor formation and progression based on the genes involved. For example, in about half of all prostate cancers, the TMPRSS2 gene fuses with the ERG gene in the presence of the androgen dihydrotestosterone. The fusion of these genes could possibly be caused when the proteins that are involved in regulating the activity of genes (called transcription factors) bring together genes that are not normally close. As the male hormone is involved in regulating the activity of the TMPRSS2 gene, it could promote the formation of TMPRSS2: ERG fusion genes. The androgen DHT also reduces the activity of a particular gene known as the PIWIL 1 gene; (the PIWIL 1 gene protects cells from genetic rearrangement by stopping the DNA in chromosomes from breaking) thereby enhancing the formation of fusion genes in non-malignant prostate cells.

Formulation of Model Equations

We assume that mutation occurs in the following ways:

- Formation of fusion genes TMPRSS2:ERG
- Changes in the p53 gene
- Inheriting HPC1 or BRCA gene

We also assume that the hormones involved in prostate cancer formation are:

- The androgens comprising of testosterone and dihydrotestosterone (DHT)
- Estrogen
- Insulin-like Growth Factor-1 (IGF-1)

And that growth rate is exponential.

We let

$P = \text{total population of cells in the prostate gland}$

$H = \text{production of hormonal imbalance}$

$M = \text{mutated DNAs in the prostate gland}$

$G_N = \text{normal cell population in the prostate gland}$

$G_H = \text{growth of cells enhanced by hormonal imbalance}$

$G_M = \text{growth of cells enhanced by mutations}$

Then;

$$\frac{dP}{dt} = \begin{pmatrix}\text{normal growth}\\ \text{of prostate cells}\end{pmatrix} + \begin{pmatrix}\text{cells due to growth enhanced}\\ \text{by hormonal imbalance}\end{pmatrix} + \begin{pmatrix}\text{cells due to growth enhanced}\\ \text{by mutations}\end{pmatrix}$$

i.e.

$$\frac{dP}{dt} = \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M$$

where

$\alpha_1 = \text{a parameter that measures the normal growth of cells}$

$\alpha_2 = \text{a measure of growth enhanced by hormonal imbalance}$

$\alpha_3 = \text{a measure of growth enhanced by mutations}$

And

$$\frac{dG_M}{dt} = \begin{pmatrix}\text{cell growth enhanced}\\ \text{by mutations}\end{pmatrix} - \begin{pmatrix}\text{recovered cells due to repair effect of tumor}\\ \text{suppressor genes on mutating DNA}\end{pmatrix}$$

i.e.

$$\frac{dG_M}{dt} = \beta_1 G_M - \beta_2 G_M \qquad (\text{where } \beta_2 \text{ may be positive or negative})$$

where,

β_1 = a parameter that measures the growth of mutated cells

β_2 = a measure of the repair effect of tumor suppressorgenes on mutating DNA

Finally,

$$\frac{dG_H}{dt} = \begin{pmatrix}\text{hormone level due}\\ \text{to production}\end{pmatrix} + \begin{pmatrix}\text{effect of diet on}\\ \text{the prostategland}\end{pmatrix} + \begin{pmatrix}\text{genetic}\\ \text{effect}\end{pmatrix} - \begin{pmatrix}\text{hormone usage}\\ \text{in the body}\end{pmatrix}$$

i.e.

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H$$

where

γ_1 = a measure of hormone production level that causes hormonal imbalance

γ_2 = a measure of effect of diet on the hormonal level of the prostategland

γ_3 = a measure of genetic effect on hormonal imbalance

γ_4 = a measure of hormone usage in the body correcting the hormonal imbalance.

From the above, we obtain the systemof equations below

$$\frac{dP}{dt} = \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M \qquad (1)$$

where

$$\frac{dG_M}{dt} = \beta_1 G_M \quad \beta_2 G_M \qquad (2)$$

and

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H \quad \gamma_4 G_H \qquad (3)$$

SOLUTIONS TO MODEL EQUATIONS

We now present the solutions to our model equations

$$\frac{dP}{dt} = \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M \qquad (1)$$

where

$$\frac{dG_M}{dt} = \beta_1 G_M - \beta_2 G_M \qquad (2)$$

and

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H \qquad (3)$$

from (2),

$$\frac{dG_M}{dt} = \beta_1 G_M - \beta_2 G_M = (\beta_1 - \beta_2) G_M$$

$$\frac{dG_M}{G_M} = (\beta_1 - \beta_2) dt \qquad \textit{and solving gives:}$$

$$G_M = C_0 e^{(\beta_1 - \beta_2) t} \tag{4}$$

From (3),

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H$$

$$\frac{dG_H}{dt} = (\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) G_H$$

Solving this gives;

$$G_H = C_1 e^{(\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) t} \Rightarrow G_H = C_1 e^{\lambda t} \tag{5}$$

where $\lambda = \gamma_1 + \gamma_2 + \gamma_3 - \gamma_4$

Substituting (4) and (5) in (1) gives:

$$\frac{dP}{dt} = \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M \tag{1}$$

$$\frac{dP}{dt} = \alpha_1 C_2 e^{\mu t} + \alpha_2 C_1 e^{\lambda t} + \alpha_3 C_0 e^{(\beta_1 - \beta_2) t} \tag{6}$$

where

$G_N = C_2 e^{\mu t}$ since the normal population growth is exponential

and μ = rate constant for the normal population growth of prostate cells

$$dP = \left(\alpha_1 C_2 e^{\mu t} + \alpha_2 C_1 e^{\lambda t} + \alpha_3 C_0 e^{(\beta_1 - \beta_2) t} \right) dt$$

$$\int dP = \int \alpha_1 C_2 e^{\mu t} dt + \int \alpha_2 C_1 e^{\lambda t} dt + \int \alpha_3 C_0 e^{(\beta_1 - \beta_2) t} dt$$

$$P = \frac{1}{\mu} \alpha_1 C_2 e^{\mu t} + \frac{1}{\lambda} \alpha_2 C_1 e^{\lambda t} + \frac{1}{\beta_1 - \beta_2} \alpha_3 C_0 e^{(\beta_1 - \beta_2) t} + e C^3 \tag{7}$$

$$= A \left(\frac{1}{\mu} \alpha_1 C_2 e^{\mu t} + \frac{1}{\lambda} \alpha_2 C_1 e^{\lambda t} + \frac{1}{\beta_1 - \beta_2} \alpha_3 C_0 e^{(\beta_1 - \beta_2) t} \right)$$

$$= A \left(\frac{1}{\mu} b_1 e^{\mu t} + \frac{1}{\lambda} b_2 e^{\lambda t} + \frac{1}{\beta_1 - \beta_2} b_3 e^{(\beta_1 - \beta_2) t} \right) \tag{8}$$

where $b_1 = \alpha_1 C_2$, $b_2 = \alpha_2 C_1$, $b_3 = \alpha_3 C_0$.

Equilibrium State Equations

An equilibrium state refers to the state of a system in which all competing influences are balanced; it is a state of a system which does not change. If the dynamics of a system is described by a differential equation (or a system of differential equations); then equilibrium can be estimated by setting a derivative (all derivatives) to zero.

For an equilibrium state we must have that, from equations (1) - (3),

$$\frac{dP}{dt} = \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M = 0 \quad (9)$$

$$\frac{dG_M}{dt} = \beta_1 G_M - \beta_2 G_M = 0 \quad (10)$$

and

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H = 0 \quad (11)$$

Thus from (10) we have;

$$(\beta_1 - \beta_2) G_M = 0$$

$$\text{If } G_M \neq 0 \Rightarrow \beta_1 - \beta_2 = 0 \quad (12)$$

$$\Rightarrow \beta_1 = \beta_2 \quad (13)$$

(13) Implies that the rate at which mutated cells grow equals the repair effect of tumor suppressor genes on the mutating DNA. Physically this condition only holds for a disease free state and it might explain why some men can live without having prostate cancer.

We can see that in (12) β_2 takes on a positive value to nullify the effect of β_1. We had earlier defined β_2 as being positive or negative. If β_2 takes on a negative value then it means that the rate at which the tumor suppressor genes are working is minimal compared to the rate at which the mutated cells are multiplying, hence a significant change in the normal population of prostate cells, and a disease condition sets in.

From (11),

$$\gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H = 0$$

$$(\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) G_H = 0$$

$$\text{If } G_H \neq 0 \Rightarrow \gamma_1 + \gamma_2 + \gamma_3 - \gamma_4 = 0 \quad (14)$$

$$\text{and } \Rightarrow \gamma_4 = \gamma_1 + \gamma_2 + \gamma_3 \quad (15)$$

(15) implies that the rate at which the body uses hormones is affected by the normal rate of production of those hormones and the effect of diet on hormonal level as well as the individual's genetic makeup. Equations (14) and (15) describe an equilibrium state whereby there is a balance between the hormonal production and usage in the body such that the contribution of hormonal imbalance to the growth of prostate cancer is eliminated. Such a state is physically obtainable.

From (9),

$$\text{since } \alpha_1 G_N + \alpha_2 G_H + \alpha_3 G_M = 0$$

$$\alpha_1 G_N = -(\alpha_2 G_H + \alpha_3 G_M)$$

$$\text{or } G_N = -\frac{1}{\alpha_1}(\alpha_2 G_H + \alpha_3 G_M)$$

$$\text{If } G_H = 0 \text{ and } G_M = 0$$

$$\text{then } G_N = 0 \text{ satisfying}$$

$$\frac{dP}{dt} = 0.$$

Here if there is no growth enhanced by hormonal imbalance and that enhanced by mutation, then there will be no change in the total population of prostate cells over time, thus an equilibrium state is maintained; and a man over the age of 45 is assured that with the passage of time he is not exposed to the risk of having prostate cancer.

Stability Equations

Every solution $X = \Phi(t)$ of the linear system $\dot{X} = A(x)$ (where A is a real constant matrix) is stable if the eigen values of A have a negative real part.

Every solution $\Phi(t)$ of the linear system is unstable if at least one eigen value of A has a positive real part.

We shall now establish the stability of our model equations by testing for the stability of equations (2) to (3) since we can infer the stability of (1) from the result we obtain from the test.

From (2) and (3),

$$\frac{dG_M}{dt} = \beta_1 G_M - \beta_2 G_M$$

$$\frac{dG_H}{dt} = \gamma_1 G_H + \gamma_2 G_H + \gamma_3 G_H - \gamma_4 G_H$$

we obtain the system below

$$\begin{bmatrix} G'_M \\ G'_H \end{bmatrix} = \begin{bmatrix} \beta_1 - \beta_2 & 0 \\ 0 & \lambda \end{bmatrix} \begin{bmatrix} G_M \\ G_H \end{bmatrix}$$

where $\lambda = \gamma_1 + \gamma_2 + \gamma_3 - \gamma_4$

if we let ε be the eigen values then,

$$\begin{vmatrix} \beta_1 - \beta_2 & 0 \\ 0 & \lambda \end{vmatrix} - \varepsilon \begin{vmatrix} 1 & 0 \\ 0 & 1 \end{vmatrix} = 0 \Rightarrow \begin{vmatrix} (\beta_1 - \beta_2 - \varepsilon) & 0 \\ 0 & (\lambda - \varepsilon) \end{vmatrix} = 0$$

$$(\beta_1 - \beta_2 - \varepsilon)(\lambda - \varepsilon) = 0 \Rightarrow \beta_1\lambda - \beta_2\lambda - \varepsilon\lambda - \beta_1\varepsilon + \beta_2\varepsilon + \varepsilon^2 = 0$$

$$(\beta_1 - \beta_2)\lambda - \lambda\varepsilon - (\beta_1 - \beta_2)\varepsilon + \varepsilon^2 = 0$$

If we let $\beta_1 - \beta_2 = y$,

then

$$y\lambda - \lambda\varepsilon - y\varepsilon + \varepsilon^2 = 0 \Rightarrow \quad \varepsilon^2 - (\lambda + y)\varepsilon + y\lambda = 0$$

$$\varepsilon = \frac{(\lambda + y) \pm \sqrt{(\lambda + y)^2 - 4\lambda y}}{2} \quad = \frac{(\lambda + y) + \sqrt{(\lambda + y)^2 - 4\lambda y}}{2} \quad \text{or} \quad \frac{(\lambda + y) - \sqrt{(\lambda + y)^2 - 4\lambda y}}{2}$$

(*i.*) if $\sqrt{(\lambda + y)^2 - 4\lambda y} > \lambda + y$

$$\Rightarrow (\lambda + y)^2 - 4\lambda y > (\lambda + y)^2$$

$$\Rightarrow 4\lambda y < 0 \quad \text{and} \quad \lambda y < 0$$

$$\Rightarrow \quad (a.)\ y < 0 \ \text{and} \ \lambda > 0$$

$$or \quad (b.)\ \lambda < 0 \ \text{and} \ y > 0 \qquad (16)$$

$$(a.) \Rightarrow (\beta_1 - \beta_2) < 0 \quad \text{and} \quad (\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) > 0$$

$$(\beta_1 - \beta_2) < 0 \Rightarrow \beta_1 < \beta_2$$

Meaning that the inhibitory action of the tumor suppressor genes is greater than the effect of the mutating cells on the prostate gland and

$$(\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) > 0 \Rightarrow \gamma_1 + \gamma_2 + \gamma_3 > \gamma_4$$

(*b.*) $\lambda < 0$ *and* $y > 0$

$$\Rightarrow (\gamma_1 + \gamma_2 + \gamma_3 - \gamma_4) < 0 \quad \text{and} \quad (\beta_1 - \beta_2) > 0$$

$$\Rightarrow \gamma_1 + \gamma_2 + \gamma_3 < \gamma_4 \quad \text{and} \quad \beta_1 > \beta_2$$

In the first case; $(a.)$, stability can be guaranteed since the tumor suppressor genes have more effect than the mutating effect.

However, even though the hormonal imbalance can occur, it can be controlled. This establishes the only possible condition for stability in the human system to guarantee the non-occurrence of prostate cancer.

In the second case; $(b.)$, since the effect of the suppressor genes cannot stop the mutating of the gland cells, we see that even when the hormonal imbalance can be controlled, it may be very difficult to control mutation since this is a natural occurrence. Hence the possibility of the occurrence of prostate cancer is more eminent here than in the first case and hence the instability in the condition of the individual with regards to prostate cancer.

$(ii.)$ We now consider the condition of having

$$\begin{aligned}
&\sqrt{(\lambda + y)^2 - 4\lambda y} \;<\; (\lambda + y) \\
&\Rightarrow (\lambda + y)^2 - 4\lambda y \;<\; (\lambda + y)^2 \\
&\Rightarrow 4\lambda y > 0 \;\; and \;\; \lambda y > 0 \\
&\Rightarrow \left.\begin{array}{l} \lambda > 0 \quad and \quad y < 0 \\ or \quad y > 0 \quad and \quad \lambda < 0 \end{array}\right\}
\end{aligned} \tag{17}$$

This is exactly the same conditions we obtained in the previous case (in equation 16);

hence the same conclusions apply here.

MODEL SIMULATIONS

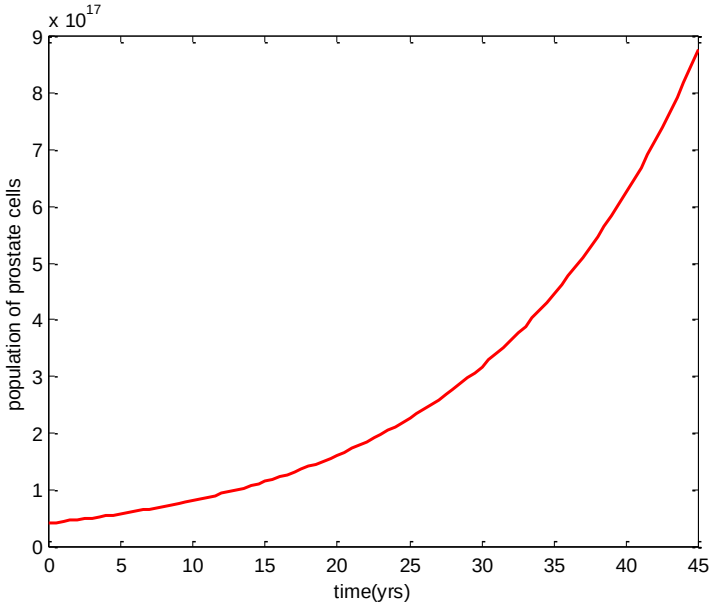

Fig 1. Graph showing the total population of prostate cells at 45 years

$t = 0 : 0.5 : 45; A = 1.9802; \alpha_1 = 1.9989; C_2 = 0.7143 \times 10^{15}; \alpha_2 = 0.1667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0428; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.4545; \gamma_3 = 0.0714; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191$

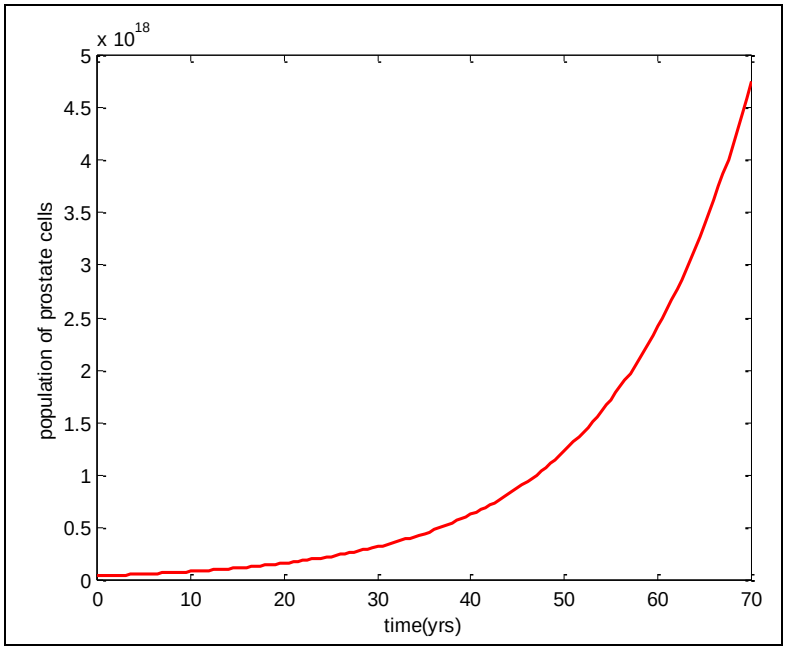

Fig 2: Graph showing increase in the total population of prostate cells at 70 years

$t = 0 : 0.5 : 70; A = 1.9802; \alpha_1 = 1.9989; C_2 = 0.7143 \times 10^{15}; \alpha_2 = 0.1667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0428; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.4545; \gamma_3 = 0.0714; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191$

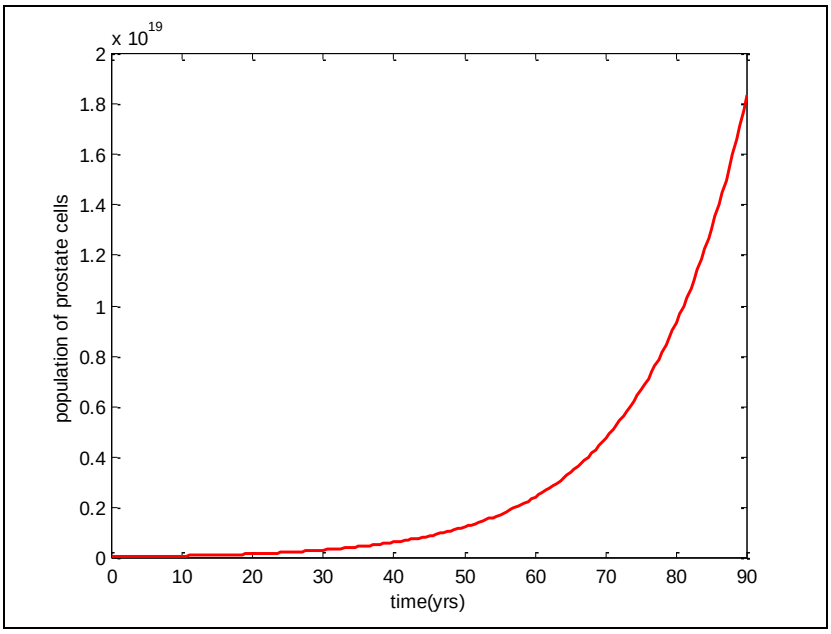

Fig 3: Graph showing increase in the total population of prostate cells at 90 years

$t = 0 : 0.5 : 90; A = 1.9802; \alpha_1 = 1.9989; C_2 = 0.2854 \times 10^{15}; \alpha_2 = 0.1667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0428; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.4545; \gamma_3 = 0.0714; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191$

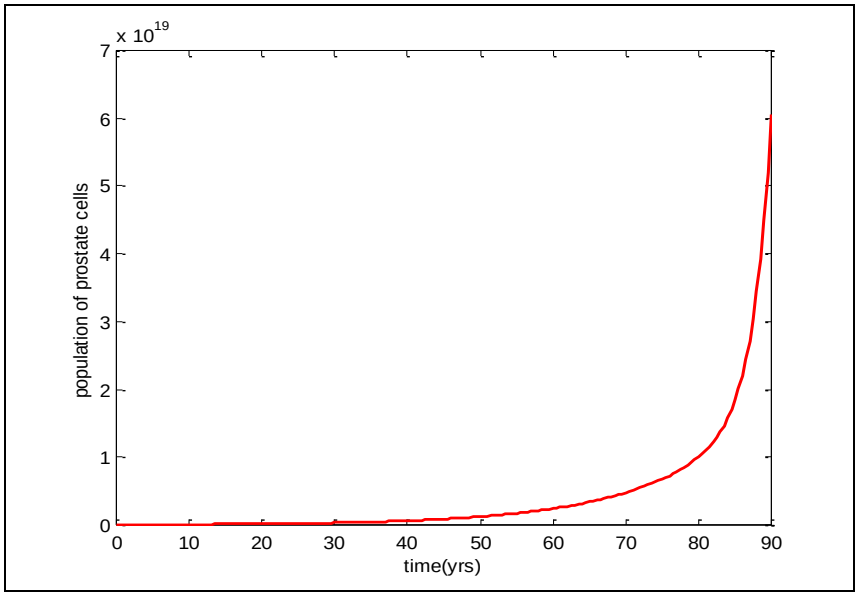

Fig 4: Graph of $\beta_1 > \beta_2$ with $\gamma_1 + \gamma_2 + \gamma_3 > \gamma_4$

$t = 0 : 0.5 : 90; A = 1.9802; \alpha_1 = 1.9989; C_2 = 0.7143 \times 10^{15}; \alpha_2 = 0.1667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0428; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.2909; \gamma_2 = 0.5595; \gamma_3 = 0.2784; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191$

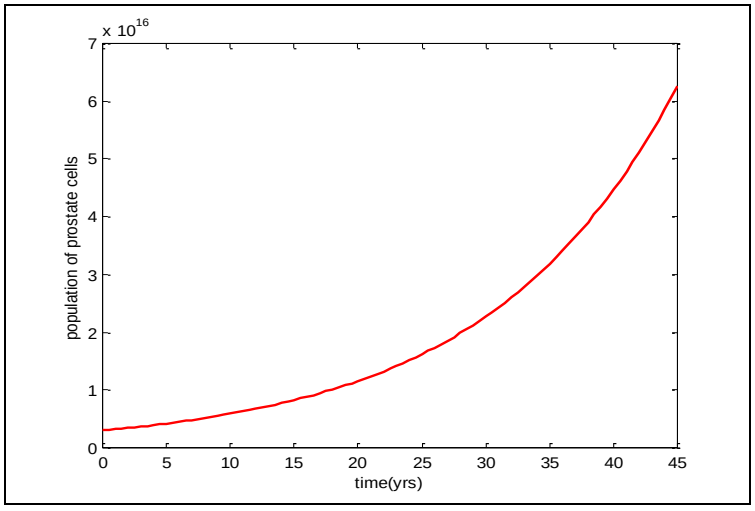

Fig 5: Graph of $\beta_2 > \beta_1$ and $\gamma_1 + \gamma_2 + \gamma_3 < \gamma_4$ at 45 years

$t = 0 : 0.5 : 45; A = 1.9802; \alpha_1 = 0.1429; C_2 = 0.7143 \times 10^{15}; \alpha_1 = 0.0667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0028; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.4545; \gamma_3 = 0.0714; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191 \times 10^3$

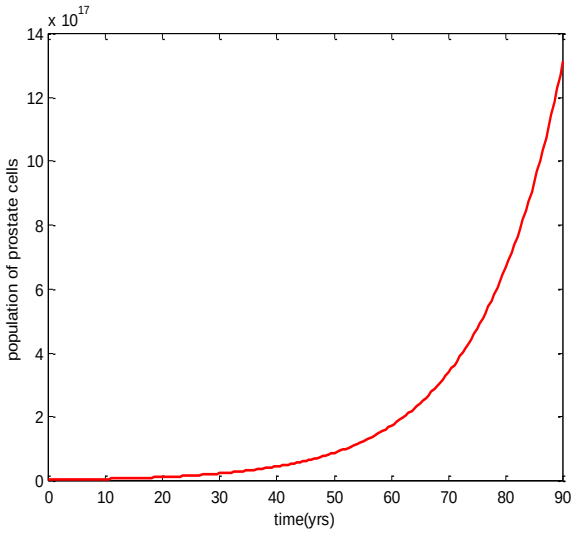

Fig 6: Graph of $\beta_2 > \beta_1$ with $\gamma_1 + \gamma_2 + \gamma_3 < \gamma_4$ at 90 years

$t = 0 : 0.5 : 90; A = 1.9802; \alpha_1 = 0.1429; C_2 = 0.7143 \times 10^{15}; \alpha_2 = 0.0667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0028; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.4545; \gamma_3 = 0.0714; \gamma_4 = 0.7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191 \times 10^3$

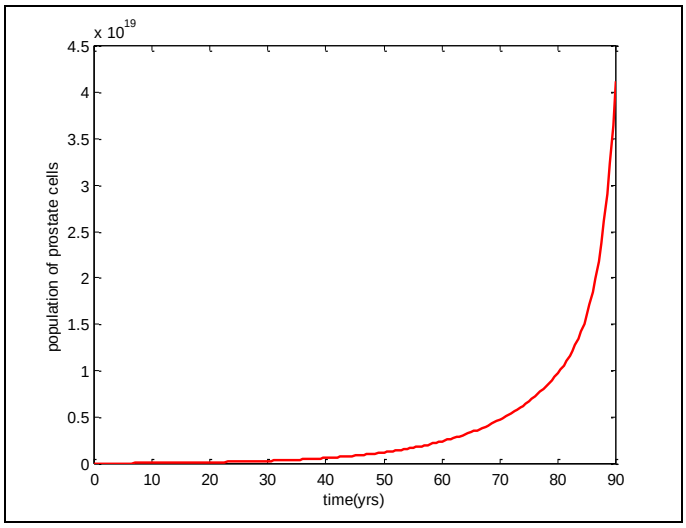

Fig 7: Graph showing effect of increasing α_2

$t = 0 : 0.5 : 90; a = 1.9802; \alpha_1 = 1.9989; C_2 = 0.7143 \times 10^5; \alpha_1 = 0.1667; C_1 = 0.0333 \times 10^5;$

$\alpha_3 = 0.0428; C_0 = 0.2854 \times 10^5; \mu = 0.0676; \gamma_1 = 0.0909; \gamma_2 = 0.9595; \gamma_3 = 0.0714; \gamma_4 = 0..7143;$

$\beta_1 = 0.1990; \beta_2 = 0.0191$

Discussion

In this section, we shall discuss the results we have obtained from our simulations which we have done by considering some experimental values and assigning suitable values to our parameters. Though we do not have exact experimental results all through, we hope that our simulations will show reasonable behavior.

We observe the gradual increase in the population of cells in the prostate gland in figs 1-3. In fig 1, the population is $8 \cdot 8 \times 10^{17}$ cells at 45 years, and in fig 2, it increases to $4 \cdot 75 \times 10^{18}$ at 70 years while in fig 3 the population increases to

$1 \cdot 82 \times 10^{19}$ at 90 years. This shows that the cells in the prostate gland gradually grow and increase in number with increase in time. Though physically, the growth rate may not be the same with different individuals, and may not correspond exactly with the values obtained here. And for some individuals with developing or advanced prostate cancer, the growth may be more spontaneous.

In fig 4, having $\beta_1 > \beta_2$ and increasing the sum of $\gamma_1, \gamma_2, \gamma_3,$ so that it is greater than $\gamma_4,$ leads to an increase in the prostate gland cell population, implying that if the effect of the mutating cells is greater than the inhibitory effect and with the contribution from the imbalance of hormones, there is more chance for one to develop prostate cancer.

If we increase β_2, (the repair effect of the suppressor genes), so that it is greater than β_1, (the rate at which the cells are mutating) and reduce α_1, (the rate at which the normal cells are growing), with the sum of $\gamma_1, \gamma_2, \gamma_3,$ less than γ_4, and with the other contributing factors from α_2 and α_3 reduced; we see a decrease in the total cell population of the prostate gland over time. This is illustrated in fig 5 and fig 6 where the total population of cells at 45 years is $6 \cdot 2 \times 10^{16}$ and at 90 years is 13×10^{17} respectively. The implication is that if some of these contributing factors can be considerably controlled, then the risk of having prostate cancer will be reduced.

In fig 7, increasing γ_2, the measure of effect of diet on the hormonal level of the prostate gland is observed to cause an increase in the total population of the prostate cells. We observe the level of the population at $4 \cdot 1 \times 10^{19}$ cells at 90 years. This shows that the diet we consume also contributes to the growing risk of prostate cancer in our population. Hence care should be taken as to the food we eat; we ought to eat healthy to stay healthy, avoid consuming a lot of red meat and high fat dairy products to ensure good prostate health.

Summary

We observe from our model and simulations that having some of these factors contributing to the growth of prostate cancer under control it is possible to have the occurrence of the disease prevented even with the effect of advancing age. We hope that this work will provide a clear understanding of the processes involved in the growth of the prostate cancer and possibly help in the prevention of the disease, and that such understanding will bring about positive results to the benefit of those living with the disease.

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