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Mathematical Modelling of Hormonal Contraceptives and Cervical Cancer Risk

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Abstract:
The kind of cancer which related with the cervix and that affects the cells of the cervix is called as the cervical cancer. The relationship between hormonal contraceptives (birth control pills) and cervical cancer risk is a complex and evolving area of research. In order to examine the association between hormonal contraceptives, or birth control pills, and cervical cancer risk both with and without vaccination. Mathematical model of cervical cancer built using the Human Papillomavirus. The model is constructed using an ordinary differential equation, and its validity is subsequently confirmed by the application of mathematical analysis methods. Building an accurate model requires obtaining relevant and trustworthy data on the length of birth control pill use and the risk of cervical cancer.

Keywords: Human Papillomavirus, Numerical Solution, hormonal contraceptives, Cervical Cancer.

1. Introduction:

Generally, the organ or the tissue from which a cancer originates determines its name. Multiple organs and tissues in the female body might be impacted by cancer. Ovarian cancer, Breast cancer cervical cancer, Uterine cancer are the list of the cancer which afflict the women more in their life. The part where the vagina and the uterus is joined is called as the cervix. Where the specific type of the cancer is formed is called as the cervical cancer [13,14]. Generally it is caused due to the infections transmitted by sexually intercourse such as high-risk kinds of HPV (human papillomavirus) are the primary cause of most cervical cancers. All human bodies are made up of cells. Cells growths of the normal body divides to form the new cells. Initially in childhood, normal cells divide more quickly to enable growth in all individuals.

The majority of cells in an adult are only divided in order to replace damaged or dead cells. The body's cells naturally divide and expire. The natural cell in the human body divides and multiplies in order to maintain the equilibrium condition of cell population and to balance natural cell death. Uncontrollably growing aberrant cells are the result of mutations in healthy cells.

The human body experiences unchecked and rapid cell development, which gives rise to cancer. A collection of about 100 diseases that impact the human body are collectively referred to as "cancer" [1-4]. Numerous cancer disorders can appear in the human body.

Generally speaking, the name of the cancer is derived from the name of the area that is affected by the disease; a few examples of these include breast, cervical, brain, lung, blood, and bone cancers. More than half of all cervical cancer cases worldwide, or over 250,000 incident cases annually, are found in the Asia Pacific region [1,5]. Prevention efforts of the Cervical cancer in the region are challenged by the fact that there are more women above the age of 15 [2,6] and that there are epidemiological disparities between and within the countries. The most common cause of cervical cancer in women is the infection with HPV. Population is divided into the four groups to build the mathematical model. The number of the infected women with HPV. The number of susceptible women, the number of infectious HPV women who are infected with cervical cancer and the number of infectious HPV women who are not infected with cervical cancer are the two additional compartments. Two more compartments is due to the possibility that people with HPV infection could be or might not also have cervical cancer.

Mathematical Model of Cervical Cancer

Assumption in model:

1. All the women and the girls after15 years- Susceptible population.
2. There is cervical cancer death and natural death.
3. Before infected by HPV full vaccinated --Vaccinated susceptible population
4. Population divides into the four compartments.

Let,

Women population's birth rate is denoted by -bh

Women population's death rate of -μh

Total number of women -Np

Number of susceptible women – X1

Number of women who have received HPV - X_2

Number of Women with HPV Infectious without use of birth control pills X3

Number of Women with HPV Infectious without Long-term use of birth control pills – X_4

Number of women populations who obtain vaccination and develop insusceptibility vX_1

Chances of HPV infection in women who do not take birth control pills – Pv

Cervical cancer risk factors for women who use birth control tablets and have HPV - pc

The model for cervical cancer is constructed by dividing the model into four compartments. The 4 compartments are the numbers of women who is susceptible(X1), infected with HPV (X2), infected with HPV but don't use the contraceptive pills but are not yet infected with cervical cancer (X3) and the infected women with HPV used the birth control pills but are not yet infected with cervical cancer (X4) are the two additional compartments. The flow diagram of the model is as shown as follows:

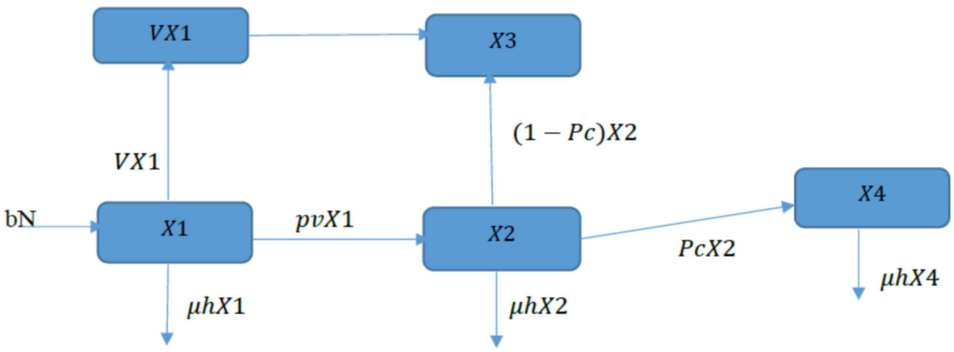


Figure1. Flow diagram of Model with all compartments

Mathematical model Analysis-

Model analysis is necessary to produce the result and to handle parametric factors in a simulation study. These assumptions apply to the strategies that have been reviewed.

(1) It is considered that vaccination, which occurs between the ages of 9 and 12, offers complete, lifetime protection in case of the infections of HPV-16/18 after successful completion of three doses.

(2) The model determines the demotion in the risk of the cervical cancer at different ages using the date which is available on age-specific incidence of cervical cancer and distribution of HPV-16/18 type in cancer, and also the anticipated effectiveness of vaccine and its coverage. Vaccine recipients are still vulnerable to infection from additional high-risk HPV strains that are not protected against by the vaccine.

(3)Depending on the target age group (35, 40, 45), the frequency (once, twice, or three times in a lifetime), and the initial screening test (HPV, DNA testing, visual inspection, cervical cytology) and visits count required to confirm diagnosis ,obtain initial test results and receive appropriate treatment, screening methods can also vary. After the initial screening visit, in between the age of 30 to 35, follow-up screenings are conducted every in five years. There have been other assumptions regarding screening processes, such as the belief that women utilize birth control tablets. The Excel-based approach also calculates the number of cancer deaths and cases of cervical cancer that may have been averted, translating them into final health outcomes.

$$\frac{dX_1}{dt} = bN - p_\nu X_1 - \mu_h X_1 - \nu X_1 \qquad (1)$$

$$\frac{dX_2}{dt} = p_\nu X_1 - (1 - p_c)X_2 - (p_c + \mu_h X_2) \qquad (2)$$

$$\frac{dX_3}{dt} = (1 - p_c)X_2 - \mu_h X_3 + \nu X_1 \qquad (3)$$

$$\frac{dX_4}{dt} = p_c X_2 - \mu_h X_4 \qquad (4)$$

Introduce variables Defined by $x_1 = \frac{X_1}{N}$,

$x_2 = \frac{X_2}{N}$,

$x_3 = \frac{X_3}{N}$ and $x_4 = \frac{X_4}{N}$

$$\frac{dx_1}{dt} = \mu_h(1 - x_1) - (p_\nu + \nu)x_1 \qquad (5)$$

$$\frac{dx_2}{dt} = p_\nu x_1 - (1 - p_c)x_2 - (p_c + \mu_h x_2) \qquad (6)$$

$$\frac{dx_3}{dt} = (1 - p_c)x_2 - \mu_h x_3 + \nu x_1 \qquad (7)$$

$$\frac{dx_4}{dt} = p_c x_2 - \mu_h x_4 \qquad (8)$$

From constructed model of the cervical cancer given in equation (5), (6), (7), (8), identify the stationary points. And undertake stationary point's stability analysis:

Stationary Points:

A point $x*$ in the real line R is considered a stationary point of the one-dimensional ordinary differential equation $x'= (x)$ if it meets the condition $f\ (x*)$ =0. Stationary point is also called as the Equilibrium point., To get the stationary point of the model equation (5), (6), (7), (8), set the right hand sides of each of the four equations in (5), (6), (7), and (8) concurrently equal to 0. and solve, to get the following equations :

$$\boldsymbol{x_1}^* = \frac{\boldsymbol{\mu_h}}{\boldsymbol{\mu_h + p_v + v}} \tag{9}$$

$$\boldsymbol{x_2}^* = \frac{\boldsymbol{p_v\ \mu_h}}{(\boldsymbol{\mu_h + p_v + v})(\boldsymbol{1+\mu_h})} \tag{10}$$

$$\boldsymbol{x_3}^* = \frac{(\boldsymbol{1-p_c})\boldsymbol{p_v + v(1+\mu_h)}}{(\boldsymbol{\mu_h + p_v + v})(\boldsymbol{1+\mu_h})} \tag{11}$$

$$\boldsymbol{x_4}^* = \frac{\boldsymbol{p_c\, p_v}}{(\boldsymbol{\mu_h + p_v + v})(\boldsymbol{1+\mu_h})} \tag{12}$$

Stationary Points-

It is now possible to assess the stability of this equilibrium point, $P=(x1*,x2*,x3*,x4*)$, by (i) creating the Jacobian matrix, (ii) figuring out the Eigen values of the Jacobian matrix, and (iii) figuring out the signs of these Eigen values at the equilibrium point.

Equilibrium Point's Positivity

Restricted that the four compartment population sizes which can reach a non-negative steady state in order to demonstrate the biological fullness and well-defined nature of the models (5), (6), (7), and (8). As a result, we define the parameter condition as $\mathbb{R}4 = \{(x,,,):x,x,x,x\geq 0\}$. The equilibrium points need to satisfy these non-negativity constraints. In order to ensure that $x1,2,x3,x4\geq 0$ for any value of the parameters $\mu h,pv,pc,v\geq 0$ discovered in the dimensionless version of the model is positive, the mathematical and biological model of cervical cancer is thus adequately described.

Stability Analysis of the Equilibrium Point P ($\boldsymbol{x_1}^*$, $\boldsymbol{x_2}^*$, $\boldsymbol{x_3}^*$, $\boldsymbol{x_4}^*$)

The Jacobian matrix for the model equations (5), (6), (7), and (8) is provided by; this matrix is used to examine the local stability of equilibrium or stationary sites.

$$J = \begin{bmatrix} -\mu_h - p_v - v & 0 & 0 & 0 \\ p_v & -(1+\mu_h) & 0 & 0 \\ v & (1-p_c) & -\mu_h & 0 \\ 0 & p_c & 0 & -\mu_h \end{bmatrix}$$

At the stationary point (x_1*,x_2*,x_3*,x_4*) the Jacobian matrix takes the form

$$J(x_1^*, x_2^*, x_3^*, x_4^*) = \begin{bmatrix} -\mu_h - p_v - \nu & 0 & 0 & 0 \\ p_v & -(1+\mu_h) & 0 & 0 \\ \nu & (1-p_c) & -\mu_h & 0 \\ 0 & p_c & 0 & -\mu_h \end{bmatrix}$$

The characteristic equations of matrices

$$(\lambda+\mu h+p_v+v)\ (\lambda + (1+\mu h))\ (\lambda+\mu h)(\lambda+\mu h)=0$$

The four Eigen values of the Jacobian matrices at the equilibrium point are as follows.,

$\lambda_1 = -(\mu h+p_v+v)$

$\lambda_2 = -(\lambda+\mu h)$

$\lambda_3 = -\mu h$

$\lambda_4 = -\mu h$

Based on the algebraic sign of the Eigen values $\lambda 1$, $\lambda 2$, $\lambda 3 and\ \lambda 4$ of the Jacobian matrix, we can ascertain the type of equilibrium points. At the equilibrium point, the dimensionless system (5), (6), (7), and (8) that describes cervical cancer is stable since all of the Eigen values are less than zero (negative).$P= (x_1^*,\ x_2^*, _3^*, x_4^*)$

Results: In biological systems, equilibrium points are fundamental for homeostasis, where internal conditions are regulated to maintain stability. For example, in the human body, temperature, blood pressure, and pH levels are regulated around equilibrium points to ensure optimal functioning.

Numerical Analysis for the constructed cervical cancer model

Visualizing the cervical cancer risk based on the duration of birth control pill use can be done using various visualization techniques. It uses logistic regression to model the relationship between the duration of pill use and the probability of cervical cancer. The scatter plot shows the actual data points, and the red curve represents the logistic regression model's estimated probabilities.

To illustrate the connection between the length of pill use and the presence of cervical cancer.

Generates 100 random values between 0 and 1 for the predictor variable X, scales these values to be between 0 and 5. Creates the binary response variable Y.

To demonstrate the concept of logistic regression and the visualization of estimated probabilities. A scenario where the probability of developing cervical cancer increases with the duration of pill use assumed. X represents the duration of birth control pill use in months, and assumed duration is a maximum of 20 months. The probability of developing cervical cancer increases after 10 months $X \geq 10$ The logistic regression model is trained on data, and the logistic regression curve is plotted.

Duration of pill use in months	probability of cervical cancer range	predictor variable X	Binary response variable Y	Cervical cancer status
1 - 3	0	1		
4- 6	0 – 0.1	2	0	No
7-9	0.15 – 0.2	3	0	No
10- 12	0.2 – 0.3	4	1	Yes
12 - 14	0.4 – 0.5	5	1	Yes

14 - 16	0.6 – 0.7	6	1	Yes
16 – 18	0.8 – 0.9	7	1	Yes
18 -20	0.9 - 1	8	1	Yes

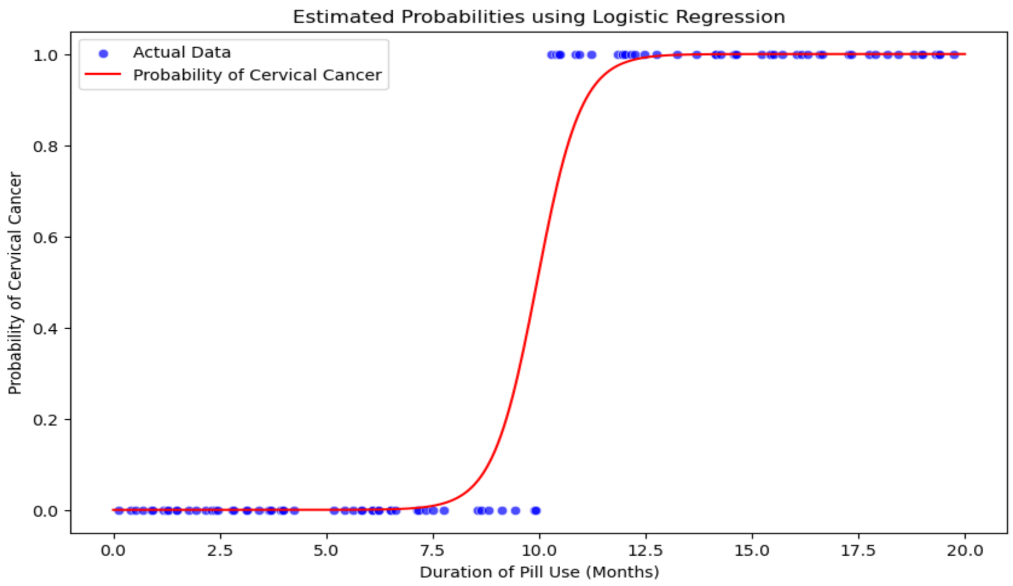
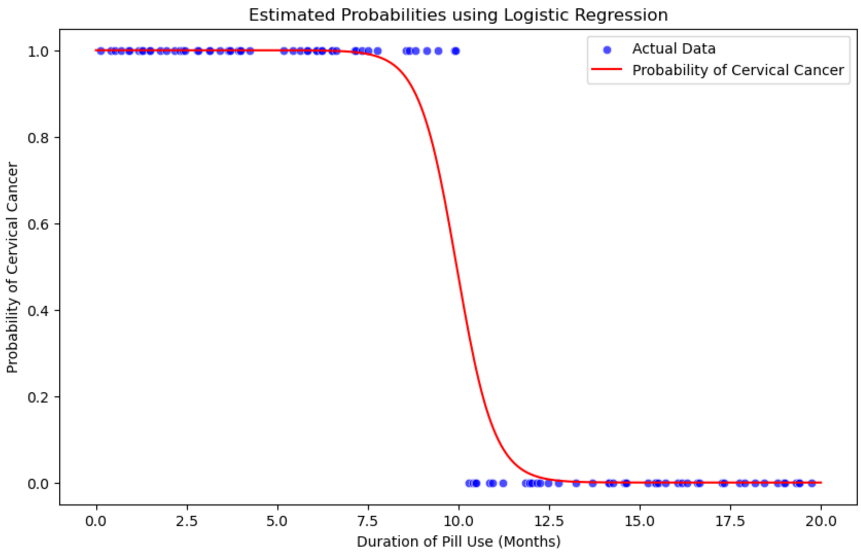


Figure2. Transmission of HPV and Cervical cancer with contraceptives (birth control pills) used (increased risks)

Assumed a scenario where the probability of developing cervical cancer decreases with the duration of pill use. X represents the duration of birth control pill use in months, and assume a duration maximum of 20 months. The probability of developing cervical cancer decreases after 10 months (**(X < 10)**

Duration of pill use in months	probability of cervical cancer range	predictor variable X	Binary response variable Y	Cervical cancer status
1 - 3	0.9 - 1	1	1	Yes
4- 6	0.8 – 0.9	2	1	Yes
7-9	0.6 – 0.7	3	1	Yes
10- 12	0.4 – 0.5	4	1	Yes
12 - 14		5	1	No
14 - 16	0.2 – 0.3	6	0	No
16 – 18	0.15 – 0.2	7	0	No
18 -20	0 – 0.1	8	0	No



Figur3. *Transmission of HPV and Cervical cancer with* contraceptives (birth control pills) used (decreased risks

To analyze data and identify potential associations between both increased and decreased risks of cervical cancer When it comes to the relationship between birth control pill use and cervical cancer, risk of cervical cancer without birth control pill use the findings are expressed as relative risks, odds ratios, or hazard ratios rather than as a simple equation.

A simplified representation a statistical association might be expressed:

$$\text{Relative} \quad \frac{\text{Cervical Cancer risk with Birth Control Pill Use}}{\text{Cervical Cancer risk without Birth Control Pill Use}} \quad \text{Risk = = R}$$

- If R.> 1, It implies a higher risk connected to the usage of birth control pills.
- If the R< 1, It implies that there is less risk involved in using birth control pills.

Discussion:

Cervical cancer risks have been linked to long-term usage of birth control pills, both positively and negatively, based on a population-based random sample of married women. And the relationship between the two is complex. Sensitivity analyses evaluate the potential impact of ambiguous parameters and assumptions on the outcomes. As previously mentioned, predictions of the model that mean reduction in cervical cancer mortality with HPV vaccination are subject to a number of dubious assumptions [13, 16, 21, 24, 35]. For instance, if the currently available HPV vaccines have significant herd immunity effects, partially shield against further strains of HPV and reduce other HPV-16/18-associated cancers, and the benefits of vaccination may exceed those reported in baseline analyses. After making their sexual debut if girls receive vaccinations, if effectiveness is reduced in adolescents infected with HIV, and if not vaccinated targeted HPV types are more common and are linked to pre-cancerous and cancer, the benefits may be less than anticipated (at least in some circumstances).

Probability of cervical cancer risk with long term use of birth control pills Decreased Risk:
Risk of cervical cancer is reduced if there **is** long-term use of birth control. Above studies have suggested that birth control pills used for a long time may be associated with a decreased risk of developing cervical cancer. The potential protective effect may be related to the hormonal changes induced by the use of birth control pills, including:

Factors that may contribute to a decreased risk:

1. **Hormonal Regulation:** Birth control pills regulate hormonal levels, and this hormonal balance may influence the risk of cervical cancer.
2. **Reduced HPV Persistence:** Hormonal contraception might affect the persistence of HPV, a cervical cancer’s major risk factor. Reduced HPV persistence could contribute to a lower risk of developing cervical cancer.

Probability of increased risk of the cervical cancer due to maximum use of the birth control pills
Birth control pills contain hormones (estrogen and progestin) that can influence the cervical environment. The hormonal changes may affect the persistence of HPV, which is the major risk factor for cervical cancer. Conversely, some studies have suggested a potential increased risk of cervical cancer associated with long duration use of contraceptive pills.

Factors that may contribute to an increased risk include:

1. **HPV Infection:** Primary cause of causing cervical cancer is the infection of HPV which cannot be protected by just using the birth control pills. Hence if a woman is using the contraceptive pills and caused by HPV, the risk of causing the cervical cancer may be present. Regardless of birth control pill use, the presence of high-risk HPV type’s infections significantly contribute to cervical cancer risk. Hormonal changes induced by birth control pills may have varying effects on the cervix and the risk of cancer.
2. **Individual Variation:** The risk of the cervical and use of the birth control pill may vary among individuals. Factors such as age, overall health, and other risk factors play a role. Individual health characteristics, genetic factors, and lifestyle choices can impact cervical cancer risk. Each person's situation is unique.
3. **Smoking:** Women who use birth control pills and smoke may face an increased risk.

Conclusion:
HPV vaccination, safe sex practices, and other preventive measures play a crucial role in reducing cervical cancer risk. Ongoing research continues to deepen our understanding of the relationship between hormonal contraceptives and cervical cancer risk. Different types of hormonal contraceptives may have varying effects. For example, combined oral contraceptives containing both estrogen and progestin and progestin-only contraceptives may have different impacts on cervical cancer risk. While some studies suggest a potential decrease in overall risk, there are indications that hormonal contraceptives might be linked with more risk in specific subgroups, such as women with persistent HPV infections. Smoking is a one of the cervical cancer’s risk factor, and interaction

between hormonal contraceptives and smoking may influence risk. Other individual factors and lifestyle choices can also play a role. Regular cervical cancer screenings (Pap smears and HPV tests) are essential for early identification and prevention of the disease, regardless of the use of contraceptives. Women are advised to get vaccinated against HPV, as it is the main preventive measure against cervical cancer. A system is stable and unchanging when opposing factors are balanced, which is known as an equilibrium point. It's crucial to speak with medical specialists for tailored advice based on a person's unique health history, risk factors, and other factors.

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