Models in Medicine: HPV and Cervical Cancer

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Abstract

One of the most important aspects when studying a disease is working to find a solution or treatment. This often involves the introduction of one or more vaccines to assist the patient in getting back to a well state after contracting the disease. In the paper *Mathematical Model for the Natural History of the Human Papillomavirus Infection and Cervical Carcinogenesis*, health stages for women aged 15 to 85 are given and used to simulate the effects that HPV has on patients over time. This model is a stepping stone in working towards a prevention strategy for HPV, which can lead to cervical cancer, and helping prolong the effects of the infection, or even completely eliminating it from certain patients. Throughout this paper, we will discuss a basic model for studying a disease, and relate it to the larger problem of finding a treatment for HPV and cervical cancer.
# Contents

1 Introduction  
2 Background  
3 Mathematical Approach for the Toy Model  
4 Mathematical Approach for the HPV and Cervical Cancer Model  
5 Conclusion  
6 References
1 Introduction

The human papillomavirus is a common disease in the United States that can lead to cervical cancer in women. HPV is complex and treatment depends upon patient characteristics and what stage the patient is in when they begin the treatment. In this paper, we will start by studying a "toy" example for a patient who has some disease (in this case the type of disease is irrelevant, but let’s call it Disease A) so that it can later be applied to a larger example, such as the HPV and cervical cancer case; this case is more complex but uses a similar procedure. After introducing a vaccine or medication for Disease A and determining whether or not it would prolong the life of a patient, we can determine if some sort of vaccine or medication would also assist with HPV and cervical cancer. This is extremely important in the real world, because although cervical cancer is considered rare in the United States (affects less than 200,000 per year) and treatment depends on the stage that the patient is in, this model can save the lives of women, whether it be prolonging life, or completely ridding the individual of the virus.

The Markov model for the HPV virus which leads to cervical cancer is shown below. Without the "toy" example, this model would be immensely difficult to interpret. We will begin by analyzing a disease model with only three possible states for a patient: well, sick, and dead. This model does not take into account patients’ personal characteristics, so it would not be an accurate model to describe a real life disease, but it gives us a better idea of how to understand a large model with a higher number of possible states.

Figure 1: Markov model for HPV and cervical cancer (Myers, 2000)
After analyzing the "toy" example, it is much easier to interpret the HPV and cervical cancer model that is represented in Mathematical Model for the Natural History of the Human Papillomavirus Infection and Cervical Carcinogenesis. There are twelve states in the large model pictured above, and some of these states can be combined for simplicity, while still making sense with regard to a real life model. We will look at five states for the HPV and cervical cancer model: well, undetected HPV, low/high grade SIL, cervical cancer, and dead. These states will be used to study two patients who are in different age groups in order to study the difference between them, and to figure out the best stage in which they should be given treatment.

2 Background

A decision tree models the prognosis of a patient subsequent to the choice of a management strategy (Sonnenberg, 1993). In this case, we are introducing a vaccine for a certain virus, and we can model the events that can occur based on complications that can happen during the sickness, or based on treatment given to the patient for the disease. The decision tree model will contain a "subsequent prognosis" for patients, which shows the states in which the patient can move. For example, if a patient is well, they can become sick, but patients who are dead cannot move anywhere afterwards, because it is unrealistic for them to come back to life. In a real case, these prognoses depend upon particular characteristics that patients have, such as their age, gender, rate at which the virus spreads, etc. The "toy" problem will not take into account such characteristics. However, the larger model will take age into account, so that we can compare more than one patient and study the outcome based on when they are given treatment.

A method for estimating life expectancy for a patient is a Markov model. Markov models are especially useful when a decision problem involves a risk that occurs over time. Consequences of events that have ongoing risk are:

- The times at which the events occur are uncertain so the outcome for the patient can depend on the time that the virus enters the patient.
- A given event may occur more than once. For example, if you were well, became sick, received treatment, and are well again, there is still a risk of contracting the virus a second time.

Markov models assume that patients are always in one state of health, also known as a Markov state, so the next state depends only on the current state. Movement through these states are modeled as transitions from one to the other, and visualized as arrows. An example of a basic model is shown in Figure 2.
The HPV and cervical cancer model started with twelve states, and some of the states have been combined to simplify the model, with justification. For example, low and high grade SIL states have been combined because of the similarity between them. SIL (squamous intraepithelial lesions) are seen in abnormal Pap test results. Low-grade SIL show that cervical cells are changing abnormally, but the changes are mild and usually go away on their own. High-grade SIL mean that cervical cells are changing more severely, and can lead to cancer quicker than those of low-grade. However, both types of lesions appear on the surface of the cervix, so they are similar enough to combine because they are around the same level of severity. When combining two states, such as low and high grade SIL, the average of the transitional probabilities is used. Some states are also completely disregarded, such as "death from other cause", because this model is concerned only with death from cancer.

3 Mathematical Approach for the Toy Model

As pictured in the background information, the basic Markov model includes three possibilities for a patient’s health: well, sick, and dead. The matrix below shows the transitional probability of each state of health that we will use for the "toy" problem. Transitional probability is the probability that a patient goes from one state to the next in a single cycle. Those listed as "zero" in the matrix are probabilities that do not allow movement between states; for example, if a patient is dead, they are unable to transition to other states, so the probability of being well or sick after someone is dead will be zero. The entry \( P_{ij} \) is the probability of a patient transitioning from state \( i \) to state \( j \).

\[ P_{ij} \]
Table 1: P Matrix

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>WELL</td>
<td>0.6 0.2 0.2</td>
</tr>
<tr>
<td>DISABLED</td>
<td>0 0.6 0.4</td>
</tr>
<tr>
<td>DEAD</td>
<td>0 0 1</td>
</tr>
</tbody>
</table>

Figure 3: Transition matrix (Sonnenberg, 1993)

The plot below is a visualization of the above matrix, repeatedly applied over time. Given an initial state $x_0 = (w_0, s_0, d_0)$, we find the state at cycle $t$ by $\bar{x}_t = (P^T)^t \bar{x}_0$. This can be seen in Figure 3, which corresponds to the transition matrix defined in Table 1. The black line represents patients who are well, blue represents sick patients, and red represents dead patients.

Figure 4: Plot of transition matrix

The $P$ matrix makes the assumption that if a patient becomes sick, they can no longer return to being well. This is where the introduction of a vaccine/medication becomes important, because it gives the patient the opportunity to become well again. The plots below show a change in the probability of becoming well after being sick; instead of being zero, the probability for wellness increases by 0.05 as the plots progress, so the new matrix is:

$$P = \begin{bmatrix}
0.6 & 0.2 & 0.2 \\
\alpha & \alpha/2 & \alpha/2 \\
0 & 0 & 1
\end{bmatrix}$$

(1)

with vaccination effectiveness $\alpha = 0.05n$ for $n = \{0, 1, ..., 6\}$. 
In the final plot, the probability of becoming well after being sick is $\alpha = 0.3$. This brings down the probability of fatal outcomes, so patients who would have died after being sick now have a chance of living longer. This means that the vaccine or medication that was introduced for Disease A is saving patients who could not become well again in the first model; this is also where the plot seems to become stable and the gap between well and sick is getting larger, so more patients are saved in the longterm. In other words, this is a measure of the effectiveness of the vaccine/medication. The higher the value of $\alpha$ and the more lives the vaccine/medication saves, the more effective it is at treating the virus.

This model also implies that patients can cycle back and forth between well and sick states. However, there are still chances for these patients to have a prolonged life, rather than dying out immediately after they have contracted the disease; this is where the magnitude of the gap between well and sick states becomes important.
For the HPV and cervical cancer problem, Table 2 is used to determine the transitional probability between states. Since the model has been cut down to five states, only the probabilities pertaining to those states will be taken into account. For low and high grade SIL, the average of the two transitional probabilities will be used in the final matrix. For this particular problem, the time step is 18 months, so all probabilities are converted to fit that interval. However, the plots will show the time in segments of 12 months, in order to simplify interpretation.
The factors of interest in the HPV and cervical cancer model are the age of the patient, and the state of health in which they are given vaccination. Two patients in different age groups will be introduced to a vaccine during both the HPV stage and the lesions stage. This will be used to determine if there is a difference in the effectiveness of the vaccine depending on the stage that it was presented, and if the outcome differs between patients of two age groups.

TABLE 2. Transition probabilities and incidence rates* of preinvasive human papillomavirus (HPV) disease: Markov model

<table>
<thead>
<tr>
<th>Parameter (reference no.)</th>
<th>Base case</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of HPV infection, age 15 years</td>
<td>0.10</td>
<td>0–0.25</td>
</tr>
<tr>
<td>Prevalence of low-grade SIL† age 15 years</td>
<td>0.01</td>
<td>0–0.1</td>
</tr>
<tr>
<td>Age (years)-specific incidence of HPV infection (5, 6, 27, 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
<td>0.5–2 × base estimate</td>
</tr>
<tr>
<td>16</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>24–29</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Age (years)-specific regression rate, HPV infection (HPV to Well) (26, 28, 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>0.7/18 months</td>
<td>0.6–0.9/18 months</td>
</tr>
<tr>
<td>25–29</td>
<td>0.5/18 months</td>
<td>0.45–0.8/18 months</td>
</tr>
<tr>
<td>≥30</td>
<td>0.15/18 months</td>
<td>0.1–0.2/18 months</td>
</tr>
<tr>
<td>Progression rate (HPV to low-grade SIL) (26, 28, 31)</td>
<td>0.2/36 months</td>
<td>0.15–0.3/36 months</td>
</tr>
<tr>
<td>Proportion of infections progressing directly to high-grade SIL (26, 28, 31)</td>
<td>0.1</td>
<td>0.05–0.5</td>
</tr>
<tr>
<td>Regression rate (age (years)) (low-grade SIL to HPV or Well) (27, 32–34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–34</td>
<td>0.85/72 months</td>
<td>0.6–0.8/72 months</td>
</tr>
<tr>
<td>≥35</td>
<td>0.4/72 months</td>
<td>0.3–0.6/72 months</td>
</tr>
<tr>
<td>Regression rate (high-grade SIL to low-grade SIL or Well) (27, 32–34)</td>
<td>0.35/72 months</td>
<td>0.3–0.5/72 months</td>
</tr>
<tr>
<td>Proportion of high-grade SIL reverting to Well (27, 32–34)</td>
<td>0.5</td>
<td>0–0.5</td>
</tr>
<tr>
<td>Progression rate (high-grade SIL to stage I cancer (8, 9, 35–38)</td>
<td>0.4/120 months</td>
<td>0.3–0.5/72 months</td>
</tr>
</tbody>
</table>

* Rates are converted to probabilities in the model.
† SIL, squamous intraepithelial lesion.

Figure 8: Table 2 (Myers, 2000)
The transition matrix for a fifteen year old patient is shown below:

\[
P = \begin{bmatrix}
0.9 & 0.1 & 0 & 0 & 0 \\
0.7 & 0.1 & 0.2 & 0 & 0 \\
0.7 & 0.2 & 0 & 0.1 & 0 \\
0 & 0 & 0 & 0.83 & 0.17 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\] (2)

The visualization of the above matrix is shown in Figure 8. The black line represents well patients, the blue line represents HPV, the red line represents lesions, the green line represents cancer, and the cyan line represents death. The plot is shown over 70 years; the assumption is that the patient has the potential to live to be about 85 years old.

The vaccination will be introduced first in the HPV state. As in the toy model, the \( \alpha \) value will be 0.05. The new matrix is:

\[
P = \begin{bmatrix}
0.9 & 0.1 & 0 & 0 & 0 \\
0.7 + \alpha & 0.1 - \alpha/2 & 0.2 - \alpha/2 & 0 & 0 \\
0.7 & 0.2 & 0 & 0.1 & 0 \\
0 & 0 & 0 & 0.83 & 0.17 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\] (3)

with vaccination effectiveness \( \alpha = 0.05n \) for \( n = \{0, 1, \ldots, 3\} \).
The final plot shows the details of the range of density at \( \alpha = 0.15 \), so that the plot lines can be more easily seen. As \( \alpha \) increases from 0 to 0.15, the death rate decreases by about 3%. Throughout all plots, it is obvious that the higher the value of \( \alpha \), the more effective the vaccination.

The vaccination will also be introduced in the lesions state; the \( \alpha \) value will stay at 0.05. The new matrix is:

\[
P = \begin{bmatrix}
0.7 & 0.2 - \alpha/2 & 0 & 0.1 - \alpha/2 & 0 \\
0.9 & 0.1 & 0.2 & 0 & 0 \\
0.7 + \alpha & 0.1 & 0 & 0.83 & 0.17 \\
0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\] (4)
For the lesions plots, as \( \alpha \) increases from 0 to 0.15, the death rate decreases by about 5%. The difference between death rate when vaccination is introduced during the HPV and lesions states is approximately 2%. This indicates that, for a fifteen year old patient, vaccination is more effective when introduced at the later health stage. This is counterintuitive, yet plausible mathematically and medically. We can use this information to determine if the same outcome is true for an older patient.

For a thirty-five year old patient, the transitional matrix differs slightly. Overall, it is less likely for an older patient to contract HPV, but it is more difficult to treat HPV once it’s contracted. This leads to patients staying in the HPV stage over a longer period of time. The matrix for a thirty-five year old patient is listed below.
\[ P = \begin{bmatrix} 0.99 & 0.01 & 0 & 0 & 0 \\ 0.15 & 0.65 & 0.2 & 0 & 0 \\ 0.7 & 0.24 & 0 & 0.06 & 0 \\ 0 & 0 & 0 & 0.83 & 0.17 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \] (5)

The visualization for the above matrix is shown in Figure 13. The colored lines will indicate the same stages as they did for the fifteen year old patient. The plot covers 50 years, still assuming that the patient can live to be 85 years old.

![Figure 14: Thirty-five year old patient](image)

Because the probability of moving from the lesions state to the cancer state is so small for this patient \((P_{34})\) in the matrix, the \(\alpha\) value was chosen to be smaller than 0.05, as used above. This will give a similar interpretation as using a larger \(\alpha\) value, but the progression will be in smaller increments.

The new matrix for the thirty-five year old patient, with the introduction of a vaccine at the HPV state, is shown below.

\[ P = \begin{bmatrix} 0.99 & 0.01 & 0 & 0 & 0 \\ 0.15 + \alpha & 0.65 - \alpha/2 & 0.2 - \alpha/2 & 0 & 0 \\ 0.7 & 0.24 & 0.06 & 0 \\ 0 & 0 & 0.83 & 0.17 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \] (6)

where \(\alpha = 0.02n\) for \(n = \{0, 1, ..., 5\}\).
Figure 15: HPV: $\alpha = 0.02$

Figure 16: HPV: $\alpha = 0.04$

Figure 16: HPV: $\alpha = 0.06$

Figure 16: HPV: $\alpha = 0.08$
The final plot shows the details of the $\alpha = 0.1$ figure, so that the plot lines can be more easily seen. As $\alpha$ increases from 0 to 0.1, the death rate decreases by about 0.03%. Similar to the fifteen year old patient, the higher the value of $\alpha$, the more effective the vaccination.

The vaccine is also introduced at the lesions stage for the thirty five year old patient. The new matrix is:

$$P = \begin{bmatrix}
0.99 & 0.01 & 0 & 0 & 0 \\
0.15 & 0.65 & 0.2 & 0 & 0 \\
0.7 + \alpha & 0.24 - \alpha/2 & 0 & 0.06 - \alpha/2 & 0 \\
0 & 0 & 0 & 0.83 & 0.17 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix} \quad (7)$$

where $\alpha = 0.02n$ for $n = \{0, 1, ..., 5\}$.
For the lesions plots, as \( \alpha \) increases from 0 to 0.1, the death rate decreases by about 0.06%. The difference between death rate when vaccination is introduced during the HPV and lesions states is approximately 0.03%. This indicates that, for a thirty-five year old patient, vaccination is more effective when introduced at the later health stage. This matches the results of the younger patient, but the overall effectiveness of the medication is much less for the older patient.

5 Conclusion

The "toy" model with only three stages (that don’t take into account the personal characteristics that patients may have) is very limited, but it is apparent that regardless of the disease, a vaccine or medication is an important factor in lowering the rate of fatality. The more effective the treatment is, the higher the chance a
patient has of staying in the well state or moving back to the well state after sickness; this can be translated to the HPV and cervical cancer model.

Vaccination for both a fifteen year old patient and the thirty-five year old patient resulted in a lower death rate when introduced at both the HPV and lesions stages. The most important conclusion that was made from the HPV and cervical cancer model is that the treatment was more effective for both patients when introduced during the lesions state. This result is interesting because generally, one would assume that the earlier a patient is treated, the less likely they are to contract a disease, but in this case, HPV was the earlier health state.

Overall, it is important for a patient of any age to receive vaccination if there is a chance that it will better their health. For a real case, we can conclude that a higher level of treatment leads to a decrease in fatality, but early treatment does not always lead to the best possible results.

6 References

