Evolutionary Ecology of Human Papillomavirus: Trade-offs, Coexistence, and Origins of High-Risk and Low-Risk Types

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Background. We address the ecological and evolutionary dynamics of human papillomavirus (HPV) that lead to the dichotomy between high-risk (HR) and low-risk (LR) types. We hypothesize that HPV faces an evolutionary tradeoff between persistence and per-contact transmission probability. High virion production enhances transmissibility but also provokes an immune response leading to clearance and limited persistence. Alternatively, low virion production increases persistence at the cost of diminished transmission probability per sexual contact. We propose that LR HPV types use the former strategy and that HR types use the latter. Sexual behaviors in a host population determine the success of each strategy.

Methods. We develop an evolutionary model of HPV epidemiology, which includes host sexual behavior, and we find evolutionarily stable strategies of HPV.

Results. A slow turnover of sexual partners favors HR HPV, whereas high frequency of partner turnover selects for LR. When both sexual behaviors exist as subcultures in a population, disruptive selection can result in the coevolution and ecological coexistence of both HR and LR HPV types.

Conclusions. Our results indicate that the elimination of HR HPV through vaccines may alter the evolutionary trajectory of the remaining types and promote evolution of new HR HPV types.

Human papillomavirus (HPV) is the most common sexually transmitted infectious agent worldwide. It can cause or facilitate cervical cancer and other epithelial malignancies [1]. More than 100 HPV types [2] have been identified and are typically classified as low-risk (LR) or high-risk (HR) based on their proclivity to cause cancer. Most HPV types are LR, and only a few, such as HPV 16 and 18, commonly lead to cancer [3]. Distinct molecular differences separate LR and HR HPV types [4], and their course of infection in a host and their transmission between hosts varies. However, the mechanisms linking the evolutionary dynamics of HPV and the sexual activities of human hosts are not well understood.

Both HR and LR types of HPV have independently evolved twice in the α genus [2], suggesting convergent evolution in HR and LR forms. This suggests that each type represents a phenotypic strategy that successfully exploits consistent ecological opportunities with human populations.

The classic evolutionary trade-off for viruses is virulence versus per-contact transmissibility [5]. More virulent phenotypes produce more virions, increasing the probability of transmission between hosts. However, excessive virion production may either kill the host or trigger a more vigorous immune response. Natural selection often favors intermediate phenotypes, although some ecological circumstances may promote extremes of persistence or virulence [6, 7].

No HPV type is particularly virulent in the sense of directly causing host death. Perhaps because HPV is vulnerable to vigorous immune responses, the majority of HPV infections clear within 1 year [8]. LR types, which
produce more virions [9], are typically cleared by the immune system more quickly than HR types [10]. The significance of these differences will become apparent below.

We propose that the central trade-off governing HPV phenotypes is virion production, which affects both per-contact transmissibility and the length of infection prior to immune clearance. We hypothesize that this produces 2 divergent strategies. LR HPV types use high virion production to maximize transmissibility per contact while tolerating a shorter persistence time because of immune stimulation. HR HPV types produce fewer virions, which reduces the per-contact transmission rate but permits longer infection time and a greater number of sexual contacts.

We find that the relative advantage of each HPV strategy depends on the sexual behaviors in a human population. In our model, HR gains an ecological advantage in a host population, with sexual behavior characterized by monogamous relationships maintained for months to years. LR gains an ecological advantage in a host population in which individuals are serially monogamous, having a high turnover rate of partners. Here, we develop a simple ecological susceptible-infectious-resistant model that includes the sexual behaviors of the host population. We demonstrate that subpopulations will exert different selection pressure on HPV, resulting in speciation into LR and HR phenotypes. In reality of course, most human populations exhibit great diversity of sexual activities and individual behaviors change with time. We find that this promotes ecological coexistence of HPV types. Finally, we examine the dynamics of removing dominant populations from the HR niche through vaccination and the likely evolutionary consequences.

**THE MODEL**

We start with a susceptible-infected-resistant model for the epidemiology of HPV in humans [11] (Table 1). We let the humans be celibate or in a relationships, resulting in 9 different states (Figure 1). There are 3 celibate states of susceptible (S), infected (I), or resistant (R). There are 6 states representing the possible relationships between S, I, and R individuals: SS, SI, SR, II, IR, and RR (Table 1).

For simplicity, we assume that the total sexually active human population size, N, remains constant and sex implicit (allowing it to slowly change does not alter the results). Individuals who die or become permanently nonsexually active are replaced by adding new individuals to the susceptible celibate pool. We let celibate individuals encounter each other at random, and after encounter, individuals have some probability of entering into a relationship (η). Relationships have a probability of breakup (δ), or a relationship may also end by the death of a member. When a relationship ends, surviving members return to their corresponding celibate states.

HPV infection dynamics are determined by the rate of infection of S individuals (S becoming I) and the rate of infection clearance by I individuals (I becoming R). New infections can only occur in an SI relationship. The rate of infection for

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**Table 1. Equations Governing the Dynamics of the Model**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
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<tbody>
<tr>
<td>( \frac{dS}{dt} = \mu (N - S_C) + (\delta I_C + \mu) I_S + \frac{1}{2} (S_I + S_R) - (\eta I_C + m S_C + m S_I) )</td>
<td>Growth rate of celibate susceptible</td>
</tr>
<tr>
<td>( \frac{dI}{dt} = (\delta + \mu) I_S + (\frac{1}{2} (S_I + S_R) - (\eta + z I_R + \mu + m) R_C + m I_C) )</td>
<td>Growth rate of celibate infected</td>
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<td>( \frac{dR}{dt} = (\delta + \mu) R_S + z (u) I_C + z (u) R_C + z (u) R_C + z (u) R_C + z (u) R_C + z (u) R_C )</td>
<td>Growth rate of celibate resistant</td>
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<tr>
<td>( \frac{dS}{dt} = \eta \left( \frac{S_I}{S_I + S_R + S_C} \right) - (2\mu + \delta) S_I )</td>
<td>Growth rate of susceptible in relationship with susceptible</td>
</tr>
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<td>( \frac{dI}{dt} = 2\eta S_C \left( \frac{S_I}{S_I + S_R + S_C} \right) - (2\mu + \delta + z I_R + \mu + m) S_I )</td>
<td>Growth rate of susceptible in relationship with infected</td>
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<td>( \frac{dR}{dt} = 2\eta I_C \left( \frac{S_I}{S_I + S_R + S_C} \right) - (2\mu + \delta + z I_R + \mu + m) I_I )</td>
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<td>Growth rate of infected in relationship with infected</td>
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<td>( \frac{dI}{dt} = 2\eta R_C \left( \frac{S_I}{S_I + S_R + S_C} \right) - (2\mu + \delta + z I_R + \mu + m) I_I )</td>
<td>Growth rate of infected in relationship with resistant</td>
</tr>
<tr>
<td>( \frac{dR}{dt} = \eta \left( \frac{S_I}{S_I + S_R + S_C} \right) - (2\mu + \delta) R_R )</td>
<td>Growth rate of resistant in relationship with resistant</td>
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**Figure 1.** The social dynamics for how individuals transition from being celibate to being in sexual relationships (thin solid arrows) and the transmission dynamics of human papillomavirus (HPV) as it spreads by infecting susceptible (thick solid arrow) and decreases as infected individuals become resistant (dotted arrows). The 9 states include the 3 celibate pools of individuals (S, I, and R) and the 6 combinations of relationships. The challenge for HPV emerges from the limited opportunity for spread. Only 1 state (SI) provides an opportunity for new infections (with transmission rate ψ), whereas all 4 states with infected individuals (II, SI, I, and RR) provide opportunities for elimination (with transition rate of z). Table 1 gives the equations describing the mathematical model corresponding to the graphical compartmental model depicted here.
individuals in a SI relationship is determined by the frequency of sex \((a)\) and the per-sex transmission probability \((b)\).

We let all \(I\) individuals, regardless of relationship status, have the same probability \((z)\) of clearing the HPV infection. Only 1 of the 9 states \((SI)\) can augment the prevalence of the virus, whereas any 1 of 4 states \((I, II, SI, and RI)\) can result in a reduction. These positive and negative states represent the main selection forces that drive HPV evolution. We consider 2 scenarios. The first imagines a population in which all individuals conform to a single sexual culture. The second considers 2 somewhat different sexual subcultures. Sexual subcultures are defined by the values of the parameters \((g\) and \(d)\) that describe how frequently individuals enter into and/or break off relationships. In the 2-subculture scenario, for simplicity, we assume that sexual relationships are exclusively in the subculture. We create a mixing of subcultures by having celibates switch between subcultures at some constant per-capita rate \((m)\). Throughout, we let subculture 1 have a relatively lower rate of relationship turnover (low values for both \(g\) and \(d)\) and we let subculture 2 have a relatively high rate of relationship turnover (high values for \(g\) and \(d)\).

Although the model is couched in terms of the dynamics of the human population, it also describes the ecology of an HPV strain. To see how evolution by natural selection acts on the HPV, we let the HPV evolve an evolutionary strategy (heritable phenotypes) representing a trade-off between transmission \((b)\) and persistence \((z)\). We let \(v\) denote the evolutionary strategy that characterizes a focal HPV infection. We set the transmission probability to \(v; \beta(v) = v\). We let the clearance rate \(z\) be the reciprocal of average persistence time of an infection: \(z(v) = 1/\gamma(1 - v)\). As the transmission probability \((v)\) increases, persistence time of the infection decreases and the clearance rate increases. The variable \(u\) is vector-valued and describes the strategies of the HPV strains already present in the population. The strategy of a focal HPV infection \((v)\) becomes important in determining fitness and the fate of a rare mutant HPV strains in a population dominated by HPV types with use of strategies \(u = u_1, u_2, \ldots u_n\). The resulting model is an evolutionary game, because the value of an HPV strain possessing strategy \(v\) depends on the HPV strains already present in the population.

**Dynamics of HPV Prevalence**

When introduced into a population of susceptible individuals, the virus will either die or establish. Extinction occurs when rates of having sex, rates of transmission per sex act, probability of relationship break-ups, and probability of entering a relationship are too small, or when the rate of clearing the infection is too high. If the virus is successful, the model dynamics converge on a stable distribution of individuals among the different states.
The equilibrium prevalence (proportion of population in the infected state) in the population increases with the rate of relationship transitions (both break-ups and unions) and transmission rates (product of rate of sex and transmission per sex act). Equilibrium prevalence decreases with the clearance rate (Figure 2).

Despite a stable distribution of individuals among the 9 states, the actual life experience of any given individual varies. The model can be viewed from an individual-based perspective by rolling the dice for an individual to see whether he or she exits the population of sexually active individuals, enters into, or ends a relationship for any given time step of the model. In this way, each individual has a unique life history. The frequency distribution for the lifetime number of sexual partners of individuals in the population (Figure 3) varies with subculture (low versus high turnover). However, one cannot be certain about an individual’s subculture simply on the basis of the experiences of that individual. Even with slow turnovers of relationships, some individuals will still have numerous partners, whereas even with fast turnovers, some individuals will remain celibate or monogamous their entire lifetime. However, of importance to HPV evolution is the average behavior of individuals in each subculture. Natural selection acting on HPV will be driven primarily by average behaviors.

HPV Evolutionary Dynamics in Sexual Subcultures

In terms of natural selection, phenotypes of HPV that can persist on the lowest equilibrium level of susceptible individuals will replace and out-compete other phenotypes. Of note, only closely related HPV types, such as HPV 45 and 18, appear to compete in this manner [12]. However, competition among closely related variants is sufficient to drive evolution. Under this evolutionary pressure, HPV evolves toward a balance of persistence and transmissibility that minimizes the necessary frequency of susceptibles.

In this context, phenotypes play a consumer-resource game. This is because the level of resources (susceptible individuals) depends on the phenotypes present and their abundances. The level of resources in turn determines each phenotype’s fitness. We define viral fitness as the per-capita growth rate of infected individuals. The fitness of a phenotype depends on the phenotypes used by other viruses. The solution to such a consumer-resource game is known as an Evolutionarily Stable Strategy (ESS) [13]. An ESS is both unbeatable and convergent stable [14], meaning that the evolutionary dynamics converge on an optimal strategy.

We begin by analyzing evolution in populations with a single sexual culture (m = 0). We vary the sexual behavior of the population by varying the $g$ and $d$ parameters. Cultures with higher $g$ and $d$ have a higher average number of lifetime sexual partners (see Figure 3). The virus’s ESS level of transmissibility increases with lifetime sexual partners (Figure 4). Thus, high-turnover populations select for an LR type of HPV, and low-turnover populations select for HR HPV. The next section shows how different sexual subcultures in the population may explain the speciation and origins of LR and HR HPV types.

HPV Evolutionary Dynamics With 2 Sexual Subcultures

The model with 2 subcultures has 2 sets of equations. Subcultures are linked by the parameter $m$, which determines the per-capita rate at which individuals switch from 1 subculture to the other. What is the effect of the subculture switching rate on HPV coexistence and evolution?

We use adaptive landscapes to display evolutionary dynamics and solve for evolutionary equilibrium. The adaptive landscape plots HPV fitness as a function of a focal strategy of HPV infection for a given ecological circumstance. It shows the ecological performances of individuals from a range of phenotypes under the specific social circumstances. A convergent stable maximum of the landscape is an ESS.
For a population of evolving organisms, the slope of the fitness landscape at the population’s mean strategy determines the direction and speed of natural selection [15]. We use adaptive landscapes throughout to lead us to ESS solutions. In doing so, we assume that the ecological dynamics of the system occur much quicker than the evolutionary dynamics.

With rapid switching between subcultures (high values of $m$), most individuals will experience both sexual cultures. From the HPV perspective, this blurs the distinction between them. To the HPV, the 2 subcultures are a single resource. This creates selection pressures for the virus to adopt a strategy that does relatively well in both subcultures. Thus, evolutionarily, relatively high switching rates between subcultures leads to a single HPV with a generalist strategy that is between the 2 specialist strains that would be favored for each subculture alone (Figure 5). This would be an intermediate phenotype with moderate proliferation and persistence. This would likely be manifest as an HPV type with intermediate cancer risk.

With slow switching between subcultures (low values of $m$), a single HPV strain adopts a generalist strategy, which is at an evolutionary minimum (Figure 6). This minimum is convergent stable [16, 17]. A strategy sitting at an evolutionary minimum experiences disruptive selection. This promotes adaptive speciation [18, 19], so that 2 resident strains of HPV possessing slightly different strategies can coexist on opposite sides of the minimum. These daughter strains will then diverge and evolve in opposite directions. Thus, the diversity and temporal variation of sexual behavior in individuals in a human population result in an ESS community (epidemiology) of multiple coexisting HPV strains. Many strains possess strategies that are closer to each other than their respective subcultural specialists, because each strategy is now exposed to both subcultures. This explains the large number of HPV types found with human populations throughout the world.

Finally, we note that eradication of a single HPV type from the ESS community of several coexisting types leaves an empty niche. For instance, eradication of the HR type causes the remaining LR strain to evolve to the generalist strategy at the convergent stable minimum (Figure 6C). This may lead to speciation and re-establishment of the HR strain. Successful
eradication of HR strains may not be evolutionarily persistent, as the remaining LR strains evolve to fill the empty niche. However, as genetic studies show [20], the rate of evolutionary change may be too slow to be of importance to current human health.

**DISCUSSION**

Although the majority of HPV studies focus on its molecular biology and clinical outcomes, we view HPV in the context of its evolutionary ecology. This article addresses the following questions: (1) What evolutionary selection pressures and viral adaptations/strategies result in the observed HR and LR HPV types? (2) How does variation in human sexual activity contribute to the evolution and persistence of HR and LR types in populations? (3) What will the ecological and evolutionary consequences be of an HPV vaccine?

On the basis of mathematical models and computer simulations, we investigate how a trade-off between persistence and transmissibility coupled with sexual behavior of hosts creates the fundamental selection pressure driving HPV evolution. Fitness for a virus is its ability to spread to susceptible hosts from infected hosts. In our model, HR HPV types use a stealth approach in which the virus delays the immune response by remaining in the epithelial cells and producing relatively few virions. This phenotype persists for longer periods because of the limited immune response (this persistence may predispose these types

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**Figure 6.** Adaptive landscapes depicting a situation in which the rate of switching by humans among subcultures is relatively low. In this case, the Evolutionarily Stable Strategy (ESS) for human papillomavirus (HPV) consists of 2 strains that specialize somewhat on their respective subcultures. Starting with just a single HPV strain of either $u = 0.27$ (A) or $u = 0.34$ (B) results in a configuration of the adaptive landscapes that results in evolution towards a minimum of $u = 0.308$ (C). This favors speciation of the HPV into 2 strains. Natural selection can then achieve an ESS where strains $u_1 = 0.2$ (high-risk HPV) and $u_2 = 0.375$ (low-risk HPV) coexist at peaks of the adaptive landscape (D). Parameters for this example are $\gamma = 100; c = 1; m = 0.0005; \mu = 0.001, \phi_1 = 0.05, \phi_2 = 0.5, \eta_1 = 0.2, \eta_2 = 0.5$, and $\alpha = 1$.
to transform human cells). Daud et al [21] showed that HR HPV interferes with the Toll-like receptors of the innate immune system as part of its strategy for persistence. However, the penalty of this strategy is the production of fewer virions and reduced probability of transmission at each sexual contact. Clinically, these infections are inconspicuous, such as the flat lesions of HPV 16 and 18. On the other hand, the LR types, by producing large numbers of virions, achieve higher transmission probabilities per sexual contact. However, this strategy also stimulates the immune system, resulting in more-rapid elimination. Clinically, this infection manifests as genital warts (types 6 and 11), which act as virus factories. Studies have shown that HR HPV types are more persistent than are LR HPV types [10, 22, 23]. In terms of transmissibility, Oriel [24] showed that genital warts result in 60% viral transmission between partners. Of course, the more relevant metric is the per sex act transmission, which requires detailed knowledge of sexual contacts and infections status. To our knowledge, there is no study to date that has published this information.

For HPV, the value of a given phenotype along this persistence-transmissibility continuum depends on the sexual behavior of the host population, specifically the turnover rate of sexual relationships. To persist, HPV requires some turnover of sexual partners in the host population; exclusive, life-long monogamous relationships do not support HPV. In our model, we consider 2 sexual subcultures: (1) low turnover, in which sexual relationships are exclusive and transient but relatively stable (eg, lasting from months to years), and (2) high turnover, in which sexual contacts are more frequent and relationships have a typical duration of days to months. Our models demonstrate that low turnover selects for HR HPV types, because longer (but not life-long) monogamous relationships favor a viral strain that has high persistence but low transmissibility. On the other hand, high turnover favors the LR HPV strategy with high transmissibility but low persistence. We also find that different sexual subcultures in the human population promote the coexistence of HR and LR HPV types and, under some conditions, can result in selection for intermediate, generalist strains of HPV. Adaptive speciation of these generalists into HR and LR types can also occur, consistent with data showing that both types have independently evolved twice in the α genus. In reality, sexual behavior in humans is highly varied and can change over time under the influence of social factors. Identifying clearly defined groups in the human population is difficult and potentially controversial. Sex workers clearly represent a high-turnover group. Ecologically, HR HPV types, particularly HPV 16, are almost invariably more abundant in all studied groups, including sex workers [25–28]. Our model provides several reasons for this observation. HR HPV is more persistent, which can lead to higher prevalence than LR. Furthermore, surveys of human sexual activities indicate typical behaviors more consistent with our low turnover subculture [29, 30]. Seroprevalence studies should indicate more exposure and clearance of LR types if our hypothesis is correct, but a skew in prevalence may make exposure to HR strains more likely. Comparative studies using the same methods are needed; for instance, a comparison of sex workers to low-turnover groups in the same population.

Studies of papillomavirus in other animals with less varied sexual behavior may be instructive. For example, bonobos (Pan paniscus) use sex for social purposes beyond reproduction, such that individuals have frequent sex with multiple partners. In bonobos, papillomavirus diversity is considerably lower that that found in human populations, consisting of a type evolutionarily related to LR types 6 and 11 [31]. Thus, in a species with a high turnover of sex partners, only LR HPV types are present, as our model would predict.

Our model requires several caveats. For the purposes of modeling the factors favoring HR and LR strains, we assumed that all HPV phenotypes compete for susceptible individuals. Epidemiologically, this amounts to full immune cross-reactivity between HPV phenotypes. In reality, this may only be true for very closely related HPV types. There is no cross-reactivity between distantly related HR and LR HPV types [12]. Cross-reactivity may be another aspect of HPV phenotype that promotes the coexistence and diversification of HPV strains. Competition for susceptible hosts produces the divergent selection that explains the origins and evolutionary maintenance of HR and LR HPV types. As the HPV types diverge, they may also be under selection to lose cross-reactivity. This results in the ghost of competition past [32], in which 2 previously competing species evolve phenotypes that no longer directly influence each other’s fitness or ecology.

We also assume that HPV evolves and responds to natural selection. Molecular clock studies suggest that HPV evolves very slowly (estimated at a rate of 1% nucleotide change per 100 000 to 1 000 000 years) [20]. Molecular clock studies generally assume a constant rate of evolutionary change. In our model, as the HPV strains traverse the adaptive landscape, the rate of adaptive evolution can initially be very high but then slows to zero as the strain approaches its ESS. Thus, HPV strains may be capable of rapid evolution but appear relatively static when close to their ESS.

Does our model of HPV evolutionary ecology provide insight into management strategies for HPV? There will undoubtedly be an ecological and evolutionary response to the vaccine. Ecologically, it should reduce the prevalence of these types by reducing the resource pool available to them (number of susceptible individuals).

Evolutionarily, the eradication of HR HPV type will leave an open niche, causing other types to evolve and fill this HR niche. This scenario of course relies on the fact that HPV strains compete with one another and are able to evolve sufficiently fast. Perhaps more realistically, the vaccine will not completely eradicate a targeted HPV type, but rather act as a strong selective force. There has been discussion in the literature about the possibility of
these reductions changing the prevalence of other types through interactions among different HPV types [33, 34]. There is some evidence for associations between specific HPV types [35].

Nevertheless, on the basis of our models, absence of an HPV type should select for initial evolution toward a generalist phenotype, but there is reasonable probability of eventual speciation back to the original strains. We advise close, long-term monitoring of HPV types in human populations following vaccination efforts to detect evolutionary changes.

In conclusion, an evolutionary ecology perspective of HPV identifies the major selective forces and evolutionary trade-offs that govern the interactions of HPV with humans. Our approach provides insight into the critical parameters governing HPV-human ecology and identifies key parameters that should be measured in future research.

Notes

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