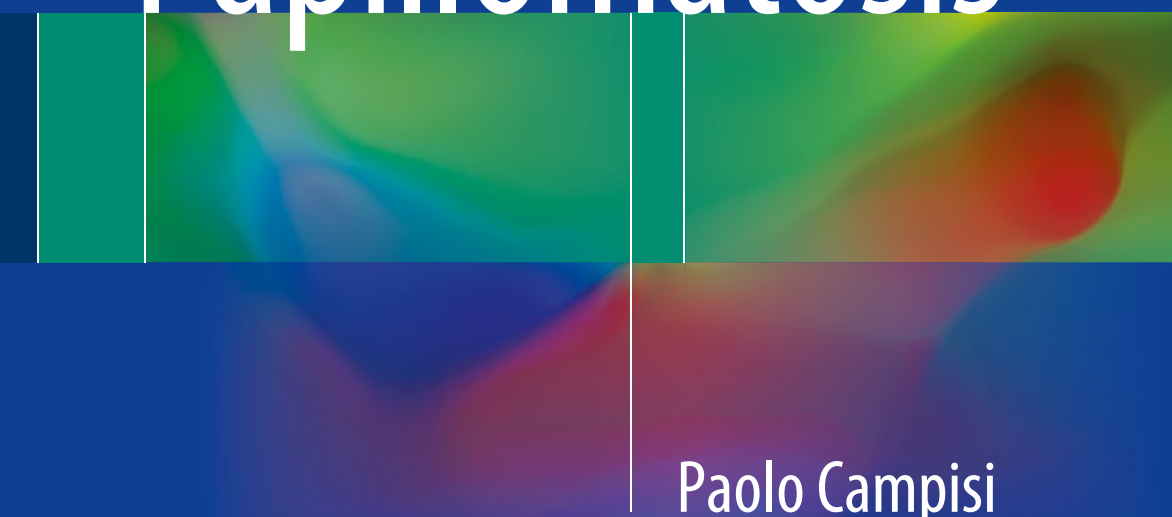
Recurrent Respiratory Papillomatosis



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This collaborative work is dedicated to the children and adults that courageously live with recurrent respiratory papillomatosis. Together we will advocate for the prevention of RRP and strive for the development of novel, effective treatments.

Foreword

It is with great pleasure and honour that I write the foreword to this most impressive book on RRP edited by a trusted friend and colleague, Dr. Paolo Campisi.

As a retired paediatric otolaryngologist/head and neck surgeon, I dealt first-hand with many patients suffering from this disease. Throughout my education as a resident and during my career for more than 30 years, I witnessed the pain, suffering and disruption of quality of life of child, parent and family alike. In my early years, I sensed frustration amongst all the health-care providers, myself included, and researchers with the lack of understanding and effective treatment options available for these children. To put it bluntly, we were poorly equipped and lacking on all fronts. With pure motivation to relieve pain and suffering, we all wanted to do better, and so we did.

Course crude debulking techniques performed via direct laryngoscopy were replaced with innovative microsurgical techniques, powered instrumentation and laser technology with the intent of producing better voice outcomes.

A fresh understanding of the disease—including its epidemiology, proposed aetiology and relationship to the human papilloma virus and cancer—brought new interest to the table from many research groups, from both the adult and paediatric research realm alike. This research translated into a variety of new treatment options and trials from interferon to cidofovir. Initial response to these treatments incited both optimism and controversy, making efficacy and safety a paramount consideration. Vaccine technology not only offered another treatment option but also weighed heavily in the prevention of the disease. A better understanding of the epidemiology and transmission of disease allowed surgeons to better inform and advise patients and families. Intervals between treatments were optimized and outcomes could be better predicted. Parental guilt was replaced by knowledge and optimism.

RRP is an example of how a single disease with both paediatric and adult implications can excite and promote collaboration from a variety of disciplines from the social, clinical, research and public health worlds. The pressing need to find better treatments and ultimately a cure for those suffering from RRP will continue to drive this collaborative effort into the foreseeable future.

I congratulate Paolo and his dedicated team of contributing authors, truly experts in their field, for bringing their knowledge together in what can arguably be described as the best single-source reference ever published on RRP. Thank you all!

Toronto, Canada Vito Forte, MD, FRCSC

Contents

Chapter 1
Fundamental Biology of Human Papillomaviruses

Meghan Lambie and Scott V. Bratman

1.1 Introduction

Papillomaviruses are a family of non-enveloped double-stranded DNA viruses that infect a number of different species including birds, cows, and humans. The human papillomavirus (HPV) can be found globally, with very little impact of geographic location on prevalence infection (De Villiers et al. 2004; Forman et al. 2012). HPV causes abnormal cellular proliferation within infected tissues, which can be broadly categorized as *mucosal* or *cutaneous*; HPV types that infect mucosal tissues are the cause of many benign neoplastic conditions such as condylomata acuminata (genital warts) and recurrent respiratory papillomatosis, and those types that infect cutaneous tissues are the cause of common skin warts (verrucae). HPV gained attention following the discovery that it is the causative agent in cervical cancer (zur Hausen 1976, 1996). Since, it has also been shown to be involved in the genesis of some head and neck cancers, as well as penile, vaginal, vulva, and anogenital cancers (Forman et al. 2012).

Over 170 different HPV types have been sequenced to date (de Villiers 2013), a number that has been rising steadily with the improvement of sequencing methods. It can be difficult to ascertain the precise portion of the population that is infected at any given time, as in most cases the virus remains latent or shows no symptoms. Up to 80% of sexually active women harbor a genital HPV infection at any one time, and men are thought to be similarly afflicted (Antonsson et al. 2000; Donne et al. 2010; Doorbar et al. 2015). One challenge of assessing the prevalence

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of HPV has been that not all cells within an infected tissue contain HPV genomes, requiring the sampling of a large area in order to confidently give a negative diagnosis (Donne et al. 2010).

The contrast between the common prevalence of the virus and the relatively small number of individuals who experience symptoms lends credence to the theory that HPV is most often a commensal entity rather than a disease-causing pathogen (Antonsson et al. 2000). Nonetheless, HPV infection can lead to numerous diseases in humans. The profound impact of this class of pathogens on human health has spurred the development of vaccines with the potential to significantly reduce the incidence of HPV infections and HPV-associated diseases (Dochez et al. 2014). Multiple vaccines are now approved for human use and are being incorporated into population-based vaccination schemes.

Several factors will limit the immediate impact of vaccines on HPV prevention, guaranteeing the continued prevalence of HPV-associated diseases for the foreseeable future. First, the available vaccines provide protection against only a small subset—albeit the most common—of the HPV types that cause human disease. Second, most HPV-associated diseases have a long latency (years to decades) following initial infection and colonization of tissues by the virus. Third, a negative social stigma toward vaccines that prevent sexually transmitted diseases has reduced uptake of HPV vaccines in some segments of society. Finally, the high cost of these proprietary vaccines means that for now, wealthy developed countries derive the greatest benefit (Moody and Laimins 2010; Dochez et al. 2014). Thus, the need for knowledge of the management and treatment of HPV-associated diseases will remain for years to come.

1.2 Genetics and Types of HPV

HPV types carry differential risk of causing invasive malignancy (Donne et al. 2010; Doorbar et al. 2015). Types that are more likely to cause invasive malignancy are referred to as *high-risk* types (Fernandes 2013). High-risk HPV types (the most commonly studied being types 16 and 18) have been determined to be the causative factor in 99% of cervical cancers (Walboomers et al. 1999). RRP is most commonly caused by two low-risk HPV types—6 and 11—which are also associated with benign warts and other hyper-proliferative lesions (Donne et al. 2010; Fernandes 2013). Invasive malignancy is very rare in low-risk types, affecting only a small percentage of patients with cervical infections or RRP (Donne et al. 2010).

1.2.1 Genomic Organization of HPV

HPVs are small, non-enveloped viruses with a genome of approximately 8000 base pairs, contained in a single closed double-stranded circular DNA episome (Fernandes 2013; Doorbar et al. 2015). Within the genome there are eight open reading frames that are divided into three regions:

- The **early region** (E) includes six open reading frames encoding the E1, E2, E4, E5, E6, and E7 proteins. E1 and E2 regulate expression of viral transcripts. E4 controls viral release and viral genome replication. E5, E6, and E7 contribute to host cell division, which can sometimes lead to neoplastic transformation (Tsakogiannis et al. 2012; Fernandes 2013). Overall these proteins are responsible for subsistence of the virus within infected human cells.
- The **late region** (L) encodes two histone-like capsid proteins, L1 and L2, which provide the structure to the HPV virus (Kajitani et al. 2012). The major protein capsid of the virus is L1, with L2 joining pentamers of L1 to stabilize the structure.
- The **long control region** (LCR) is a noncoding region that regulates the transcription of viral genes, including oncogenes E6 and E7. It is an approximately 1 kb long binding site for both positive and negative transcriptional regulators.

The specific genes and their functions have been summarized in Table 1.1. The genome of HPV, despite containing few gene templates, displays complex gene expression programs with several possible alternative splice sites. These are controlled by both cellular and viral transcription factors, mainly within the LCR, as well as by the methylation of viral genomic sequences by the host cell (Kajitani et al. 2012).

Table 1.1 HPV gene functions at a glance

Viral gene	Viral life cycle	Transformation and oncogenesis	Immune modulation
E1	DNA helicase activity. Regulates viral gene transcription		
E2	Regulates early gene promoter	Knockout due to integration of viral genome can cause deregulation of E6/E7 expression	
E4	Control of viral release and genome replication	Involved in viral genome amplification	
E5	Stimulates mitogenic signals of growth factors, including EGFR	Involved in inhibition of apoptosis as well as triggering differentiation	Interferes with MHC class 1 complex presentation
E6	Viral oncogene. Inactivates p53. Regulates many other cellular components	Significant. Prevents cell cycle arrest and apoptosis triggered by E7 activities	Inhibits cytokines including interferon
E7	Viral oncogene. Inactivates Rb. Regulates many other cellular components	Significant. Triggers reentry into the cell cycle and continued cell division	Inhibits cytokines including interferon
L1	Major capsid protein		HPV vaccine target
L2	Minor capsid protein		

1.2.2 HPV Taxonomy

The L1 open reading frame is the most conserved region in the HPV genome and has, therefore, been used to define papillomavirus types. Distinct HPV types are characterized by greater than 10% dissimilarity to the closest known type within the L1 open reading frame (De Villiers et al. 2004). A great deal of sequence similarity also exists in the E1, E2, and L2 open reading frames, with somewhat less conservation of the E4, E5, E6, and E7 open reading frames (De Villiers et al. 2004).

HPV types are categorized by *genus* into five main groups: *alpha*, *beta*, *gamma*, *mu*, and *nu* (Fig. 1.1). Members of the same genus harbor greater than 60% nucleotide sequence identity within the L1 open reading frame and greater

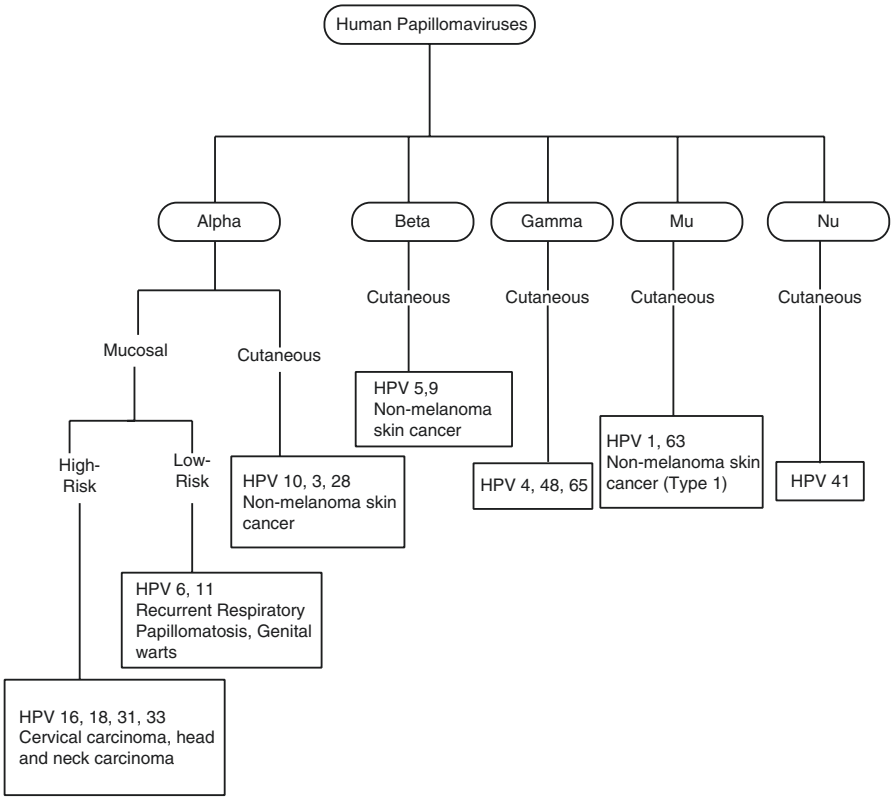

Fig. 1.1 Phylogeny of HPV types. HPV genuses are shown at the first division level. Most studied HPV subtypes exist within the alpha or beta genus. HPV types can either be mucosal or cutaneous, and mucosal subtypes are further subdivided into high and low risk based on potential for malignant transformation. Representative HPV types are shown below each subcategory, along with most common malignancies associated with those types

than 45% identity across the entire genome (De Villiers et al. 2004). Within each genus of HPV types are groupings referred to as *species* or *clade*. To be within the same species, HPV types must share between 60% and 70% of their nucleotide sequence (De Villiers et al. 2004). As mentioned above, HPV types are at least 10% dissimilar from one another, and additional subtypes may exist with nucleotide sequence dissimilarity of 2–5% (noted, e.g., as HPV6c and HPV6d) (Donne et al. 2010).

The division of HPV types by genetic similarity does not necessarily indicate functional similarity. For example, HPV-6 and HPV-11, which are the major contributing factors to RRP, share the same pathology as well as the same phylogenic subtype. In contrast, HPV-2 and HPV-4 are unrelated genetically, but both result in similar cutaneous papillomas (De Villiers et al. 2004).

In addition to the genetically determined phylogeny described above, HPV types are characterized by their predilection for infecting mucosal or cutaneous squamous epithelia. All HPV types infect stratified squamous epithelial tissues. Most of the symptomatic diseases result from types that colonize mucosal squamous epithelia, including high-risk HPV types that cause anogenital and oropharyngeal carcinomas as well as low-risk HPV types responsible for condylomata acuminata and RRP (Fernandes 2013). Alternatively, some HPV types such as HPV-2 and HPV-4 cause cutaneous lesions that infect the keratinized skin surface and are thought to be a risk factor for nonmelanoma skin cancer (Weissenborn et al. 2005). Most mucosal HPV types are of the alpha genus, and most cutaneous types are of the beta genus, although some overlap exists. In comparison to these types, relatively little is known regarding HPV types in the gamma, mu, and nu genera, from which most infections are asymptomatic (Tommasino 2014). These differences in disease states are possibly linked to variation in transmission and propagation of the virus, as well as differences in immune recognition and clearance (Doorbar et al. 2015). These significant divisions of HPV types, as well as the common malignancies seen with each division, are highlighted in Fig. 1.1.

1.3 Virus Life Cycle

HPV infects stratified squamous epithelial tissues, and its life cycle is closely tied to the biology of cellular differentiation within such tissues. The reasons for this particular tropism are not entirely known, although most evidence points toward tissue-specific transcription factors as opposed to cell surface receptors as the primary restrictive factor (Doorbar et al. 2015). Once the virus gains entry into epithelial cells, it embarks upon a well-characterized life cycle that is non-lytic, which in part explains its relative ubiquity and comparatively infrequent symptoms. Immune-mediated clearance and the function of putative viral oncogenes are what differentiate transient infections that go unnoticed from benign papillomas and metaplastic lesions that can progress to invasive carcinomas.

1.3.1 Viral Entry

The HPV virus initially infects cells within the basal layer of the stratified squamous epithelia at the site of infection (Moody and Laimins 2010; Groves and Coleman 2015). The infective viral particle resembles an icosahedral capsid, composed of the late region proteins, L1 and L2 (Doorbar et al. 2012). These proteins are able to interact with heparin sulfate proteoglycans, as well as possibly laminin or integrin α6 to facilitate cell entry (Giroglou et al. 2001). Micro-wounds within the epithelia allow viral entry and replication. As epithelial cells divide during wound healing, viral episomes gain entry to the nucleus (Groves and Coleman 2015). Low-risk HPV types are particularly dependent on the signaling produced by healing cells to facilitate viral episome maintenance, gene expression, and persistence of infection (Doorbar et al. 2012). Conversely, high-risk HPV subtypes, which can drive cell proliferation, may engage in alternative mechanisms for cell entry and persistence of infection (Doorbar et al. 2012; Doorbar et al. 2015).

The HPV DNA uncoats and sheds the capsid structure and utilizes cellular machinery to enter the nucleus (Kajitani et al. 2012). Upon reaching the nucleus, the virus exists in episomes (Groves and Coleman 2015).

1.3.2 Viral Maintenance and Genome Amplification

Upon nuclear entry, transcription of early genes is initiated. Most early genes (excluding E4) induce cell proliferation, leading to an increase of cells in the area that contain the viral genome (Fernandes 2013). At this time, there is very low expression of viral proteins and genetic material, allowing the virus to evade immune detection (Doorbar et al. 2015). The HPV genome does not encode polymerases or most of the other machinery necessary for DNA replication and relies solely on the host proteins for viral DNA synthesis. The lone exception is the E1 protein, which functions similarly to human DNA helicase (Moody and Laimins 2010; Satsuka et al. 2015).The viral E1 and E2 proteins bind at the origin of replication, which allows the recruitment of cellular polymerases and other cellular proteins that are required for replication (Moody and Laimins 2010; Kajitani et al. 2012).

Many transient viral infections may affect epithelial cells that are subsequently shed or cleared by the immune system. Persistent infection is thought to occur as a result of colonization of stem cells in the basal compartment of the epithelium (Doorbar et al. 2012). These cells by definition have the capacity for self-renewal and can give rise to differentiating cells within the stratified squamous epithelium. By infecting basal stem cells, HPV can persist in the long-lived stem cell compartment and also be passed on to differentiating daughter cells.

As the basal cells give rise to differentiating progeny within the stratified squamous epithelium, HPV episomes are maintained in both cell compartments. Viral genome replication is coupled to cell division; ensuring sufficient genetic material

is passed on to the mother and daughter cells. Within differentiating daughter cells, expression of E1, E2, E6, and E7 is maintained, and expression of E4 increases. The E4 protein promotes a dramatic acceleration in viral genome replication (Fernandes 2013). Meanwhile, E6 and E7 act together to ensure that cells reenter S phase of the cell cycle. The daughter cells travel upward in the stratified epithelium throughout the amplification process, as shown in Fig. 1.2 (Fernandes 2013).

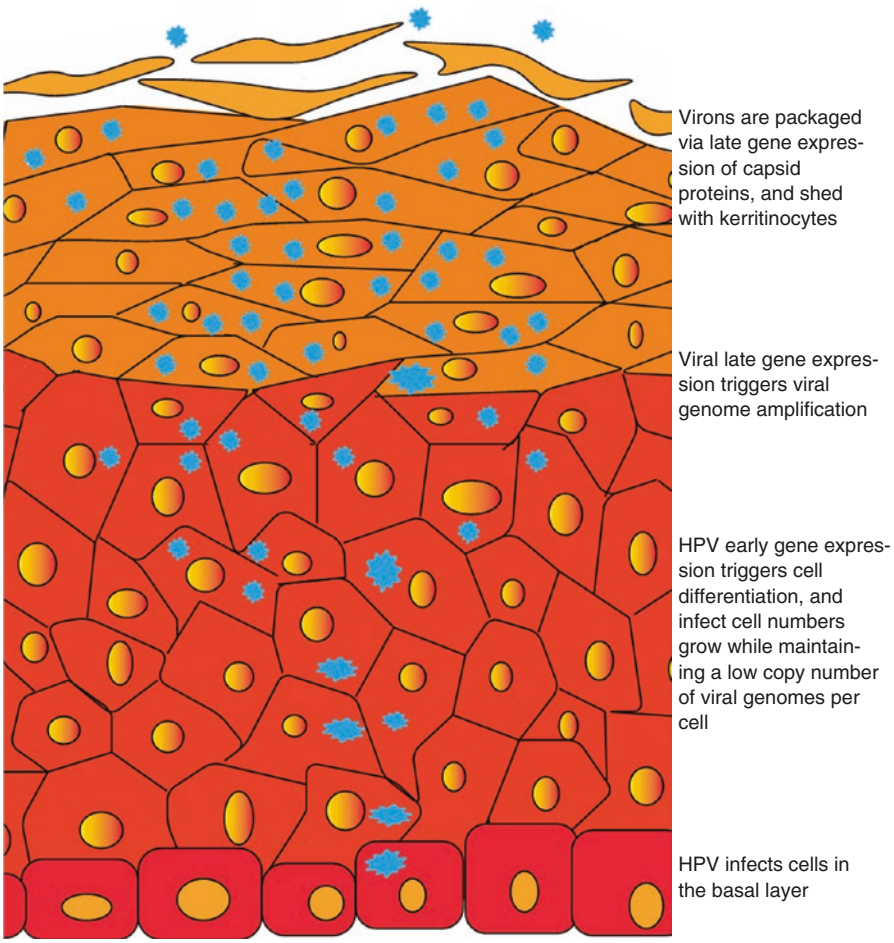

Fig. 1.2 Visualization of viral life cycle and amplification. The HPV virus initially infects cells in the basal layer, entering through micro-wounds. Wound healing promotes cell replication, and the virus is able to further induce cell division, resulting in the growth of the number of infected cells within the area. During this process, the viral genome is kept at a relatively low copy number to help evade immune detection. As the infected cells differentiate and reach the upper layers of the epithelia, viral gene replication is triggered and viral copy number significantly increases. Viral late gene expression leads to the production of functional virions that are shed with the keratinocytes, where they can infect new hosts

Upon reaching the superficial layers of the epithelium, the activity of the late promoter is stimulated (Doorbar 2005). This activation results in expression of viral capsid proteins (late proteins L1 and L2) as well as an upregulation of viral genes that are involved in DNA replication, without altering the activity of E6 and E7 that are required for maintaining the proliferative action of the host cell (Doorbar 2005). As a result, the viral genome copy number increases from 50–200 to several thousand copies per cell (Fernandes 2013; Doorbar et al. 2015). At the terminal stages of cell differentiation, E2 mediates the downregulation of E6 and E7, and the cell exits the cell cycle upon terminal differentiation (Fernandes 2013).

1.3.2.1 Specific Activities of E6 and E7

The E6 and E7 proteins are expressed from a single mRNA transcript. Expression of E6 and E7 is under the control of E2, which represses transcription upon binding to the LCR (Bernard et al. 1989). The primary influence of E6 and E7 proteins on the viral life cycle stems from inhibition of the G1/S cell cycle checkpoint. This causes the transition into S phase in cells that would otherwise not be dividing (Doorbar et al. 2012), which allows the viral genome to replicate, amplify, and eventually be packaged and released. Thus, cell proliferation is a secondary effect that results from the release of the G1/S checkpoint in infected cells.

The E6 and E7 proteins interact primarily with p53 and Rb, respectively. Key downstream cellular processes affected by the E6 and E7 proteins are highlighted in Fig. 1.3. The phenotypic differences seen between the high- and low-risk types relate to the efficiency by which binding and inactivation occur. Key differences in the actions of high- and low-risk protein effects are outlined below.

The E7 protein is structurally similar to the adenovirus E1A protein and shares its 3-domain structure. It was this similarity that leads to the efficient determination that the retinoblastoma (Rb) tumor suppressor was the target of the E7 protein (Dyson et al. 1989; Klingelhutz and Roman 2012). The second conserved domain of E7 (as well as E1A) contains an LXCXE motif, which interacts directly with Rb and its two related proteins, p107 and p130 (Oh et al. 2004). Rb is a critical gene in regulating the cell cycle. Rb negatively regulates the E2F family proteins, resulting in their inactivation during Go and G1 phases of the cell cycle. Under normal conditions, the E2F transcription factors are the regulators of the G1 exit and progression to S phase (McLaughlin-Drubin and Munger 2009). Upon activation of E2F family proteins, transcription of cyclin A and E occurs, leading to expression of CDK2 and entry into S phase (Tommasino 2014) (Fig. 1.3). High-risk E7 protein binds to Rb with tenfold greater affinity (White et al. 1994). E7 binding to Rb leads to its inhibition in low-risk HPV types and proteasomal degradation in high-risk types (Klingelhutz and Roman 2012). E7 has also been shown to bind directly to the CDK inhibitors, p21WAFI, CIPI, and p27KIPI, neutralizing their cell cycle inhibitory effects (Moody and Laimins 2010; Tommasino 2014). Finally, the E7 protein alters chromatin structure within host cells as a result of Rb inhibition. Specifically, E7 counteracts Rb-dependent histone deacetylase (HDAC) regulation

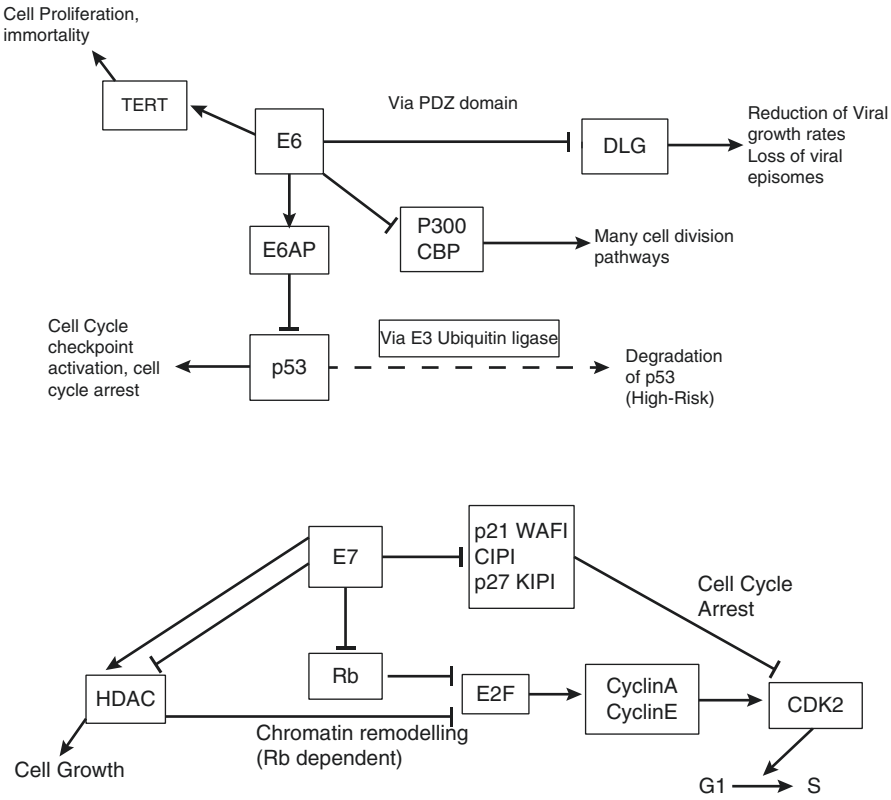

Fig. 1.3 Significant cell signaling pathways of HPV E6 and E7 proteins. E6 and E7 proteins inhibit tumor suppressor proteins p53 and pRb, respectively. The E6 protein associated with the E6-associated protein (E6AP) degrades p53 via an E3 ubiquitin ligase in high-risk HPV types. This association is seen in low-risk types, but does not lead to the degradation of p53; instead a loss of function is seen. The lack of p53 activity results in a loss of the G1/S cell cycle checkpoint arrest. Via a PDZ domain, E6 is able to inhibit DLG and associated proteins, preventing the complex from exerting its function: inhibiting viral growth rates and eliminating viral episomes. E6 can interact with other proteins to enhance cell proliferation and prevent cell senescence. The E7 protein inhibits Rb, which under normal cellular conditions prevents the cell from reentering the cell cycle via the G1 to S phase transition. With Rb activation, E2F is inhibited, preventing cyclin A/E and CDK2 activation. E7 has also been shown to inhibit other proteins that ultimately result in CDK2 deactivation. Finally, E7 binds HDAC proteins, which contributes to unrestrained cell growth through aberrant chromatin remodeling

of E2F-regulated genes. Moreover, Rb-independent interaction of E7 with HDAC has been shown to promote cell growth (Brehm et al. 1999).

The deregulation of the cell cycle induced by E7 function causes levels of the G1/S cell cycle checkpoint protein, p53, to increase which leads to cell cycle arrest (Moody and Laimins 2010). Both high- and low-risk HPV E6 proteins inactivate p53 function to relieve this cell cycle arrest, but only high-risk E6 is able to incite the ubiquitination and degradation of the protein (Klingelhutz and Roman 2012).

Specifically, high-risk E6 proteins interact with E6-associated protein (E6AP), forming a complex that binds to the DNA binding domain of p53 and leading to its degradation via E3 ubiquitin ligase (Fig. 1.3) (Scheffner et al. 1993). While low-risk E6 proteins can also form a complex with E6AP, they do not incite ubiquitination, suggesting that alternate mechanisms of p53 inhibition are more relevant, and ubiquitination targets of the E6 and E6AP complex are unclear (Brimer et al. 2007). The E6 protein itself can also bind to p53 to inhibit function in both high- and low-risk types (Lechner and Laimins 1994), and this is believed to be the main mechanism by which low-risk HPV types inhibit p53 activity (Moody and Laimins 2010).

E6 can also inhibit the activities of p300 and CREB-binding protein (CBP), which are transcriptional co-activators involved in many pathways relevant to cellular differentiation and proliferation (Patel et al. 1999; Moody and Laimins 2010). One of the downstream transcriptional targets of p300/CBP signaling is p53 itself. E6 proteins from both high- and low-risk HPV types bind to p300/CBP; however the inhibition by the low-risk HPV6 E6 was only 50% as efficient as that by the high-risk HPV16 E6 (Patel et al. 1999).

An additional mechanism by which high-risk HPV E6 proteins promote cell cycle continuation and progression is through inhibition and degradation of the tumor suppressor, DLG. High-risk HPV E6 proteins harbor a PDZ binding motif (PDM) located at the C terminus of the protein (Doorbar et al. 2015), which facilitates binding to the PDZ domain within DLG. This binding results in the degradation of DLG and an augmentation in cellular growth rate (Pim et al. 2000; Pim and Banks 2010). Blocking the interaction between HPV16 E6 and DLG was shown to reduce the cellular growth rate and lead to a loss of viral episomes (Brimer et al. 2007; Nicolaides et al. 2011). While low-risk HPV E6 proteins are also critical for maintenance of viral episomes (Oh et al. 2004), unlike high-risk HPV E6 proteins, they are apparently unable to induce the degradation of DLG (Brimer et al. 2007).

The E6 protein has also been shown to interact with telomerase-related enzymes, leading to an increase in TERT transcription. This allows indefinite proliferation and the maintenance of cellular immortality, although this is only seen in high-risk HPV types (Klingelhutz and Roman 2012; Tommasino 2014). There are many additional known targets of the E6 protein; however their exact cellular functions are unknown (Tommasino 2014).

1.3.3 Virus Synthesis and Release

When the basal daughter cell approaches the surface of the stratified epithelium, it reaches terminal differentiation, and encapsulation of the viral genome is triggered (Kajitani et al. 2012; Doorbar et al. 2015). Alternative RNA splicing facilitates the turnover from early to late gene translation (Kajitani et al. 2012). The capsid proteins, L1 and L2, are expressed and transported into the nucleus where capsid assembly takes place. L2 is guided into the nucleus through its association with

host protein, DAXX. PML bodies attract high levels of L2 protein and act as a scaffold to facilitate viral capsid assembly. L1 is then recruited to these sites. L1 is sufficient for viral capsid assembly, but this process is more efficient in the presence of L2 (Doorbar 2005). On the surface layer, dying keratinocytes undergo a change lose their mitochondrial oxidative phosphorylation capability, decreasing the overall pH of the viral environment. As a result, disulfide bonds form between L1 proteins, which stabilizes the capsid structure (Buck et al. 2005; Doorbar et al. 2015). Virus maturation occurs as keratinocytes become cornified cells that are shed along with mature packaged virions (Bryan and Brown 2001). Encapsulated virions are then released from the shedding cells into the environment, where they can survive for greater than 1 week prior to reinfection into a new host (Roden et al. 1997).

1.4 Pathogenesis of HPV

Most HPV infections are cleared within 6–12 months without lasting effects (Tommasino 2014). However, HPV is the causative agent in a number of neoplastic conditions that have a significant impact on human health. It is therefore important to consider the many factors involved in the transition from viral colonization to a disease state.

1.4.1 Role of HPV in RRP

Recurrent respiratory papillomatosis (RRP) is a rare disease affecting children. RRP is characterized by periods of recurrent growth of lesions in the mucosal surfaces of the upper airways. HPV is the causative agent and is found within 91–100% of lesions (Draganov et al. 2006), with the variety arising from different sequencing methods used to detect HPV. With modern methods, it can be assumed that all cases of RRP are caused by HPV infection.

Interestingly, the copy number of the HPV genome seen in RRP, at around 10^2–10^7 copies per μg, is significantly higher than that seen in carcinomas of the cervix, pharynx, and larynx (Donne et al. 2010). Additionally, dramatic changes in copy number are seen throughout the course of the disease (Major et al. 2005). Increased copy number of HPV DNA is considered to be associated with severity in RRP (Major et al. 2008).

Despite the ubiquity of HPV exposure, RRP remains a rare disease entity. The reasons for the discrepancy are not well understood, and no clear biomarkers have been confirmed to predict RRP incidence in children. Immune status is thought to be a major contributor to RRP, as those with immunodeficiency (e.g., organ transplant and AIDS patients) experience more severe disease course in

other HPV-associated diseases (Doorbar 2005; Stern et al. 2007). Likewise, immune function likely influences RRP progression in children. A prospective study of 20 children with RRP examined disease severity and course compared to immunological factors measured at regular intervals of 6 months over the course of the study (Stern et al. 2007). In this small study, the ratio of CD4 + T cells to cytotoxic CD8 + T cells was reduced in RRP patients compared to matched negative controls (Stern et al. 2007). Other studies have found additional differences between the immune function (both innate and adaptive immunity) of RRP patients and controls (Bonagura et al. 2010; Lucs et al. 2015). Nonetheless, no single host immune factor identified to date can fully explain the diagnosis or severity of RRP.

1.4.2 Neoplastic Transformation by E6 and E7

The neoplastic transformation of HPV stems in large part from disruption of the tumor suppressor proteins p53 and Rb by E6 and E7, respectively. Low-risk E6 and E7 cause aberrant cell proliferation within stratified squamous epithelia leading to warts, RRP, and other benign papillomatous conditions. The development of invasive malignancy is uncommon in tissues infected with low-risk HPV types. In RRP, for example, approximately 3–6% of cases (<1% in juvenile cases) develop into a malignant carcinoma (Donne et al. 2010). High-risk E6 and E7 impart a massively greater risk for progression toward invasive malignancy due to higher potency of p53 and Rb inhibition.

The role of E6 and E7 proteins in neoplastic transformation can be illustrated by the way they promote the hallmarks of cancer. First described by Hanahan and Weinberg in 2000 (Hanahan 2000) and expanded in 2011 (Hanahan and Weinberg 2011), the hallmarks of cancer describe a rational framework for understanding processes that lead to neoplastic transformation. The E6 and E7 proteins perturb pathways involved in several of the hallmarks, including:

- *Sustaining proliferative signaling*
- *Evading growth suppression*
- *Resisting cell death*
- *Enabling replicative immortality*
- *Activating invasion and metastasis*
- *Deregulating cellular energetics*

E6 and E7 promote these hallmarks of cancer through additional mechanisms other than p53 and Rb inhibition. For instance, high-risk E6 promotes *evasion of growth suppression* through inhibition of cell-to-cell contact and loss of cell polarity (Pim et al. 2000; Pim and Banks 2010), and high-risk E7 *deregulates cellular energetics* (McLaughlin-Drubin and Munger 2009). Cellular metabolism in HPV-infected cells is shifted away from mitochondrial respiration and oxygen consumption toward anaerobic glycolysis, a change that is triggered in part by E7 expression (McLaughlin-Drubin and Munger 2009).

1.4.3 Neoplastic Transformation by Additional Mechanisms

The expression of E6 and E7 is integral to neoplastic transformation of HPV-infected tissues. Nonetheless, E6 and E7 are insufficient to induce invasive malignancy in the absence of additional "second hit" mutations. Supporting this, high-risk E6 and E7 expression is able to cause immortalization of human keratinocytes in culture (Brehm et al. 1999), but activation of additional oncogenes is necessary to induce tumors when the cells are injected into mice (McLaughlin-Drubin and Munger 2009).

A number of processes contribute to accumulation of second hit mutations that promote invasive malignancy. First, passive accumulation of random mutations is far more likely to occur within replicating cells than in uninfected quiescent cells. Second, innate antiviral APOBEC-mediated mutagenesis, which is meant to damage foreign viral DNA, also can result in collateral damage within host oncogenes and tumor suppressors (Rebhandl et al. 2015). Third, viral genome integration leads to activation of oncogenes or inactivation of tumor suppressors through varied mechanisms. Fourth, chromosomal instability resulting in aneuploidy and rearranged chromosomes (Duensing and Münger 2002) is tolerated by HPV-infected cells as a result of p53 inhibition (White et al. 1994). Thus, a multitude of processes can lead to increased mutagenesis and heightened genomic instability, which ultimately can disrupt normal cellular and tissue homeostasis.

Integration of the viral genome into the host DNA, while not essential, contributes to the development of invasive malignancy (Moody and Laimins 2010; Tommasino 2014). As described above, host genes that are activated or disrupted by viral integration can directly drive oncogenesis. Moreover, disruption of the E2 gene upon linearization of the viral genome results in higher expression of E6 and E7. Virus integration into the host genome often occurs at the E2 locus, therefore disrupting gene function (Donne et al. 2010). However, recent high-throughput sequencing studies have revealed that viral integration in cervical cancer can occur at other viral loci in addition to E2 (Hu et al. 2015), so this mechanism might not be necessary for the development of invasive malignancy.

Despite the variety of mechanisms by which HPV can induce a neoplastic change, as mentioned previously, very few HPV infections even with high-risk types cause neoplasia. Persistence of the virus is the critical factor in neoplastic transformation (Moody and Laimins 2010; Doorbar et al. 2012). Immune-mediated clearance of acute infections eliminates the risk of transformation (Tommasino 2014). Individuals whose immune systems fail to clear the virus, however, are at risk. With persistence, unrestrained cellular division can continue.

1.4.4 Evasion of Immune-Mediated Clearance

Evasion of the immune recognition and clearance is critical for HPV to infect and persist within epithelial tissues. Several intrinsic characteristics of HPV allow it to counter immune detection. First, the virus produces no cell death or viral lysis. Second, the entire viral life cycle occurs within intact epithelial cells resulting in no

virus entering the bloodstream. Third, viral replication does not promote inflammation (Doorbar et al. 2015). In addition, there are a number of molecular mechanisms by which HPV evades both adaptive and innate immunity.

1.4.4.1 Mechanisms of HPV Evasion of Adaptive Immunity

HPV actively blocks antigen presentation in infected keratinocytes. HPV-related tumors experience a loss of major histocompatibility complex (MHC) I, which is required for antigen recognition by T cells (Kanodia et al. 2007). E5, E6, and E7 each contribute to reduced MHC-I expression on the surface of infected cells (Kanodia et al. 2007). Moreover, many viral peptides are similar in composition to human peptides; thus, endogenous mechanisms for self-tolerance are co-opted by the virus to minimize immune recognition (Kanodia et al. 2007).

1.4.4.2 Mechanisms of HPV Evasion of Innate Immunity

Under normal conditions, keratinocytes express pathogen recognition receptors (PRRs), which recognize specific pathogen-associated molecular patterns (PAMPs) (Stanley 2012; Zhou et al. 2013). Two classes of PRRs drive recognition of HPV by keratinocytes: Toll-like receptors (TLR family) and nucleotide-binding domain—leucine-rich repeat-containing PRRs (NLR family) (Stanley 2012).

TLR activation triggers an antiviral response through type I interferon (IFN) signaling (Zhou et al. 2013). In HPV-infected cells, E7 blocks the antiviral effects of type I IFN signaling (Stanley 2012). In addition, E6 inhibits transcription of type I IFN mRNAs (Stanley 2012; Doorbar et al. 2015) as well as downstream JAK-STAT activation by type I IFN (Stanley 2012; Doorbar et al. 2015).

The NLR response is routinely elicited by keratinocytes during cell injury and stress. Downstream signaling following NLR binding triggers interleukin 1 (IL-1) secretion (Stanley 2012). IL-1 secretion is critical for the activation of antigen-presenting cells of the skin and mucosa. Both E6 and E7 dampen the IL-1 response seen upon NLR activation (Stanley 2012).

1.5 Summary

The HPV family displays striking diversity in nucleotide sequence, but there is much in common in the manner by which distinct HPV types infect human tissues and cause disease. Despite a small and relatively simple genomic makeup, perturbations caused by HPV infection can activate many of the classic hallmarks of cancer. Viral factors are able to co-opt normal homeostatic processes within infected cells and squamous epithelial tissues to establish persistent infections, evade host immune detection, and activate neoplastic pathways.

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Chapter 2
The Epidemiology of Recurrent Respiratory Papillomatosis

Paolo Campisi

Abbreviations

APSU	Australian Paediatric Surveillance Unit
CDC	Centers for Disease Control and Prevention
HLA	Human leukocyte antigen
HPV	Human papillomavirus
ICD	International Classification of Diseases
JoRRP	Juvenile-onset recurrent respiratory papillomatosis
KIR	Killer-cell immunoglobulin-like receptors
PPV	Positive predictive value
RRP	Recurrent respiratory papillomatosis

2.1 Epidemiology: A Global Perspective

For rare conditions such as juvenile-onset recurrent respiratory papillomatosis (JoRRP), it is important to have a firm understanding of the epidemiology of the disease. This is only possible by combining the collective experience of multiple centers as individual institutional experience is typically limited. Collaborative efforts are necessary to define the clinical and economic burden the condition poses to the health-care system and guide public health initiatives such as vaccination programs. For the patient, understanding the disease is important for patient and family counseling, the development of novel primary

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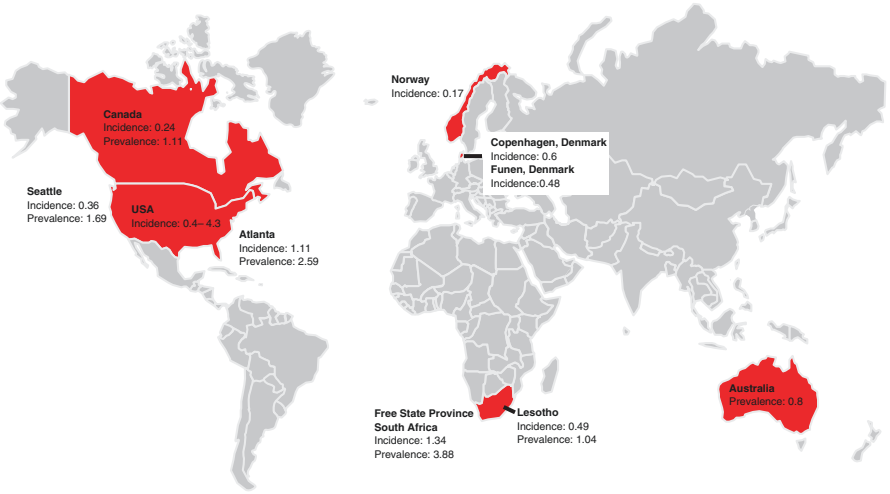

Fig. 2.1 Global reported rates of incidence and prevalence of JoRRP. Rates are per 100,000 children

and adjuvant treatment strategies, and early detection or mitigation of serious complications such as lower airway dissemination of papillomas and malignant transformation.

Several health-care jurisdictions have developed databases and registries at a regional or national level with the common goal of understanding JoRRP. The results of these efforts have been reported from health-care regions in North America, Europe, Australia, and Africa (see Fig. 2.1).

2.1.1 Africa

Estimates of incidence and prevalence for JoRRP have been reported for the Free State province of South Africa and Lesotho, a small country of 1.9 million people geographically situated within South Africa (Seedat 2014). The Free State province has a population of 2.75 million people, and all cases of JoRRP from the Free State and Lesotho are managed at the same referral center. The retrospective study reviewed all cases in patients under the age of 15 years presenting between January 2011 and December 2013. The estimates of incidence and prevalence were calculated based on midyear populations of children aged 0–14 years published by Statistics South Africa and the Lesotho Bureau of Statistics.

During this 3-year period, 31 new cases of JoRRP were diagnosed in the Free State province with an average incidence of 1.34 per 100,000 per year. Year over year, the incidence fluctuated between 0.52 and 2.36 per 100,000 population per year. The average prevalence was 3.88 per 100,000 per year (range, 3.10–4.73 per 100,000 population per year). The median age at diagnosis was 4.3 years, and the male to female ratio was 1:1.21.

In comparison, 10 new cases of JoRRP were referred from Lesotho, indicating an incidence of 0.49 per 100,000 and a prevalence of 1.04 per 100,000 population per year. The median age at diagnosis was slightly lower at 3.8 years, and the male to female ratio was 4:1. The variability in the statistical measures is expected in jurisdictions with relatively small populations. Moreover, the measures of incidence and prevalence are probably an underestimation due to more difficult access to medical care for patients from remote communities and the high rate of poverty in the Free State province and Lesotho. Although not specifically studied, the high prevalence of coinfection with HIV may account for the higher incidence and prevalence rate reported for Africa compared to populations in Europe, Australia, and North America.

Estimates of disease burden have also been reported for academic referral centers in cities in Ghana and Nigeria. In 2012, Baidoo and Kitcher retrospectively reviewed the theater records at the ENT Unit of Korle Bu Teaching Hospital, Accra, Ghana (Baidoo and Kitcher 2012). Over a 10-year period, 69 patients were treated for RRP. The median age of the patients was 8.5 years (range 2–54 years). Forty-eight (70%) of the patients were children 10 years of age or younger. The patients were subjected to a high cumulative rate of tracheostomy of 14.5%. The authors recognized the need to avoid tracheostomy to prevent the distal airway spread of papillomas. However, limitations to accessing medical care in remote communities rendered the need for tracheostomy unavoidable.

A similarly large proportion of pediatric patients were identified in two studies from Nigeria. In Ibadan, Nigeria, 74.4% of RRP patients were children (Nwaorgu et al. 2004). In Enugu, Nigeria, an 11-year review of 54 cases of RRP revealed that 51.8% of patients were children (Mgbor et al. 2005). Epidemiological data from South Africa, Lesotho, Ghana, and Nigeria confirm that RRP has a significant pediatric footprint.

2.1.2 Australia

Efforts to estimate the incidence and prevalence of JoRRP in Australia have been spearheaded by Novakovic and Brotherton. In a recently published study, Novakovic and colleagues reported the results of a retrospective review of pediatric RRP cases presenting at three tertiary pediatric hospitals in New South Wales (Novakovic et al. 2016). Cases were identified from hospital records using ICD-10 codes and RRP-related procedure codes. The local epidemiological results were subsequently applied to national hospital separations data to estimate national disease prevalence.

The retrospective review at the three pediatric hospitals in New South Wales identified 30 cases of JoRRP with a median age of onset of 36 months. There was a small female preponderance (57%). The use of ICD-10 codes to identify cases was found to have a very high positive predictive value of 98.1%. Assuming the high positive predictive value was consistent nationally, the local data was applied to national hospital separations data. This exercise revealed a national (estimated)

JoRRP prevalence rate of 0.8 per 100,000 children <15 years of age between 2000 and 2013. The peak rate of 1.1 per 100,000 was found in 5- to 9-year-old children.

The limitations of this study design include the need for a consistent positive predictive value of ICD-10 codes across hospitals, the regional distribution of RRP treatment to specialized centers, and missing local data from private hospitals.

Australia has also established an Australian Paediatric Surveillance Unit (APSU) that facilitates the national active surveillance of uncommon diseases of childhood including JoRRP (Deverell et al. 2014). APSU uses standardized case definitions and distributes a report card to 1400 practicing pediatricians and child health specialists every month. Response rates have remained at approximately 90% for the past 20 years. In the 2013 APSU report, there were six confirmed cases and one probable case of JoRRP in 2012 and one confirmed case and two probable cases in 2013. The data suggests there has been a decline in the incidence of JoRRP. This reporting structure has its limitations but may prove useful in the surveillance of JoRRP in the postvaccination era.

2.1.3 Europe

JoRRP epidemiological data have been reported for several geographical areas of Europe including Denmark, Norway, the United Kingdom, and France. Robust data have been reported for the Scandinavian countries but is very limited for the rest of Europe.

In 1988, Bomholt identified and analyzed the clinical course of 23 patients treated for RRP in the Copenhagen region during a 4-year period (Bomholt 1988). Although the age range of the patients was 3–67 years (median 18 years), all patients presented with RRP in childhood. Between 1980 and 1983, seven new cases of JoRRP presented out of an at-risk population of 300,000 children aged 0–14 years, indicating an incidence of 0.6 per 100,000 children.

The incidence of JoRRP was calculated for another Danish subpopulation by Lindeberg and Elbrønd in 1990 (Lindeberg and Elbrønd 1990). They calculated the incidence of RRP in patients that lived in Funen or Jutland at first presentation between 1965 and 1984. The population of this area is approximately 2.8 million persons. They classified presentations at 20 years of age or younger as "juvenile." The observed incidence of JoRRP for patients below 20 years of age was 0.36 per 100,000. Adjustments to include only cases with presentation of JoRRP below 15 years of age resulted in an incidence of 0.48 per 100,000 children.

Omland and colleagues conducted a study to estimate the incidence of juvenile and adult RRP in two Norwegian regions with a combined population of 3.7 million inhabitants (Omland et al. 2012). All patients were treated in three hospitals. Patients were identified with ICD-10 codes, procedure codes, and electronic pathology archives. The search protocol identified 115 patients treated between 1987 and 2009, of which 22 patients had a juvenile onset of disease. JoRRP was defined as disease onset before puberty. The overall incidence of JoRRP was 0.17 per 100,000

children per year. The median age at diagnosis was 4 years with a 3:1 male preponderance. The analysis did not detect a statistically significant change in incidence over the study period.

Estimates of incidence and prevalence of JoRRP have not been reported for other European countries. In the United Kingdom, epidemiological data is limited to a retrospective review of cases treated at Christie Hospital and the Manchester Royal Infirmary, Manchester (Hartley et al. 1994). The study analyzed 59 cases of RRP presenting between 1974 and 1992. Twenty of the 59 patients were children under 16 years of age at disease onset. The study revealed that HPV 11 was more often detected in younger patients and that all seven patients with distal airway disease at presentation were children. In another UK study, consultant members of the British Association of Paediatric Otorhinolaryngology were surveyed regarding the management of patients with RRP (Tasca et al. 2006). Although information regarding 103 patients was elicited, there is no breakdown of data according to the age of the patients. A poignant conclusion of the study was the recognition of the need to establish a centralized national database to which consultants can report cases.

In 2009, an attempt to initiate a database that could serve as a European multicenter epidemiological study was proposed by a group in Lyon, France, under the leadership of Froehlich (Carvalho et al. 2009). This group published a retrospective study of RRP cases in a tertiary care teaching hospital and developed a standardized intake questionnaire. Between January 2005 and July 2007, 72 patients were entered into the RRP database. Of the patients registered, 24 had JoRRP defined as diagnosis before the age of 12 years. The mean age at first treatment was 5 years with a small female preponderance. Although this study represented the first data registry of RRP patients in France and Europe, no further updates have been published by this group.

2.1.4 North America

The first estimates of incidence and prevalence of JoRRP in the United States (and worldwide) were derived from a survey study by Strong and colleagues in 1976 (Strong et al. 1979). The survey was distributed to 4200 practicing otolaryngologists in the United States. Responses were received by 51% of the surgeons identifying 1500 new cases of RRP in all age groups, 56% of which were children 16 years of age or younger. The authors estimated the national incidence of JoRRP at 0.4 per 100,000 children. This value was surprisingly similar to future rates reported for Scandinavian countries and Canada.

In 1995, Derkay championed a second national survey study of otolaryngologists in the United States (Derkay 1995). A three-page survey was administered to all active US members of the American Society of Pediatric Otolaryngology (ASPO), American Broncho-Esophagological Association (ABEA), and 1000 board-certified otolaryngologists practicing in the United States through a random mailing list provided by the American Academy of Otolaryngology—Head and Neck Surgery.

More than 1300 surveys were mailed out and 315 were returned. The highest response rates were from ASPO members (81%) and surgeons in a full-time academic practice (77%). The survey identified 2354 new pediatric cases over a 12-month period. Based on US census data, the incidence of JoRRP in children 14 years of age and younger was estimated at 4.3 per 100,000 children. The estimated incidence rate is almost tenfold higher than previously reported for the United States and other health jurisdictions. The higher response rate from ASPO members and full-time academics may have skewed the national incidence estimate. The survey also identified 5970 active cases (in the preceding 3 years), requiring 16,597 surgical procedures over a 12-month period at an estimated cost of $109 million (USD). Extralaryngeal spread was identified in 31% of children, 13 children developed squamous cell carcinoma, and 14% required a tracheostomy. Interestingly, there were only four sibling sets identified in this large series of patients.

A meticulous calculation of the incidence of JoRRP in two US cities with a similar population was reported by Armstrong and colleagues in 2000 (Armstrong et al. 2000). The authors recruited the participation of 240 physicians in a 24-county area of Atlanta and an 8-county area of Seattle. The physicians were requested to identify all patients under the age of 18 years treated for JoRRP during the 1996 calendar year. The study protocol identified nine new cases of JoRRP in Atlanta and three cases in Seattle. Using 1990 US Census data, the authors calculated the incidence of JoRRP in Atlanta at 1.11 per 100,000 and in Seattle at 0.36 per 100,000. The prevalence for Atlanta and Seattle was estimated at 2.59 per 100,000 and 1.69 per 100,000, respectively. The study demonstrated that when studied at a smaller scale, there may be regional differences in incidence and prevalence of JoRRP.

A novel approach to estimate the incidence and prevalence of JoRRP in the United States was completed with medical claims insurance databases representing both privately and publicly insured children. The study by Marisco and colleagues was the first to assess differences in epidemiology in large, geographically and socioeconomically diverse source populations (Marisco et al. 2014). Study populations were derived from the two databases using predefined algorithms. Children aged 0–17 years were identified with continuous health plan coverage for at least 90 days (or 30 days if born in 2006) during the 2006 calendar year. ICD and procedure codes were used to identify potential cases followed by chart validation protocols to calculate the positive predictive value (PPV) of the claims-based algorithms. The overall PPV-adjusted incidence of JoRRP in 2006 was 0.51 per 100,000 in privately insured children and 1.03 per 100,000 in publicly insured children. The peak incidence was identified in children aged 0–4 years for both privately and publicly insured children. The PPV-adjusted prevalence of JoRRP in 2006 was 1.45 per 100,000 in privately insured children and 2.93 per 100,000 in publicly insured children. The PPV of the incidence and prevalence algorithms was 34% and 52%, respectively. Nonetheless, the discrepancy in calculated incidence and prevalence between privately and publicly insured children suggests a higher susceptibility and severity of disease in children with lower socioeconomic status.

In Canada, a population-level national database was developed through a JoRRP Working Group that networked all tertiary pediatric referral centers (Campisi et al.

2010). Canada represents an ideal location for a JoRRP database because of the universal health-care system and strict centralization of specialized pediatric care to tertiary centers. In addition, the population is large enough to derive accurate measures of incidence and prevalence but small enough to thoroughly collect population-level data. The Canadian national database was predicated on a well-defined case definition of JoRRP, a strategy to accurately identify cases across the country, a stable JoRRP Working Group membership, a standardized case report form, and a centralized database. Twelve academic pediatric centers contributed to the database. Between 1994 and 2007, 243 cases of JoRRP were identified nationally. Almost 50% of the cases were identified in Ontario and Quebec, the most populous provinces in the country. The 243 children underwent more than 3000 surgical procedures during the time frame of the study, providing approximately 837 patient-years of retrospective observation.

When the incidence and prevalence data was analyzed regionally, the rates of incidence were highly variable year over year. This is not unexpected given the rare occurrence of the condition. This finding demonstrates that a sufficiently large population is required to derive meaningful epidemiological measures. Nationally, the incidence rate was calculated at 0.24 per 100,000 children aged 14 years or younger. The prevalence rate was 1.11 per 100,000 children. These values are actual measures, not estimates. The median age at diagnosis was 4.4 years (range 1 month–14 years) with a slight male preponderance. Patients underwent a median of seven surgical procedures throughout the course of their disease.

The Canadian national database is currently being used as a platform for the surveillance of incident and prevalent cases of JoRRP following the introduction of provincial HPV vaccination strategies introduced in 2007. The ongoing surveillance study will be further addressed later in the chapter.

2.2 The Natural History of JoRRP

A thorough understanding of the clinical course of JoRRP is important for patient and family counseling, anticipating disease progression and complications, and the interpretation of therapeutic interventions. The characteristics of the natural history of JoRRP have been pieced together from several studies with large cohorts of patients. For example, the initial results from the US national registry for JoRRP, which analyzed the clinical course of 399 children, revealed that children diagnosed under the age of 3 years were 3.6 times more likely to require more than 4 surgical procedures per year (Armstrong and Derkay 1999). This study also demonstrated that the mean duration of the disease was 4.4 years. This basic information regarding clinical course is very important to prepare the parents of newly diagnosed children to cope with the financial and psychological challenges they are likely to encounter.

In a follow-up study of the US national registry for JoRRP, clinical course—defined as the number of anatomical sites involved with papillomas—was characterized over a follow-up period of 4.3 years.(Reeves et al. 2003) The updated registry

included 603 children that underwent a mean of 5.1 surgeries annually. The analysis revealed that the vast majority of children (74.2%) had stable disease over time and 5.8% showed progression of papillomas to new anatomical sites and 17.9% had no evidence of disease for at least 1 year. Unfortunately, the study was not designed to measure any change in the rate of surgery required year over year.

Changes in the rate of surgery over time, however, have been addressed by population-level studies in Denmark and Canada. In 2004, Silverberg and colleagues published a study that captured and mapped the clinical course of all children with confirmed RRP born in Denmark between 1974 and 1993 (Silverberg et al. 2004). The authors identified 57 patients with JoRRP with a median age of onset of 5.5 years. The most relevant finding was a high rate of surgery required for the first few years after diagnosis which decreased as the patient aged. This was found for most (67%) of the patients. The surgery rate decreased over time from 1.2 to 0.3 surgeries per person-year for children aged 5 to 10 years and from 0.8 to 0.1 surgeries per person-year for children aged 10 to 15 years. Another important finding was that children diagnosed under the age of 5 years had a significantly higher rate of surgery than children diagnosed older than 5 years.

A similar decrease in the rate of surgery over time was observed in a cohort of 67 patients treated between 1994 and 2004 at the Hospital for Sick Children in Toronto, Canada (Hawkes et al. 2008). The 67 patients underwent a total of 926 surgical procedures with a median number of 9 surgeries per patient. In the study, nonlinear modeling equations were developed to describe the time course of required surgeries. For the entire cohort, the mean annual surgery rate decreased by 12% per year. Further modeling demonstrated that 27 patients (59%) had a decelerating rate of surgeries with time, 17 (37%) had a constant rate of surgery, and 2 (4.3%) had an accelerating rate of surgery based on a median follow-up period of 3 years.

The important observation of a decreasing rate of surgery over time in the majority of patients must be considered when interpreting uncontrolled therapeutic trials with novel surgical techniques or adjuvant therapies. Failure to consider the natural clinical course of JoRRP will lead to the erroneous conclusion that the intervention being studied caused the observed decrease in surgical rate.

2.3 Risk Factors for the Acquisition of JoRRP and Disease Severity

There are several studies in the medical literature that have assessed the risk factors for the acquisition of JoRRP and disease severity. A recent systematic review by Niyibizi and colleagues thoroughly and succinctly summarized the findings of 32 observational studies encompassing a total of 2287 JoRRP cases (Niyibizi et al.

Table 2.1 Summary of factors increasing the risk of acquisition of JoRRP

Risk Factor	Description	Studies
Maternal factors		
Maternal age	Mother < 20 years	Shah et al. (1998) and Silverberg et al. (2004)
Maternal genital warts during pregnancy	Active condylomata	Silverberg et al. (2004)
Birth order	First born	Shah et al. (1998)
Vaginal delivery duration	Duration > 10 h	Silverberg et al. (2004)
Host genetic and immune response factors		
HLA alleles	Presence of DRB1*, DQB1* susceptible alleles	Gelder et al. (2003), Gregoire et al. (2003), and Bonagura et al. (2004)
KIR and HLA gene combinations	DRB1/DQB1 susceptible alleles associated with KIR3DS1, KIR2DS1, KIR2DS5	Bonagura et al. (2010)

2014). The purpose of the systematic review was to summarize the risk factors that render a patient susceptible to JoRRP and a severe clinical course.

The risk factors for the acquisition of JoRRP can be broadly classified as either maternal factors or host genetic and immune response factors. The factors that increase the risk of acquiring JoRRP are summarized in Table 2.1. The most significant factors include a low maternal age, birth order, maternal genital warts during pregnancy, and the presence of specific HLA alleles. Factors that do not increase the risk of acquiring JoRRP include a history of RRP in the biological parents and serum immunoglobulin levels (Gerein et al. 2006; Stern et al. 2007).

Severe or aggressive JoRRP has been defined in many ways including a very young age at presentation, the need for four or more surgical procedures per year, the need for more than ten surgical procedures over the course of the disease, papillomata involving multiple anatomical regions of the airway, peak severity score, peak surgical frequency, distal airway spread, pulmonary involvement, the need for a tracheostomy, malignant transformation of the disease, and others. The literature suggests that the most important risk factors for the development of severe disease include a young age at presentation and infection with HPV 11 (Niyibizi et al. 2014). Other factors that have been studied include socioeconomic status, maternal pregnancy factors, and host genetic and immune response factors. The risk factors shown to predispose to severe disease are summarized in Table 2.2. Factors that have not been shown to increase the risk of severe disease include the sex and race of the patient, low socioeconomic status, and viral load (Armstrong and Derkay 1999; Reeves et al. 2003; Gabbott et al. 1997; Leung et al. 2007; Gerein et al. 2005).

Table 2.2 Summary of factors increasing the risk of developing severe or aggressive JoRRP

Risk Factor	Description	Studies
Age at presentation	Younger age (<2–5 years at presentation) associated with severe disease	Gabbott et al. (1997), Armstrong and Derkay (1999), Snowden et al. (2001), Reeves et al. (2003), Silverberg et al. (2004), Wiatrak et al. (2004), Leung et al. (2007), Shehata et al. (2008), Buchinsky et al. (2008), Campisi et al. (2010), and Omland et al. (2014)
HPV genotype	Infection with HPV 11 associated with severe disease	Rimell et al. (1997), Rabah et al. (2001), Wiatrak et al. (2004), Gerein et al. (2005), Draganov et al. (2006), Shehata et al. (2008), Buchinsky et al. (2008), Carvalho et al. (2009), and Seedat et al. (2010)
Host genetic and immune response factors		
IL-2, IL-2 receptor	Levels lower in severe cases	Snowden et al. (2001)
HLA alleles	Presence of DRB1*, DQB1* susceptible alleles	Bonagura et al. (2004)
KIR genes	Lack of KIR genes 3DS1 and 2DS1 associated with severe disease	Bonagura et al. (2010)

2.4 Surveillance

As mentioned earlier in the chapter, understanding the epidemiology of rare conditions (such as JoRRP) through databases, registries, and collaboration across academic institutions is important for many reasons. The reasons include mitigation of risk factors of disease acquisition and severity, gauging the economic burden on the health-care system, development and study of novel treatments, and guiding public health policy decisions such as the funding of vaccination programs.

The introduction of HPV vaccines in 2006 to prevent cervical cancer presented a unique opportunity to prevent various other malignant and nonmalignant HPV-related diseases such as RRP. Commercially available vaccines were designed to protect against infection with HPV 6 and 11 (and other subtypes) which were recognized as the cause of RRP. The hope was that the widespread vaccination of young women and men would promote a "downstream" reduction in RRP by either protecting the next generation of youth from HPV or decreasing the rate of genital warts in the general (vaccinated and unvaccinated) adult population, a known risk factor for the vertical transmission of HPV from mother to child. Indeed, a precipitous drop in the rate of genital warts has already been documented in many countries with a high level of HPV vaccine uptake.

As this phenomenon is unfolding, it has become very apparent that accurate estimates of the incidence and prevalence of JoRRP at baseline will be required to detect any decreases in JoRRP after the introduction of vaccination programs.

Surveillance programs for JoRRP are already in effect in Australia and Canada and will soon be initiated in the United States. The Australian Paediatric Surveillance Unit (APSU), mentioned above, has been monitoring the rate of JoRRP incidence since 2011. APSU has extended its program by surveying pediatric otolaryngologists, designing a case reporting form, and offering HPV typing to all incident cases (Brotherton et al., Abstract presented at IPV 2017). The rate of JoRRP declined from 0.3 per 100,000 children under the age of 15 years in 2012 to 0.04 per 100,000 in 2016. A longer-term surveillance is required to determine if the decreasing trend will be sustained as JoRRP incident rates are known to fluctuate year over year.

In Canada, the JoRRP Working Group has been monitoring the incidence and prevalence of JoRRP since 2007 when HPV vaccination programs were initiated. Ten-year surveillance data will be complete at the end of 2017. Interim analysis of data at the end of 2012 (5-year follow-up) has revealed an approximately 25% reduction in the incidence and prevalence of JoRRP nationally (unpublished data). In the United States, Derkay has initiated a registry protocol to monitor the national prevalence of JoRRP through a multi-institutional infrastructure sponsored by the Centers for Disease Control and Prevention (CDC) in Atlanta, USA. The registry plans to enroll pediatric cases (0–17 years of age) for a period of 2 years. Approximately 45 centers have been identified for collaboration. The CDC will provide HPV typing for all registered cases. No data is available at this early stage of the project.

The encouraging developments in vaccine technology and observed decreases in JoRRP in Australia and Canada are unprecedented. The emerging data may herald an era in which the eradication of JoRRP is considered possible.

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Chapter 3
Monitoring Public Health Impact of HPV Vaccination on RRP

Vidisha Singh, Elissa Meites, and Adam Klein

Abbreviations

4vHPV	Quadrivalent HPV vaccine
9vHPV	Nonavalent HPV vaccine
ACIP	Advisory Committee on Immunization Practices
AORRP	Adult onset recurrent respiratory papillomatosis
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CSTE	Council of State and Territorial Epidemiologists
DNA	Deoxyribonucleic acid
ENT	Ear, nose, and throat
EVMS	Eastern Virginia Medical School
HPV	Human papillomavirus
ICD	International Classification of Disease
JORRP	Juvenile onset recurrent respiratory papillomatosis
MSM	Men who have sex with men
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health

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NNDSS	National Notifiable Disease Surveillance System
PPV	Positive predictive values
RRP	Recurrent respiratory papillomatosis
UK	United Kingdom
US	United States

3.1 Introduction

Recurrent respiratory papillomatosis (RRP) is a condition marked by benign, wart-like lesions in the respiratory tract as a result of infection with human papillomavirus (HPV) types 6 and/or 11. These types are categorized as low-risk or non-oncogenic types and together are responsible for greater than 90% of all cases of anogenital warts (Wiley et al. 2002). Two forms of RRP exist, juvenile onset (JORRP) and adult onset (AORRP), reflecting age of symptom onset (Lacey et al. 2006). Studies have demonstrated that the majority of patients with JORRP become symptomatic and are diagnosed before 5 years of age, whereas AORRP presents later in life with much more age variability and peak incidence between 20 and 40 years of age (Strong et al. 1976; Armstrong et al. 1999; Derkay 2001). Although RRP is rare, this disease presents a significant health and economic burden for persons affected, particularly for those with JORRP (Derkay 1995). A report from the first JORRP registry in the United States (US) found that children aged 0–18 years undergo an average of 5 surgeries per year and as many as 21 in a single year (Reeves et al. 2003). Complications of RRP are rare but may arise due to natural disease progression and malignant transformation or as a result of iatrogenic intervention (Derkay 2001).

Monitoring of health conditions serves to determine the magnitude of the problem, identify affected populations and their risk factors, detect rare complications, and identify opportunities for prevention (Thacker and Berkelman 1988). For RRP, current incidence and prevalence estimates in the United States are imprecise due to limited populations under study and infrequent measurements (i.e., cross-sectional studies) (Larson and Derkay 2010; Marsico et al. 2014). For this reason, more accurate methods of defining the burden would be helpful. While it is known that HPV acquisition is a prerequisite for developing RRP, other risk factors are not well understood for either AORRP or for JORRP (Shah et al. 1998; Ruiz et al. 2014). Ongoing monitoring could help identify important risk factors and detect rare complications.

Since the introduction of the first HPV vaccine in 2006, infections with HPV type 6 and 11 can be considered preventable (Centers for Disease Control and Prevention et al. 2015). Given the availability of vaccine with high efficacy against the HPV types responsible for RRP in both males and females, widespread uptake of quadrivalent (4vHPV, Gardasil) or nonavalent (9vHPV, Gardasil 9) HPV vaccine among the target age groups has the potential to prevent new cases of RRP (Shah et al. 1998; Centers for Disease Control and Prevention 2010; Markowitz et al. 2014).

In 2006, the first national recommendation from the Advisory Committee on Immunization Practices (ACIP) recommended HPV vaccination for routine use among females at age 11 or 12 years (and through age 26 years if not previously vaccinated) (Markowitz et al. 2007). In 2009, a permissive recommendation was made for males; in 2011, ACIP recommended routine vaccination of males at age 11 or 12 years (and through age 21 years if not previously vaccinated)[1]; and in 2016 the ACIP updated the recommendation to a 2-dose schedule for adolescents initiating HPV vaccination before their 15th birthday (Centers for Disease Control and Prevention 2011; Markowitz et al. 2014; Meites et al. 2016). One potential population impact of 4vHPV and 9vHPV vaccination may be an overall decrease in RRP incidence, which could result from decreased number of infections with HPV types 6 and 11 among vaccinated persons and their partners (Larson and Derkay 2010). Ongoing monitoring of RRP may reveal differences in incidence among vaccinated and unvaccinated individuals, providing important evidence of HPV vaccine impact.

Data collected through monitoring may aid in the implementation of public health interventions, both preventive (i.e., HPV vaccination programs) and therapeutic (i.e., antiviral medications or operative procedures). Furthermore, monitoring can be used to assess the potential impact of interventions, which might include prevention of both JORRP and AORRP, improved quality of life for affected persons, and reduced healthcare costs associated with the condition.

3.1.1 Challenges to Monitoring

RRP presents unique challenges for monitoring (Derkay 1995). Rare health outcomes generally require studies with large sample sizes to detect enough cases to make accurate population-level estimates, which can be a logistic and financial strain on monitoring systems for RRP (Nsubuga et al. 2006). Furthermore, standardized case definitions have not yet been established at the national level for JORRP or AORRP. A useful attempt was made by subject matter experts with the 2006 RRP Task Force, who agreed to define clinically relevant JORRP as: "(1) a history of symptomatic breathing, swallowing, and/or voice problems in children 14 years of age and younger; (2) the presence of wart-like lesions in the upper aerodigestive tract; and (3) histopathology demonstrating pedunculated masses with finger-like projections of nonkeratinized stratified squamous epithelium supported by a core of highly vascularized connective tissue stroma" (Campisi et al. 2010). Nevertheless, inconsistencies abound throughout the literature. For example, JORRP has been denoted as RRP beginning anywhere from birth until varying upper age bounds, ranging from 12 to 18 years (Marsico et al. 2014; Derkay 1995; Armstrong et al. 2000; Campisi et al. 2010; Larson and Derkay 2010).

[1] HPV vaccination is also recommended for men who have sex with men (MSM), for transgender persons, and immunocompromised persons through age 26 years for those who were not adequately vaccinated previously.

Non-standardized case definitions affect the ability to correctly identify cases, thus distorting the true magnitude of JORRP and AORRP burden among the general population.

Additional monitoring challenges presented by this rare disease include the lack of a standard method for documenting RRP-related health encounters (i.e., no consistent diagnostic or procedure code in International Classification of Disease (ICD)-9 or ICD-10) and the variety of study methodologies used to estimate RRP burden (Armstrong et al. 1999). Studies conducted using specific populations are not necessarily generalizable, and methods involving convenience sampling may introduce selection bias. Because neither HPV nor RRP is a nationally notifiable condition in the United States, a variety of case identification and sampling methods have been used to understand the scope of the issue. The lack of a standardized and ongoing system of monitoring RRP in the United States contributes to a limited understanding of its epidemiology (Centers for Disease Control and Prevention 2016; Lee and Thacker 2011).

3.1.2 Estimates of Disease Burden

In the United States, efforts to better understand the burden of RRP over the decades have yielded varying estimates of its prevalence and incidence. Specifically, a variety of study designs, case definitions (i.e., age distinction between JORRP and AORRP), and study populations have resulted in these differing burden estimates (Table 3.1). One of the earliest US studies conducted in 1995 by the RRP Task Force surveyed otolaryngologists nationwide and reported that RRP incidence among children less than 14 years old was 4.3 per 100,000, while a two-city study in the following year reported incidence and prevalence among children <18 years old were 1.11/100,000 and 0.36/100,000 in Atlanta and Seattle, respectively (Derkay 1995; Armstrong et al. 2000). Furthermore, in the United States, few studies exist which estimate the incidence of RRP among adults as compared with children.

Studies have been conducted outside the United States as well. A Danish study found that between 1969 and 1984 in the regions of Funen and Jutland, juvenile and adult incidence was similar (0.362 per 100,000 children <20 years of age and 0.394 per 100,000 adults, respectively) (Lindeberg and Elbrond 1990, 1989). An Australian study used administrative claims data from 1998 through 2008 in order to determine the utility of claims codes in identifying true cases and determining JORRP burden nationally. They reported JORRP prevalence of 0.6–1.1 per 100,000 persons <20 years old (Novakovic et al. 2010). A cross-sectional online survey designed to gather aggregate totals of both child and adult RRP patients being treated in 2015 in the United Kingdom (UK) was sent to ear, nose, and throat (ENT) consultants in nearly all of the National Health Service (NHS) trusts and boards of England, Scotland, Wales, and Northern Ireland. This study found a reported 1.42 cases of RRP/100,000 persons among the general population (Donne et al. 2016).

Table 3.1 Recurrent respiratory papillomatosis (RRP) incidence and prevalence, by study characteristics

Study	Type of study	Study period	Onset (age)	Incidence per 100,000 persons	Prevalence per 100,000 persons	Country/study population
Lindeberg and Elbrond (1990)	Population-based registry	1968–1984	Juvenile (<20 years)	0.362	–	Denmark/Funen and Jutland
			Adult	0.394	–	
Bomholt (1988)	Population-based registry	1980–1983	Juvenile (0–14 years)	0.6	0.8	Denmark/Copenhagen
			Adult	0.8	2.3	
Omland et al. (2012)	Population-based registry	1987–2009	Juvenile (<18 years)	0.17	–	Norway/Oslo and Akershus
			Adult	0.54	–	
Derkay (1995)	National registry	1993–1994	Juvenile (<14 years)	4.3	–	United States
			Adult (>15 years)	1.8	–	
Campisi et al. (2010)	National registry	1994–2007	Juvenile (0–14 years)	0.24	1.11	Canada
Armstrong et al. (2000)	Population-based registry	1996	Juvenile (<18 years)	1.11	2.59	United States, Atlanta
				0.36	1.69	United States, Seattle
Novakovic et al. (2010)	Administrative claims	1998–2008	Juvenile (<20 years)	–	0.6–1.11	Australia
Marsico et al. (2014)	Administrative claims	2006	Juvenile (<18 years)	–	1.03	United States/publically insured
				–	0.51	United States/privately insured
Donne et al. (2016)	Nationally representative health survey	2014–2015	Juvenile and adult	–	1.42	United Kingdom

3.2 Types of Monitoring Studies

Several types of public health monitoring are useful for identifying and quantifying areas of need and, ultimately, informing public health action. The particular approach selected is a function of its objective, intended area of response (i.e., policy decisions, resource allocation, program implementation), and the type and frequency of data collected (i.e., health status data, laboratory specimens, self-report information) (Thacker and Berkelman 1988; Nsubuga et al. 2006). For many public health information systems, the patient-clinician interaction serves as the primary source of data. Thus, healthcare provider participation in reporting health conditions is critical for building the evidence necessary to meet public health objectives (Meites et al. 2013). Monitoring trends in genital warts (due to HPV types 6 and 11) and RRP will be useful to guide strategies for reducing its overall burden in the United States. Although neither HPV infection, nor genital warts, nor RRP is a notifiable condition through the National Notifiable Disease Surveillance System (NNDSS), alternative means for estimating the scope of RRP could include other surveillance systems, nationally representative surveys, analyses of data from registries and collaboratives, and administrative claims databases (Centers for Disease Control and Prevention 2016).

3.2.1 Surveillance Systems

National public health surveillance involves the ongoing collection and analysis of data with coordination between local, state, territorial, and national public health partners (Lee and Thacker 2011). Currently, there are no national surveillance systems in the United States which systematically monitor RRP, although such monitoring could be useful for identifying annual disease burden. As previously mentioned, a prominent national surveillance system in the United States is the NNDSS, which uses standardized tools for voluntary electronic case reporting of nationally notifiable diseases and conditions among 57 jurisdictions (Centers for Disease Control and Prevention 2016; Adams et al. 2015). Each year, the Centers for Disease Control and Prevention (CDC) and Council of State and Territorial Epidemiologists (CSTE) revise the annual list of nationally notifiable conditions, which may be infectious or noninfectious. Within each state or jurisdiction, however, the list of mandatory reportable conditions is revised according to applicable state or local law (Thacker and Berkelman 1988; Gostin 2000). For example, although it is not a nationally notifiable condition, RRP is reportable in the state of Florida (Florida Department of Health 2014).

3.2.2 Nationally Representative Health Surveys

Nationally representative health surveys collect individual-level data through self-report from volunteer participants and often are used to support surveillance systems in assessing health status of a population. Currently there are no national

surveys which adequately capture RRP diagnoses in the United States. The National Center for Health Statistics (NCHS) at CDC oversees multiple programs which conduct surveys to provide national data on health and disease. Data obtained from these surveys may be used to further study trends associated with specific subpopulations or to evaluate public health programs (Ivankovich et al. 2013; Sirken et al. 2011). One NCHS survey in particular, the National Health and Nutrition Examination Survey (NHANES), gathers a range of demographic and health-related information on adults and children and conducts laboratory testing, including testing for type-specific HPV (Centers for Disease Control and Prevention 2015). However, because national surveys sample broadly to reflect national profiles of health conditions, they are not well suited to detect rare diseases such as RRP (Nsubuga et al. 2006).

3.2.3 Registries and Collaboratives

Health registries target a specific disease or health status, as compared with national health surveys which generally collect a broad range of information from a representative sample of households and individuals (National Institutes of Health 2016). Databases and registries are useful for public health surveillance efforts and particularly important for rare disease detection. In the United States, the RRP Task Force collected pilot data for a national registry by mailing surveys to members of otolaryngology professional societies and a sample of ENTs in clinical practice. This study obtained data on incidence, prevalence, demographics, and course of disease for patients with JORRP (onset age <14 years) or AORRP (onset age >15 years) during 1993–1994 (Derkay 1995). After adjusting for survey response rate, national disease burden and cost projections were calculated using census data.

The following year, a population-based study aimed to collect accurate data on JORRP (onset <18 years) burden in two geographically defined cities, Atlanta and Seattle. All practicing ENTs within chosen counties of each city were contacted to identify active JORRP patients residing in each study area in 1996. Patient demographics and course of disease history were obtained from medical records, and study findings confirmed JORRP as a rare condition in each city (Armstrong et al. 2000). This study represented a more complete method of ascertaining JORRP incidence and prevalence due to its defined catchment area (metropolitan area) for case identification. While disease estimates obtained were also used to extrapolate national JORRP burden, the study demonstrated that burden ascertainment is feasible on a smaller, more manageable scale.

From 1997 to 2002, a JORRP national registry, established by the CDC, Eastern Virginia Medical School (EVMS), along with the RRP Task Force collected information on cases in order to more closely understand the epidemiologic characteristics of the disease among children <18 years old. JORRP incident and prevalent case data from 22 tertiary care centers during 1996–2002 were collected as well as follow-up measurements about disease progression and treatment (Reeves et al. 2003). Although this study used convenience sampling for case identification, participating hospitals were a fairly large sample of major tertiary care sites throughout

the United States. In 2015, CDC and EVMS initiated an ongoing JORRP monitoring study as a pilot registry for assessing HPV vaccination impact on JORRP incidence in the United States (Singh et al. 2017). This study enrolls both incident and prevalent cases from a convenience sample of hospitals where pediatric RRP patients are treated to evaluate demographic and disease characteristics, HPV type, and maternal characteristics related to JORRP. These data are part of an ongoing monitoring study which aims to detect trends in disease prevalence and incidence post HPV vaccine introduction in the United States.

RRP registries have also been established in such regions as France, Canada, and the United Kingdom (UK) (Carvalho et al. 2009). One of the more comprehensive databases is the JORRP national database in Canada which retrospectively assessed cases among children ≤14 years old who were diagnosed or treated between 1994 and 2007. Cases were identified through participation from ENT society members, and nearly all centers treating JORRP were captured (thus, achieving a relatively representative sample). The development of a centralized database containing over a decade of standardized case reporting enabled detection of trends in incidence and prevalence of JORRP (1.11/100,000 and 0.24/100,000, respectively). Two major advantages in this particular setting are Canada's universal healthcare access and its centralized specialty care, both of which increase representativeness of the data collected (Campisi et al. 2010).

Studies in Scandinavia used population-based registries to assess RRP incidence over time, among other disease-related trends. In the regions of Funen and Jutland, a retrospective study was conducted to collect data on active and existing RRP patients treated at 14 ENT departments from 1963 through 1986. From this registry of 231 patients, a subset of incident cases in the two regions was used to further examine characteristics of juvenile (<20 years) and adult (≥20 years) RRP (Lindeberg and Elbrond 1989, 1990). The broad time period of data collection for this registry was particularly useful for assessing trends in incident cases. In Norway, a population-based study identified all RRP patients treated from 1987 through 2009 in order to assess incidence over the 20-year period. RRP case identification from ENT patient registries used ICD codes, procedure codes, and histopathological confirmation. These studies further demonstrate the use of registries in well-defined areas, which enables more complete data collection and subsequent disease estimates (Omland et al. 2012).

Tissue banks provide another approach to gathering data on RRP. A National Institutes for Health (NIH) funded study from 2002 assembled a broad-based RRP DNA repository with the goal of identifying susceptibility loci in RRP patients across the United States (Buchinsky et al. 2004). One such example is the RRP tissue bank at Emory University, which currently enrolls both incident and prevalent cases and collects papilloma tissue, blood, and saliva samples from each subject.[2] These banks become a resource for identifying trends in disease incidence, surveying demographic data, genomic testing, examining the relationship between disease burden and novel therapeutic management or HPV vaccination, HPV typing, and

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determining the prevalence of malignant degeneration. Although such a regional collection does not provide information for the general population, it does create a data pool from a tertiary level center from which trends may be extrapolated.

Disease collaboratives involving multiple treatment centers deserve mention as a means of generating large enough datasets to assess treatments for rare conditions. The North American Airway Collaborative (https://noaac.net/), a relatively new collaborative, has already better elucidated the demographics of idiopathic subglottic stenosis (Gelbard et al. 2016). Currently, there is no formal RRP collaborative, but there does exist a long-standing RRP Task Force, which has served as a catalyst for single and multi-institutional research studies, as well as a source for treatment recommendations and guidelines (Derkay 1995). RRP is a condition that could well benefit from a collaborative, as it is rare, making it a challenge to gather data and assess treatment protocols.

3.2.4 Administrative Claims Databases

Another tool for RRP monitoring includes the use of administrative claims databases. These databases contain large amounts of data on healthcare utilization through standardized collection, making them ideal for capturing data on rare conditions if cases can be identified accurately. Data sources such as Centers for Medicare and Medicaid Services (CMS) data, private insurance providers, and hospital discharge records contain procedure and/or billing codes which may indicate a particular condition (Riley 2009). Certain challenges with use of such data, however, include the lack of any specific claims codes for RRP as well as the defined populations which do not necessarily lend to generalizability of findings (Marsico et al. 2014; Riley 2009).

A US-based study in 2006 leveraged public and private medical claims databases in order to estimate JORRP burden among children <18 years old. A set of ICD-9 and Current Procedural Terminology (CPT) codes commonly used to diagnose and treat JORRP were selected by practicing otolaryngologists, applied to the age-eligible population in order to identify suspect cases, and confirmed via individual medical chart review. It was found that the positive predictive value (PPV) of claims codes overall was 52.1% for prevalent cases and 33.7% for incident cases. Prevalence of JORRP was 1.03/100,000 among publically insured and 0.51 among privately insured (Marsico et al. 2014). Despite its limitation to insured populations, this strategy represents the utility of such existing databases to characterize burden of RRP nationally.

In Australia, Novakovic and colleagues utilized discharge records from a tertiary pediatric children's hospital to conduct a retrospective chart review and calculate burden of JORRP cases spanning 1998–2008. ICD-10 codes and procedure codes most likely to be RRP related were used to calculate PPV of individual diagnostic and procedure codes, apply them to the national hospital discharge database, and estimate national JORRP burden. They found the highest predictive ICD-10 code

was “benign neoplasm of the larynx” and estimated a JORRP prevalence of 0.6–1.1 per 100,000 persons <20 years old. Notably, the claims codes collected did not represent unique patients; thus, PPVs, incidence, and prevalence estimates were not direct measures.

Administrative claims data may serve as a useful tool for ongoing RRP monitoring despite some challenges presented by claims codes and specific populations covered by the databases (e.g., those insured, seeking care at a particular hospital, etc.). These large, frequently updated datasets can capture rare diseases; however, further work would be needed to address the lack of specificity of the codes used to identify cases.

3.3 Discussion

Data from monitoring and surveillance of RRP can provide clinicians and public health practitioners with important information about disease burden, risk factors, and incidence trends in the vaccine era. Course of disease information may be useful for evaluating and building evidence in support of various treatment interventions. RRP is not reportable, and monitoring RRP through national surveys is not reliable because it is a rare condition. Ideally, a national registry or database that is continuously updated through coordination with otolaryngology clinics for case identification would allow monitoring of RRP. Monitoring activities aim to characterize disease burden and detect changes in both the incidence and prevalence of RRP. An essential component of these aims is the clinician role in case reporting, care management, and disease prevention (Meites et al. 2013). It is through clinician support and collaborative efforts toward public health goals that so many monitoring activities and subsequent public health action are achieved.

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Chapter 4
Advances in Vaccine Technology

Julie Ahn, Simon R.A. Best, and David E. Tunkel

4.1 Introduction

Human papillomaviruses (HPVs) are the cause of the most common sexually transmitted infections in the USA, and about half of these infections are with "high-risk" HPV subtypes (Hariri et al. 2011), which can cause cancer. HPV subtypes 16 and 18 ("high risk") cause most HPV-associated cancers (Lowy and Schiller 2012; Centers for Disease Control and Prevention 2012) such as cervical cancer and oropharyngeal cancers. Recurrent respiratory papillomatosis (RRP) is caused by infection with HPV types 6, 11, or both.

The three Food and Drug Administration (FDA)-approved vaccines that prevent HPV infection, Gardasil, Gardasil 9, and Cervarix, are L1-based prophylactic vaccines that appear highly effective in protecting against new HPV infections. These L1 vaccines do not provide broad protection against multiple HPV subtypes, and studies have shown that L2-based vaccines may be the solution to this limitation (Jagu et al. 2009). Neither L1- nor L2-based vaccines have any therapeutic capability against established HPV infection, so therapeutic vaccine technologies using DNA- and peptide-based vaccines are under development (van der Sluis et al. 2015; Trimble et al. 2015). In this chapter, we will review the role of L1 and L2 vaccines in preventing HPV infections and also look at the current research on therapeutic vaccine technology.

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4.2 History of Vaccine Development

Human papillomavirus (HPV) is the causative agent for a number of serious illnesses, including cancer of the cervix in women, squamous cell carcinoma of the head and neck in adults, and recurrent respiratory papillomatosis (RRP) in children. The research and development of a prophylactic HPV vaccine has focused on eliminating the risk of cervical cancer in women, as the association between HPV infection and head and neck cancer was made fairly recently and the population impact of RRP in children is much smaller than that of cancer of the cervix in women. We would expect that an effective HPV vaccine aimed at the suspect virus subtypes, and widely administered, will favorably impact the incidence of head and neck cancer and RRP, and future studies will likely determine such benefits (Guo et al. 2016). We will briefly summarize the history of development of vaccines for HPV.

In 1991, Jian Zhou and Ian Frazer at the University of Queensland, Australia, developed a noninfective recombinant viruslike particle (VLP) of L1, the major papillomavirus virion protein, that was able to induce a cellular immune response (Angioli et al. 2016; Brotherton and Ogilvie 2015). Two years later, at the National Cancer Institute, a VLP structural analog of HPV type 16 was synthesized. This VLP was the basis of the HPV vaccine that was developed in parallel, at the aforementioned institutions as well as at the University of Rochester and Georgetown University. This HPV vaccine was subsequently licensed by Merck.

Gardasil, a quadrivalent vaccine with activity against HPV types 6, 11, 16, and 18, was approved by the FDA for use in the USA in June 2006. In 2007, The Advisory Committee on Immunization Practices (ACIP) recommended that this vaccine be administered to women between 9 and 26 years of age (Markowitz et al. 2007). In 2009, Cervarix, a bivalent vaccine with activity against HPV types 16 and 18, was approved by the FDA and recommended by the ACIP (Handler et al. 2015). The FDA approved the use of quadrivalent HPV vaccine for males between 9 and 26 years of age in October of 2009, and vaccination of males was recommended by ACIP in 2010 (Castle and Maza 2016).

Australia was the first country to adopt widespread vaccination against HPV, with a national vaccination program administering the quadrivalent vaccine since 2007. Over 70% of the target 12–13-year-old female population received three doses of vaccine (Garland 2014). A 77% reduction in infection with vaccine-type virus has been demonstrated in this group, as well as >90% reduction in genital warts and similar reduction in high-grade cervical lesions. The effects of broad vaccination on the incidence and disease burden from RRP remain to be seen, as surveillance for RRP as part of the Australia vaccination program commenced in late 2011.

Since 2006, HPV vaccines have been licensed in over 100 countries. By 2012, immunization programs in over 40 countries have included vaccination against HPV (Markowitz et al. 2012). In the USA, coverage with one dose of HPV vaccine in girls aged 13–17 years increased from 25% in 2007 to 49% in 2010. In 2010, three-dose HPV vaccine coverage was only 33%. The introduction of HPV vaccine programs has had social, legal, and policy concerns in the USA that have impacted wider coverage.

The development and introduction of the HPV vaccine included careful assessment of vaccine safety. In prelicense studies of >20,000 women for the quadrivalent vaccine and >30,000 women for the bivalent vaccine, no differences were seen in serious adverse events, autoimmune disease, or deaths between vaccine and control groups (Herrero et al. 2015). Over 144 million doses of quadrivalent vaccine and over 41 million doses of bivalent vaccine had been distributed throughout the world by the end of 2013. Passive surveillance, active monitoring, and population-based studies all support the safety of the available HPV vaccines, with syncope the most commonly reported postvaccination adverse event and no evidence of vaccine-associated serious harms.

There are presently three HPV vaccines commercially available, quadrivalent vaccine against HPV types 6, 11, 16, and 18 (Gardasil, Merck), bivalent vaccine against HPV types 16 and 18 (Cervarix, GlaxoSmithKline), and nine-valent vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9, Merck).

The vaccine of choice when considering population reduction of the incidence of recurrent respiratory papillomatosis most likely would be vaccines protective against HPV types 6 and 11, the causative agents of RRP (Derkay and Wiatrak 2008). Otolaryngologists have encouraged the use of the quadrivalent (and now the nine-valent) vaccine, as Cervarix does not contain types 6 and 11 (Jeyakumar and Mitchell 2011). The role for HPV vaccine as an adjuvant therapy of RRP is debated, as some investigators have reported benefit (Young et al. 2015) and others have shown no effect on postvaccination RRP behavior (Hermann et al. 2016). Vaccine-type specific immune response in RRP patients has been demonstrated after vaccination (TjonPianGi et al. 2016; Makiyama et al. 2016). It has been suggested that an increase in HPV-neutralizing antibodies by vaccination of pregnant women who already have condyloma may passively protect newborns at risk for contracting RRP (Shah 2014). It is most probable that the greatest benefits of HPV vaccine for RRP will come from reduction of maternal HPV infection and condyloma, with resultant decrease in vertical transmission of HPV to susceptible children.

4.3 L1 Vaccines

4.3.1 Biology

HPV vaccines based on L1 VLPs have shown great efficacy in protecting against HPV infection (Harro et al. 2001). L1 is a major capsid protein of the papillomavirus that can self-assemble into viruslike particles (VLPs). VLPs allow for safe and easy vaccine production, and these particles induce strong immune responses (Suzich et al. 1995). Recombinant L1 VLPs induce a high initial serum HPV type-specific neutralizing antibody response and are strongly immunogenic (Schiller and Lowy 1996). Commercial HPV VLP vaccines are delivered intramuscularly and induce adaptive immune responses. The antibodies neutralize the HPV virion by preventing endocytosis into the epithelial basal cells. The antibodies reach the

basement membrane through the dermal capillary network or an exudate caused from tissue injury to the epithelium (Harper et al. 2010). Neutralizing antibodies at the site of infection prevent initial L1 binding of the virus to the basement membrane.

4.3.2 Indications/Implementation

Cervarix, Gardasil, and Gardasil 9 are the current FDA-approved L1 vaccines. The target population for prophylactic L1 vaccines is children before they are sexually active and exposed to HPV (Hildesheim et al. 2007). Gardasil and Gardasil 9 are approved for use in females from age 9 to 26 years for the prevention of HPV-related cervical, vulvar, vaginal, and anal precancerous/cancerous lesions and genital warts (Table 4.1). Gardasil is also approved for male patients aged 9–26 years and Gardasil 9 for males between ages 9 and 15 years. Cervarix is approved only for females between 9 and 25 years of age, for the prevention of cervical cancer.

The current L1 vaccines are designed to be given in a series of three injections over a 6-month period. Many countries, however, are studying two-dose regimens, rather than three doses, to reduce cost and improve compliance. In such a study of Cervarix, women that received two doses of Cervarix had as much protection from HPV 16/18 as women that received three doses, over a 4-year study period (Kreimer et al. 2011). Other studies have also shown that the protective efficacy of two doses of Gardasil (Dobson et al. 2013) or Cervarix (Romanowski et al. 2011) was comparable to that of three doses in young adolescents.

The number of doses recommended and vaccination requirements (gender, target age, etc.) vary around the world. Although the World Health Organization recommends two doses of Gardasil, a three-dose regimen is still recommended in the USA. The specifics of HPV vaccination protocols also vary state by state in the USA (State Vaccination Requirements 2016). For example, the District of Columbia and Virginia require HPV vaccination for girls entering sixth grade, but parents may opt out. Rhode Island requires all boys and girls entering seventh grade to be vac-

Table 4.1 Current FDA-approved HPV vaccines and recommendations for use

	Gardasil	Gardasil 9	Cervarix
Gender	Females and males in the USA	Females and males in the USA	Females
Age (years)	9–26	Females 9–26 and males 9–21	9–25
Recommended age (years) at vaccination	11–12 in the USA	11–12 in the USA	11–12 in the USA
HPV types covered	HPV 6, 11, 16, and 18	HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58	HPV 16 and 18
Dosing regimen	3 over 6-month period	3 over 6-month period	3 over 6-month period

cinated against HPV infection. School-based immunization programs are in effect in many countries including Canada, Malaysia, Indonesia, and several European countries.

4.3.3 Efficacy

During FDA trials of Gardasil and Cervarix, both vaccines were shown to be effective in preventing almost 100% of cervical infections with HPV 16 and 18. Gardasil 9 is about 97% effective in preventing cervical, vulvar, and vaginal disease caused by the five additional HPV types (Chatterjee 2014). All three L1 vaccines protect against HPV 16 and 18 infections, which cause about 70% of cervical cancers and 86–95% of HPV-related non-cervical cancers (Gillison et al. 2008). Gardasil also protects against HPV 6/11 infections – the subtypes responsible for about 90% of genital warts (Koutsky et al. 2002) as well as RRP.

The efficacy of L1 vaccines has been studied in multiple countries, and studies of long-term efficacy are still ongoing. In Denmark, vaccination was associated with a 45% reduction in genital warts in girls 16–17 years of age (Ferris et al. 2014). In the aforementioned Australian HPV vaccination program, a high proportion of girls are vaccinated with Gardasil. As a result, the incidence of genital warts fell in vaccinated females and even in unvaccinated males (Fairley et al. 2009). This is an example of herd immunity, where genital wart cases decreased in heterosexual men after the introduction of HPV vaccination in women.

HPV vaccination in males has also been well studied, not only because they are at risk of HPV infections, but because sexual behavior and HPV infection significantly affect their female or male sexual partners. A HPV study of men conducted in Brazil, Mexico, and the USA found that the overall HPV infection prevalence was 65.2% in this male study population (Giuliano et al. 2008a). One study on HPV in males showed a reduced risk of cervical cancer in women whose male partners had multiple sexual partners and were circumcised compared to women whose male partners were uncircumcised (Castellsague et al. 2002). This difference was due to an almost four-fold lower rate of HPV infection in the circumcised group of men. HPV prevention in both men and women will reduce the probability of viral transmission and will thus reduce the risk of HPV-related diseases. Studies of HPV vaccination in the male population demonstrate protective effects against HPV-associated diseases of genital warts (Giuliano et al. 2011) and anal intraepithelial neoplasia (Palefsky et al. 2011), even though males seem to have a lower immune response to HPV infections (Giuliano et al. 2008b; Dunne et al. 2006) compared to women.

As of yet, there is no conclusive data about the minimum antibody levels necessary for HPV VLP protection against infection or about the role of memory B cells if antibody levels decrease. It is encouraging that in animal models vaccinated with commercial L1 vaccines, very low concentrations of antibody have been found to be protective (Day et al. 2010). In humans, long-term data have shown that Gardasil

protects at least 8 years (Lowy and Schiller 2012) and Cervarix at least 9 years (Centers for Disease Control and Prevention 2012). A study in Denmark, Iceland, Norway, and Sweden is evaluating the long-term effectiveness and safety of the HPV vaccine in young women (Nygård et al. 2013). The long-term efficacy for the newer Gardasil 9 is not yet known.

4.3.4 Limitations

These highly effective commercially available prophylactic HPV L1 vaccines are very expensive. Gardasil and Cervarix each cost more than $100 per dose, and these vaccines require refrigeration. The VLPs for both Gardasil and Cervarix are complexed with aluminum salts and need to be refrigerated in a liquid state, making transportation difficult and costly. Although many insurance plans and programs now cover HPV vaccination in the USA, distribution and implementation in developing countries is very difficult.

Vaccine acceptance and compliance are hampered by high cost, the need for multiple injections to complete the full immunization course, and the sporadic and sometimes limited access of most adolescents to health care. In the USA, the vaccination rate for girls aged 13–17 years for at least one dose was 54% and for the completion of all three doses was only 33% ((CDC) CfDCaP 2013). School-based programs in the UK, Australia, and some parts of Europe have ≥80% vaccination rates. Many countries are therefore trying to implement a two-dose protocol. The European Medicines Agency approved a two-dose Cervarix schedule for girls aged 9–14 years, but three doses are recommended for girls older than 14 years.

HPV L1 vaccines are ineffective at protecting against non-vaccine HPV types. The neutralizing epitopes in the L1 protein are not cross-reactive among subtypes. There is also no therapeutic activity of vaccines against established HPV infection (Hildesheim et al. 2007; Schiller et al. 2012). The HPV-infected basal epithelial cells do not express detectable levels of L1 and/or L2 and therefore cannot be targeted by the immune response from these vaccines (Schiller et al. 2008).

Adverse reactions to Gardasil and Cervarix are unusual. Pain or swelling at the injection site is a common side effect. Other reactions include fatigue, fever, gastrointestinal symptoms, headaches, and anaphylaxis (Bayas et al. 2008). The National Vaccine Injury Compensation Program provides compensation for people that require medical care as a result of vaccination.

The presumed sexual implications of administration of HPV vaccines to teens and preteens have caused some parents and a number of religious and conservative groups to oppose routine HPV immunization. A study on college-aged women reported that HPV vaccination did not affect their decisions on condom use or other birth control (Ports et al. 2014). Nevertheless, vaccine critics continue to report public concerns regarding about encouragement of risky sexual practices by such vaccination (Constantine and Jerman 2007; Marlow et al. 2009).

4.3.5 Future Directions

The search for a more cost-effective, stable vaccine that provides broader protection against all oncogenic HPV types is ongoing. The current L1 vaccines are VLP based and require 360 copies of the L1 protein, which is one of the costly steps in HPV vaccine production. A capsomere-based vaccine may be a more cost-effective alternative, with efficacy similar to the VLP-based vaccines. Only five copies of the L1 protein are required, and the vaccine can be produced in bacteria, with reduced cost (Fraillery et al. 2007).

4.4 L2 Vaccines

4.4.1 Biology

The type-specific nature of L1 vaccines makes it economically and biologically unfeasible to keep adding more and more subtypes to prophylactic L1 vaccines. A pan-HPV type vaccine would therefore be ideal, a concept that has led to research into L2 vaccines. L2 is a minor papillomavirus capsid protein that is required for infection and is highly conserved among HPV types. Unlike L1, the major determinants of L2 that neutralizing antibodies can recognize are not exposed when virions are free in solution. However, they are exposed after the virion binds to the basement membrane, where furin cleavage of the N-terminus of L2 occurs. The N-terminal region is highly conserved among HPV types and can induce protective immunity in animal papillomavirus models.

4.4.2 Indications/Implementation

Studies have shown that there are conserved protective epitopes between residues of L2, suggesting that L2 can provide broad protection against many HPV subtypes (Wu et al. 2015). Part of the L2 protein, between amino acids 20 and 38, is conserved in many high-risk HPV subtypes. Broad-spectrum neutralizing antibodies are induced, and similar to HPV L1 vaccines, L2 vaccines could be protective against potential infection. Therefore, the target populations for L2 vaccines are the same as for L1 vaccines, children and adolescents prior to HPV exposure that can occur during sexual activity.

4.4.3 Efficacy

Although there are no commercially available HPV L2 vaccines and human L2 vaccine trials have not been conducted, animal studies have demonstrated protective immunity of L2 against HPV infection (Karanam et al. 2009a; Schellenbacher et al.

2013; Jagu et al. 2013). In a mouse model, the oral administration of L2 displayed on *L. casei* induced systemic and mucosal cross-neutralizing effects (Yoon et al. 2012). In a cervicovaginal mouse model, L2 showed in vivo neutralization (Roberts et al. 2007). Mice vaccinated with the L2 vaccine synthesized with *L. casei* induced neutralizing antibodies against multiple oncogenic HPV types, including 16, 18, 45, and 58. The ability to mass-produce L2-based vaccines in bacteria would reduce production costs (Karanam et al. 2009b).

4.4.4 Limitations

Unfortunately, L2 is weakly immunogenic compared to L1 VLPs (Roden et al. 2000). L2-induced titers are at least ten times lower than the titers induced by L1 (Pastrana et al. 2005). The weak immunogenicity of L2 can be overcome by linking together short amino acid sequences of L2 from different oncogenic HPV types or displaying L2 peptides on a more immunogenic carrier (Jagu et al. 2009; Tumban et al. 2012). In addition, adenovirus types can be used as platforms for capsid display of foreign antigens in order to induce protective immunity (Fraillery et al. 2007; Wang and Roden 2013; Sharma et al. 2013; Farrow et al. 2014).

4.4.5 Future Directions

Several groups are researching various L2-based vaccines, often in conjunction with therapeutic vaccines that will treat established disease and while the L2 component will prevent new infections. TA-CIN/GPI-0100 and pNGVL4a-hCRTE6E7L2 DNA vaccine are some of the current L2 vaccines that show promise in protection against cervical cancer. These studies are being conducted in both animals and humans. A study of the pNGVL4a-hCRTE6E7L2 DNA vaccine in mice demonstrated a strong E6- and E7-specific CD8+ T-cell response after vaccination with electroporation as well as eliciting a strong L2 response that would prevent against pan-HPV infections (Peng et al. 2014).

4.5 Therapeutic Vaccine Technology

4.5.1 Biology

One of the major limitations of L1 and L2 vaccines is that they lack a therapeutic role; that is, they will not treat established HPV-related disease. An effective therapeutic vaccine would clear viral infections by directing the immune system

to produce cytotoxic T cells primed against the foreign HPV antigens that target the infected tissue. A therapeutic DNA vaccine therefore contains a foreign antigen, which for HPV-associated diseases is usually the oncogenic proteins E6 or E7, as well as a mechanism for expressing that foreign antigen in native tissue using mammalian promotors encoded in the DNA vaccine plasmid. The DNA vaccine is injected and expressed by native tissue, driving foreign antigen expression in antigen-presenting cells (APCs), which stimulate a CD4+ and CD8+ T-cell response against the target antigen. The generation of cytotoxic T cells specific for the target antigen will then clear HPV-expressing cells which contain this foreign antigen. Because the entire E6 or E7 protein is delivered via the DNA vaccine, major histocompatibility complex (MHC) restriction and antigen length is not a limitation with DNA vaccines, since each patient will process these proteins in a different way and present them to the immune system in their own unique immunologic background.

Peptide vaccines function by identifying the major immunologic epitopes for the target protein, again usually HPV E6 or E7, and directly delivering these short, optimized, and immunologically stimulating proteins by injection. The HPV antigenic proteins are directly taken up by dendritic cells and are presented in association with MHC pathways on HLA molecules. This presentation will again generate cytotoxic CD8+ T cells that will eliminate the virally infected cells. In this approach, the proteins are designed and optimized for certain MHC molecules, restricting their use to patients with that particular MHC class (Gérard et al. 2001).

With either approach, HPV-induced immunosuppression in the tumor microenvironment is a concern for many patients with HPV-associated diseases, and finding ways to overcome this local immunologic suppression is a key challenge.

4.5.2 Indications/Implementation

Therapeutic vaccines, unlike the prophylactic L1 and L2 vaccines, can potentially treat patients with active HPV-associated diseases and therefore have broad theoretic applicability to any HPV-associated disease. Because peptide or DNA plasmid administration alone is usually weakly immunogenic, therapeutic vaccines are delivered with electroporation or gene gun. Electroporation in particular has been used in human trials and functions by increasing the permeability of the plasma membrane using an electrical current at the site of the DNA vaccine delivery. This allows robust entry of DNA plasmid into native cells with resultant high levels of antigen expression. Gene gun delivers DNA vaccine-coated gold particles to the dendritic cells in the dermis by using an air-powered needless system. These techniques significantly enhance the levels of antigen expression within the cells (Best et al. 2009).

4.5.3 Efficacy

While there are no commercially available therapeutic vaccines at present, the efficacy of therapeutic vaccines in humans and animal models has been studied. In several animal models, calreticulin (CRT) DNA vaccines induce potential antitumor effects against HPV cell lines by targeting the E7 protein (Peng et al. 2006). Therapeutic vaccines are also undergoing testing in humans. In a recent landmark study, VGX-3100 is the first therapeutic vaccine to be effective against cervical intraepithelial neoplasia grade 2/3 (CIN2/3) associated with HPV 16 and 18 (Trimble et al. 2015). It is composed of synthetic plasmids that target HPV 16 and 18 E6 and E7. VGX-3100 is given intramuscularly by electroporation at 0, 4, and 12 weeks. In a randomized, placebo-controlled trial, almost 50% of vaccinated patients had histopathological regression as compared to 30% of patients who received placebo. Most patients who received vaccine experienced local injection reactions, but there were no serious adverse events.

Peptide vaccines have also been tested in humans. Kenter et al. demonstrated the therapeutic efficacy of a peptide vaccine against HPV 16 for vulvar intraepithelial neoplasia (Kenter et al. 2009). Vaccination with synthetic peptides for E6 and E7 of HPV 16 is effective for 12–24 months for treatment of vulvar intraepithelial neoplasia. The vaccine most likely induces a T-cell response.

4.5.4 Limitations

Therapeutic vaccines cannot provide broad treatment against multiple HPV types as the targeted E6 and E7 antigens are type specific. However, since treatment of specific patients with established disease is the goal of therapeutic vaccination (rather than broad protection of an uninfected population), this is less of a downside than it is for prophylactic vaccination with L1 vaccines. Generating a robust immune response with DNA vaccines or peptide vaccines is the major challenge in humans, and strategies to increase immunogenicity include vaccination delivery techniques or the use of adjuvants like cytokines, chemokines, or Toll-like receptor (TLR) ligands. An effective vaccine would likely require high levels of target gene expression in transfected cells for a prolonged period of time in order maintain a sustained immunologic response. However, it is important to note because DNA-based vaccines cause expression of potentially oncogenic proteins – HPV E6 and E7 – to prime the immune system; these DNA sequences need to be altered to reduce their oncogenic potential to avoid secondary malignancies.

4.5.5 Future Directions

With the recent favorable results of the first human trials of DNA vaccines for HPV-associated diseases, there is substantial interest in using this technology to treat the spectrum of HPV-related diseases. DNA vaccines can be used to target HPV 6 and

11, and preclinical work has already been performed in this area to demonstrate that an immune response can be elicited against viral proteins from these "low-risk" HPV types (Peng et al. 2016; Peng et al. 2010). As methods are developed to enhance the immunogenicity of these therapeutic vaccines, DNA vaccine technology will likely play a role in future treatment of a broad array of HPV-associated diseases, including RRP.

4.6 Conclusions

HPV vaccination for the prevention of HPV-associated disease is one of the great successes of modern medicine. From the initial detection of HPV DNA in cervical lesions in 1976, barely 30 years elapsed before there was a FDA-approved vaccine that offers robust protection for an entire generation of girls and boys against new HPV infection. However, these L1 vaccines currently in use do not offer broad protection against all HPV types. Implementation has been difficult due to cost, formulation, and the requirement for multiple doses. Therefore, research continues into novel technology such as L2 vaccines which could offer true pan-HPV protection. For those with active HPV-related disease, therapeutic vaccines offer an elegant way to harness the immune system, targeting the foreign antigen present in the HPV-infected cells with the hope of providing a cure for these devastating diseases. With regard to RRP, a disease that seems to be caused almost exclusively by two HPV types, types that are included in the protection afforded by Gardasil and Gardasil 9, wide acceptance and administration of these prophylactic vaccines are the best hope for marked reduction in the number of patients affected by this disease.

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Chapter 5
Human Papillomavirus Vaccination: Making Sense of the Public Controversy

Talía Malagón and Eduardo L. Franco

Abbreviations

CIN	Cervical intraepithelial neoplasia
CRPS	Complex regional pain syndrome
HPV	Human papillomavirus
MSM	Men who have sex with men
NCI	National Cancer Institute
POTS	Postural orthostatic tachycardia syndrome
RCT	Randomized clinical trial
STI	Sexually transmitted infection
US	United States
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

5.1 Introduction

Controversies surrounding the human papillomavirus (HPV) and other vaccines generally dispute their effectiveness, safety, utility, and ethical use, and have changed remarkably little over time since vaccines' introduction. Opposition to the smallpox vaccine has existed since at least the mid-nineteenth century following the passing of the Vaccination Acts in the United Kingdom, which were seen as infringing upon individual self-determination (Wolfe and Sharp 2002). More recently, the

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retracted 1998 publication of a hypothesized link between the measles-mumps-rubella vaccine and autism (Wakefield et al. 1998) (RETRACTED) generated much concern over vaccine safety and undermined public confidence in vaccines, despite the subsequent convincing evidence rejecting any causal association (DeStefano and Thompson 2004). Not surprisingly, the HPV vaccine has been among the most scrutinized and controversial vaccines since its first licensure in 2006. The agent that it targets is a sexually transmitted infection (STI) that causes cancer (uterine cervix, vagina, and vulva in women, penis in men, and anal and oral cancers in both genders), which heightens the public attention that it attracts, especially in the era of rapid and widespread communication exchange brought by the Internet and social media.

Public scrutiny of vaccination practices is important. Vaccines are interventions given primarily for preventive purposes to healthy individuals. The average expected benefit must be balanced against any potential harm associated with vaccination. Professional, political, and financial stakes can influence how the benefits and harms of vaccination are valued. Consequently, public scrutiny and continual evaluation of the value of HPV vaccines are desirable. Fundamentally, HPV vaccine controversies can be traced to a differential understanding and weighting by stakeholders of the risks, costs, and benefits associated with vaccination. Regrettably, many of these controversies have arisen from misinformation and disregard of scientific evidence, stemming from distrust of institutions, the pharmaceutical industry, and biomedical technologies (Briones et al. 2012; Dyer 2015; Kata 2010).

In this chapter, we aim to discuss various public criticisms directed against HPV vaccination as well as the weight of the evidence surrounding each. Broadly, HPV vaccine controversies can be classified in the following categories of concerns:

1. Efficacy and effectiveness (*Will HPV vaccines prevent the health outcomes we want them to prevent?*)
2. Safety and risk (*Are the HPV vaccines safe? Do they entail unintended risks?*)
3. Utility (*Do we need HPV vaccines? Do the benefits of vaccination outweigh the costs/risks?*)
4. Ethics (*Are HPV vaccination practices moral?*)

5.2 Efficacy and Effectiveness

5.2.1 Lack of Evidence of HPV Vaccines' Efficacy Against Cancers

The reduction of mortality and morbidity attributable to HPV-associated cancers is generally the primary aim of HPV vaccination programs. Many have criticized the wide-scale implementation and recommendations of HPV vaccination programs on the grounds that HPV vaccines have not been proven to prevent any cancers (Abdelmutti and Hoffman-Goetz 2009; Dyer 2015; Lippman et al. 2007; Syrjänen

2010; Tomljenovic and Shaw 2013; Tomljenovic et al. 2013). Critics have argued that the etiological link between HPV infection and cervical cancer is too poorly understood to warrant wide-scale vaccination, given that many women who are infected with HPV never develop cervical cancer, and many precancerous lesions may regress spontaneously (Lippman et al. 2007; Rail and Lippman 2015; Tomljenovic and Shaw 2012b; Tomljenovic and Shaw 2013).

Phase III HPV vaccine clinical trials have shown extremely high prophylactic efficacy against the intermediate endpoints of persistent infections, genital warts, high-grade cervical lesions, high-grade anal lesions, and vulvar/vaginal lesions with vaccine-type HPVs in women and men who were not previously infected with those types (Beachler et al. 2016; Future II Study Group 2007; Garland et al. 2007; Giuliano et al. 2011; Joura et al. 2015; Joura et al. 2007; Paavonen et al. 2009). These trials did not evaluate efficacy against cervical cancer and other cancer outcomes for ethical and practical reasons. Firstly, it would not be ethical to allow precancerous lesions to progress to cancer in participants; lesions are treated upon detection. Secondly, the progression from initial infection to cervical cancer is a decade-long process (Schiffman et al. 2007); it would be unfeasible to prolong trials over decades to evaluate eventual efficacy against cancer.

There is overwhelming epidemiological evidence causally linking HPV infection with precancerous cervical lesions and cervical cancer. The World Health Organization's (WHO) International Agency for Research on Cancer concluded 20 years ago that there was sufficient evidence to classify many HPV types as group 1 human carcinogens (Cogliano et al. 2005). As HPV DNA detection methods have improved, studies have confirmed that oncogenic HPV DNA can be detected in almost 100% of cervical cancers and in a substantial proportion of oropharyngeal (89–95%), anal (93%), and genital cancers (63–88%) (Bosch and de Sanjose 2003; Chaturvedi 2010; Muñoz 2000). The comparison of cancer cases to controls reveals that exposure to oncogenic HPV types is associated with an enormous relative increase in the risk of developing cervical and other HPV-related cancers, consistent with a causal effect (Bosch et al. 2002; D'Souza et al. 2007; de Martel et al. 2012; Muñoz et al. 2006). The association between HPV and cervical cancer is one of the strongest ever observed for a human cancer. Though most individuals will clear their HPV infections, for many women the infections may persist for years, causing precancerous cervical intraepithelial lesions (CIN) which can eventually progress to cancer (Khan et al. 2005; Schiffman et al. 2007). Infection with an oncogenic HPV type is widely considered to be a necessary cause of cervical cancer (Franco et al. 1999; Muñoz 2000) and an important contributing cause of oropharyngeal, anal, and genital cancers (Chaturvedi 2010). This implies that all cervical cancers and a significant proportion of other HPV-associated cancers would not have occurred had the initial HPV infection been prevented. Given the solid scientific evidence supporting the role of HPV infection and high-grade lesions in the development of cervical cancer, the demonstrated efficacy against these endpoints strongly supports the assertion that the vaccine will also prevent HPV-associated cancers.

Even if we accept that the efficacy of HPV vaccines against associated cancers is undemonstrated, the opposition to vaccination on these grounds ignores the proven

efficacy of HPV vaccines against other disease outcomes. The prevention of warts and precancerous lesions already provides substantial benefits to vaccinated individuals independently of eventual efficacy against cancer (Drolet et al. 2015).

In short, that clinical trials did not evaluate HPV vaccine efficacy against cervical cancer does not constitute a valid argument against HPV vaccination given the weight of the scientific evidence causally linking HPV infection with various cancers and other health outcomes. Given the long latency between onset of HPV infection and the initial neoplastic stages in cervical cancer, there has not been enough time for HPV vaccination to have made an impact on the incidence of cervical cancer; however, HPV vaccination has already had a measurable impact in reducing the incidence of precancerous lesions of the cervix (Baldur-Felskov et al. 2014; Crowe et al. 2014; Mahmud et al. 2014). Critics argue that cytology screening precludes the need for HPV vaccination due to its demonstrated effectiveness at preventing cervical cancer through detection and treatment of precancerous lesions (Rail and Lippman 2015; Tomljenovic and Shaw 2012b). The logical conclusion that preventing these lesions via vaccination will attain the same objective is lost on them.

5.2.2 HPV Vaccine Efficacy Not Demonstrated in Preadolescents

Because HPV vaccines are prophylactic and HPV is sexually transmitted, HPV vaccination programs and recommendations generally target preadolescents before they initiate sexual activity. However, clinical trials assessed HPV vaccine efficacy in older adolescents and adults. Some have questioned whether it is warranted to recommend vaccination and implement routine vaccination programs in age groups where vaccine efficacy has not been demonstrated (Lippman et al. 2007; Nature Biotechnology 2007; Reist and Klein 2007; Thompson and Polzer 2012).

Phase III clinical trials evaluated HPV vaccine efficacy in adult populations for both ethical and practical reasons. Preadolescent populations are largely sexually inexperienced and have low rates of infection (Cubie et al. 1998). The invasive examinations required to assess efficacy against infection and precancerous lesions would not have been ethical to perform in younger populations, who would receive very little benefit from the examination. The efficacy of the vaccine would not have been assessable before many years due to the low incidence rate of infection until later adolescence and early adulthood.

Though efficacy was not assessed in preadolescents, vaccine safety and immunogenicity trials have bolstered the evidence basis for vaccine use in this age group. Comparisons of clinical trials in preadolescent, adolescent, and adult populations show that HPV vaccines have similar safety and tolerability profiles in all age groups (Block et al. 2006; Reisinger et al. 2007). Furthermore, the vaccine-induced antibody titers in preadolescents are non-inferior and potentially even superior to

those observed in older participants following three doses (Block et al. 2006; Dobson et al. 2013). Experimental evidence strongly supports neutralizing antibodies as the source of vaccine-induced immunity against new HPV infections (Day et al. 2010). This suggests that the vaccine should also lead to high efficacy in younger age groups, given the high efficacy observed in adult populations with similar antibody titers.

Surveillance studies are now starting to show the impact of HPV vaccination in the first cohorts of girls vaccinated in early adolescence. A 64% reduction in HPV-6/HPV-11/HPV-16/HPV-18 infection prevalence has already been observed in girls 14–19-year-olds in the 6 years following vaccine licensure in the United States despite only moderate (51%) coverage (Markowitz et al. 2016). Similar important reductions in infection prevalence and genital warts incidence have been observed in girls in this age group in many other countries that have implemented HPV vaccination (Drolet et al. 2015).

In conclusion, the recommendation to vaccinate preadolescents was justified based on available epidemiological evidence at the time of vaccine licensure and is increasingly bolstered by emerging surveillance data of girls vaccinated in early adolescence.

5.2.3 Limited HPV Type Protection and Type Replacement

Current HPV vaccines only protect against a handful of all HPV types. This limited protection has led to concerns that even if the vaccines are efficacious against infection with some HPV types, vaccination may still not reduce long-term cancer incidence because other non-vaccine HPV types may still cause cancer (Baden et al. 2007; Reist and Klein 2007; Tomljenovic and Shaw 2012b).

The first licensed HPV vaccines (Gardasil and Cervarix) were formulated to protect against HPV-16 and HPV-18. These types are responsible for the vast majority of cervical, anal, oropharyngeal, and genital cancers that are HPV positive (Backes et al. 2009; de Sanjose et al. 2010; De Vuyst et al. 2009; Kreimer et al. 2005; Li et al. 2011). Although approximately 11% of cervical cancers have traces of DNA of multiple HPV types, different attribution methods consistently estimate the proportion of cervical cancers due to HPV-16/HPV-18 to be around 70% (Vaccarella et al. 2011). There is also evidence that vaccines provide some cross protection against other related HPV types (Brown et al. 2009; Wheeler et al. 2012). A newly licensed vaccine (Gardasil 9) now protects against infection with the HPV types responsible for 90% of cervical cancers (HPV-16/HPV-18/HPV-31/HPV-33/HPV-45/HPV-52/HPV-58) (Joura et al. 2015). HPV vaccines thus give a broad protection against the HPV types causing the highest burden of morbidity and mortality. Furthermore, the precancerous lesions associated with types other than HPV-16/HPV-18 do not progress to cancer as rapidly or as frequently as those caused by the latter types (Kjaer et al. 2010; Schiffman et al. 2007) and, thus, are amenable to be detected by screening, an activity that has continued postvaccination.

Even before the vaccines were licensed, researchers were aware of a potential for HPV type replacement following vaccination (Elbasha and Galvani 2005). Type replacement constitutes an increase in the prevalence of non-vaccine HPV type infections following vaccination due to the vacating of the ecological niche occupied by vaccine HPV types. Type replacement had previously been observed in the case of the pneumococcal vaccine, which similarly only targeted a limited number of pneumococcal types (Weinberger et al. 2011). However, in the case of HPV, post-vaccination surveillance studies have not observed strong marked increases in the prevalence of non-vaccine HPV types in vaccinated populations (Drolet et al. 2015). Postvaccination HPV type replacement is widely considered to be unlikely to occur for the following reasons:

1. Unlike pneumococcus, evidence does not suggest strong competitive interactions exist between HPV types which could cause type replacement (Chaturvedi et al. 2011; Thomas et al. 2000; Tota et al. 2013; Vaccarella et al. 2011; Vaccarella et al. 2013). Furthermore, this competitive interaction would have to be stronger than the cross protection induced by vaccines for type replacement to occur (Elbasha and Galvani 2005).
2. The potential for new HPV types to quickly evolve to fill the ecological niche left by HPV-16/HPV-18 is also very unlikely given the slow mutation rate of HPV (Van Doorslaer 2013).
3. Finally, non-vaccine HPV type infections have a significantly lower risk of oncogenic progression than HPV-16/HPV-18 infections (Guan et al. 2012; Khan et al. 2005; Kjaer et al. 2010). Even if some type replacement were eventually to occur, it is unlikely that this would substantively undermine the effectiveness of vaccination against HPV-associated cancers.

In conclusion, HPV vaccines protect against infections with the HPV types that cause the highest disease morbidity and mortality. The potential for competing risks from other types and type replacement are becoming increasingly less important with the advent of new multivalent vaccines targeting more HPV types that cause nearly all HPV-associated cancers. Moreover, any HPV types which could increase in prevalence do not have high oncogenic potential and thus would not substantially diminish vaccination effectiveness.

5.3 Safety and Risk

5.3.1 Serious Adverse Events Associated with Vaccination

Despite the substantial evidence now supporting HPV vaccines' safety, an association between vaccination and various adverse events remains one of the most contentious public controversies surrounding the vaccine (Franco et al. 2012). From the time of vaccine licensure, some researchers expressed the opinion that the implementation of large-scale programs was premature in light of the fact that there were

no long-term data on the vaccine's safety (Tomljenovic and Shaw 2012b). They advocated for more data on vaccine safety before integrating HPV vaccine into existing programs, generally invoking the precautionary principle as a justification. Over time, they have maintained that the link between HPV vaccines and various rare serious adverse events has not been given due attention by the scientific community (Dyer 2015; Tomljenovic and Shaw 2012a; Tomljenovic and Shaw 2012b). HPV vaccine safety is also a recurring concern for the public, and various anti-vaccine groups oppose HPV vaccines on purported safety grounds, as described by several investigators (Bingham et al. 2009; Darden et al. 2013; Hendry et al. 2013; Kata 2010; Ogilvie et al. 2010).

The claim that there were no long-term data on HPV vaccine efficacy before vaccine program implementation is debatable. Aluminum adjuvants in vaccines had been in use for some 60 years and are widely regarded as safe (Global Advisory Committee on Vaccine safety 2014; Lindblad 2004). Various randomized controlled trials (RCTs) of the HPV vaccines had for vaccine licensure been performed in thousands of young girls and women followed up to 4 years to assess vaccine safety, immunogenicity, and efficacy, and further RCT results in women, men, and children were also published in subsequent years (Block et al. 2006; Castellsague et al. 2015; Einstein et al. 2011; Future II Study Group 2007; Garland et al. 2007; Giuliano et al. 2015; Harper et al. 2006; Munoz et al. 2009; Paavonen et al. 2009; Reisinger et al. 2007; Schwarz et al. 2014; Vesikari et al. 2015; Villa et al. 2006). RCTs are the strongest source of evidence for efficacy and safety outcomes and are the gold standard for scientific health research. The strength of the evidence comes from the randomization of individuals to the HPV vaccine or the control group. The randomization ensures that HPV vaccinated and unvaccinated individuals are similar in terms of their risk factors for HPV infection, disease, and adverse events. When randomization is successful, differences in the rate of outcomes between the groups can then generally be interpreted as an effect of the vaccine. The pooling of data across Gardasil trials shows that the risk of serious adverse events was very similar between the 11,778 participants receiving Gardasil and 9680 participants receiving the placebo both in the 15 days following injection (0.5% and 0.4%, respectively) and over the entire study period (0.9% and 1.0%, respectively) (Food and Drug Administration 2006). Pooling of data across Cervarix trials similarly shows that for almost 30,000 girls and women who received the vaccine, the rate of serious adverse events was similar between participants receiving Cervarix and the control over the trial follow-up years (2.8% and 3.1%, respectively), and there was no differences in the onset of new chronic or autoimmune diseases between the vaccinated and control girls and women (Descamps et al. 2009). The most common adverse events reported in these trials were injection site pain, swelling, headache, fatigue, and fever, which were higher in the vaccine groups than in the control groups (Block et al. 2006; Future II Study Group 2007; Schiller et al. 2012). Overall, these results from large-scale RCTs indicate that HPV vaccines, while causing temporary adverse events in some individuals (pain, swelling, headache, fatigue, fever), do not increase the risk of overall serious adverse events or of chronic and autoimmune diseases.

RCTs cannot however evaluate the risk of very rare or very long-term adverse events. Various post-marketing surveillance studies have therefore been put into place in many countries in order to assess the ongoing safety of HPV vaccines. Since vaccine licensure, over 200 million doses of HPV vaccines have been distributed worldwide, providing much data to assess safety (Global Advisory Committee on Vaccine safety 2015). A first data source is the passive reporting of adverse reactions and case reports of diseases identified in vaccinated individuals. For example, the Vaccine Adverse Event Reporting System (VAERS) in the United States (US), the Canadian Adverse Events Following Immunization Surveillance System in Canada, and the Yellow Card Scheme in the United Kingdom collect reports of adverse event experienced by vaccine users. In the United States, as of 2014, 25,176 adverse event reports have been made to the VAERS for 67 million doses of Gardasil distributed (Stokley et al. 2014). The most commonly reported adverse events to passive reporting systems are injection site reactions, dizziness, syncope, nausea, and headache (van't Klooster et al. 2011; Slade et al. 2009; Stokley et al. 2014). Case reports have been published of very rare and serious adverse events detected in vaccinated individuals, such as primary ovarian insufficiency, Guillain–Barré syndrome, anaphylaxis, venous thromboembolism, multiple sclerosis, cerebral vasculitis, complex regional pain syndrome (CRPS), and postural orthostatic tachycardia syndrome (POTS) (Brinth et al. 2015; Brinth et al. 2015; Global Advisory Committee on Vaccine safety 2015; Gruber and Shoenfeld 2015; Ojha et al. 2014; Slade et al. 2009). However, the causal interpretation of passive reporting systems and case reports is very limited because there is no comparator. Vaccinated individuals are still subject to a background rate of disease and mortality from other causes. Diseases and adverse health outcomes could coincidentally arise around the same time as vaccination from unrelated reasons. Passive reporting systems and case reports are most useful to identify outcomes that can be examined more thoroughly in larger epidemiological studies.

Independent researchers and regulatory agencies such as the World Health Organization's Global Advisory Committee on Vaccine Safety regularly reexamine post-licensure surveillance data to determine whether vaccines can be causally linked to serious adverse events identified in case reports. The strongest evidence comes from observational cohort studies comparing outcomes in vaccinated and control populations. The comparison with a control population allows ascertaining whether the rate of disease in vaccinated individuals is substantially higher than would be expected in a demographically comparable unvaccinated population. For example, in a large cohort of nearly one million Swedish and Danish adolescent girls, vaccinated and unvaccinated girls had very similar incidence rates of venous thromboembolism (14 vs. 13 per 100,000 person years), epilepsy (51 vs. 72 per 100,000 person years), juvenile arthritis (38 vs. 37 per 100,000 person years), and numerous other autoimmune and neurological diseases (Arnheim-Dahlström et al. 2013). One French study showed a small absolute increase in the risk of Guillain-Barré syndrome in vaccinated girls (1/100000) (Agence nationale de sécurité du médicament et des produits de santé 2015), but this result was not replicated in other studies (Gee et al. 2011; Grimaldi-Bensouda et al. 2014; Slade et al. 2009). Overall,

comparative studies have time and time again concluded that the incidence rate of serious adverse events in vaccinated individuals is consistent with the background rates of chronic, neurological, and autoimmune diseases and that there is very little evidence suggesting that HPV vaccination causes any of these diseases (Arnheim-Dahlström et al. 2013; Chao et al. 2012; Donegan et al. 2013; Gee et al. 2011; Global Advisory Committee on Vaccine safety 2014, 2015; Grimaldi-Bensouda et al. 2014; Scheller et al. 2014; Scheller et al. 2015).

Most of the controversy generated over HPV vaccines' safety has resulted from selective reporting of safety data. Attacks on the vaccines' safety generally cite only case reports/passive reporting systems while ignoring or not reporting the stronger evidence from RCTs and comparative studies. The media often seizes on case reports of rare and serious illnesses in vaccinated individuals due to their sensational and emotive nature. Despite the rarity of these diseases and the lack of evidence supporting any causal link with the HPV vaccine, these reports have strong effects on the public's perception of the risks of vaccination. For example, a recent series of case reports of CRPS and POTS in vaccinated individuals triggered a review of the evidence by the European Medicines Agency. After a careful analysis of the case reports and epidemiological data, the agency found no evidence that the occurrence of these syndromes in vaccinated girls was different from what was expected in this age group (Pharmacovigilance Risk Assessment Committee 2015). However, in Japan the mass media and social media coverage of cases had instigated a public hysteria. In response, the Japanese Ministry of Health, Labour, and Welfare suspended the active recommendation of HPV vaccination in 2013, a decision that was politically rather than scientifically motivated. The suspension of recommendations undermined public confidence in the HPV vaccine and led to the plummeting of vaccine coverage from approximately 70% to 8% (Hanley et al. 2015; Konno et al. 2015a, b).

In conclusion, strong and consistent epidemiological evidence from both prelicensure and post-licensure studies confirms that HPV vaccines are safe and are not causally associated with serious adverse effects. The safety of the vaccine has been continuously examined by the scientific community over the years, and no signal suggesting a causal effect of the vaccine on autoimmune or neurological diseases has emerged. Unfortunately, despite this substantial body of evidence supporting vaccine safety, fearmongering and misinformation have undermined public confidence in vaccine programs in many countries.

5.3.2 Enhanced Oncogenic Progression

Some have claimed that vaccination may enhance the oncogenic progression from infection to cervical intraepithelial lesions in women who are already infected (Spinosa et al. 2011; Suba et al. 2013; Tomljenovic and Shaw 2012b; Tomljenovic and Shaw 2013). This claim is based on a post hoc sub-analysis of the FUTURE I trial of the Gardasil vaccine. In women who were already infected with and

seropositive to HPV-16/HPV-18/HPV-6/HPV-11 before vaccination, there was a higher incidence rate of high-grade lesions (CIN2/3) in women who were vaccinated with Gardasil (11.1/100 person-years) than in women vaccinated with a placebo (7.7/100 person-years) (Food and Drug Administration 2006).

This observation however does not provide evidence for the vaccine enhancing the progression from infection to CIN. Firstly, the observed difference between the vaccine and placebo groups was not statistically significant. This observation is thus likely attributable to the small sample size and is consistent with the HPV vaccine having no effect on the progression rate of already established infections. Secondly, the further comparison of the two groups reveals that the women vaccinated with Gardasil already had a higher prevalence of abnormal Pap smears before vaccination than the women vaccinated with the placebo. This suggests the higher incidence rate of CIN2/3 was also in part attributable to other preexisting risk factors in women vaccinated with Gardasil rather than any effect of vaccination. Finally, the same result was not subsequently observed in the FUTURE II trial: women previously infected with and seropositive to HPV-16/HPV-18/HPV-6/HPV-11 vaccinated with Gardasil had instead a lower CIN2/3 incidence rate (6.0/100 person-years) than women vaccinated with the placebo (6.3/100 person-years) (Food and Drug Administration 2006). Further studies have confirmed that HPV vaccines do not affect the clearance and progression rate of preexisting infections (Hildesheim et al. 2016; Hildesheim et al. 2007; Syrjanen et al. 2009).

In conclusion, there is no convincing evidence that the vaccine affects the persistence and progression of preexisting HPV infections. Furthermore, this concern has limited applicability to HPV vaccination programs targeting preadolescents before sexual debut, who will be largely uninfected.

5.3.3 Vaccination will Lead to Sexual Disinhibition

The HPV vaccines target an STI. Some parents, conservative institutions, and ethicists were initially concerned that the vaccine could cause sexual disinhibition in vaccinated preadolescents (Forster et al. 2010; McQueen 2007; Smith et al. 2008; Waller et al. 2006; Zimmerman 2006). Vaccinated adolescents might potentially increase their sexual risk behaviors and promiscuity if they perceive themselves to be protected against STIs and/or due to a normalization of sexuality at young ages. A notable example occurred in 2007–2008, when Catholic bishops in Alberta and Ontario issued statements to parents and directors of the Catholic school boards, indicating that abstinence from sexual activity was the best protection against STIs, and warning against the promotion of the message that early sexual intercourse is normative (Smith et al. 2008; Wingle 2007). Various catholic school boards subsequently voted on moral grounds not to provide the vaccine in schools (CBC News 2008). These decisions were later overturned following citizen intervention efforts (Cotter 2014; Guichon et al. 2013).

Various studies have since confirmed that preadolescents and adolescents do not increase their sexual risk behaviors after being vaccinated against HPV (Bednarczyk et al. 2012; Forster et al. 2012; Smith et al. 2015). For example, in the months following a catch-up vaccination program in England, 6% of vaccinated and 8% of unvaccinated girls 16–18 reported having initiated sexual activity since the vaccine had been offered, suggesting the receipt of the vaccine had not influenced sexual initiation rates (Forster et al. 2012). In one US study of 11–12-year-old girls eligible for vaccination, the incidence rate of diagnosis for STIs and pregnancy was 0.26/100 person-years in girls who had been vaccinated and 0.25/100 person-years in girls who had been unvaccinated in the 3 years following eligibility (Bednarczyk et al. 2012). In Canada, cohorts of girls in grade 8 eligible for school-based HPV vaccination had similar risks of pregnancy and STIs (5–6%) than cohorts of girls not eligible for vaccination (6%) during their high school years (Smith et al. 2015). The vast majority of adolescent girls still perceive safe sex practices to be important after receiving the HPV vaccine (Mullins et al. 2012).

In conclusion, the evidence suggests that exposure to HPV vaccines and to HPV vaccine programs does not change young girls' sexual behaviors, outcomes, and attitudes.

5.4 Utility

5.4.1 HPV Vaccines Are a Conspiracy Perpetuated for Profit

HPV vaccines are a marketable technology developed by pharmaceutical companies. The commercial development of HPV vaccines from proof of concept, to vaccine development, to production scale-up, to clinical trials in thousands of women, and to approval was an expensive and high-risk process that took over 10 years to accomplish (Inglis et al. 2006). Therefore, pharmaceutical companies have a vested interest in the vaccines' sale and marketability. Natural suspicion arose from the start over the influence of commercial interests over policy decisions and over the utility of HPV vaccines (Gefenaite et al. 2012; Kata 2010; Porta et al. 2008; Reist and Klein 2007; Tomljenovic and Shaw 2012b).

Vaccine opponents have argued that efficacy and safety data from HPV vaccine RCTs are suspect on the grounds that most RCTs were financed by the vaccine's manufacturers (Lippman et al. 2014; Tomljenovic and Shaw 2012b; Tomljenovic and Shaw 2013). However, in addition to the stringent oversight imposed by regulatory approval agencies, such as the US Food and Drug Administration and the European Medicines Agency, all the clinical trials were supervised by independent data monitoring committees who reviewed safety data on an ongoing basis to ensure the ethical and safety interests of trial participants. An HPV vaccine clinical trial funded by the National Cancer Institute (NCI), a public US federal agency, also later independently confirmed the efficacy and safety results obtained in manufacturer-funded RCTs

(Hildesheim et al. 2014). There is no evidence to support aspersions of scientific and ethical misconduct during clinical trials. It should also be emphasized that owing to their high cost in the tens of millions of dollars and the need for them to be conducted across multiple centers and countries, HPV vaccine trials could not be funded by any public agency or charity organization. Only large pharmaceutical companies are capable of funding such trials. The aforementioned unique example of the NCI sponsorship of an HPV vaccine trial was based on an arrangement with the manufacturer (GSK) for the NCI study site (Costa Rica) to be one of the many centers for the investigation of the candidate bivalent HPV vaccine.

Because the prevalence of HPV is high in the general population, all women (and eventually all men) were considered to be a potential market for the HPV vaccine (Nature Biotechnology 2007; Rothman and Rothman 2009). Following the licensure of Gardasil in 2006, the vaccine's manufacturer Merck aggressively marketed its vaccine in the United States. The initial marketing placed much emphasis on the risk of cervical cancer, despite the fact that cervical cancer incidence is low (and perceived as such) in developed countries (Mah et al. 2011; Rothman and Rothman 2009). Merck's marketing tactics included lobbying for public funding of the HPV vaccine and vaccination mandates, contributions to political campaigns and women's health groups, educational grants to professional medical associations, and direct to consumer ads (Colgrove et al. 2010; Haber et al. 2007; Rothman and Rothman 2009). In a particularly controversial example, Merck contributed thousands of dollars to the campaign of a Texas governor, who subsequently signed an executive order to make HPV vaccination mandatory which was later revoked (Nature Biotechnology 2007). Merck eventually ceased lobbying efforts for mandatory vaccination in the United States following the negative public reaction. Nevertheless, the ensuing polemic acted as a catalyst for many of the controversies surrounding HPV vaccines' safety, effectiveness, and utility, and considerably increased the public distrust of pharmaceutical companies and government vaccination policies. Many individuals believe that vaccines are a conspiracy foisted upon the public by pharmaceutical industries and governments for profit (Kata 2010; Madden et al. 2012). The involvement of vaccine manufacturers in the policy process exacerbated this perception.

In conclusion, commercial interests have influenced policy decisions and public perceptions of HPV vaccines. However, the value of HPV vaccines is a question that has been substantially evaluated independently by many public health experts and researchers, as discussed below.

5.4.2 Safe and Effective Interventions to Prevent Cervical Cancer Already Exist

Cervical cancer screening tests have existed for many decades, and countries with screening programs have seen substantial declines in cervical cancer incidence and mortality (Gustafsson et al. 1997; Sigurdsson 1999; Vizcaino et al. 2000). While

cervical cancer remains the second most incident female cancer in developing countries, it is now only the tenth most incident cancer in developed countries, in large part due to screening (Kane et al. 2012). Papanicolaou cytology, the test used for screening, is safe and acceptable to most women. Most cervical cancers are detected in under-screened or never-screened women (Andrae et al. 2008; Kirschner et al. 2011; Leyden et al. 2005). Some have argued that wide-scale HPV vaccination is not warranted in the current epidemiological context as there is a low disease burden of cervical cancer thanks to cervical cancer screening. This argument was notably used by Finnish health authorities as a justification for not implementing HPV vaccination after licensure (Syrjänen 2010). Many fear that the focus on vaccination, whose long-term value is yet unproven, could detract from the use and improvement of cervical cancer screening, whose value has been demonstrated (Harper et al. 2010; Lippman et al. 2007; Tomljenovic and Shaw 2013). However, this argument ignores the following weaknesses of cervical cancer screening which can be counteracted through vaccination.

A single cytological screening test for cervical cancer has a relatively low sensitivity (55–90%) to detect prevalent high-grade lesions (Arbyn et al. 2008). Unlike vaccination, the success of cervical cancer screening programs is predicated on repeated testing of women over their adult lives. The necessity for repeated testing and follow-ups presents a substantial burden on health-care systems, as well as on women. For example, cervical cancer screening is estimated to annually cost the US 6.6 billion USD and the UK 208 million GBP (Brown et al. 2006; Chesson et al. 2012). For every case of cervical cancer that is detected by screening, there is an additional 50–100 women with cytological abnormalities and precancerous lesions that are discovered by screening and require proper diagnosis, treatment, and/or long-term follow-up every year (Centers for Disease Control and Prevention 1994). Despite the significant efforts deployed to ensure program quality, many cancers are still diagnosed in women for whom the screening program fails due to a false negative test, inadequate management, loss to follow-up, or interval cancer incidence (Janerich et al. 1995; Kirschner et al. 2011; Leyden et al. 2005). Moreover, screening is not effective against all cervical cancers. Screening is not very effective at preventing cervical cancers in women under 25 years (Lonnberg et al. 2012; Sasieni et al. 2009) or at preventing adenocarcinomas of the cervix, whose incidence rates have been increasing in many countries (Bulk et al. 2005; Lönnberg et al. 2015; Smith et al. 2000).

Though many advocate for increasing screening compliance and reducing program inefficiencies, it is uncertain how successful such interventions would be in reducing cervical cancer incidence and mortality. Screening coverage has stalled over the past decade in many countries despite efforts (Centers for Disease Control and Prevention 2013; Habbema et al. 2012; Machii and Saito 2011), reflecting the difficulty of reaching many marginalized women who have little or no contact with health systems. The declines in incidence and mortality rates of cervical cancer have likewise plateaued in many countries (Dickinson et al. 2012; Habbema et al. 2012; Lönnberg et al. 2015; Syrjänen 2010; Vaccarella et al. 2013), suggesting we may have nearly reached the maximal benefits of cervical cancer screening.

The focus on cervical cancer screening also ignores the other HPV-associated diseases that could be prevented through HPV vaccination. Genital warts are highly distressing and lead to non-negligible health-care costs (Chesson et al. 2012; Ostensson et al. 2015); their incidence has markedly declined in age groups targeted by HPV vaccination programs (Ali et al. 2013; Drolet et al. 2015). Oropharyngeal, anal, vulvar, vaginal, and penile cancers are also not prevented through cervical cancer screening but could be prevented through HPV vaccination. Rare put potentially fatal juvenile-onset recurrent respiratory papillomatosis might potentially also be prevented in the long-term by vaccination, as mothers may transmit their vaccine-induced HPV antibodies to their children (Shah 2014).

HPV vaccination also has indirect beneficial effects on unvaccinated individuals called herd effects. Herd effects occur because protected vaccinated individuals no longer become infected and transmit the infection to others. HPV vaccines are thus expected to reduce infection incidence in both vaccinated and unvaccinated individuals. This is not the case for cervical cancer screening, which benefits only the woman being screened. Some critics have claimed that realizing vaccine herd effects would require a high vaccination coverage to manifest (Harper et al. 2010), but this is demonstrably untrue as herd effects can immediately accrue following vaccination from reduced HPV transmission. For example, surveillance data has already shown that genital wart incidence decreased in unvaccinated heterosexual males following the implementation of female-only HPV vaccination programs in Australia (Ali et al. 2013) and that HPV vaccine type prevalence has declined in both vaccinated and unvaccinated female adolescents in the United States (Kahn et al. 2012; Markowitz et al. 2013).

Some argue that Pap tests and treatment procedures used in cervical cancer screening are much safer than vaccines and consequently that the large-scale use of vaccines with unknown risks is not ethically justifiable (Tomljenovic and Shaw 2012b). However, screening and treatment procedures do entail well-documented harms that should be weighed against potential adverse effects of vaccination. Cervical lesion treatment procedures can cause pain, bleeding, and psychological distress (O'Connor et al. 2016; Sharp et al. 2009). Cervical lesion treatment is also associated with marked subsequent increases in adverse obstetric outcomes such as preterm deliveries, miscarriages, low birth weight, and perinatal mortality (Arbyn et al. 2008; Kyrgiou et al. 2006; Kyrgiou et al. 2014). These adverse obstetric effects are not associated with HPV vaccination (Baril et al. 2015; Garland et al. 2009). Many women undergoing screening are of childbearing age, and many of them will be at risk for these adverse effects of screening over their lifetimes. HPV vaccination may substantially reduce these adverse effects by reducing the incidence of cervical lesions.

In conclusion, though cervical cancer screening has been a very effective intervention, it is likely that countries with long-standing screening programs have already reaped most of the benefits that can be achieved through screening. Primary prevention of HPV infection through vaccination presents substantial advantages, notably herd effects, and the prevention of a variety of health outcomes that cannot be prevented through cervical screening alone. The pitting of vaccination against screening is counterproductive and presents a false dichotomy, as both should be deployed as part of a comprehensive cervical cancer prevention program.

5.4.3 *HPV Vaccines Are Too Expensive and Not a Cost-Effective Use of Resources*

HPV vaccines are among the most expensive childhood vaccines on the market. Upon licensure, a three-dose course of Gardasil cost some 360 USD (The Lancet 2013). Over the years, critics have questioned whether public financing of HPV immunization programs is a cost-effective use of resources (Lippman et al. 2008; Porta et al. 2008; Syrjänen 2010; Thompson and Polzer 2012; Tomljenovic and Shaw 2013), given that (as per their reasoning) (1) the long-term benefits of HPV vaccination are uncertain, (2) the cost of the vaccine is high, and (3) the incidence of cervical cancer is low in most developed countries due to effective cervical cancer screening programs. Furthermore, the argument went, as the duration of vaccine efficacy is uncertain, booster shots may be required over time to maintain protection, further increasing the cost of HPV vaccine programs.

Most decision modeling analyses however agree that vaccinating preadolescent girls against HPV represents a cost-effective intervention in high-income countries using reasonable willingness-to-pay thresholds (Brisson et al. 2013; Jit et al. 2008; Konno et al. 2010; Olsen and Jepsen 2010; Seto et al. 2012). This is due largely to the sizeable gains in life years from averted cervical and other HPV-related cancers but is also due to the projected increases in quality of life and the costs saved from reduced treatment and management of vaccine-preventable cervical cancers, high-grade cervical lesions, and genital warts. In other words, providing the vaccine to preadolescent girls is generally concluded to give good value for money even at a high cost per dose and on top of existing cervical cancer screening. Public health HPV vaccination recommendations often explicitly factor in these cost-effectiveness considerations (Canadian Immunization Committee 2014; Markowitz et al. 2007). Modeling analyses do predict that vaccination of women past adolescence becomes decreasingly cost-effective (Jit et al. 2008; Kim and Goldie 2008), which supports vaccine policies targeting preadolescent girls before sexual debut. This is because many women will already have been infected by late adolescence and adulthood, reducing the cost-effectiveness of vaccination at these ages.

The high retail cost of the vaccine and lack of infrastructures for vaccine delivery in adolescents have constituted significant barriers in resource-restrained settings with competing priorities (Kane et al. 2012). HPV vaccination is predicted to be cost-effective in most low- and middle-income countries, however, when assuming a tiered vaccine cost by country according to income (Fesenfeld et al. 2013; Goldie et al. 2008; Jit et al. 2014). These countries generally have a much higher cervical cancer incidence and mortality than high-income countries and would substantially benefit from vaccination. Not surprisingly, however, cost-effectiveness analyses are highly sensitive to the vaccine price and discount rate.

Modeling analyses have consistently concluded that the vaccine protection should last at least 10–20 years in order for vaccination of preadolescents to be cost-effective, as these will constitute the years during which they will be most at risk for HPV infection (Elbasha et al. 2007; Jit et al. 2008; Kim and Goldie 2008). Though

the duration of HPV vaccine protection remains uncertain, current evidence suggests that HPV vaccines should provide long-lasting immunity. The longest clinical trials which accumulated almost 10 years of follow-up data did not show any waning of vaccine efficacy against HPV-16/HPV-18 infections and associated lesions over time, which suggests that protection lasts much longer than 10 years (Ferris et al. 2014; Naud et al. 2011). Models of antibody titers predict that mean antibody titers will remain above those associated with natural infection for at least 20 years (David et al. 2009; Fraser et al. 2007). These lines of evidence suggest HPV vaccine protection should be long-lasting; there is no current indication that booster shots will be needed to maintain protection. Furthermore, in light of the natural history of HPV infection and cervical cancer, it is conceivable that the critical period for protection is during the late adolescence years, when the uterine cervix is at its most vulnerable phase with exposure of the metaplastic epithelium in the ectocervix (Schiffman et al. 2007). Vaccination in the preteen years should thus offer maximum protection even if it eventually declines.

In conclusion, economic analyses suggest that HPV vaccine programs targeting adolescent girls are a cost-effective intervention in many settings, even in countries with existing screening programs.

5.5 Ethics

5.5.1 Lack of Consent and Infringement of Self-Determination

Because public health interventions such as vaccination are enacted to increase the overall health of the population possibly against individual preferences, they can be perceived as paternalistic and infringing upon individual self-determination (El Amin et al. 2012; Schmidt 2012). The past few decades have seen a societal shift toward the rejection of paternalism, the rise of the well-informed patient, and skepticism of science and authority (Gray 1999; Kata 2010). Many controversies hinge upon a perceived undermining of self-determination in HPV vaccination practices due to misleading communication strategies, lack of information, and coercive methods.

Some have criticized the framing of HPV vaccines by health authorities and vaccine manufacturers as anticancer vaccines addressing a public health crisis, conflating HPV with cervical cancer (Mah et al. 2011; Rail and Lippman 2015; Thompson 2013; Thompson and Polzer 2012; Tomljenovic and Shaw 2012b; Tomljenovic and Shaw 2013). Critics advance that the risk of cervical cancer and other HPV-associated cancers has been misleadingly amplified and the harms of vaccination concealed in communications in order to increase the public acceptability of HPV vaccines. Consequently, they argue that HPV vaccination practices are not ethical given that parents and children cannot give an informed consent to vaccination (Lippman et al. 2014; Rail and Lippman 2015). For example, promotional materials for HPV vaccines have emphasized cervical cancer as the second leading cause of

female cancer mortality worldwide while failing to distinguish that this mortality rate is much lower in developed countries due to screening (Rothman and Rothman 2009). However, as discussed in previous sections, analyses of vaccine utility suggest that HPV vaccination does provide a substantial relative reduction in cervical cancer risk for very little harm. The framing of HPV vaccines as anticancer vaccines is also consistent with vaccine programs' stated aims of reducing the health burden of HPV-associated cancers and not the eradication of HPV infection.

Parents still often feel they lack the necessary information to assess the harms and benefits of HPV vaccination and make an informed decision (Hendry et al. 2013). Public health agencies have over the years employed various communication strategies aimed at parents and preadolescents such as promotional materials, awareness campaigns, in-class education sessions, and consent forms (La Vincente et al. 2015; Watson et al. 2009; Wilson et al. 2012). However, many individuals distrust the information provided by authorities, either because they do not feel public health policies take into account their own individual needs or because of a general distrust of authority (Braunack-Mayer et al. 2015; Gefenaite et al. 2012). For example, parents in some countries fear that HPV vaccines are a government conspiracy to sterilize their daughters, notably in Peru where the government has historically enacted coercive sterilizations in the name of public health (Bingham et al. 2009; Bosch 2002). This creates the unfortunate situation where the public may reject the information provided in favor of other sources such as the Internet or social networks. Health-care provider recommendation of HPV vaccines can help increase vaccine uptake, especially where vaccination is not school-based (Cates et al. 2010; Gamble et al. 2010; Rahman et al. 2015). This may be because they are perceived to be responding to patient's individual needs rather than acting as government agents obligated to enforce policy.

In some instances, the state has taken coercive action to increase HPV vaccination coverage. In the United States, bills were introduced in 23 states to make HPV vaccination mandatory for school attendance, with two states eventually enacting the mandate (Colgrove et al. 2010). These mandates for HPV vaccines were not well received by a variety of stakeholders due to the manufacturer's excessive influence in the policy process, the non-transmissibility of HPV in the classroom, and antipathy toward governmental coercion (Charo 2007; Colgrove et al. 2010; Haber et al. 2007). Mandates for previous vaccines had been justifiable on the public health grounds of preventing the harms from the transmission of infection in the classroom. However, HPV is not transmissible in a classroom setting, which undermines a public health justification for school-entry mandates. Moreover, HPV vaccines are generally framed as anticancer vaccines, a non-transmissible disease, which emphasizes personal care over public health and an individualistic determination of the risks and benefits of vaccination (Mah et al. 2011; Thompson and Polzer 2012). Analysts have generally concluded that coercive mandates to increase HPV vaccination lack ethical justification (Opel et al. 2008; Zimmerman 2006).

In conclusion, public health arguments have had less traction in the case of HPV vaccines than for other vaccines. Instead, the discourse surrounding HPV vaccines has revolved around the self-determination of risks and benefits of vaccination.

Although public health authorities have the ethical obligation of enabling an informed consent to vaccination, it is often challenging to provide this information due to increased demand for individually tailored information and mistrust of institutions.

5.5.2 Those Who Would Benefit Most Are Least Likely to Get Vaccinated

Because more advantaged individuals are generally better able to avail themselves of health interventions, there is concern that HPV vaccination might contribute to increase health inequalities in HPV-associated diseases (Lippman et al. 2007; Polonijo and Carpiano 2013; Thompson 2013). HPV-associated cancer incidence and mortality are generally higher in ethnic minorities, those with low education, and those living in areas of low socioeconomic status (Benard et al. 2008; Braaten et al. 2005; de Vries et al. 2015; New Zealand Ministry of Health 2008; Singh et al. 2004). The inequality between countries is even sharper: nearly 90% of all cervical cancer deaths occur in developing countries, ostensibly due to low screening coverage and availability (Torre et al. 2015). Vaccine uptake is affected by the social determinants of health, and the disadvantaged individuals who would benefit most from HPV vaccination may also be the least likely to get vaccinated. The lack of resources and infrastructures in low-income countries which impede cervical cancer screening also impede the implementation of HPV vaccination programs. Of the 57 countries having implemented HPV vaccination by 2014, only a minority were low-income countries (Herrero et al. 2015).

One potential response to this issue would be vaccination strategies targeting groups at higher risk of HPV infection and HPV-associated diseases. However, previous experience with the hepatitis B vaccine showed that the targeted vaccination of high-risk groups such as intravenous drug users and men who have sex with men (MSM) did not lead to a high vaccine uptake in the United States, which led to the decision to recommend universal infant vaccination instead (Centers for Disease Control and Prevention 1991). Targeted HPV vaccination would therefore be unlikely to succeed in preventing HPV infection and reducing health inequalities. Targeted vaccination strategies also run the risk of stigmatizing the targeted population. While some have argued that universal access to vaccination does little to address the plight of marginalized social groups (Mah et al. 2011; Thompson and Polzer 2012), universal vaccination can arguably be considered to be in line with a social justice objective.

Publically funded school-based HPV vaccination programs have demonstrably been most effective at increasing overall vaccination coverage and increasing vaccination coverage in more disadvantaged groups (Hansen et al. 2015; Hughes et al. 2014; New Zealand Ministry of Health 2008; Sinka et al. 2014). Marginalized preadolescents may underutilize health services but generally have a high school attendance rate in developed countries. For example, a study in Canada showed that

clinic-based delivery led to decreased vaccination coverage in girls from low socioeconomic neighborhoods compared to girls from high socioeconomic neighborhoods (34 vs. 41%), while school-based delivery led to increased vaccination coverage (83 vs. 79%) (Musto et al. 2013). Similarly, school-based delivery in New Zealand helped achieve a higher vaccination coverage in Pacific and Maori girls (78–88%) than in girls of European descent (63%) (Poole et al. 2012).

Vaccine reimbursement also substantially affects uptake. The inclusion of HPV vaccines in the Vaccines for Children reimbursement program in the United States likely contributed to increasing the vaccine coverage in adolescent girls living below the poverty level (67%) than in girls who live at or above the poverty level (55%) (Elam-Evans et al. 2014).

Universal vaccination also provides more herd effects, which can contribute to reducing health inequalities. Disadvantaged social groups with a higher cancer incidence are predicted to have larger absolute health gains from vaccination at equal coverage (Blakely et al. 2014). Even if disadvantaged individuals have a lower vaccine uptake, they should still benefit indirectly from the reduced transmission of HPV. Even if girls who eventually under-screen have a low vaccine uptake, their incidence rate of cervical cancer is likely to decrease, and absolute inequalities in the incidence rate of cervical cancer are likely to diminish postvaccination (Malagon et al. 2015). Unvaccinated girls should therefore still indirectly benefit from universal vaccination programs.

HPV vaccines could also reduce inequalities between countries, as vaccine delivery may be more feasible to implement in some contexts than routine cervical cancer screening (Tsu and Levin 2008). Programs are underway to bridge the health equity gap between high- and low-income countries. Starting in 2011, tiered vaccine prices allowed the introduction of HPV vaccines in some middle-income countries. In 2013, the GAVI alliance started supporting the introduction of HPV vaccines at lower prices in developing countries thanks to a price agreement with Merck & Co. (The Lancet 2013). Since then, GAVI has approved their support for demonstration programs in 20 countries and the national introduction of vaccination in Rwanda, Uganda, and Uzbekistan (Hanson et al. 2015). However, unlike cervical cancer screening, the benefits from HPV vaccination in low-income countries would still require decades to accrue and are unlikely to reduce inequalities in the short term.

In conclusion, questions of social justice have been and continue to be important in shaping HPV vaccination practices worldwide, reflecting the increasing attention being given to health equity in public health.

5.5.3 Gender-Neutral Vaccination

HPV vaccination was originally framed as a woman's health issue (Mah et al. 2011). Cervical cancer has the highest incidence rate of all HPV-associated cancers and has the strongest causal link with HPV infection (de Martel et al. 2012). HPV vaccines were initially tested and approved for use in women, and most vaccination programs

initially targeted girls only. However, there has always been discomfort with the idea of a gender-targeted vaccine (Prue 2016; Tjalma and van Damme 2006). Men also suffer from HPV-associated cancers and genital warts. Unlike cervical cancer, there is no screening program to prevent HPV-associated cancers in men, thus HPV vaccination represents a unique preventive intervention for these cancers. Because HPV is transmitted sexually, the vaccination of both boys and girls is also seen as a way for both genders to share the responsibility for sexual health (Luyten et al. 2014; Thompson and Polzer 2012). Nevertheless, the routine vaccination of boys was not universally adopted following the quadrivalent HPV vaccine's FDA approval for boys in 2009 (Centers for Disease Control and Prevention 2010).

The biggest reason for the slow adoption of vaccination of boys against HPV has arguably been issues of cost-effectiveness. The vaccination of girls already leads to substantial herd effects in boys due to the reduced female-male transmission of HPV. Transmission models predict that the routine vaccination of boys only provides marginal additional benefits both to men and women in the reduction of HPV infection and cervical cancer incidence (Brisson et al. 2011; Jit et al. 2008). However, the addition of boys to publicly funded vaccination programs roughly doubles the cost of HPV vaccination programs. Cost-effectiveness analyses have repeatedly concluded that adding boys to routine vaccination programs is unlikely to be incrementally cost-effective when there is good vaccination coverage in girls (Burger et al. 2014; Chesson et al. 2011; Jit et al. 2008; Kim et al. 2007; Laprise et al. 2014; Pearson et al. 2014). They also universally conclude that increasing vaccination coverage in girls is more cost-effective than vaccinating an equivalent fraction of boys. The vaccination of boys against HPV might however become cost-effective at a lower vaccine cost (Burger et al. 2014; Laprise et al. 2014; Pearson et al. 2014).

Nevertheless, many HPV-associated cancers are diagnosed in MSM who are unlikely to benefit much from the herd effects of girls-only vaccination. In Australia, there has been a marked 82% decrease in the diagnosis of genital warts in heterosexual men <21 years, but only a 25% decrease in MSM (Ali et al. 2013). Anal cancer is 17 times more likely to be diagnosed in MSM than in heterosexual men (Daling et al. 2004). HPV vaccination is an intervention which could increase health equity for a demographic group that historically has been marginalized and underserved by health systems. However, it is debatable whether a targeted vaccination of MSM is an effective strategy. Many men may not identify or disclose themselves as MSM until well after the initiation of sexual activity (Rank et al. 2012; Zou et al. 2014), and vaccine effectiveness and cost-effectiveness decline sharply as MSM age into early adulthood (Kim 2010). Boys and men who opt for vaccination may feel stigmatized by a targeted intervention. A gender-neutral vaccination program is thus desirable from a social justice perspective, as it would ensure that boys have equal access to the intervention at ages when it will be most effective and would likely lead to the highest coverage in males.

The increasing scrutiny of health-care budgets has placed pressure on governments to justify health expenditures on cost-effectiveness principles. Nevertheless, some jurisdictions have now endorsed gender-neutral vaccination for health, political, and ethical reasons (Centers for Disease Control and Prevention 2011; National Advisory Committee on Immunization 2012).

5.6 Conclusions

A large body of evidence supports the prevailing scientific opinion that HPV vaccines are efficacious, safe, and cost-effective. Although some financial interests have been involved in the promotion and implementation of HPV vaccination, arguably health, cost-effectiveness, social justice, and political considerations have been the most important elements shaping HPV vaccine policies worldwide. Increased efforts should be made to provide reliable scientific evidence to the relevant stakeholders (parents, children, health-care providers) to enable informed consent and to ensure that worldwide the individuals most at risk for HPV-associated diseases have access to HPV vaccines.

Controversy in public health often stems from a strong polarization of opinions between proponents and opponents regarding scientific evidence. Generally, each camp will selectively cite reports which uphold their positions, amplifying the divide in opinions (Cope and Allison 2009; Trinquart et al. 2016). Many of the controversies associated with HPV vaccines fall into this pattern, with the vast majority of researchers being in favor of vaccination but with a minority of voices persistently opposed. Though there has been much scrutiny of the financial conflicts of interest in the case of HPV vaccines, it is likely that nonfinancial conflicts of interest (political, academic, ideological, religious) have been very important in shaping the public narrative and have led to personal allegiances and expectations regarding the harms and benefits of vaccination. Nonetheless, increasing amounts of surveillance data have started to demonstrate the effectiveness and safety of HPV vaccines, as evidenced by declines in HPV infection, genital warts, and cervical lesions without any notable increase in serious adverse effects (Drolet et al. 2015; Markowitz et al. 2016; Vichnin et al. 2015). This suggests that the prevailing scientific opinion supporting the promotion and implementation of vaccination continues to be correct and based on good evidence.

Public health institutions must increasingly respond to public controversies with effective communication and policies. Public health messages compete with many other alternative information sources which individuals use to inform their decisions such as the media, the Internet, and social networks, many of which contain misinformation (Dunn et al. 2015; Habel et al. 2009; Kata 2010; Madden et al. 2012; Smith et al. 2008). Parents often cite a lack of transparency and information regarding the risks and benefits of vaccination as a major concern (Hendry et al. 2013). Unfortunately, providing educational materials to parents may not significantly influence vaccine acceptability (Dempsey et al. 2006). This may be because public health authorities can only provide information regarding population-level aggregate risks and benefits of an intervention and not the particular risks and benefits for each individual (Braunack-Mayer et al. 2015; Serpell and Green 2006). Nonetheless, public confidence in vaccines is undermined when public health policies are perceived to be contradictory or unduly influenced by commercial interests. Notable examples include the disastrous plummeting of vaccine coverage following the suspension of active recommendations of HPV vaccination in Japan, the public

backlash which followed the industry lobby for vaccine mandates in the United States, and the government suspension of demonstration projects for HPV vaccination in India following advocacy group pressure (Colgrove et al. 2010; Hanley et al. 2015; Larson et al. 2010). Public health policies should be evidence-based and transparent and be perceived as such.

Ongoing public scrutiny of HPV vaccination practices remains important. In the coming years, the role of cervical cancer screening in the age of HPV vaccination will become a key controversial subject (Franco et al. 2006). The decline in the prevalence of HPV infection and of precancerous lesions will lead to a substantial decrease in the performance of screening tests (Franco et al. 2009). As the predictive value of screening is expected to decline, screening protocols will have to be redesigned in order to maintain program quality while keeping an acceptable trade-off between the benefits and harms of screening. This will likely generate much debate due to the uncertainty regarding the impact of changes in screening protocols and the public's perception of these changes. The controversies related to HPV vaccination will thus continue to evolve in the coming years.

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Chapter 6
Impact on Quality of Life

Neil K. Chadha

Abbreviations

HRQOL	Health-related quality of life
HUI3	Health Utilities Index version 3
JORRP	Juvenile-onset recurrent respiratory papillomatosis
PVHI	Pediatric Vocal Handicap Index
PVOS	Pediatric Voice Outcome Survey
PVRQOL	Pediatric voice-related quality of life
RRP	Recurrent respiratory papillomatosis
SF36	Short Form 36
VAPP	Voice Activity and Participation Profile
VHI	Vocal Handicap Index
VHI10	Vocal Handicap Index-10
VoiSS	Voice Symptom Scale
VOS	Voice Outcome Survey
VRQOL	Voice-related quality of life

6.1 Introduction

Although challenging to define precisely, quality of life is comprised of broad concepts that affect global life satisfaction, including health, housing, employment, safety, relationships, education and leisure. The concept of quality of life has become

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increasingly important in healthcare, and those life concerns that are most affected by health or illness are termed “health-related quality of life” (HRQOL). HRQOL encompasses methodologies and measures for quantitative evaluation of the effects of an illness on a patient’s physical and mental well-being (Bergner 1989).

Early instruments relied on expert assessment to evaluate a patient’s life quality in terms of their dependence on medical care and mobility, using “objective” rating scales. Later instruments were developed that assess a patient’s own “subjective” responses to multi-item questionnaires, providing ratings in a number of life domains, such as emotional health, physical health and social well-being. These questionnaires, such as the Short Form 36 and the HUI3, are deliberately generic, as they can be applied to a variety of medical conditions. This wide applicability is advantageous when comparing the impact of differing health conditions for resource allocation or cost-benefit analysis, but has a disadvantage in lacking the sensitivity to detect subtle changes, and lacks the specificity for the manifestations unique to individual illnesses.

Increasingly HRQOL has been recognized as an important outcome measure to evaluate and compare treatment interventions in more homogenous diseases. For this purpose, a disease-specific HRQOL measure would be advantageous and needs to be designed specifically to assess the quality of life domains and symptoms relevant to the health condition being assessed. In this chapter, the quality of life issues that manifest in RRP are discussed, together with a review of the historical usage of HRQOL measures in RRP clinical research and their findings.

6.2 Health Quality Impacts of Recurrent Respiratory Papillomatosis

Recurrent respiratory papillomatosis (RRP) is the second most common cause of hoarseness and the most common benign neoplasm of the larynx children. RRP is a viral infection caused by the human papillomavirus (HPV), most commonly types HPV 6 and HPV 11. RRP can be categorized into two clinical subgroups: juvenile onset (JORRP) and adult onset. JORRP appears to be the most common and most aggressive form of this condition and is typically diagnosed before a child is 5 years of age.

The most common symptom manifestation of RRP is a voice that is persistently hoarse, weak, low pitch, breathy, or strained. In more severe cases, an affected individual may have aphonia (i.e., loss of voice). The bulk and location of the papillomatous lesions in the larynx, and thereby how they interfere with normal vocal cord function, likely explains the variability of voice defects. Lesions that occur on the true vocal cords, particularly those affecting the anterior commissure, can cause hoarse voice early, with relatively small lesions. As the volume of tumor increases with disease progression, difficulty breathing can occur through reduction in the airway diameter by the lesions. This is frequently associated with inspiratory and/or

expiratory stridor, as the lesions cause turbulent airflow through the larynx. In mild cases, the voice and airway symptoms of RRP may develop gradually over several months or years, but in aggressive cases, symptoms may progress rapidly. The most common presentation in young children is a weak hoarse cry, persistent cough, difficulty swallowing, and stridor. Although airway compromise is more common in children with JORRP, breathing difficulties may also occur in adults, particularly with exertion and exercise. The natural history of RRP varies, with most children requiring repeated endoscopic surgical debulking to ensure airway patency and adequate voice quality.

The potentially profound effects of RRP on the airway and voice have led to widespread interest in the use of HRQOL measures to assess the impact of RRP in comparison to other medical conditions, to explore the natural history of the condition, and as an outcome measure to evaluate interventions. The number of surgical procedures required during the lifetime of a child with severe RRP to maintain their airway patency and voice may in some cases be over 100. Therefore, it has long been suspected that in addition to the voice and breathing HRQOL effects of RRP, the need for frequent surgical treatments itself likely results in physical and emotional distress for affected patients and their families.

6.3 Overall Health Versus Disease-Specific Quality of Life Measures

Several instruments exist that can be used to measure HRQOL in RRP, including generic, disease-specific, and symptom-specific instruments. Generic instruments are designed to investigate aspects of health that are of universal importance and thereby allow comparisons of HRQOL among different patient populations. By contrast, a disease-specific instrument attempts to capture the specific impact of a disease on a patients' functioning and well-being, with domains that aim to be more sensitive to clinically important differences of the disease in question. The first widely recognized disease-specific instrument for measuring HRQOL in RRP was proposed by Derkay et al. in 1998 (Derkay et al. 1998). This scoring system consisted of two parts: a "clinical score" based on the patient's voice, stridor, respiratory distress, and urgency of surgery (see Fig. 6.1) and an "anatomical score" based on number of laryngeal subsites affected. Although the Derkay-Coltrera anatomical score has become widely used for both clinical and research purposes, the Derkay-Coltrera clinical score has not since been employed or validated as a HRQOL tool.

Unfortunately, there does not currently exist a validated, disease-specific tool for measuring HRQOL in RRP. As the most common symptom manifested by RRP-affected individuals is a change in voice quality, tools measuring voice-related QOL have largely become surrogate tools for measuring RRP HRQOL. Fortunately, there exist a number of validated voice-specific quality of life measures that were designed to assess the severity of any voice disorder. Although not specific to RRP, these

CLINICAL COMPONENT OF DERKAY-COLTRERA STAGING ASSESSMENT FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

1. Describe the patient's voice today:

normal __ (0); abnormal __ (1); aphonic __ (2)

2. Describe the patient's stridor today:

absent __ (0); present with activity __ (1); present at rest __ (2)

3. Describe the urgency of today's intervention:

scheduled __ (0); elective __ (1); urgent __ (3); emergent __ (4)

4. Describe today's level of respiratory distress:

none __ (0), mild __ (1); moderate __ (2); severe __ (3); extreme __ (4)

Total for questions 1-4("Clinical score") = ____ (/ maximum 12)

Fig. 6.1 Clinical score, modified from the Derkay-Coltrera RRP staging/severity score (Derkay et al. 1998)

instruments can be easily applied to RRP and thereby have provided the opportunity to compare the impact of this condition on voice-related quality of life in comparison to other conditions that affect voice.

6.4 General Health-Related Quality of Life Measures in RRP

The first application of a general HRQOL measure to RRP occurred in 2000, when Hill et al. used the Short Form 36 (SF36) questionnaire in a group of adults with RRP (Hill et al. 2000). The SF36 is a 36-item, patient-reported survey of health that consists of 8 domains including physical, social and mental health. Although this study was limited by its small size and incomplete response rate (26 respondents of 36 contacted), it provided novel evidence that RRP scored lower than the general population in generic HRQOL, particularly in the domains of "role limitation (physical)," "energy/vitality," "pain," and "social functioning." This effect was much more apparent in those individuals with greater disease volume. Differences from the general population existed but were small in the domains of "mental health" and "general health perception."

The general HRQOL of a pediatric RRP population was first studied by Lindman et al. in 2005, employing the Pediatric Quality of Life Inventory (PedQL 4.0) (Lindman et al. 2005). PedQL is a 23-item survey validated in children and

adolescents that includes both child self-report and parent self-report in the domains "physical," "emotional," "social," and "school functioning." The study included 22 otherwise healthy children between 2 and 18 years. The study found PedQL scores were worse in all domains in the RRP children than expected in healthy children. Additionally, the child self-report scores for RRP children aged 5 to 18 years, were similar for those expected from children with other chronic diseases.

The concept of health utility measurement has gained importance as it provides a method for the valuation of health in economic evaluation, such as the calculation of quality-adjusted life years (QALYs). This method of general HRQOL measurement was first applied to RRP through the use of the multi-attribute Health Utilities Index version 3 (HUI3) (Chadha et al. 2010). The HUI3 is a measure of health utility and quality of life validated in the pediatric population, consisting of eight domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, each with 5–6 levels of ability/disability. The study included all 20 children with active RRP at the center, with age range of 17 months to 17 years. The mean HUI3 score was 0.76 on a scale of 0 (death) to 1 (perfect health). This was comparable to cystic fibrosis in a similarly-aged population (Chadha et al. 2010).

A further study obtained data on utility using the 15D Questionnaire, which consists of questions on 15 domains of HRQOL. This study aimed to see the HRQOL impact of JORRP on adults later in life. The population included 18 of 32 adult RRP patients known to the center (Ilmarinen et al. 2011), aged 22 to 71 years old, an average of 40 years from first diagnosis. In that study, HRQOL gave a mean score of 0.91, which was only slightly lower than the score for controls (0.95), but all except four of the participants were in complete remission with no active disease, and the groups' interval since the last surgical procedure ranged from 1 to 27 years.

An attempt was made to explore the burden on a family of having child with RRP, using the Impact on Family Life Scale (IFS). This is a validated 27-item scale that measures a caregiver's perception of the impact caring for a child with a chronic health condition has on family life, using four dimensions (economic, social, familial and strain). The median IFS for the 20 children with active JORRP included in the study was 0.75 (0 = least impact, 1 = most impact) (Chadha et al. 2010). High total scores on IFS are concerning for potential correlation with maternal psychiatric symptoms, poor child health, poor child adjustment and increased child hospitalizations.

6.5 Voice-Related Quality of Life Measures in RRP

Historically, severity and outcome in voice disorders were measured from the clinician's perspective, using for example, perceptual measures, imaging, or acoustic measurements. Subsequently physicians and speech and language therapists treating these individuals have developed a vast array of patient-reported measures, many of which could be considered measures of HRQOL as they include questions on the functional, physical, psychological/emotional, and social effects of voice

Instrument	VHI	VHI10	VRQOL	VOS	VAPP	VoiSS	PVHI	PVRQOL	PVOS
No. of items	30	10	10	5	28	30	23	10	4
Domains:									
Communication				X	X	X			X
Social			X	X	X	X		X	X
Emotional	X	X	X		X		X	X	
Physical	X	X	X				X	X	
Functional	X	X	X				X	X	
Work/School				X	X	X			
Voice sound and variability						X			

Fig. 6.2 Branski et al. compared nine adult and pediatric voice-related quality of life measures, demonstrating the considerable variation in content and addressed domains (VHI, Vocal Handicap Index; VHI10, Vocal Handicap Index-10; VRQOL, voice-related quality of life; VOS, Voice Outcome Survey; VAPP, Voice Activity and Participation Profile; VoiSS, Voice Symptom Scale; PVHI, Pediatric Vocal Handicap Index; PVRQOL, pediatric voice-related quality of life; PVOS, Pediatric Voice Outcome Survey) (Branski et al. 2010)

dysfunction (see Fig. 6.2) (Branski et al. 2010). Many of these tools were adapted for children, and they have undergone varying degrees of validation in different populations with voice disorders. With the major impact on RRP individuals being most commonly voice-related, tools measuring voice-related QOL have largely become surrogate tools for measuring RRP HRQOL.

The first study to measure voice-related QOL in RRP using a validated pediatric tool was by Chadha et al. in 2010, employing the pediatric voice-related quality of life (PVRQOL) tool, a 10-item questionnaire exploring the impact of voice dysfunction on physical, emotional, and social interaction in children. This study found the 20 included children with RRP had a mean PVRQOL score that was substantially worse than shown in other studies of children with common pediatric voice diseases, such as unilateral vocal cord paralysis or vocal cord nodules (Chadha et al. 2010).

A study of 34 adult RRP patients aged 25 to 85 years, some many years into remission, used the Voice Handicap Index (VHI) which is a validated voice-related quality of life measure (van Nieuwenhuizen et al. 2010). This study found two-thirds of individuals had at least a mild voice handicap. A similar study employing the VHI in adults who were largely in remission from previous JORRP from Ilmarinen et al. found no statistically significant difference in voice-related QOL compared to controls, although all the RRP patients had either a mild or moderate voice handicap (Ilmarinen et al. 2011).

In a study of 143 adults attending a voice clinic with various laryngeal pathologies, the 20 adults with RRP had a mean VHI which was similar to the scores from the subjects with the other laryngeal pathologies, such as vocal cord polyp, vocal cord cyst, unilateral Reinke's edema, vocal cord nodules, and sulcus vocalis, although less severe than the VHI scores in subjects with unilateral vocal cord

paralysis (Stuut et al. 2014). A more recent study employing a modification of the VHI with a reduction from 30 questions to 10 questions (VHI-10), showed a mean pre-op score of 18 out of 40 at the time of surgery for 93 procedures in 43 adults with RRP (Kupfer et al. 2016), suggesting a mild to moderate voice handicap.

6.6 Correlation Between Disease Severity and Quality of Life Measures

The majority of studies on the efficacy of RRP interventions have focused on the extent of disease in the airway, as measured by the bulk of disease and number of affected subsites in the larynx. This anatomical method of assessing disease severity has been popularized by the widespread use of the Derkay-Coltrera anatomical scoring system. Although this provides a useful and consistent measure of disease activity, until study began of HRQOL in RRP it was unclear whether the disease severity as assessed by the clinician observing disease bulk had any relevance to the disease severity as reported by patients' QOL. Chadha et al. were the first to explore this and somewhat surprisingly found that the Derkay-Coltrera disease anatomical score did not correlate well with voice-specific or overall health utility measures (Chadha et al. 2010). This finding confirmed anecdotal impressions that the anatomical extent of papilloma within the larynx may not in itself be a reliable predictor of the negative impact of RRP on health and voice. Although it is clearly of interest in the assessment of new therapeutic agents to look for a reduction of papilloma extent within the airway, the patient-centered outcomes of health-related and voice-related quality of life should also be considered in future therapeutic trials.

Another study of adult RRP subjects attempted to use a multivariate regression analyses to look for a correlation between voice-related QOL and disease severity. They included a number of factors, including age of onset, time between surgical procedures, disease location, and time since last surgical procedure, to explore whether there may significant predictors for VHI scores. They found the only significant predictors for worse VHI were a shorter time since the last surgical procedure and a passive coping style, with disease anatomical factors not significant predictors (van Nieuwenhuizen et al. 2010).

Kupfer et al. designed their study of 46 adult patients with active RRP specifically to explore whether there may be a correlation between the anatomical disease extent and the voice-related quality of life at the time of each surgery (Kupfer et al. 2016). They retrospectively collected data on 93 procedures in these patients, including the Derkay-Coltrera anatomical score at the time of the procedure and the most recent VHI-10 score within at least 30 days. They found a statistically significant correlation between these variables with a worse VHI in those individuals with more extensive anatomical disease. This study suggested that the VHI-10 may therefore be considered a good indicator of disease severity, reflecting both voice-related QOL and anatomical disease severity (Kupfer et al. 2016).

Unfortunately, a limitation of that work was that each procedure was considered separately for statistical analysis, and therefore multiple data points were derived from an individual patient in several instances, creating a potential bias weighted toward those patients.

6.7 Areas for Further Work

The need for a validated and distinct disease-specific HRQOL measure for RRP has been discussed in the literature but to date remains elusive (Lindman et al. 2005; Chadha et al. 2010). The development of such an instrument would involve multiple steps, including open-ended interviews, focus group interviews, and field testing. The number of subjects involved would likely require a multi-institutional collaborative effort, in view of the rarity of this condition. Once validated, such a tool would be useful as both a clinical and research outcome measure, benefiting from being more specific to RRP and therefore more sensitive to subtle change than generic HRQOL measures.

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Chapter 7
Contemporary Management of Recurrent Respiratory Papillomatosis in Adults

R. Jun Lin and Clark A. Rosen

7.1 Introduction

Recurrent respiratory papillomatosis (RRP) are benign epithelial growths that have been shown to associated with human papilloma virus (HPV) infection. Low-risk HPV subtypes 6 and 11 are the most common etiologic agents. RRP may manifest during either childhood or adulthood. The incidence of adult-onset RRP has been reported between 3 and 10 per 1,000,000 (Lindeberg and Elbrond 1990). It presents most commonly between ages of 20 and 40, with a higher prevalence in men (Cohn et al. 1981). The adult form of RRP is typically considered less aggressive compared to the juvenile form. This perception may have also arisen from the smaller airway size and therefore increased susceptibility to symptoms secondary to disease in the pediatric population. Surgical removal is the standard of treatment; however surgery is not curative. Adjuvant treatments including local and systemic therapies are available for aggressive disease. Adjuvant treatments will be discussed in a separate chapter. Given the recurrent nature of the disease, surgical goals focus on disease control, maintenance of airway patency, and preservation of voice while minimizing the sequela of multiple surgeries, e.g., vocal fold scar, anterior glottic web formation, etc.

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7.2 Surgical Management

7.2.1 Office-Based Procedures

Office-based laryngological procedures have been gaining increasing popularity since the 1990s (Woo 2006). Advances in technology, such as the development of high-definition chip-tip endoscopes and flexible fiber-based laser systems, are contributing factors to this upswing. Chip-tip endoscopes provide dramatic improvement in image and video resolution. The working channel in therapeutic laryngoscopes, bronchoscopes, and esophagoscopes provides a conduit through which additional flexible instruments, for example, drip catheters, biopsy forceps, and injection needles, can be utilized to administer medications and perform laryngological procedures. Lasers of different wavelengths, such as the pulsed dye laser (PDL), pulsed KTP (potassium titanyl phosphate) laser, and CO_2 (OmniGuide™ fiber or FiberLase™) laser, are offered in a flexible fiber-based configuration that can be delivered through the therapeutic endoscopes.

Other advantages of office-based procedures include real-time evaluation of voice, true vocal fold closure and mucosal vibration, as well as immediate assessment of treatment results. In addition, given the recurrent nature of RRP, performing unsedated procedures in the clinic setting translates into decreased cumulative risk of general anesthesia, decreased recovery time, and reduced missed time from work or school. Further, office-based RRP treatments may present a healthcare cost savings incentive. One study showed that savings of greater than $5000 were realized for every procedure performed in the office versus the operating room (OR) (Rees et al. 2007). Performing unsedated RRP treatments in the endoscopy suite is another alternative that maintains the cost savings benefit of office-based procedures while eliminating added costs to the clinic, e.g., equipment, staff, laser fibers, and laser machine (Hillel et al. 2015). This is also an effective approach for practices that cannot support procedures in the office setting.

Office-based laryngological procedures have been shown to be safe and well-tolerated. Koufman et al. reported 443 cases of laser procedures in the office, 212 (52.2%) of which were RRP patients (Rees et al. 2006). Only four complications (0.9%) were reported, including one vasovagal event, two vocal fold hemorrhages, and one broken PDL laser tip in the airway, which was immediately retrieved with cup forceps. In a series of 328 patients who underwent unsedated in-office PDL laser treatments, the average comfort score was 7.4 (10 being minimal discomfort) and 87% of patients preferred to undergo in-office procedures (Zeitels et al. 2004).

Zeitels et al. first described laser treatment of laryngeal papillomas in the office (Zeitels et al. 2004). This group performed 82 office-based treatments in 51 patients with recurrent vocal fold dysplasia or RRP using a 585-nm PDL. Only five procedures were aborted due to inadequate exposure or discomfort. Of those who were successfully treated, 88% had 50% disease involution, while the remaining 12% had 25% to 50% disease regression. The longer pulsed 532-nm KTP laser was trialed and adopted for the management of RRP a few years later (Zeitels et al. 2006a). The laser is preferentially absorbed by oxyhemoglobin, and its increased pulse length

allows for more consistent intravascular coagulation, thus less bleeding (Zeitels et al. 2006b; Broadhurst et al. 2007). It has now become a widely used fiber-based laser treatment modality for office-based management of RRP.

Small RRP lesions may also be removed by cold steel in the office using peroral instruments or biopsy forceps through the working channel of therapeutic laryngoscopes. However these approaches are very limited. This chapter will concentrate on laser treatments of RRP in the clinic setting.

7.2.1.1 Indications

Patient selection and shared decision-making are imperative. The pre-procedure discussion should include the nature of the procedure as well as the steps involved. A patient's willingness to cooperate and anxiety should be assessed. Generally a patient is not considered a suitable candidate for unsedated office-based procedures if he or she is anxious and having a difficult time tolerating diagnostic flexible laryngoscopy. In addition, a sensitive gag reflex may preclude the patient from having an unsedated procedure. Other factors to consider include the patient's anatomy, general health status, and RRP disease burden. The patient must have a sufficiently patent nasal passage to allow a 2.1-mm channeled laryngoscope (outer diameter 5.0 mm) to pass through. For patients who are not healthy enough to undergo general anesthesia, unsedated procedures are good alternatives. However, these patients may still need to be monitored during the procedure. In which case the procedure can be performed in an endoscopy suite or in the OR with continuous monitoring capabilities. Studies in the literature demonstrate that epithelial dysplasia can be identified in up to 50% of patients with RRP, while malignant transformation occurs in less than 3% of the cases (Schraff et al. 2004; Baumann et al. 2009). For this reason, the authors believe that the very first RRP surgery should be performed in the OR for proper disease staging, as well as for obtaining representative biopsies.

7.2.1.2 Setup/Equipment

The procedure is typically performed with one assistant while the patient sits upright in a chair (Mallur and Rosen 2012). Additional details and educational information for laryngology assistants can be found in the article by Mallur and Rosen (Mallur and Rosen 2012). The surgeon needs to be mindful of the amount of topical lidocaine administered during the procedure. The total dosage of 4% lidocaine applied is 2 mg/kg to a maximum of 5 mg/kg. Intranasal anesthesia is administered topically with nasal pledgets soaked in a 50:50 mixture of 4% lidocaine and oxymetazoline (Afrin™). The oropharynx and larynx are anesthetized using a nebulizer treatment of 3 mL of 4% lidocaine (Fig. 7.1). After passing a flexible laryngoscope with a 2.1-mm working channel through the nostril, the epiglottis and the true vocal folds are further anesthetized by dripping 4% lidocaine using a cannula through the working channel.

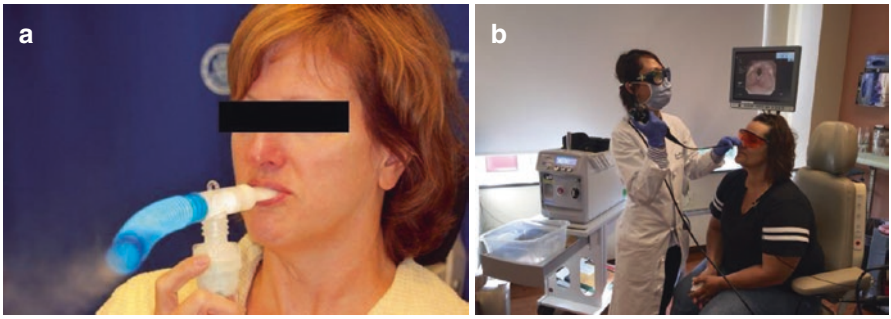

Fig. 7.1 Procedure setup. (**a**) Patient is receiving a nebulizer treatment of 3 mL of 4% lidocaine pre-procedure. (**b**) Patient positioning and procedure room setup. Note the KTP laser machine on the left side of the room. Both the surgeon and the patient are wearing laser-safe goggles. There are two monitors in the room, one for the surgeon and one for the assistant (the second monitor is outside the picture). [(**a**) was adapted from Fig. 33.3 in Rosen and Simpson (2008)]

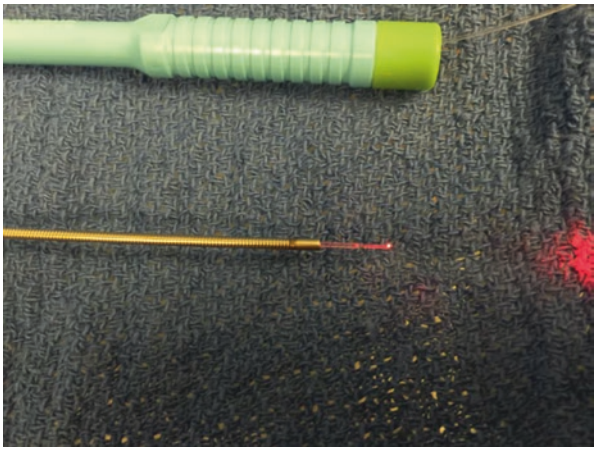

Fig. 7.2 KTP laser fiber-catheter system. The KTP laser fiber is passed through a catheter to prevent scratching the inside of the working channel of the laryngoscope. The entire system is then passed through the working channel. Note the KTP laser fiber past the distal end of the catheter. The KTP fiber length can be easily adjusted during the procedure

Once the patient is adequately anesthetized, laser precautions should be ensured before the procedure begins. All individuals in the procedure room should wear laser safety goggles. A laser warning sign should be posted outside the door. The KTP laser fiber is first passed through a protective catheter to prevent scratching the inside of the working channel of the laryngoscope (Fig. 7.2). While the surgeon is holding the laryngoscope, the assistant can pass the laser fiber catheter unit through the working channel. The laser fiber is then aimed at the RRP lesions for treatment. Common laser settings include a power of 30 W to 35 W, 15-ms pulse width, and two pulses per second (pps). Total joules and time of laser exposure are recorded for each procedure. The end-tissue effects are also recorded. A 5-point classification system was created describing common end-tissue effects seen during KTP laser treatment (Table 7.1 and Fig. 7.3) (Mallur et al. 2014). The surgeon may start with the most conservative KTP effects and increase as needed. Depending on the

Table 7.1 The pulsed 532-nm potassium titanyl phosphate (KTP) laser treatment classification

Treatment classification	Description
KTP V	Noncontact, angiolysis
KTP 1	Noncontact, epithelium intact, epithelium blanched
KTP 2	Noncontact, epithelium disruption, slight "craters" in epithelium
KTP 3	Select contact or noncontact, epithelial ablation without tissue removal
KTP 4	Contact, epithelial ablation with tissue removal

Note: Table adapted from Mallur et al. (2014)

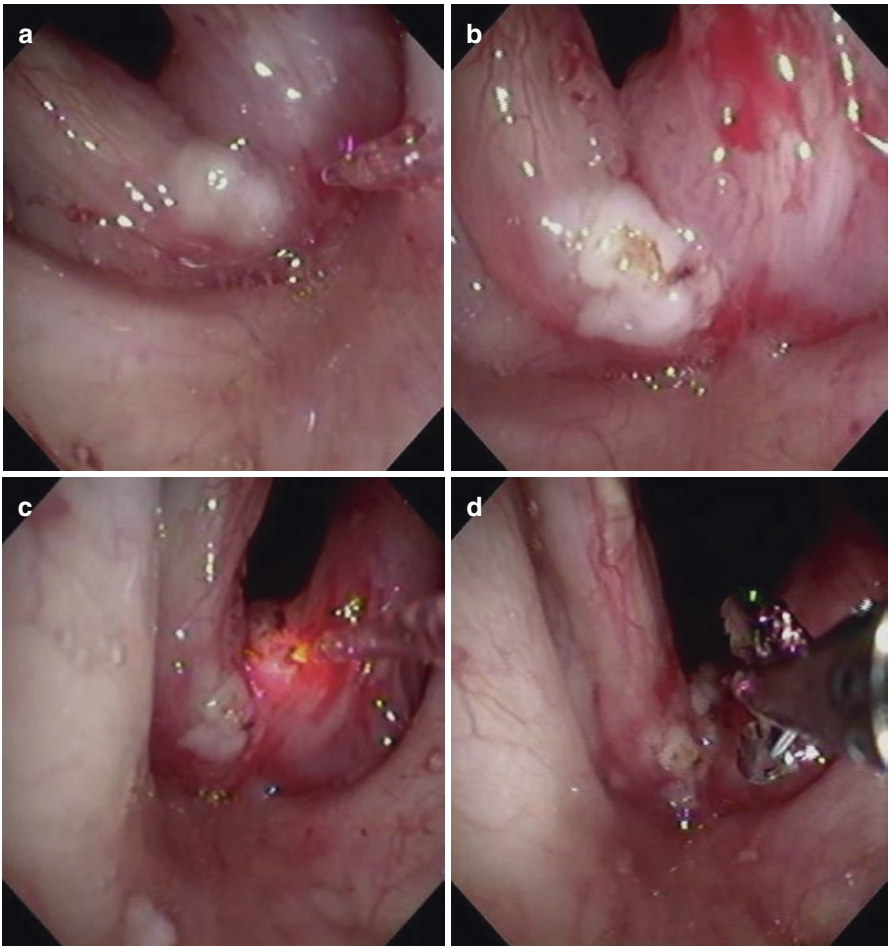

Fig. 7.3 Various end-tissue effects from KTP treatment. (**a**) KTP 1; (**b**) KTP 2; (**c**) KTP 3 using contact mode; (**d**) RRP debris can be removed using flexible grasping forceps through the working channel of a laryngoscope

location of the RRP lesion, different KTP end-tissue effects are desired. For example, at the anterior commissure, it is preferable to have a treatment effect of KTP 4 on one vocal fold and a KTP 1 on the contralateral vocal fold. This prevents having two raw surfaces contacting each other resulting in anterior glottic web formation. Due to the laryngeal local anesthesia provided, the patient is advised to remain NPO for 2 h after the procedure.

7.2.1.3 Advantages/Disadvantages

Office-based pulsed KTP laser treatment of RRP lesions helps patients to avoid multiple general anesthetics as more than one treatment is usually required in this patient population. It allows "touch-up" removal of small RRP lesions. The patient is unsedated; thus he or she can drive to and from the clinician's office before and after the procedure. In addition, postsurgical recovery time is less compared to those performed in the OR, which translates into less time missed from work or school. Disadvantages include that it is time-consuming for treating bulky RRP lesions and that the treatment is not as precise as when the patient is under general anesthesia. It is also difficult to perform a biopsy and provide KTP laser treatment at the same session due to decreased effectiveness of the laser secondary to bleeding. Complications of office-based KTP laser treatment include vasovagal reaction, epistaxis from passing the laryngoscope through the nose, and anterior glottic web formation.

7.2.2 Operating Room Procedures

Operative microlaryngoscopy has been a long-standing and effective treatment for RRP. This is performed under general anesthesia using principles of phonomicrosurgery (Rosen and Simpson 2008). Patients can typically be intubated with a size 5 endotracheal tube. For those with subglottic or tracheal RRP, jet ventilation or apneic methods can be considered. The largest laryngoscope should be utilized for visualization of the RRP site(s). The laryngoscope may need to be repositioned multiple times during the surgery for optimal exposure of the targeted lesions. Risks of these operating room procedures include those associated with suspension microlaryngoscopy, such as throat pain, jaw pain, tongue swelling, taste change, chipped teeth, and lip or gum lacerations. RRP patients tend to have multiple surgeries; thus there is a risk associated with cumulative general anesthesia as well as vocal fold scarring and anterior glottic web formation. Different surgical techniques are available, and utilization of each technique is dependent on lesion characteristics, equipment availability, and surgeon preference. Specific advantages and disadvantages of each technique are described below.

7.2.2.1 CO_2 Laser

CO_2 laser has been a traditional treatment for RRP. It has an emission wavelength of 10,600 nm and is absorbed by intracellular water. Therefore CO_2 laser, when coupled to an operating microscope, can effectively vaporize RRP lesions with precision, resulting in minimal bleeding. Dedo reported a series of 244 patients with RRP treated with CO_2 laser every 2 months (Dedo and Yu 2001). He achieved disease remission in 37% of his patients, disease clearance (no recurrence in 3 years) in 6%, and cure of disease (no recurrence in 5 years) in 17%.

Laser safety precautions are paramount in the OR. The laser beam can reflect off metal from the laryngoscope and injure eyes or skin in it's path. A misfire may also hit patient tissue(s) that are not protected by a wet towel to absorb the laser energy. In addition, laser smoke, or plume, has been found to contain active viral DNA, which is a potential source of infection (Kashima et al. 1991). In the oxygen-rich environment provided by anesthetic gases, airway fire can be a possibility. Low FiO_2 setting (<30%) should be utilized when at all possible. Saline pledgets are placed in the airway to protect the endotracheal tube. The patient's face is wrapped with wet towels. All OR personnel should wear laser safety goggles. Smoke evacuators are necessary to further reduce laser plume. Laser warning signs are posted outside the OR door. Disadvantage of the CO_2 laser includes thermal injury to the surrounding normal tissue, with a theoretical risk of implanting viral particles into those areas. CO_2 laser has long been considered a workhorse in otolaryngology. Recent advances in technology including micromanipulators and scanning laser delivery systems have made it into a more powerful operative tool in laryngologic procedures. The use of a CO_2 laser requires the laser to be used frequently by the surgeon and well maintained by the laser team at its facility.

7.2.2.2 KTP Laser (pulsed)

Photoangiolytic lasers such as the KTP selectively ablate the papilloma microvasculature with limited thermal injury to the surrounding tissue due to their selective absorption by oxyhemoglobin. KTP was first reported as a treatment modality for RRP during microlaryngoscopy under general anesthesia in 2007 (Burns et al. 2007). This study described 35 procedures performed on 23 patients. Approximately 80% of the cohort achieved more than 90% disease regression with no new laryngeal webbing. Typically KTP laser settings in the OR are the same as office-based settings as described previously. Standard laser safety precautions should apply (see above). KTP end-tissue effects are recorded as described in office-based procedures.

7.2.2.3 Microdebrider

Powered instrumentation for RRP removal first came into use in the early 2000s. Two studies have shown that the microdebrider reduced operative time and caused minimal soft tissue effects (El-Bitar and Zalzal 2002; Patel et al. 2003). Microdebriders allow removal of laryngeal RRP lesions without causing thermal damage. Collection of specimens is available if the tissues are captured in a filtration sock placed on the suction apparatus. The specimens are collected piecemeal rather than en bloc. Nonetheless the tissues obtained through a microdebrider have been shown to be suitable for pathological diagnosis (McGarry et al. 1997), and it is routinely done in endoscopic sinus surgery. There is no plume exposure compared to CO_2 laser treatment. In addition, microdebrider has been associated with equivalent postoperative pain and improved voice quality compared to CO_2 laser (Pasquale et al. 2003). It may also result in cost savings as expensive laser equipment and personnel are not required. Bleeding intraoperatively can be controlled by submucosal infusion of epinephrine prior to surgical excision or application of epinephrine-soaked pledgets on the surgical site post lesion removal. The smallest microdebrider blade should be used first. The authors typically use a 2.9-mm Skimmer blade (Medtronic®, Minneapolis, Minnesota). The microdebrider should have a starting setting of 500 rpm and can be adjusted accordingly. The microdebrider blade should be held approximately 1–2 mm over the RRP lesion, allowing the suction from the microdebrider to draw the RRP tissue toward the blade and therefore away from the underlying deep tissue. This technique is great for bulky, pedunculated RRP lesions. Its main disadvantage is that the instrument is large in size and sometimes it may obstruct the operative view. When used with great control and good visualization, precision RRP removal can be achieved.

7.2.2.4 Cold Steel

Cold steel techniques include microflap removal or cup forceps removal of RRP (Rosen and Simpson 2008). These techniques, particularly microflap, allow precise removal of the entire RRP-involved epithelium, providing tissue for biopsy. Similar to using the microdebrider, there is no plume exposure. Disadvantages include longer operative time. Hemostasis can be achieved by submucosal infusion of epinephrine prior to elevation of the microflap and/or by application of epinephrine-soaked cotton pledgets on the surgical site post lesion removal. This technique is ideal for isolated, discrete RRP lesions located on the free edge of the vocal fold.

7.3 Controversies in Surgical Management of Adult-Onset RRP

7.3.1 Office-Based Versus Operating Room Treatment of RRP

The treatment of RRP in the office and the operating room has its pros and cons. Deciding on where to treat the patient depends on whether the clinic is equipped to perform in-office procedures, the ability of the patient to tolerate an awake

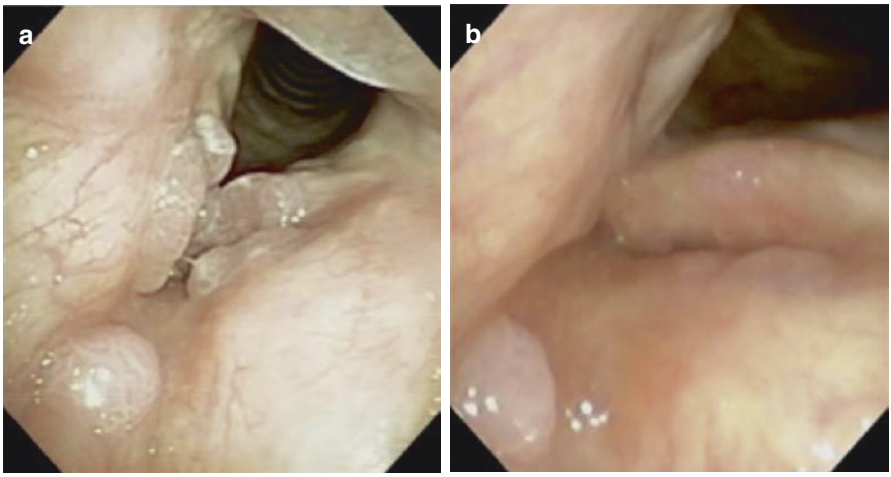

Fig. 7.4 Different disease burden in the same patient. (**a**) Large amount of RRP lesions which is best managed in the OR; (**b**) after initial OR management, small amounts of RRP lesions remained on the superior surface of the left vocal fold and at the petiole of the epiglottis. These lesions were managed in the office using KTP laser

procedure, and the RRP disease burden (Fig. 7.4). In general the first RRP treatment should be performed in the OR for proper staging of the disease and for tissue sampling. Biopsy can be performed in the office as well. Unlike performing a biopsy for laryngeal leukoplakia, the final pathologic diagnosis of RRP is not affected by the biopsy forceps size. The issue with in-office biopsy, however, is that it may not be as precise as that in an anesthetized patient. In addition, the biopsy will inevitably result in bleeding. The blood can absorb laser energy, thus limiting its effect on the intended RRP lesion target. Therefore, direct microlaryngoscopy remains the definitive diagnostic procedure for laryngeal pathologies. Office-based treatments can be considered for subsequent RRP management if the patient can tolerate unsedated procedures and have a small amount of remaining disease.

7.3.2 Surgical Interval

There is currently no consensus on surgical interval in adult RRP patients. The goal of treatment focuses on eradication of disease, airway maintenance, and preservation of voice. However this varies significantly based on disease severity and individual patient preference. Setting up a regular surgical interval may be appropriate if the patient has a significant disease burden that cannot be removed by one surgical procedure, or if the patient has rapid disease regrowth. Each procedure is typically separated by 4 to 6 weeks allowing previous surgical sites to heal prior to the next surgery. Anterior commissure disease is usually staged to prevent anterior glottic web formation. One side is treated first followed by a second treatment 4 to 6 weeks later. Alternatively different KTP end-tissue effects can be applied on either side of

vocal fold to prevent the formation of two contacting raw surfaces. Once disease is under control, patients can have regular surveillance with "touch-up" procedures as needed in the clinic or in the OR.

7.3.3 Biopsy Interval

Rates of moderate or severe epithelial dysplasia in adult-onset RRP vary widely, ranging from 10% to 55% (Karatayli-Ozgursoy et al. 2016). Malignant carcinoma-ex-papillomatosis is reported to occur at a rate between 2% and 5% in different study series (Karatayli-Ozgursoy et al. 2016; Lee et al. 2008). In a recent retrospective review of 159 adult- and juvenile-onset RRP patients, 6% of patients were diagnosed with dysplasia, while 5% were diagnosed with carcinoma-ex-papillomatosis. Gender, tobacco use, or cidofovir injections were not associated with the development of dysplasia or carcinomas. All carcinoma-ex-papillomatosis cases were in pediatric patients and were pulmonary in origin, consistent with the anecdotal observation that pulmonary dissemination is associated with a higher risk of malignant transformation of RRP (Derkay and Faust 2010).

HPV 11 has been shown to be associated with a more aggressive RRP course (Mounts and Kashima 1984; Omland et al. 2014). Gerien et al. reported 13% of patients with severe RRP developed malignant transformation over the course of 27.2 ± 8.0 years (Gerein et al. 2005). All of these patients were HPV 11 positive. In the same study series, six patients had pulmonary disease and four of these patients developed a malignant lung tumor over the observation period of 14.6 ± 6.3 years. These patients were also HPV 11 positive. Therefore initial RRP lesion biopsy and HPV viral typing are important in patient counseling in terms of expectations on the natural history of disease as well as the risk of malignant transformation. Currently there is no clinical guideline suggesting a regular RRP biopsy interval and what that interval should be. Whether the RRP lesions require a biopsy depends on patient's symptomology and surgeon's clinical judgment. In patients with a more aggressive HPV subtype, e.g., HPV 11, biopsies should probably be performed on a more frequent basis. In addition, regular chest imaging such as a chest x-ray should be considered in this patient population to rule out pulmonary spread.

7.4 Summary

RRP is a disease of the upper airway that most commonly involves the larynx and is primarily managed by surgical excision. With advances in modern technology, RRP treatment can be performed both in the operating room as well as in the clinic setting. Different surgical techniques are available depending on equipment availability and surgeon preference. No clear consensus exists in terms of surgical or biopsy intervals for patients with RRP.

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Chapter 8
Contemporary Management of Recurrent Respiratory Papillomatosis in Children

Sarah N. Bowe and Christopher J. Hartnick

8.1 Introduction

Recurrent respiratory papillomatosis (RRP) is a rare disease, yet represents the most common benign neoplasm of the larynx in children. While the primary symptom is hoarseness, these changes in voice may go unnoticed with potentially devastating consequences due to airway obstruction. This chapter will focus on the contemporary management of RRP in children. Virology will be discussed briefly, focusing specifically on disease severity. Clinical features, including history, physical exam, and airway endoscopy with staging assessment, will be provided. The main emphasis will be directed at surgical management including cold-steel, microdebrider, and laser techniques, as well as anesthesia considerations. A brief discussion on combination therapy, in which adjuvant treatment is paired with surgical management, will be reviewed. Finally, we will present novel opportunities for personalized medicine using cell culture techniques on tumor specimens.

8.2 Virology

While the infectious origin of recurrent respiratory papillomatosis was long suspected, it was not until 1980 that human papillomavirus (HPV) DNA was identified by Southern blot hybridization within laryngeal papillomas. Subsequently, the same virus was identified in condylomata acuminata, suggesting a common etiological

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agent for both conditions (Quick et al. 1980). Juvenile-onset RRP is primarily the result of infection with HPV-6 and/or HPV-11.

Some HPV types have been reported to cause more aggressive disease than others. In 1984, Mounts and Kashima demonstrated that HPV-6c was characterized by extensive anatomical spread of disease, higher frequency of operations, and a need for tracheotomy (Mounts and Kashima 1984). Similarly, Padayachee and Prescott retrospectively reviewed 20 cases of laryngeal papillomatosis and found that disease caused by HPV-6 tended to be more aggressive than that caused by HPV-11 (Padayachee and Prescott 1993).

In contrast, most of the published data suggest that RRP attributable to infection with HPV-11 tends to be more aggressive in severity and clinical course. Rimell et al. performed a retrospective analysis of 19 patients with pediatric RRP. Human papillomavirus typing was performed on paraffin-embedded biopsy specimens using PCR techniques. The authors found that HPV-11 was significantly associated with an earlier and more aggressive airway obstructive course, with greater necessity for tracheostomy, compared to HPV-6 (Rimell et al. 1997). Using similar techniques, Rabah et al. performed viral typing on 61 laryngeal biopsy specimens. Patients with HPV-11 were more likely to have longer periods of disease activity, more procedures per patient, per year, and required more surgical procedures compared to patients with HPV-6. In addition, three of the HPV-11 patients developed invasive papillomatosis and bronchogenic squamous cell carcinoma, with two of these succumbing to the disease (Rabah et al. 2001).

Until 2004, the literature examining the impact of HPV type on severity of disease was performed largely by retrospective data analyses, often using paraffin-embedded pathological specimens, years after the surgical procedure. In 1993, Wiatrak et al. developed a 10-year prospective, longitudinal study, assessing epidemiological factors, extent of disease using a novel scoring system, and HPV type (Wiatrak et al. 2004). Of the 58 specimens undergoing HPV typing, those with HPV-11 were significantly more likely to have higher severity scores, require more frequent surgical intervention, and require adjuvant therapy to control disease progression. In addition, HPV-11 patients were significantly more likely to develop tracheal disease, require tracheotomy, and develop pulmonary disease (Wiatrak et al. 2004).

While many studies had examined the association between HPV types and clinical disease behavior, none had simultaneously accounted for other variables, particularly age. For example, Rabah et al. noted a statistically significant difference in age of diagnosis in patients with HPV-11 (36.2 months) compared to those with HPV-6 (48.2 months) (Rabah et al. 2001). Buchinsky and colleagues utilized fresh, laryngeal biopsy specimens obtained in collaboration with the RRP Task Force to further examine this relationship (Buchinsky et al. 2008). One hundred and eighteen patients with JORRP with at least 1 year of clinical data and infected with a single HPV type were analyzed. A priori, the authors defined "aggressiveness" as the total number of surgeries >10, frequency of surgery >4 times per year, distal involvement, and presence of tracheostomy. The odds of a patient with HPV-11 running an aggressive course was 3.9 times higher than that of patients with HPV-6 ($p = 0.017$)

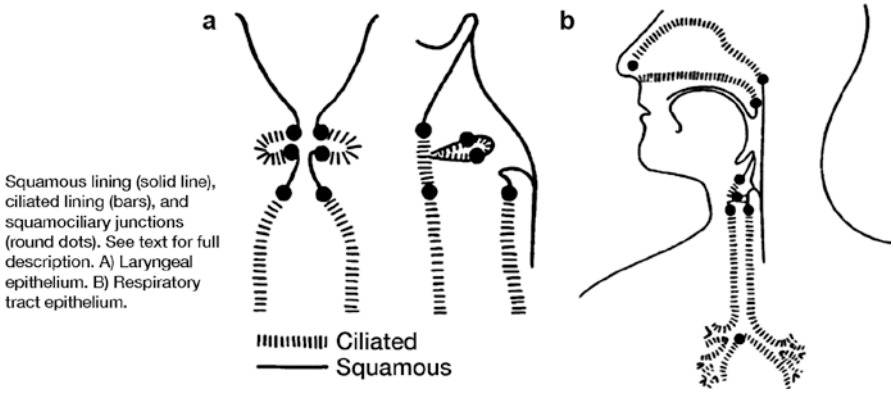
(Buchinsky et al. 2008). It was also noted that patients with HPV-11 were diagnosed at a younger age (2.4 years) than were those with HPV-6 (3.4 years) ($p = 0.014$). Thus, by both multiple linear regression and multiple logistic regression, HPV type was only weakly associated with disease course, when simultaneously accounting for age (Buchinsky et al. 2008).

In summary, early, retrospective studies provided conflicting results, with some suggesting HPV-6 behaved more aggressively (Mounts and Kashima 1984; Padayachee and Prescott 1993), whereas others supported HPV-11 (Rimell et al. 1997; Rabah et al. 2001). In their prospective work, Wiatrak et al. found numerous markers of disease severity in patients with HPV-11 viral type compared to those with HPV-6 (Wiatrak et al. 2004). Buchinsky and colleagues confirmed that HPV-11 is associated with a more aggressive clinical course. Furthermore, they identified that HPV type is correlated with age of the patient, and this is why one sees an association between HPV type and clinical course, if not simultaneously controlling for the age of the patient (Buchinsky et al. 2008).

8.3 Clinical Features

8.3.1 History

Recurrent respiratory papillomas have a predilection for anatomic sites where ciliated and squamous epithelia are juxtaposed. Subsequently, the larynx is the most common site of disease, specifically the mid-zone of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricles, and the undersurface of the vocal folds (Fig. 8.1, Kashima et al. 1993). It is therefore unsurprising that the most



Squamous lining (solid line), ciliated lining (bars), and squamociliary junctions (round dots). See text for full description. A) Laryngeal epithelium. B) Respiratory tract epithelium.

Fig. 8.1 Anatomic representation of laryngeal (**a**) and respiratory tract (**b**) epithelium indicating squamociliary junctions at which recurrent respiratory papilloma predilection occurs (Republished with permission from Kashima et al. 1993)

common presenting symptom is hoarseness. In an infant, however, hoarseness may only manifest as mild voice change or weak cry going undiagnosed as long as a year or more. In these cases, progression of disease may lead to airway obstruction arising secondarily (Derkay 1995). In contrast, lesions arising outside the glottis may first present with progressive airway symptoms, including stridor. As a result, they may be misdiagnosed as laryngomalacia, vocal nodules, croup, allergies, asthma, or bronchitis (Wiatrak et al. 2004).

The clinical setting in which dysphonia presents will dictate the acuity of the evaluation. Certainly, in a child presenting in severe respiratory distress, airway management will take precedence over voice concerns. In contrast, a patient presenting in the ambulatory setting, with a chronic or recurrent voice disturbance, may undergo a more systematic evaluation (Faust 2003). When possible, a complete history, including birth, medical, and surgical, is necessary, in addition to a detailed voice history.

Factors pertinent to birth history include maternal age, number and method of previous deliveries, and history of HPV infection. It is assumed that the majority of children with RRP acquire the disease by vertical transmission, occurring during delivery through an infected birth canal. Overt maternal condylomata are seen in more than 50% of mothers who give birth to children with RRP (Hallden and Majmudar 1986). It has also been noted that patients with JORRP are not only delivered vaginally, but also the firstborn child to a young woman (<20 years old). It is hypothesized that primigravid mothers have a longer second stage of labor, resulting in prolonged exposure to genital HPV. In addition, recently acquired lesions are more likely to shed virus than long-standing lesions, exacerbating the risk in younger women (Shah et al. 1998).

There are multiple medical conditions, which can both cause and exacerbate dysphonia, including allergies, asthma, bronchitis, and gastroesophageal reflux disease (GERD). Of these, GERD has been implicated as a potential risk factor for RRP, as well as complications following surgical management. In fact, patients with severe RRP, requiring multiple surgeries and poor response to systemic therapy, showed a significant decrease in recurrence after therapy for GERD (Borkowski et al. 1999). In addition, antireflux therapy in patients considered “high risk” based on frequency of procedures and disease at the anterior commissure has been shown to reduce the presence of soft tissue complications, specifically scarring and laryngeal web formation (Holland et al. 2002).

A thorough surgical history is necessary to identify surgical procedures that may place the recurrent laryngeal nerve at risk (e.g. ligation of persistent ductus arteriosus). In addition, details of previous intubation should be documented, including circumstances necessitating intubation, difficulty of intubation, tube size, length of time of intubation, and need for re-intubation following extubation (Faust 2003). This same approach should be utilized when considering any intubations that occurred in the perinatal period.

Vocal history, including time of onset, precipitating causes, chronology, exacerbating or alleviating factors, and severity, should be obtained. Additionally, it is pertinent to assess for symptoms that may represent disturbances with swallowing (e.g. dysphagia, aspiration) or breathing (e.g. stridor).

8.3.2 Physical Examination

Children who present with dysphonia must undergo an organized and thorough physical examination. Regardless of the setting, every evaluation must begin with a rapid assessment for respiratory distress. The respiratory rate should be assessed, as well as changes in the rate that may indicate fatigue. The patient should be observed for the presence of nasal flaring or the use of accessory neck or chest muscles. Finally, evidence of cyanosis may indicate impending respiratory collapse. If there is evidence of significant distress, further examination is best undertaken where equipment for endoscopic evaluation, airway intubation, and possible tracheostomy is readily available. Depending on resource capabilities, this may be the emergency room, pediatric intensive care unit, or operating room.

Assessment of vital signs, particularly pulse oximetry, can provide objective information on respiratory status (Derkay and Faust 2015). However, oxygen saturation may not be the most reliable indicator of disease severity in proximal (i.e., laryngeal or tracheal) airway obstruction, since the mechanism of hypoxemia in such cases is frequently hypoventilation. Due to the principles of the alveolar gas equation, partial carbon dioxide tension of the arterial blood ($PaCO_2$) increases disproportionately to decreases in arterial hemoglobin oxygen saturation by pulse oximetry (SPO_2) (Fouzas et al. 2011). As a result, clinical appearance is generally more reliable, as infants can appear to maintain adequate perfusion up until the point of sudden decompensation.

Auscultation is often considered the most important part of the evaluation (Derkay and Faust 2015). With the aid of a stethoscope, listening over the nose, open mouth, neck, and chest may help localize the site of respiratory obstruction. Changes in the normal respiratory cycle, which consists of a shorter inspiratory phase and longer expiratory phase, may be assessed. While stridor may begin as inspiratory, it often progresses to biphasic as airway obstruction worsens. Fluctuation in the quality of the stridor with changes in position may assist with diagnosis. For example, children with RRP do not generally experience changes due to the static nature of the lesions, whereas infants with laryngomalacia improve in the prone position (Derkay and Faust 2015).

In a stable patient with dysphonia, a complete head and neck examination is essential. The ears should be examined for evidence of previous or current otologic disease. A thorough, age-appropriate hearing assessment should be performed. Nasal examination should identify any septal deviation or turbinate abnormalities, as well as the presence of rhinorrhea or polyps. Oropharyngeal examination includes inspection of the structural integrity and mobility of the palate. In some cases, papillomas may be noted in the oral cavity or oropharynx, as it has been noted as the most frequent site of extralaryngeal spread, which occurs in approximately 30% of children with RRP. Palpation should be performed to evaluate for the presence of any neck masses. Finally, the cranial nerves should be assessed.

8.3.3 Airway Endoscopy

Flexible fiber laryngoscopy provides the cornerstone for evaluation in the dysphonic patient. When the scope is passed into each nasal cavity, choanal patency can be assessed. At the level of the nasopharynx, adenoid size and velopharyngeal function can be determined. With continued passage, the position and function of supraglottic and glottic structures, including the true vocal cords, can be observed. Finally, inspection of mucosal and squamous surfaces for the presence of masses or lesions within the oropharynx, hypopharynx, and larynx is possible. Video recording of the fiber-optic examination allows for frame-by-frame review, which can be helpful in an uncooperative patient in whom the examination must be performed quickly. In addition, it provides opportunities for education of the patient and family (Faust 2003).

Histologically, recurrent respiratory papillomatosis is associated with mucosal proliferation resulting in multiple fingerlike projections with a central fibrovascular core covered by stratified squamous epithelium (Abramson et al. 1987). Two growth patterns are possible. When microscopic, the mucosal surface can exhibit a velvety appearance due to a superficial spreading configuration (Derkay and Faust 2015). The macroscopic or exophytic growth pattern is more noticeable. These lesions are pink to white in color, are sessile or pedunculated, and exhibit "cauliflower" or "grapelike" projections (Fig. 8.2).

At the completion of a thorough history, physical, and fiber-optic examination, it should be possible to diagnose nearly all cases of recurrent respiratory papillomatosis. However, there are occasional cases that require operative endoscopy for diagnosis (Faust 2003). Any patient in which there is a suspicion for RRP but who

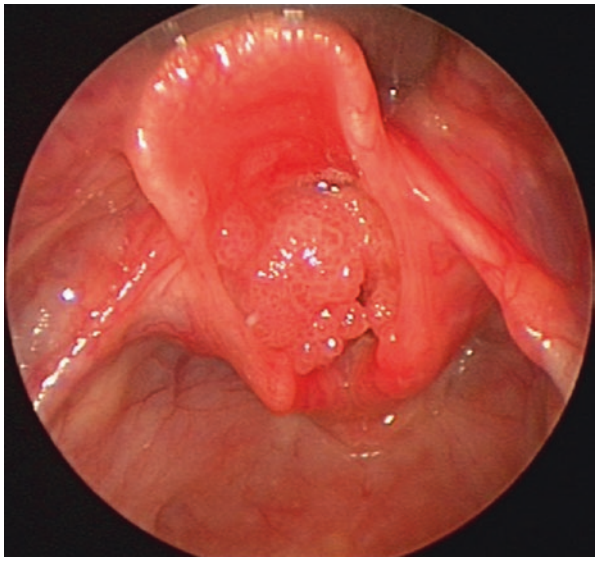


Fig. 8.2 Gross appearance of bulky, exophytic papillomatosis during laryngoscopy

is unable to tolerate flexible laryngoscopy should be evaluated in the operating room under anesthesia. In addition, due to the variety of sites in which RRP may present, including the undersurface of the vocal folds, operative endoscopy may be necessary to provide enhanced visualization in order to obtain an accurate diagnosis (Kashima et al. 1993).

8.4 Anesthesia Considerations

Anesthesia management in patients with recurrent respiratory papillomatosis can be challenging. As with any laryngeal surgery, the anesthesiologist and surgeon must share the same space in order to maintain control of the airway and treat the disease process. As a result, effective communication between the anesthesiologist and surgeon during preoperative planning and intraoperative management is paramount. Anesthetic technique may be modified depending on the child's age, suspected diagnosis, underlying impairment of oxygenation and ventilation, and potential treatment modalities (Swanson et al. 2015).

In spontaneous ventilation, the patient maintains their own respiratory effort, resulting in an unobstructed operative field, aiding in diagnosis and management. Anesthesia can be induced with either IV (sodium thiopental, ketamine, or propofol) or inhalation (sevoflurane) agents with oxygen (Swanson et al. 2015). With inhalation techniques, the delivered concentration requires a delicate balance that is high enough to prevent coughing and laryngospasm but also low enough to avoid cardiovascular depression and apnea. This can be difficult to achieve with short-acting agents. Thorough topical anesthesia with 4% lidocaine, delivered either by atomizer or syringe, can provide additional anesthesia and reduce systemic requirements. When using topical lidocaine, it is important to remain cognizant of the maximum dosage limits based on the child's weight. In addition, adjunctive agents, such as propofol infusion, may be used to reduce or replace the need for inhalational anesthesia (Swanson et al. 2015).

The apnea-(re)intubation technique provides unobstructed access to the larynx but only on an intermittent basis (Swanson et al. 2015). Induction is performed along with topical anesthesia of the airway prior to intubation. The laryngoscope is inserted until adequate exposure is achieved, at which point it is placed into suspension. The tube is then withdrawn, and the surgeon may proceed with diagnosis or treatment while the patient is apneic. The tube can then be replaced under direct visualization if carbon dioxide rises or oxygenation falls. These efforts can be repeated until the procedure is complete (Swanson et al. 2015). While it can provide visualization and access similar to spontaneous ventilation, concerns have been raised about potential viral spread due to repeated placement of the endotracheal tube (Derkay and Faust 2015).

In cases in which continuous intubation is planned, the use of a wrapped or "laser-safe" endotracheal tube is advised in order to protect the tube from accidental ignition during laser use (Derkay and Faust 2015). While the tube is protected, the

cuff remains susceptible to rupture and should be covered with moist surgical cottonoids. As an added measure of protection, the cuff is filled with saline. Methylene blue or other visible dyes are generally mixed with the saline to help detect cuff perforation. Regardless, the tube remains in the operative field throughout the procedure, potentially reducing visualization, particularly in the posterior glottis and subglottis (Derkay and Faust 2015).

Jet ventilation provides another anesthetic alternative with complete visualization of the glottis. Induction requires the use of an IV anesthetic, such as propofol, with a muscle relaxant. After topical anesthesia is provided, the suspension laryngoscope is introduced with attached jet-ventilating device (Swanson et al. 2015). Due to the high pressures involved, it is preferable to place the jet cannula proximal to the end of the laryngoscope. In this location, however, there is the potential risk of disseminating papilloma further into the tracheobronchial tree (Derkay and Faust 2015). The use of jet ventilation is also limited in patients with higher disease burden, as it predisposes them to serious complications. In particular, with large laryngeal lesions, narrowed airways, or ball-valve lesions, high degrees of outflow obstruction may occur, resulting in increased intrathoracic pressure with subsequent pneumothorax or pneumomediastinum (Derkay and Faust 2015). Inadequate muscle relaxation can also produce outflow obstruction. Therefore, jet ventilation requires a certain level of experience on behalf of the anesthesiologist, prior to considering its use.

In some cases, patients present with severe, acute respiratory distress that may require tracheostomy. In general, tracheostomy has been approached with hesitation in the management of RRP surrounding concerns that the mucosal injury may initiate the progression of disease to the distal airway (Cole et al. 1989; Kashima et al. 1993). For example, in a series of 40 patients with lower airway RRP in Russia, placement of a tracheostomy tube was noted to be the basic cause of papilloma extension in 92.5% of patients (Soldatski et al. 2005). In contrast, Shapiro and colleagues noted that their tracheostomy patients presented at a younger age with more widespread disease, often involving the distal airway prior to tracheotomy (Shapiro et al. 1996). Thus, whether the tracheostomy itself predisposes the mucosa to papillomatous spread or whether the necessity of tracheostomy indicates a more severe state remains unclear. Regardless, in cases in which tracheostomy is unavoidable, decannulation is advised as soon as the disease burden is cleared and airway patency restored.

Several different anesthetic techniques may be utilized in the diagnosis and management of RRP. The best option will depend on the child's age, disease burden, respiratory status, and potential treatment modalities. In addition, the familiarity and comfort of the anesthesiologist and surgeon must be taken into consideration. Regardless of the technique, constant communication among all members present in the operating room is essential to successful airway management.

8.5 Staging Assessment

Initial staging systems were often developed during the performance of clinical trials. While several were proposed, most researchers and clinicians had not adopted a uniform system, leading to confusion in the recurrent respiratory papillomatosis literature, as well as in communications between physicians regarding patient management. The original concept of a uniform scoring system was introduced by Kashima et al. as part of a multi-institutional study evaluating interferon therapy (Kashima et al. 1985). Unfortunately, this system had limited laryngeal subsite information such that there was no indication of the side of involvement. In addition, there was substantial subjectivity in determining the percentage of airway lumen obstruction and a lack of clinical measures of disease severity (Derkay et al. 1998). While Lusk and colleagues divided the right and left halves of the airway, this was done within the glottis only, failing to take into consideration disease outside the larynx (Lusk et al. 1987). Similar to Kashima and colleagues, there was still considerable subjectivity, as well as absent functional assessment (Kashima et al. 1985; Derkay et al. 1998).

The authors of the most frequently used assessments, along with the Task Force on RRP and the Collaborative Anti-Viral Study Group HPV Subcommittee, developed a comprehensive staging system, which incorporated functional evaluation, numerical grading of subsite involvement, and final disease severity score, as well as diagrammatic interpretation of disease burden (Figs. 8.3 and 8.4, Derkay et al. 1998). Initially, six questions are posed about the patient's clinical course, including interpretation of the patient's voice, stridor, respiratory status, and urgency of current intervention. Adding the scores for four of the six subjective assessments generates a clinical score. Then, a score of 0 to 3 (0 = absent, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion) is assigned to nine laryngeal subsites, five tracheal subsites, and six additional subsites. A total score is calculated by summing the scores from the various subsites. In addition, lesions are marked on a standardized diagram, along with biopsy and treatment sites. Finally, a total score, incorporating both the clinical and anatomic score, is generated (Derkay et al. 1998).

Some authors have demonstrated variability between intra-rater and inter-rater agreement among pediatric otolaryngologists when scoring endoscopic videotapes (Behar and Todd 1999; Todd 1997). In contrast, Hester et al. found high reliability in using the previously mentioned staging system by Derkay et al. (Hester et al. 2003; Derkay et al. 1998). Ten videotaped recordings of endoscopic assessment of patients with RRP were reviewed by 15 fellowship-trained pediatric otolaryngologists. In 90% of patients, the standard errors of the mean total score were less than 1, indicating low variance and subsequent high reliability of the total score (Hester et al. 2003). Furthermore, elements of this staging system have shown promise for their predictive value on surgical interval (Derkay et al. 2004). Seventeen patients

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

1. How long since the last papilloma surgery?____days,_____weeks,___months,____years,
2. Counting today's surgery, how many papilloma surgeries in the past 12 months?____
3. Describe the patient's voice today: ____aphonic, ____ abnormal, ____normal,____ other
4. Describe the patient's stridor today: ____ absent,____present with activity, _____present at rest,
5. Describe the urgency of today's intervention: ____scheduled,____urgent, ____emergency

1 = suface lesion, 2 = raised lesion, 3 = bulky lesion

LARYNX

Epiglottis
Lingual surface _____ Laryngeal surface _____
Aryepiglottic folds: Right ____ Left ____
False vocal cords: Right ____ Left ____
True vocal cords: Right ____ Left ____
Arytenoids: Right ____ Left ____
Anterior commisure_____ Posterior commisure _____
Subglottis _____

TRACHEA:

Upper one-third _____
Middle one-third _____
Lower one-third _____
Bronchi: Right_____ Left_____
Tracheotomy stoma_____

OTHER:

Nose _____
Palate _____
Pharynx _____
Esophagus _____
Lungs _____
Other _____

Total for all sites: _____

Fig. 8.3 Staging assessment with component clinical and anatomic score

with RRP at a large academic medical center were assessed using the staging system, and various regression models were built. As one of the significant findings, children with a total subsite score of 20, considered a high-risk category, could expect to have their next surgery 120 days sooner than children with a total score less than 20 (Derkay et al. 2004). While pilot in nature, this study provides support for continued development work on a larger scale. To help with such efforts, the staging system is now computerized and made available through the American Society of Pediatric Otolaryngology (ASPO) for use by its members and colleagues (Derkay et al. 1998).

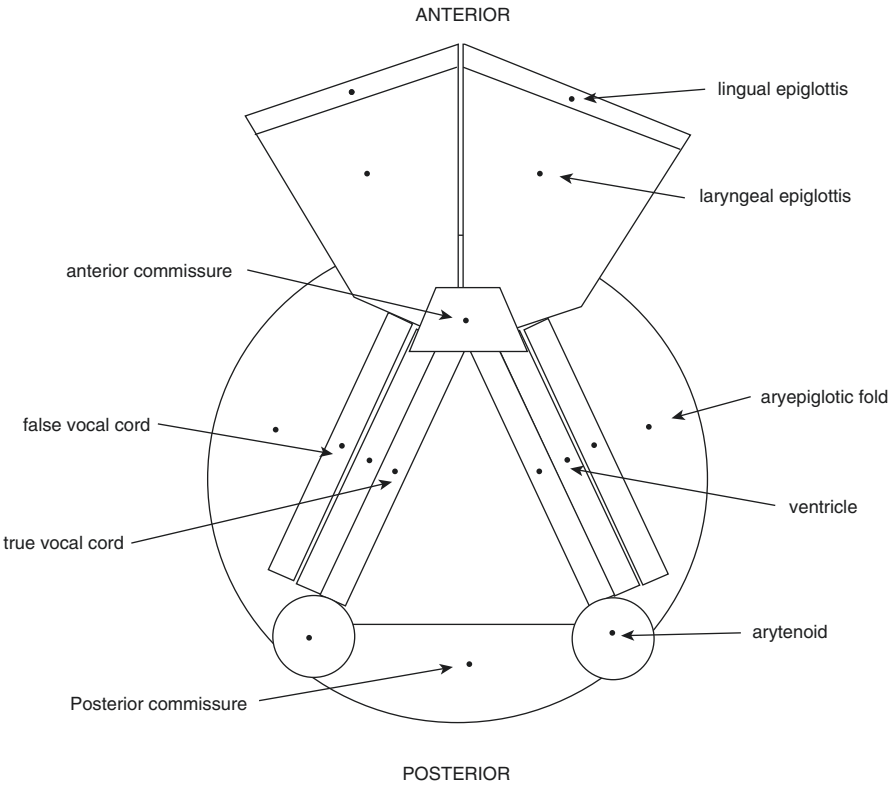


Fig. 8.4 Standardized diagram of laryngeal sites that compose anatomic score

8.6 Surgical Management

The current standard of care for pediatric RRP is focused on debulking of papillomatous lesions while preserving normal anatomical structure. The goal is to provide an adequate airway, improve voice quality, and limit complications, such as web formation or airway stenosis. The mainstay of surgical therapy has been performed using the CO_2 laser, coupled with the operating microscope (Wiatrak et al. 2004). In fact, 92% of survey respondents used the CO_2 laser as their preferred method of treatment for initially diagnosed RRP, with 70% continuing to use this modality exclusively for treatment (Derkay 1995).

The CO_2 laser has an emission wavelength of 10,600 nm and converts light to thermal energy, which is absorbed by intracellular water, effectively vaporizing the cells. The newest generation of laser microspot micromanipulators enables surgeons to use a spot size of 250 mm at 400 mm focal length and 160 mm at 250 mm focal length (Derkay and Faust 2015). Therefore, thermal energy can be delivered with

precision, reducing collateral tissue damage. The surgeon, however, must remain cognizant of deeper tissue layers and surrounding structures, particularly in difficult treatment areas, such as the true vocal cords and anterior and/or posterior commissure, as excessive laser usage may cause unacceptable scarring and abnormal vocal fold function. The smoke plume that is created contains water vapor, as well as vaporized tissue material, including active viral DNA (Abramson et al. 1990; Hallmo and Naess 1991; Kashima et al. 1991). As a result, a mechanical smoke evacuation system along with appropriate personal protective equipment, including N95 or N100 respirators, is necessary for the safety of operating room personnel (Kuhar 2013). Finally, as with all laser usage, the potential for airway fire exists, and appropriate safety precautions should be taken throughout the procedure.

Due to inherent limitations with access when using the micromanipulator partnered with the microscope, investigators began to explore alternative technologies. In 1997, Bergler et al. used argon plasma coagulation (APC) with flexible fiber endoscopy to manage a 7-year-old girl with progressive RRP, refractory to CO_2 laser and interferon-alpha treatment. APC is a monopolar electrosurgical procedure in which electrical energy is transferred to the target tissue using ionized (i.e., conductive) argon gas, without the electrode coming into direct contact with the tissue. Since the plasma follows the path of least electrical resistance, it allows treatment to occur both en face and tangentially, allowing less accessible regions to be treated. They noted very good disease control, including management of distal tracheal disease, without side effects or complications (Bergler et al. 1997).

Beginning in the late 1990s, additional laser treatment options were evaluated. Bower and colleagues evaluated the feasibility and safety of the flash pump dye (FPD) laser in a prospective nonrandomized trial comparing FPD to CO_2 laser management (Bower et al. 1998). Nine patients from 2 to 20 years of age with severe RRP were enrolled. Patients underwent CO_2 debulking of the left hemilarynx and FPD treatment of the right hemilarynx. Five patients had a 90% or more decrease in size of papillomas on the FPD-treated side 2 weeks postoperatively. The authors noted that the FPD laser coagulates, rather than vaporizes the tissue, which may limit scar formation, as well as enhance safety due to the lack of a smoke plume (Bower et al. 1998).

Using light and a variable lasing medium, the pulsed dye laser (PDL) is tuned to a specific wavelength to maximize absorption. The target chromophore for blood is 577 nm. The PDL laser works at a wavelength of 585 nm (Derkay and Faust 2015). In 1998, McMillan and colleagues investigated the use of the PDL as a minimally traumatic alternative to RRP management (McMillan et al. 1998). In their pilot study, three patients with laryngeal papillomas were treated with PDL at fluences between 6 and 10 J/cm^2 at noncritical areas using a specially designed micromanipulator. In contrast, lesions on the true vocal cords were treated with standard CO_2 laser therapy. The authors noted complete regression of the papillomas, along with preservation of the epithelial surface in the areas treated with PDL, in contrast to those treated with CO_2 (McMillan et al. 1998). In a series of ten patients, Valdez and colleagues found regression of papilloma in all patients treated with PDL. Furthermore, the authors presented the first evidence for treatment via flexible

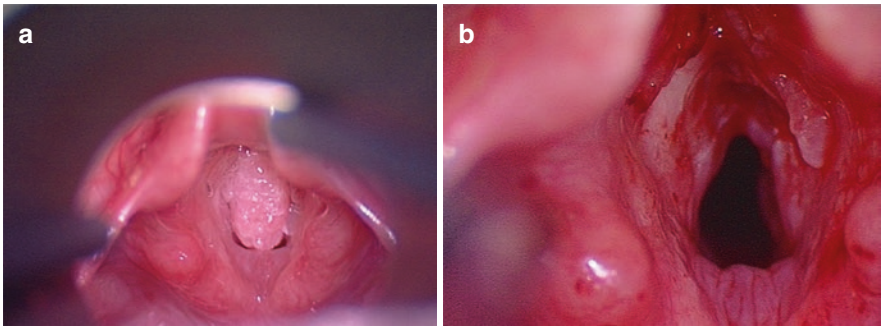


Fig. 8.5 Anterior commissure recurrent respiratory papillomatosis before (**a**) and after (**b**) pulsed dye laser treatment

fiber laryngoscopy, which was used for two of their patients (Valdez et al. 2001). Zeitels et al. managed 82 cases of recurrent glottal papillomatosis (30 cases) or dysplasia (52 cases) with PDL in the clinic using the working channel of a flexible fiber-optic laryngoscope. They noted 50% or greater disease involution in 68 cases (88%), as well as a 25–50% disease regression in the remaining 12% (Zeitels et al. 2004). In 2007, Hartnick and colleagues reported on the safety and efficacy of the PDL for treatment of juvenile-onset RRP, with particular focus on management of true vocal cord and anterior commissure disease (Fig. 8.5). Out of the 23 patients followed from 3 months to 1 year posttreatment, there was no evidence of true vocal cord scarring or anterior commissure webbing. The authors noted that PDL may allow for more aggressive surgical excision, while simultaneously maintaining voice quality, due to preservation of the vocal fold epithelium (Hartnick et al. 2007).

With their substantial experience with PDL therapy, Zeitels and colleagues noted numerous shortcomings and sought to address these limitations with the use of the potassium-titanyl-phosphate (KTP) laser (Zeitels et al. 2006). The potassium-titanyl-phosphate (KTP) laser delivers light at a wavelength of 532 nm, which is more strongly absorbed by oxyhemoglobin than the 585 nm wavelength of the PDL. In addition, bleeding associated with the PDL was often due to disruption of the vessel wall, associated with its extremely short pulse width (0.5 ms). In contrast, the pulse width for the KTP is 15 ms, allowing for more efficient and effective intravascular coagulation with slower intraluminal heating, reducing vessel wall rupture. Finally, the KTP laser output can be delivered through smaller fibers, 0.3–0.4 mm, compared to 0.6 mm for the PDL. The increased space within the operating channel provides access for suctioning blood and secretions, which can improve procedural efficiency (Zeitels et al. 2006). From July 2005 to March 2006, 36 cases of papillomatosis were all successfully managed using the KTP laser in the office setting without complications (Zeitels et al. 2006). Shortly thereafter, Burns and colleagues evaluated treatment using the KTP laser during microlaryngoscopy under general anesthesia (Burns et al. 2007). Thirty-seven patients with laryngeal papillomatosis underwent 55 procedures. Of the 35 procedures in which near-term follow-up was available via videolaryngoscopy, 90% or greater disease regression was achieved in

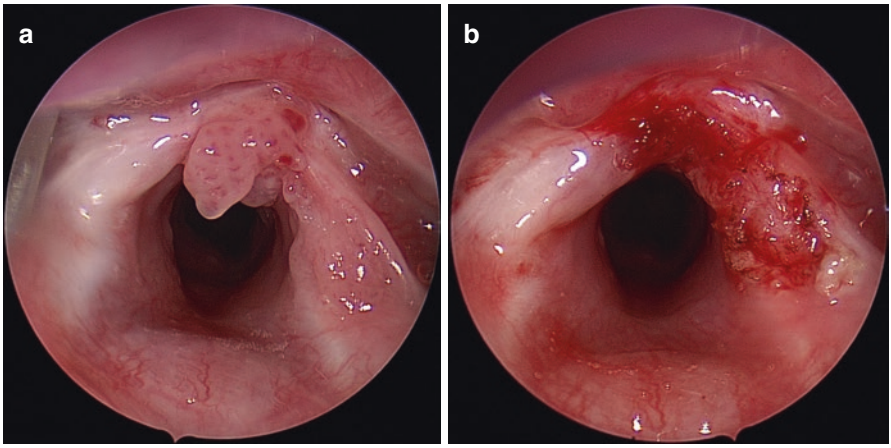


Fig. 8.6 Diffuse supraglottic and glottic recurrent respiratory papillomatosis before (**a**) and after (**b**) potassium-titanyl-phosphate laser treatment

28 of 35 (80%). All patients reported improvement in vocal function. In addition, 93% of patients had anterior commissure disease that was managed without web formation (Burns et al. 2007). Similarly, utilization of the pulsed KTP laser in the pediatric RRP population has been advised for addressing sensitive regions, including the ventricle, vocal folds, and anterior commissure, as well as sessile lesions (Maturo and Hartnick 2012) (Fig. 8.6).

Despite meticulous surgical principles, laser treatment, especially with the CO_2 laser, still requires thermal energy, which can dissipate into surrounding tissues. As a result, cold-steel excision has been utilized, particularly in the region of the true vocal cords, following the principles of phonomicrosurgery, submucosal dissection, and microinstrumentation (Derkay and Faust 2015). Zeitels and Sataloff examined the recurrence patterns of 22 patients with adult glottal papillomatosis who underwent phonomicrosurgical microflap resection. Out of the six patients that had not undergone the previous treatment, none presented with disease recurrence with at least 2 years of follow-up (Zeitels and Sataloff 1999). Further work has shown utility within the pediatric population. Thirty-two patients with juvenile-onset RRP underwent endolaryngeal microsurgery (EM). The recurrence rate was 71.9% with a mean 1.9-year interval between recurrences. Thus, EM is a safe technique providing accurate removal of papillomas, but recurrence remains common (Uloza 2000).

The newest technology to be incorporated in the therapeutic regimen for pediatric RRP is the microdebrider. Initial adaptation of the sinus microdebrider for the larynx was undertaken specifically to assist with removal of bulky, exophytic papillomatosis (Fig. 8.7). In particular, angulation and lengthening of the blade have allowed the use of the tool in a suspension laryngoscope (Myer et al. 1999). El-Bitar and Zalzal reviewed 73 operations (23 laser, 50 microdebrider) looking at postoperative complications and operative time. There were not any soft tissue complications noted within the microdebrider grouping. In addition, the

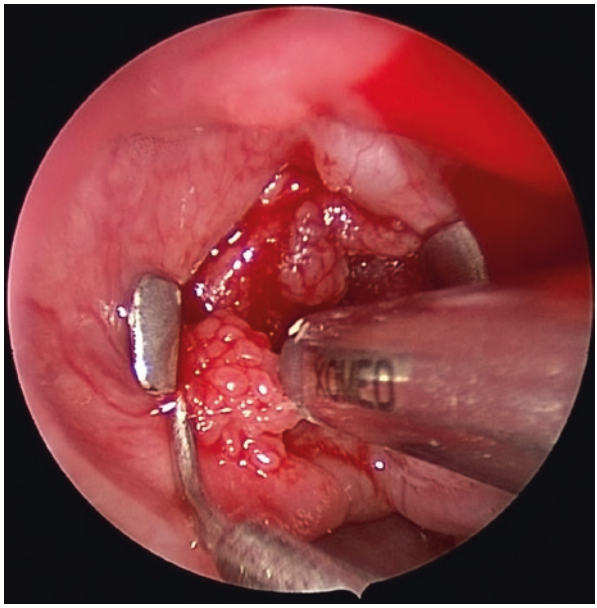


Fig. 8.7 Bulky, exophytic papilloma undergoing resection with the laryngeal microdebrider

microdebrider was less time-consuming, even though those patients had more active disease (El-Bitar and Zalzal 2002). Patel and colleagues reviewed the charts of 18 patients with RRP who were treated between December 1998 and October 2001. These patients were initially treated with the CO_2 laser (127 procedures) but were switched to microdebrider resection (50 procedures) during the review period. There was a statistically significant 26.8-min reduction in the mean operative time when microdebrider resection was compared with CO_2 laser resection. This translates to clinical significance regarding anesthetic risk, as well as treatment costs, especially when considering the mean number of procedures per patient was 10 within their cohort (Patel et al. 2003). In a small, randomized study of 19 pediatric patients, Pasquale et al. performed a direct comparison between the CO_2 laser and the microdebrider, finding equivalent 24-h postoperative pain scores, improved voice quality, shorter procedure times, and decreased procedure cost in those managed with microdebrider (Pasquale et al. 2003). In fact, an updated survey of ASPO members, performed in 2002, found that the microdebrider is now favored (52.7% of respondents) over the use of laser (41.9% of respondents), a stark comparison to the 92% of respondents who favored the CO_2 laser in the previous survey (Schraff et al. 2004; Derkay 1995).

Unfortunately, there is no treatment modality that eliminates the underlying disease process, with latent virus still present even without clinically evident papilloma. Regardless of the method of treatment, the goals remain the same: create a safe and patent airway, optimize voice quality, avoid tissue damage to decrease the spread of disease and minimize complications, reduce operative time, and increase the inter-surgical interval (Derkay and Faust 2015).

8.7 Combination Therapy (Surgical Management and Concurrent Adjuvant Treatment)

Roughly 20% of pediatric patients with RRP will require some form of adjuvant treatment, in addition to surgical management (Schraff et al. 2004). The most widely adopted criteria for initiating adjuvant therapy include undergoing more than four surgical procedures per year, rapid regrowth with airway compromise, or distal multisite spread of disease (Derkay and Faust 2015). In combination therapy, surgical management (i.e., laser) and adjuvant treatment are utilized to obtain incremental control of the disease process.

Bevacizumab (Avastin, Genentech, San Francisco, California) is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) isoforms, thus serving as a potent inhibitor of angiogenesis (Ribatti 2009). A pilot group of ten adult patients with bilateral glottal papillomatosis with established recurrence patterns following prior KTP laser therapy were treated with five bevacizumab injections along with KTP management 4–6 weeks apart. All ten patients had a greater than 90% reduction in recurrence, with four having complete resolution of the disease process. In addition, all ten patients noted substantial improvement in vocal function. Thus, bevacizumab injections were found to enhance the KTP laser photoangiolysis due to complementary mechanisms of action (Zeitels et al. 2009). A larger prospective open-label study conducted in 20 adult patients confirmed the synergistic effect between bevacizumab angiogenesis inhibition and KTP laser therapy (Zeitels et al. 2011). Maturo and Hartnick described the initial pediatric experience in three patients managed with microdebrider resection for bulky lesions, KTP laser treatment for disease at the anterior commissure and interarytenoid space, and bevacizumab injection. All three children had an increase in time interval between operations, while two had substantial decreases in their Derkay score and increases in Pediatric Voice-Related Quality-of-Life (PVRQOL) score (Maturo and Hartnick 2010). A follow-up prospective case series of ten children with severe RRP examined numerous outcome measures the year leading up to the first of three bevacizumab injections compared with the year following the third bevacizumab injection. Rogers et al. noted an increase in time between surgical procedures, decrease in number of procedures per year, decrease in Derkay staging, and improvements in all PVRQOL measures, suggesting further efficacy for the inclusion of bevacizumab as an adjuvant therapy in patients with aggressive RRP (Rogers et al. 2013).

8.8 Evaluation and Management Recommendations

Our preferred evaluation and management strategies are illustrated in Fig. 8.8. Progressive or persistent dysphonia, particularly longer than 2 weeks of duration, requires a thorough history. Certain findings from the birth history may heighten suspicion for recurrent respiratory papillomatosis, including maternal age, number

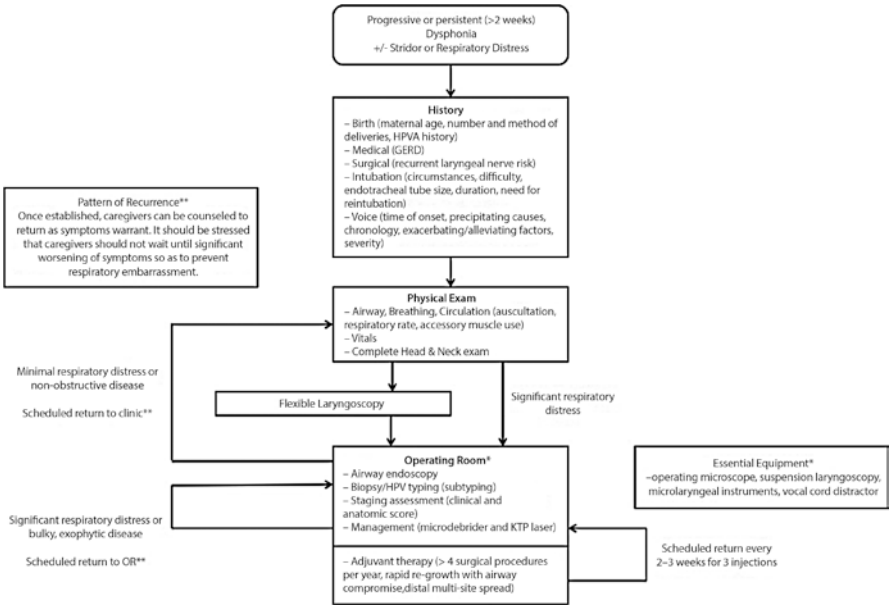


Fig. 8.8 Evaluation and management algorithm for progressive or persistent dysphonia with identification of recurrent respiratory papillomatosis

and method of deliveries, and HPV history. Further evaluation of medical, surgical, and intubation history may suggest other diagnoses. A detailed vocal history, including onset, precipitating causes, chronology, exacerbating/alleviating factors, and severity, should be obtained. Additionally, it is necessary to assess for symptoms that may represent disturbances with swallowing (e.g. dysphagia, aspiration) or breathing (e.g. stridor).

The most important component of the physical exam is an assessment of breathing, including respiratory rate, accessory muscle use, and auscultation. If significant respiratory distress is present, then laryngoscopy should be deferred until the patient can be evaluated in a setting that provides the best opportunity to maintain control of the airway and treat the disease process, preferably the operating room.

Essential equipment includes the operating microscope, suspension laryngoscopy, and microlaryngeal instruments. Our preferred resection technique incorporates a combination of microdebrider resection for bulky disease and pulsed KTP laser for sessile lesions or disease of the ventricle and vocal cords. The KTP laser is set at 35 Watts pulse power, 15 ms pulse width, and 3 pulses per second pulse rate. Utilization of a vocal cord distractor during the procedure can improve access to the airway for both oxygenation/ventilation and resection (Fig. 8.9).

Biopsy specimens are taken during the first procedure to confirm diagnosis and determine HPV subtyping. Yearly biopsy specimens should be considered to evaluate for malignant degeneration. Routine staging assessment during each trip to the operating room allows for an accurate comparison with which to assist with management decisions, including consideration for adjuvant therapy.

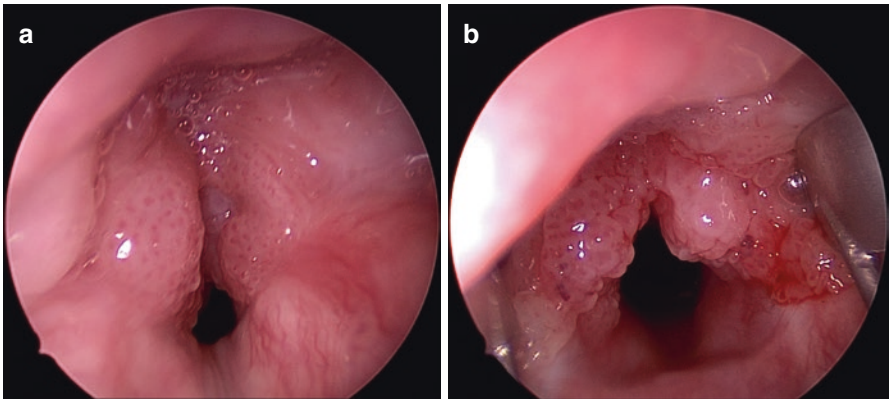


Fig. 8.9 Bulky, exophytic papilloma with near-complete obstruction of the glottis before (**a**) and after (**b**) placement of the vocal cord retractor. Enlargement of the glottis aperture can aid in spontaneous ventilation, as well as resection

Depending on the severity of symptom presentation, follow-up may be arranged for the clinic or the operating room. Overall, the key to successful management is a close working relationship with these patients and their families. A thorough understanding of the disease process is paramount, so that evaluation and treatment may be arranged sooner if there is a more progression of symptoms.

8.9 Novel Therapeutic Approaches

While several methods of adjuvant treatment, such as bevacizumab, have shown promise, none has consistently been shown to eradicate recurrent respiratory papillomatosis. One of the limitations of studying treatment in RRP was the previous lack of an appropriate cell culture system. However, Yuan and colleagues used a new cell culture technology, termed conditionally reprogrammed cells, to generate continuous cell cultures from tumor samples and normal tissue in a patient with severe, progressive RRP, including bilateral invasion of the lung parenchyma (Yuan et al. 2012). The cultures helped the authors to identify a mutation of HPV-11 that may have contributed to the observed aggressive clinical behavior. In addition, the cell cultures provided an opportunity for chemosensitivity testing of a limited number of drugs for potential clinical application. The median curative dose of vorinostat (histone deacetylase inhibitor that has shown toxicity to HPV-positive cervical cancer cells) showed selectivity for tumor cells over normal cells, and the patient was treated over the course of 12 months. By 3 months after treatment initiation, lung tumor sizes stabilized, with durable effects at 15 months (Yuan et al. 2012). This provides an example of personalized medicine in which the screening of both normal and tumor cells from a given patient has advantages for rapidly identifying plausible single or combination therapies, while diminishing the risk of adverse effects from treatment that will likely be clinically ineffective.

8.10 Conclusion

Recurrent respiratory papillomatosis, caused by infection with HPV, is the most common benign laryngeal neoplasm in children. Despite this, prolonged, extensive medical and surgical treatment is often necessary for control of the disease process. The most common clinical presentation is that of progressive hoarseness. Unfortunately, changes in voice may be missed, or papillomas may begin in extralaryngeal sites, with respiratory compromise as the initial symptom. The mainstay therapy is surgical debridement with the microdebrider currently favored over laser treatment. When laser therapy is used, the PDL and KTP are preferred over CO_2, due to preservation of the epithelial surface. Several different anesthetic techniques may be utilized with the best option depending on the child's age, disease burden, respiratory status, anesthesiologist experience, and potential treatment modalities. The goals of surgical therapy are to create a safe and patent airway, optimize voice quality, avoid tissue damage to decrease the spread of disease and minimize complications, reduce operative time, and increase the inter-surgical interval. When children require surgical therapy more than four times in 12 months or have evidence of distal spread outside the larynx, adjuvant medical therapy should be considered. Combination therapy has shown the potential for synergistic treatment effects between bevacizumab angiogenesis inhibition and KTP laser photoangiolysis. Further research using conditionally reprogrammed cells and chemosensitivity testing may identify novel therapeutics successful in eradicating RRP.

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Chapter 9
The Cidofovir Controversy

Griffin D. Santarelli and Craig S. Derkay

9.1 Background

Cidofovir is an antiviral medication that was first approved by the FDA in June of 1996. Cidofovir (trade name Vistide) was originally approved as an intravenous treatment for AIDS-related Cytomegalovirus (CMV) retinitis (Food and Drug Administration 1996). Cidofovir was developed by Gilead Sciences and its mechanism of action is directed at selective inhibition of viral DNA synthesis (Gilead Sciences n.d.). The active metabolite of cidofovir is cidofovir diphosphate, which selectively inhibits viral DNA polymerase. As the medication is incorporated into the growing viral DNA chain, it results in the reduction in rate of viral DNA synthesis. The medication was approved for intravenous use.

FDA approval of cidofovir came with warnings directed at particular patient populations: those with pre-existing renal impairment, hematologic dyscrasias, ocular hypotony, and metabolic acidosis. Because of the dose-dependent nephrotoxicity, Gilead Science recommended intravenous saline hydration and oral probenecid at time of IV drug infusion in order to facilitate renal excretion, limiting renal tubular damage. Gilead Science also recommended neutrophil counts to be monitored during infusion therapy because of the risk of developing neutropenia and intraocular pressures to be measured because of the effect on visual acuity. These risks and recommendations are specifically geared towards CMV-retinitis patients receiving intravenous cidofovir. Further commentary on complications and risks specifically in the intralesional RRP patient population is covered in further detail later in the chapter.

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The use of cidofovir has expanded over time and has come to include trials for progressive multifocal leukoencephalopathy (Segarra-Newnham and Vodolo 2001), anti-BK viral activity in renal transplant patients (Vats et al. 2003), and is also used as an investigational adjunct in RRP induced by HPV. Cidofovir was first used in 1995 as an adjunct treatment of severe RRP refractory to surgery alone (Van Cutsem et al. 1995).

9.1.1 FDA Approval/Off-Label Usage of Cidofovir

The use of cidofovir in the RRP patient population is off-label, and has not been approved by the US Food and Drug Administration (FDA) as an intralesional injection. As previously described, it is only approved for CMV induced retinitis in the AIDS population. Off-label usage of medications per the FDA can be done with the patient's best interest without regulatory approval when "intent is the practice of medicine"(FDA Regulatory Information 2016). However, for "investigational usage" when a repeated protocol is employed, it is necessary to have IRB approval. At our institution, we currently have a systematic protocol for dosing and intervals. When using a medication with an off-label indication, it is always essential to have an open conversation with the patient about the risks, benefits, as well as the uncertainty coupled with the medication. It is also in the physician and patient's best interest that a formal consent be applied to the off-label usage of any medication. Further in the chapter you will find an example of a consent form used for cidofovir at our institution.

9.2 Benefits of Cidofovir in Trials

Since the first application of cidofovir as an adjunctive treatment in severe RRP in 1995 (Van Cutsem et al. 1995), multiple studies have highlighted its benefit in reducing tumor burden longitudinally. In the original study by Van Cutsem et al. in 1995, a 69-year-old woman was injected intralesionally with cidofovir for hypopharyngeal and esophageal HPV 16 and 18 positive papillomas that were refractory to surgery. She was injected on seven different occasions. The lesions progressively responded throughout treatment, becoming smaller and flatter, until they completely disappeared.

The first published patient series was conducted in 1999 at a tertiary children's hospital where five pediatric patients with severe respiratory papillomas underwent intralesional injection with cidofovir (Pransky et al. 1999). Out of the five patients, one patient was disease free, three patients demonstrated a dramatic response, and one patient had a more moderate response.

After cidofovir showed clinical efficacy in a small patient cohort, the first long-term efficacy of cidofovir in treating RRP study was published in 2000 in a ten patient prospective case series (Pransky et al. 2000). Ten patients with severe RRP were treated with intralesional cidofovir after they failed repeated carbon dioxide laser treatments and mechanical debulking of papillomas. While there were two different treatment protocols applied in the study, the results were promising and the majority of patients either had complete response or marked improvement with a significantly reduced interval of intervention. All the patients remained healthy throughout the protocol with no clinical or laboratory evidence of adverse effects. In addition, histological studies were carried out because of the potential concern for malignant conversion of lesions, and no evidence of cancerous changes was noted.

While the original results of Pransky et al. in their ten patient prospective case series were promising, the follow-up period was approximately 1 year. In 2003, a follow-up study by Pransky et al. was conducted that evaluated ten patients treated with cidofovir throughout a six-year observational period (Pransky et al. 2003). In that study, all ten of the children completed therapy, five were disease free over a mean follow-up period of 52 months, and the remaining five patients had a decrease in their RRP severity score from 18 to 4 and no longer required further injections. In the 6 years of follow-up, no patients demonstrated adverse effects either clinically or laboratory abnormalities, and all of the longitudinal biopsies failed to demonstrate any malignant conversion.

In 2008 a prospective, double-blind, placebo controlled, longitudinal adjuvant therapy study was performed to determine the efficacy of cidofovir in the treatment of severe RRP (McMurray et al. 2008). Nineteen patients, both adult and children, were treated either with cidofovir or placebo, and patients were evaluated for both lesion response and voice improvement at two-and 12-month follow-ups. At both time intervals, there was a significant improvement ($p < 0.05$) in the Derkay Severity Score in the treatment population as well as the Voice Handicap Index. However, the same improvement was also noted in the placebo groups and there was no difference between the two groups. There is a tendency for the natural progression of the disease to follow a nonlinear time course with a decelerating rate of surgery with time (Hawkes et al. 2008), but further randomized controlled trials can elucidate the effect of adjuvant therapies on the disease severity and inter-surgical intervals.

A 2010 Cochrane Database study was published on the role of cidofovir in RRP as an adjuvant therapy (Chadha and James 2010), focusing primarily on the aforementioned study (McMurray et al. 2008). The conclusion paralleled that of the 2008 study that further studies needed to be performed in order to discern the benefits of cidofovir versus placebo longitudinally but intralesional injections do appear to have a beneficial role.

More recently a 2014 study was published assessing cidofovir's efficacy in the adult population (Grasso et al. 2014). Thirty-one adult patients with severe RRP refractory to surgery were treated with cidofovir, with 73% of patients receiving one to four treatments, and demonstrated promising results. Of the 31 treated, 26 patients

(84%) were in complete response at the time of publishing the results. None of the patients experienced renal toxicity or neutropenia. Six patients were noted to have dysplasia on histologic examination after treatment but no malignant changes were observed.

The benefits of cidofovir are not only apparent in the setting of the operating room for refractory, severe papillomatous lesions but have also shown promise in controlling growth in the ambulatory setting (Chhetri et al. 2002). Five patients, who failed to be controlled in the operating room with only debulking, were treated percutaneously with cidofovir for severe laryngeal papillomas along the vocal folds and anterior commissure. The injections were intralaryngeal. The in-office injections resulted in significant reduction in the volume of papillomatosis in all patients. There were no complications reported with the injections. Adult patients who suffer from severe disease that may not be ideal candidates for repeated anesthetics required in the operating room may be candidates for in-office procedures if the anatomical distribution of papillomas is conducive to percutaneous injection.

Throughout the literature there is a well-defined role for cidofovir as adjuvant therapy in the treatment of refractory severe papillomatous lesions induced by HPV. Further studies are needed, including a blinded, randomized, placebo controlled trial. However, the results over the last 20 years with its use have been promising in controlling an otherwise debilitating disease process.

9.2.1 Cidofovir in Non-Otolaryngology Practices

The benefits of applying cidofovir intralesionally in papillomas are not limited to the otolaryngologic practice. Recent publications in the gynecology–oncology literature have highlighted the benefits of cidofovir in a Cochrane Database review assessing treatment response in vulvar neoplasia (Lawrie et al. 2016). When comparing the medical and surgical interventions for usual-type vulvar intraepithelial neoplasia (uVIN), imiquimod or cidofovir as a topical treatment appears to be effective in about half of women treated. While the results were not standardized between medical and surgical interventions, the six randomized controlled trials assessing cidofovir's efficacy in controlling epithelial changes were promising. uVIN is an HPV mediated process and mimics RRP in viral propagation. Therefore, there is great homology in the studies geared towards RRP and vulvar/cervical epithelial changes.

9.3 Risks of Cidofovir Usage

As with any developing novel therapy, the toxicity and complications of treatment have to be understood and weighed against the benefits. The use of cidofovir intralesionally for severe RRP is not without potential complications and has been

intertwined with its usage since its introduction in 1995. The most feared and cited complication of intralesional cidofovir is the potential malignant transformation of lesions from benign papillomas to cancer.

The concern for malignant conversion of lesions stemmed from case reports highlighting potential carcinogenicity (Wemer et al. 2005). In a 1998 Belgian study evaluating the efficacy of cidofovir in severe RRP, biopsies were taken throughout the treatment process and stained for histopathology and viral typing. There was concern for two of the 17 patients because carcinoma was noted on pathologic review. However, after review of the patients' initial pathology, it was determined there was verrucous carcinoma present in the samples prior to initiating therapy. Therefore, the cidofovir was not the inciting agent in malignant conversion.

Case reports then continued to focus on the potential carcinogenicity of cidofovir (Wemer et al. 2005). A 28-year-old female was treated with intralesional cidofovir over a period of 27 months. Her initial biopsy results histologically confirmed benign papillomatous lesions with mild dysplasia but throughout her treatment the cell structure progressed to severe dysplasia. Throughout her treatment, however, there was no carcinoma in situ or malignant invasion noted. A previous study looking at the natural progression of adult RRP patients who underwent multiple surgeries without adjuvant therapy has noted a potential natural progression of disease (Hall et al. 2011). The study looked at the progression of dysplasia of lesions in 54 surgically treated patients. In the 30 patients that required multiple procedures, 9 of the 30 (30%) developed a higher dysplastic grade during the course of treatment. Of those 9, only one developed squamous cell carcinoma. While the progression of disease is less likely if benign or mild dysplasia is initially present, lesions need to be intermittently monitored regardless of therapy. Additionally, recent studies have focused on determining factors that affect the progression of dysplasia. In a recent 2016 ten-year retrospective chart review, age of disease onset was noted to be the strongest predictor of dysplastic transformation of lesions in both the adult and pediatric RRP population (Karatayli-Ozgursoy et al. 2016). The retrospective analysis, however, did not specifically comment on HPV subtypes as a contributing factor.

It is becoming more apparent that the driving force for malignant conversion is more dependent on the specific subtype of HPV that a patient is infected with. HPV types 6 and 11 are classified as the low-risk HPV subtypes and are responsible for approximately 90% of laryngeal infections in RRP (Snoeck et al. 1998). HPV 16 and 18 are the subtypes associated with greater inherent malignant potential conversion, but only occur in less than 1% of cases of laryngeal RRP (Dickens 1991a). There is a malignant transformation potential of the HPV infection with dedifferentiation of the papillomas into squamous cell carcinoma in as many as 1–4% of patients with RRP (Gron 2011). Therefore, even without the introduction of cidofovir in treatment algorithms, there is an inherent risk of malignant degeneration of papillomas based on viral induced cytologic changes. It is equally as important to identify the subtype of HPV strain in papillomatous lesions for future histopathologic studies as it is determining the degree of dysplasia for prognostic purposes.

In addition to suggested changes in human studies, animal models have identified a carcinogenic potential for cidofovir (Wutzler and Thust 2001). In a single toxicology study, rats undergoing 26 weeks of intravenous cidofovir infusion at dosages up to 1.1 times the recommended human exposure level were noted to have tumor carcinogenic changes. The treated rats were noted to have a significant increase in mammary adenocarcinomas and sebaceous gland carcinomas. However, the study included continuous treatment with cidofovir for an extended period of time and did not specifically address papillomas. Therefore, it was concluded cidofovir should be considered carcinogenic in a rat model, and potentially carcinogenic in humans.

While the long-term benefits of cidofovir have been demonstrated in limiting regrowth of papillomas, there is the potential "rebound phenomenon" after discontinuation of usage (Snoeck et al. 1998). A four patient prospective observational study in 2003 noted regrowth in three of the patients after discontinuation of treatment. The study included post-debulking injections six times in 6–8 week intervals. During treatment there was noted to be positive response in all patients; however, after completion of the trial, there was regrowth but the time interval was not noted. Two of the three patients that failed to respond also had more aggressive disease that spread beyond the glottis to include the subglottis and trachea. More extensive disease, particularly extra-laryngeal, typically requires multi-modality treatment including immunomodulating agents such as interferon.

In addition to monitoring long-term sequelae, there is also the inherent short-term risk of laryngeal histologic changes induced by injection of a foreign material submucosally. An animal model study addressed the concerns about injecting immunomodulating agents, including cidofovir, into a vocal fold (Connor et al. 2014). The histologic effects in a porcine model showed minimal inflammation, edema, and atypia after injection. There were no appreciable histologic changes in 18 pigs at 2 weeks and 4 months noted by blinded review of pathologic findings. This study supports the use of intralaryngeal injections with minimal damage to vocal fold histology locally in the short-term.

9.3.1 Long-Term Safety Profile in Human Trials

In 2009 a single case report emerged highlighting the concern for the association of squamous cell carcinoma (SCC) and cidofovir (Jeong et al. 2009). A 14-year-old patient who had been receiving treatment since the age of 4 eventually developed papilloma disease at her carina that was confirmed to be squamous cell carcinoma. During her treatment she received laser endoscopic removal, interferon therapy, indole-3-carbonol, and cidofovir. She received a total of 13

treatments of cidofovir. Years later when she had obstructive disease at her carina, as noted to be SCC, there was concern about her cidofovir treatment and malignant transformation. Not only did the patient have more aggressive disease with tracheobronchial involvement, but the patient had also undergone multi-modality therapy with other immunomodulating agents. Therefore the exact role of cidofovir in malignant transformation cannot specifically be identified as the causative agent.

More long-term studies have demonstrated the safety of intralesional cidofovir usage. A 2005 study (Shehab et al. 2005) included a MEDLINE review of 99 articles that included the use of cidofovir for severe RRP in both adults and children. Their review did not identify any patients with neoplastic changes associated with the use of cidofovir. The only complications associated with intralesional injection were rash, headache, and precordialgia.

A 2008 study specifically focused on the histologic changes associated with intralesional injection (Lindsay et al. 2008). A retrospective review of 96 patient specimens by two blinded pathologists reported that there were no cases of dysplasia identified after treatment with cidofovir. The most commonly identified finding was an increased nuclear-to-cytoplasm ratio in 8.4% of cases.

An international retrospective review of 635 patients assessed cidofovir as an adjuvant therapy in severe RRP (Tjon Pian et al. 2013). Sixteen hospitals across 11 countries evaluated both the benefits and complications of cidofovir usage via questionnaires and retrospective chart review. Their study concluded that there were no statistically significant differences in occurrence of neutropenia or renal dysfunction. Similarly, there were no differences in occurrence of upper airway and tracheal malignancies between the cidofovir treatment group and controls. This was the largest retrospective case study describing the effects of cidofovir. While there were variations in the dosage and treatment algorithms between institutions, the study was the largest of its kind to comment on the safety of cidofovir highlighting the low rates of complications.

9.4 Current Usage in Otolaryngology Practices

In a 2013 21-question survey distributed to adult and pediatric laryngeal surgeons, 82 surgeons who manage 3042 papilloma patients responded commenting on their use of intralesional cidofovir in RRP (Derkay et al. 2013). Single indications for adjuvant cidofovir included six or more surgeries per year, increasing frequency of surgery, and extralaryngeal spread in children. The dosing varied between adult and pediatric surgeons, with most adult surgeons using 20–40 mg in <4 mL and most pediatric surgeons using <20 mg in <2 mL.

9.4.1 RRP Task Force Consensus Statements

As part of the 2013 cidofovir survey conducted by Derkay et al., the RRP Task Force approved 18 consensus statements (Derkay et al. 2013):

1. Intralesional cidofovir often may be initiated for patients requiring six or more surgeries per year, or for whom the interval between surgeries is decreasing, or in children with extralaryngeal or excessively bulky papilloma disease.
2. One may occasionally consider initiating intralesional cidofovir for a combination of the following factors: patients requiring four or more surgeries per year, persistent disease at either anterior or posterior commissure, and failed response to current surgical regimen.
3. Less often, one may consider initiating cidofovir for either an incomplete response to other adjuvant therapy, request for cidofovir by the patient/parent, and (in children) disease onset prior to 3 years of age.
4. At the present time, it is not typically advised to initiate intralesional cidofovir in all (or all new) patients with RRP.
5. Intralesional cidofovir for RRP is recommended in concentrations in the range of 2.5 to 7.5 mg/ mL. Based upon the literature, doses should not exceed 3 mg/kg.
6. An endolaryngeal injection volume of <4 mL is typical in adults and adolescents, and less than or equal to 2 mL in children so as not to obstruct the airway.
7. In adults, typical doses of cidofovir do not exceed 40 mg, and a majority of surgeons administer less than or equal to 30 mg at one time, for both the office setting and direct laryngoscopy. In younger children, most surgeons use doses of cidofovir <20 mg. Up to 25% of doses administered to children are within the 30- to 40-mg range. Again, staying below 3 mg/kg is recommended.
8. A majority of surgeons practice scheduled administration of cidofovir; this tendency is more common in children. For both adults and children, surgeons who use cidofovir in a regimented fashion prefer a periodicity of administration of 2–6 weeks.
9. Based on the survey, we believe that children with RRP requiring adjuvant treatment should adhere to a scheduled regimen (i.e., not receive adjuvant treatment sporadically). Although more than half of laryngeal surgeons adhere to a scheduled regimen for adults with RRP, there was no consensus to exclusively recommend use of a scheduled regimen for all adults.
10. A typical trial of adjuvant intralesional cidofovir consists of five treatments.
11. Indefinite continuation of cidofovir is not generally advised.
12. There is a need to determine the most desirable regimen for a partial response to cidofovir (no clear consensus).
13. After a complete response, cidofovir should be discontinued, although it is common to perform one additional procedure to verify absence of recurrence.
14. Because of the risk of malignant degeneration with RRP, routine biopsies for adults with RRP should be obtained at the time of each direct laryngoscopy in the operating room (and office when feasible).

15. A similar approach to biopsy is recommended in children; at a minimum, biopsies should be obtained at initiation and in the setting of disease progression.
16. As long as one remains below the recommended maximum dosing of 3 mg/kg, it does not seem necessary to routinely screen serum chemistries, creatinine, transaminases, and the complete blood count for aberrances in the setting of intralesional cidofovir use.
17. The informed consent process should include mention of the risk of acute kidney injury in children. Adverse events including dysplasia and malignant degeneration, although possible, appear to occur with a similar frequency in patients never exposed to cidofovir.
18. Informed consent for cidofovir use should include a detailed discussion of the risks and benefits of the therapy, and state that such use is off-label. Although we found that a majority of people do not use a special consent form, this is encouraged because it may help transmit essential information and assist with special documentation of the consent process.

9.5 Future Considerations

Currently the RRP Taskforce has been discussing multiple initiatives to curtail more aggressive disease, initiate multi-modality therapy earlier in treatment algorithms, and tailor therapy to a patient's specific pathologic profile. Efforts have also been dedicated to preventing disease transmission with the newest CDC recommended Gardasil-9, nine valent vaccine. The vaccine prevents transmission of the nine most common subtypes of HPV, including subtypes 6 and 11, which are responsible for approximately 90% of laryngeal infections in RRP (Dickens 1991b). However, adaption of the vaccine has been limited and only 39% of United States' adolescent girls aged 13–17 received all three doses of Gardasil in 2014. HPV vaccination rates in boys are lower than their female counterparts and were a meager 21.6% in 2014 (CDC 2015).

While HPV vaccines have been promising in their ability to prevent transmission of disease, new treatment options are still required in order to better manage RRP patients. The goal of future interventions is to limit the number of surgical procedures and improve voice outcomes. A movement towards earlier intervention in children with adjuvant therapies is advocated because juvenile onset RRP tends to have more aggravated propagation and spreading of papillomas and quick involvement of multiple subsites due to a small larynx (Hyung-Tae and Baizhumanova 2016). Therefore, initiating adjuvant therapy earlier in children can potentially limit the spread of disease and also reduce the overall number of surgeries.

Another future consideration is the development of a personalized medical approach to a patient's specific papilloma profile. Targeted drug therapy for a patient's specific genetic profile has been employed in oncology and inflammatory diseases (Ginsburg and Willard 2009). Personalized medicine involves

incorporating a patient's unique clinical, genetic, genomic, and environmental information to specifically identify therapies that are best suited for their disease genotype. A comprehensive approach, including genomic information, can identify biomarkers and molecular events that are more susceptible to specific treatment modalities. Pharmacogenomics can also be guided by growing a patient's papilloma in the laboratory setting and testing various drugs against their unique disease state. Multiple drug therapies can be tested against the papillomas in an in-vitro setting in hopes the results translate into better control in vivo.

Finally, the majority of studies evaluating the efficacy of cidofovir have focused on intralesional injections. Future studies can include the use of intravenous cidofovir for more advanced or systemic disease. Limited case reports have been published assessing papilloma response to intravenous use of cidofovir. Four case reports have been published where patients with pulmonary extension of their RRP received intravenous cidofovir (Broekema and Dikkers 2008). The patients underwent protocols similar to those for intravenous administration of cidofovir for control of CMV-retinitis. The results were variable but dependent on prolonged periods of drug administration. Future studies can better highlight the response of systemic disease to intravenous injections as well as complications. There are also reports of inhaled cidofovir being used after conventional treatments had failed in the control of disseminated RRP in a four month old with tracheobronchial involvement (Ksiazek et al. 2011). The patient responded to inhaled treatments; however, there are no further case reports or comparisons of treatments to glean extensive details from.

9.6 Conclusion

Recurrent respiratory papillomatosis is a devastating disease with significant morbidity because of its involvement along the upper and lower airway. While surgery has been a mainstay of therapy, there is an increasing movement to adapting adjuvant therapies to better control the spread of disease. Intralesional cidofovir has had promising results with limited complications. Adapting the use of cidofovir in treatment algorithms improves voice outcomes and inter-surgical intervals. The risks and benefits should be appropriately relayed to patients prior to the initiation of therapy since it is an off-label usage of a medication. However, it should not deter the otolaryngologist from its usage in their treatment algorithm for RRP.

Summary of Clinical Studies of Adjuvant Therapies (Excluding Cidofovir) used in the Management of Recurrent Respiratory Papillomatosis Reported between 2000 and 2017 (Prepared by P. Campisi)

Study	Design	Cohort	Outcomes
		Bevacizumab	
Mohr et al. (2014)	*Case series* Intravenous: 5–15 mg/kg per dose q 2–3 weeks initially, then increase interval	*N* = 5 4 adults 1 child, 8 years of age	*Immediate response* Very good partial remission or partial response in all patients
Sidell et al. (2014)	*Case series* Intralesional injection: 5–45 mg dose × 5 doses q 4–6 weeks with 532 nm KTP laser ablation	*N* = 9 Median age 8 years Range 3–21 years	Median 58% improvement in Derkay score ↑ Median surgical interval time 2.05X
Rogers et al. (2013)	*Case series* Intralesional injection: 2.5 mg/mL × 3 doses q 2–3 weeks with 532 nm KTP laser ablation	*N* = 10 Range 18 months–18 years	Statistically significant: ↑ Median surgical interval by 5.9 weeks ↓ Median number of procedures by 4 per year ↓ Derkay score by 6 ↑ Median total PVRQOL score by 25.5 ↑ Median emotional PVRQOL score by 11.3 ↑ Median physical PVRQOL score by 14.3
Zeitels et al. 2011	*Prospective open-label trial* Intralesional injection: 7.5–12.5 mg in × 4 doses q 6 weeks into vocal fold with worse disease Opposite vocal fold sham injection with saline ± 532 nm KTP laser as needed	*N* = 20 adults with bilateral vocal fold disease	3/20—No disease in either vocal fold 16/17—Less disease in treated vocal fold 1/17—More disease in treated vocal fold 20/20 Improved: Vocal function, acoustic and aerodynamic measures of voice, VRQOL scores
		Interferon	
Suter-Montano et al. (2013)	*Case series* Peg-IFNα-2a at 180 mcg weekly × 6 months In 3rd month, +GM-CSF 400 mcg weekly × 2 months	*N* = 11 adults	3 patients had tracheostomy removed Mean improvement in VRQOL measures ↓ Number of surgical interventions required

Study	Design	Cohort	Outcomes
Nodarse-Cuni et al. (2004)	*Case series* IM injection IFNα-2b Induction: 10^5 IU/Kg in children 6×10^6 IU in adults Maintenance (up to 2 years): 5×10^4 IU/Kg in children 3×10^6 IU in adults	*N* = 169 84 adults 85 children	Relapse frequency: ↓ 74% in children ↓ 79% in adults Complete resolution in 1st presentation patients: 45% of children 88% of adults At study completion: 58% of children in remission 82% of adults in remission
Interferon and BCG			
Avramov et al. (2014)	3 Parallel case series Series 1: CO_2 laser ablation + 6–12 transdermal applications of BCG Series 2: CO_2 laser ablation + α-Interferon 3 million IU 5 times per week for 1 month, then 3 million IU 3 times per week for 1 month, then 3 million IU once per week Series 3: Surgery alone	(No mention of how patients were allocated) *N* = 16 adults *N* = 11 adults *N* = 16 adults	2/16 had a relapse (follow-up 36 months) 3/11 had a relapse (follow-up 45 months) 6/16 had a relapse (follow-up 48 months)
Interferon and Cidofovir			
Armbruster et al. (2001)	*Case report* Interferon α-2b 5 × 106 Units 3 times per week x 6 months combined with Cidofovir 5 mg/Kg per week × 2 weeks then 5 mg/Kg q 2 weeks for total 6 months	*N* = 1 adult	Regression of laryngeal and intrapulmonary disease
Indole 3 Carbinol			
Rosen and Bryson (2004)	Prospective open-label trial I3C 200 mg orally twice daily	*N* = 33 24 adults 9 children	Mean follow-up 4.8 years All patients: 33% remission 30% ↓ need for surgery 36% no response Children: 1/9—complete response 3/9—partial response 5/9—no response

Study	Design	Cohort	Outcomes
		Acyclovir	
Chaturvedi et al. (2014)	*Case series* Post-surgical oral acyclovir 800 mg 5 times per day × 5 days	*N* = 3 adults	2/3—remission at end of 1 year follow-up
		Vaccination and Immune Therapy	
Meacham and Thompson (2017)	*4 Parallel case series* Series 1: Debridement and cidofovir Series 2: Debridement and MMR Series 3: Exposure to cidofovir and MMR Series 4: Debridement only	*N* = 15 children Range 1–16 years *N* = 5 *N* = 6 *N* = 3 *N* = 1	No significant difference in number and frequency of required treatments or rates of remission across series
Beaumanis and Elmaraghy (2016)	*Case report* Quadrivalent HPV vaccine	*N* = 1 child 4 year old	Improved clinical course
Hermann et al. (2016)	Uncontrolled intervention study 3 Doses of quadrivalent HPV vaccine	*N* = 9 children Range 9–17 years	No significant difference in clinical course, anatomical score, inter-surgical interval or number of surgeries needed at 1-year follow-up
Young et al. (2015)	*Case series* Quadrivalent HPV vaccine	*N* = 20	Significant increase in inter-surgical interval 8/20—Complete remission 5/20—Partial remission
Chirila and Bolboaca (2014)	*Case series* Quadrivalent HPV vaccine	*N* = 13 Patients with recurrences after failed treatment with cidofovir	85% had no recurrence at 1-year follow-up
Lei et al. (2012)	Randomized prospective trial Arm 1: Topical MMR vaccine at site of excised lesions Arm 2: Excision only	*N* = 26 children	Longer period of remission in MMR but difference was not significant
Derkay et al. (2005)	Open-label, single arm intervention study Surgery followed by HspE7 500 mcg subcutaneously monthly × 3 doses	*N* = 27 children Range 2–18 years	At 60-weeks follow-up: Median inter-surgical interval increased 93% Stronger treatment effect in females

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Chapter 10
Malignant Transformation and Distal Airway Complications

Eleanor P. Kiell and Steven E. Sobol

10.1 Introduction

Low-risk human papillomavirus (HPV) is well recognized as the cause of recurrent respiratory papillomatosis (RRP). The virus induces proliferation of benign squamous papilloma within the aerodigestive tract leading to a number of symptoms that range from hoarseness to life-threatening airway obstruction and respiratory failure. The likelihood of this typically benign disease to progress to such devastating consequences is not entirely predictable; however it is known to recur and spread throughout the aerodigestive tract and has the potential for malignant conversion (Steinberg and DiLorenzo 1996).

There is a bimodal distribution of age of diagnosis for recurrent respiratory papillomatosis. Patients are typically categorized as juvenile onset, when diagnosed in early childhood or adolescence, or as adult onset, typically diagnosed in the third or fourth decade of life. Juvenile-onset RRP is generally regarded as the more aggressive form of the disease and as such has typically been implicated more often in these more worrisome complications of tracheobronchial extension and, to a lesser extent, malignant transformation. Malignancy has been described in patients with juvenile-onset as well as adult-onset RRP but seems to follow a different natural history. As most RRP is the result of low-risk viral subtypes of HPV, the linear progression from dysplasia to invasive carcinoma that is commonly seen in high-risk viral types of HPV has not been well

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described. This chapter will aim to discuss the natural history of, risk factors for, diagnosis and treatment of tracheobronchial extension as well as malignant transformation of RRP.

10.2 Distal Airway Complications

Recurrent respiratory papillomatosis most commonly affects the larynx. The virus has a predilection for epithelial transformation zones, where squamous and ciliated epithelia meet. The true vocal folds are most commonly affected, followed by the epiglottis and false vocal folds (Kashima et al. 1993). Though the larynx is the most commonly affected region in the upper aerodigestive tract, it is reported that 15–30% of patients experience extralaryngeal spread of the disease, but this includes the most common extralaryngeal locations of the oral and nasal cavities (Schraff et al. 2004). Just 5% of patients experience extension of the disease to the tracheobronchial tree (Derkay 1995). As noted previously, progression of disease beyond the larynx escalates a patient's risk for significant morbidity and mortality.

10.2.1 Sites of Tracheobronchial Involvement

A diagnosis of recurrent respiratory papillomatosis is suspected based on a number of clinical symptoms and confirmed by laryngoscopy and biopsy of the papillomatous lesions. If tracheobronchial extension is suspected in a patient with RRP, this must be confirmed again by endoscopy and biopsy. If tracheobronchial extension is present, the clinician should comprehensively evaluate for pulmonary disease by computed tomography (CT) scan of the lungs.

Because of the known tendency for RRP to arise at the junction of squamous epithelium and columnar epithelium, the most common sites of tracheobronchial involvement are:

- Mucocutaneous junction at a tracheostomy site, if present
- Mid-trachea, at the distal tip of the tracheotomy tube (Fig. 10.1)
- Carina

One study noted that the right proximal bronchus was consistently more severely affected than the left (Blackledge and Anand 2000). When a patient is noted to have tracheal involvement, it is imperative to investigate for pulmonary parenchymal involvement as well.

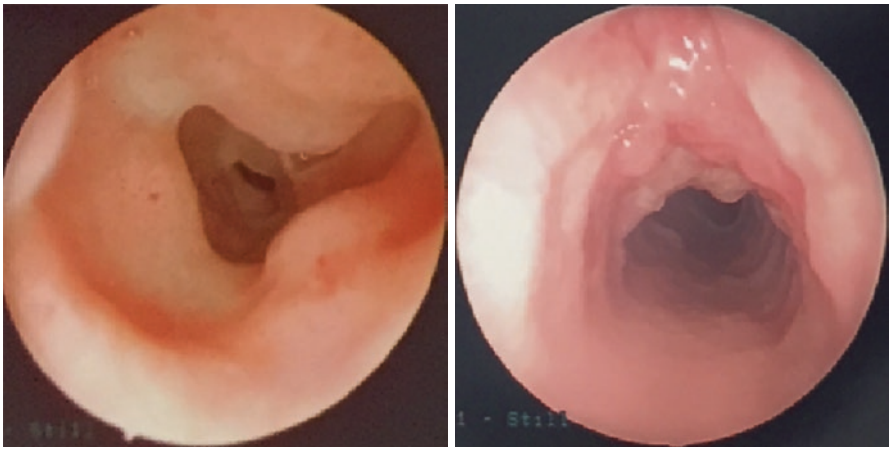

Fig. 10.1 Tracheal papilloma at the distal tip of the indwelling tracheostomy tube

10.2.2 Risk Factors for Tracheobronchial Disease

It has been well established that factors such as the presence of a tracheostomy, infection with HPV subtype 11, and juvenile onset of RRP increase the risk of distal airway spread and malignant transformation.

10.2.2.1 Tracheotomy

The relationship between tracheotomy and RRP distal to the larynx is well established. Tracheotomy is performed when a patient suffers airway obstruction. Airway obstruction may be a direct result of the bulk of the papilloma but may also be the result of scarring related to surgical treatment of the papilloma. Some have argued that those patients who require tracheotomy actually may have more aggressive disease from the outset (Blackledge and Anand 2000; Shapiro et al. 1996). Alternatively, the tracheotomy has been suggested to activate or somehow contribute to the spread of papilloma into the lower respiratory tract. Tracheobronchial extension is linked to a previous tracheotomy in as many as 95% of reported cases (Blackledge and Anand 2000; Cole et al. 1989; Soldatski et al. 2005; Weiss and Kashima 1983). It is rare that tracheal or bronchial papilloma are identified at the time of initial tracheotomy.

Most who care for patients with RRP agree that avoidance of tracheotomy is optimal. When a patient does require tracheotomy, the indication has been reported to be either "stabilization of airway" or glottic stenosis secondary to previous

surgical intervention for their disease (Blackledge and Anand 2000). In those patients who require tracheotomy, every effort is made to expedite safe decannulation. Tracheal spread of papilloma has been reported to occur in as few as 7 weeks post-tracheostomy (Cole et al. 1989) but is certainly not universally encountered in patients who undergo tracheostomy.

There is a clear association between previous tracheotomy and distal spread of papilloma. The predominant theory underlying this relationship is that by disrupting the tracheal mucosa to place the artificial airway, an iatrogenic transformation zone is created (Kashima et al. 1993). The damaged mucosa is an entry point for or the perfect environment for the virus to replicate and cause cellular proliferation and papilloma. As injured mucosa is the entry point, it has been hypothesized that tracheal mucosa injured by any means may be at increased risk for development or spread of papilloma. While this appears to be the case for chronic disruption at the distal tip of the tracheotomy tube, there does not appear to be any proven increase in neonates who require prolonged endotracheal intubation. Nor do other open airway procedures necessarily demonstrate the same increased risk. For instance, Boston et al. demonstrated that a cohort of children with RRP who also had severe subglottic stenosis successfully underwent laryngotracheal reconstruction (Boston et al. 2006).

10.2.2.2 HPV Subtype 11

It has also long been known that HPV viral subtype 11 is more aggressive than viral subtype 6. Numerous studies have demonstrated more aggressive distal complications as well as more common malignant degeneration in patients who are infected with HPV 11. While there was initially some debate in the literature regarding whether a particular subtype was significantly more likely to develop tracheobronchial extension, most agree that this is the case. The relationship was first suggested by Mounts and Kashima who found then labeled HPV subtype 6C (which has since been identified as subtype 11) to be linked with a more obstructive course (Mounts and Kashima 1984). Other studies went on to show that the infecting HPV subtype had little influence on the clinical outcomes (Rimell et al. 1992). Ultimately, studies using polymerase chain reaction were successful in correlating HPV subtype 11 with a significantly more aggressive disease course (Rimell et al. 1997). It is generally well accepted that HPV subtype 11 has a more aggressive clinical course both in tracheobronchial extension and in conversion to malignancy.

10.2.2.3 Juvenile-Onset RRP

RRP may have its onset in childhood, even in the neonatal period, or in adulthood (Derkay 1995). Generally, those with onset in childhood suffer a more aggressive form of the disease, with the less aggressive form typically occurring in adults. The age of onset of the disease is known to be a significant risk factor in prognosticating the aggressiveness of disease. Presentation in the neonatal period poses a higher risk

for tracheotomy and associated morbidity and mortality (Reeves et al. 2003; Ruparelia et al. 2003). Diagnosis before age three years versus after has been associated with 3.6 times higher likelihood of needing more than four surgical procedures per year and almost 2 times greater likelihood of having two or more anatomic sites affected (Derkay 1995). Additionally, children with disease progression are generally diagnosed at younger ages than those who remain stable or become disease-free (Wiatrak et al. 2004).

As surgical intervention is the primary mode of treatment, one measure of aggressiveness is the frequency with which a patient requires surgical intervention. One threshold for consideration of adjuvant therapies is when a patient undergoes more than four surgeries in a 12-month period. According to the National Registry for Children with RRP, which includes patients of 22 pediatric otolaryngology practices, children with RRP undergo an average of 4.4 procedures per year (Derkay 1995; Armstrong et al. 1999), thereby concluding that the majority of children could be considered for adjuvant therapy.

The presence of RRP beyond the larynx has been noted more commonly in those who are diagnosed with the juvenile-onset form of the disease as well as in those who undergo tracheotomy. There may be commonality in these groups, as Kashima et al. noted that 15% of patients with the juvenile form of the disease require tracheotomy for airway complications and management (Kashima et al. 1993).

10.2.3 Pulmonary Complications of RRP

In patients with tracheobronchial RRP, it is necessary to evaluate for pulmonary complications of the disease. Computed tomography is the most appropriate radiographic study for this evaluation.

Pulmonary complications of RRP can be categorized into those infectious complications that likely result from bronchial obstruction and those that are related to pulmonary parenchymal papilloma due to distal seeding. Patients with tracheobronchial involvement of RRP have been reported to present with pneumonia, tracheal stenosis, lung abscesses, pneumatocele, and empyema.

Pulmonary papilloma lesions begin as asymptomatic, noncalcified, peripheral nodules (Kramer et al. 1985). The lesions enlarge, develop central cavitary necrosis, and are visible on imaging with air-fluid levels (Fig. 10.2). These lesions, typical of pulmonary papillomatosis, must be differentiated from a similar but distinct pulmonary complication of pneumatocele.

Pneumatocele is the result of the necrosis of bronchopulmonary tissue followed by expansion of this cystic space. With proximal bronchial obstruction, the expiratory pressures generated within this cystic space are elevated and are then visible on chest imaging (Dines 1968). Pneumatoceles are susceptible to infection, resulting in a pneumatopycele, which requires medical management with antibiotics and may require surgical drainage. In addition to pneumatopyocele, a simple lung abscess may develop. The isolated organism is often anaerobic, requiring initial

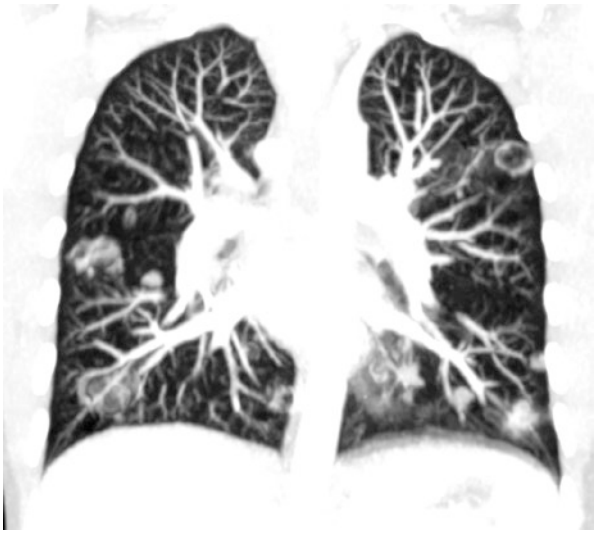

Fig. 10.2 Bilateral pulmonary papillomatosis as seen on computed tomography

intravenous antibiotics followed by a prolonged course of oral antibiotic therapy. Historically, only 10% of lung abscesses require surgical intervention (Bartlett and Gorbach 1975).

Unfortunately, with destruction of pulmonary parenchymal tissue, reduced functional capacity of the lungs develops. At this time, there exists no intervention, medical or surgical, that can consistently halt or reverse the progression of pulmonary RRP. The natural history of pulmonary RRP varies, but with ongoing pulmonary involvement, respiratory failure is likely to develop (Derkay and Wiatrak 2008).

10.2.4 Treatment for Tracheobronchial RRP

10.2.4.1 Surgical Treatment

Surgical therapy remains the mainstay of treatment for all aerodigestive papilloma that are accessible through typical endoscopic means. Surgical treatment initially involved cold surgical excision. The carbon dioxide (CO2) laser replaced cold instruments as the method of choice for removing RRP of the larynx, pharynx, upper trachea, and nasal and oral cavities (Schraff et al. 2004). Advances in the delivery of the laser, both using the micromanipulator on the operating microscope and the flexible fiber delivery system, have allowed for "vaporization" of RRP lesions with minimal bleeding and maximal precision. Drawbacks to the CO2 laser are threefold and relate to patient and caregiver safety. The first is the risk of inadvertent deflection of the laser to injure the surgical team or patient, including the indwelling endotracheal tube, which (if not appropriately protected) may ignite in

an oxygen-rich environment causing an airway fire. Second, the "plume" of smoke generated by the laser has been proven to contain active viral DNA, which is a potential source for infection (Hallmo and Naess 1991; Kashima et al. 1991; Sawchuk et al. 1989). Lastly, the laser-generated heat could cause injury to deeper laryngotracheal tissues, leading to scarring, spread of viral particles to previously unaffected tissues, and delayed local tissue healing. Other lasers, such as the potassium titanium phosphate (KTP), 585 nm flash dye, or argon laser, have also been used to treat RRP. The treatment of distal bronchial lesions has benefitted from these advances in technology. In particular, the use of lasers delivered via fiber that can also be coupled with a ventilating or flexible bronchoscope has improved the success of more distal surgical resection. More recently, powered endoscopic microdebrider has been used with good success, as shown by several groups (Pasquale et al. 2003; Patel et al. 2003; El-Bitar and Zalzal 2002). Powered microdebrider is also limited to subglottic and proximal tracheal involvement due to the physical space restraints required for exposure and the size/length of the instrument. Use of any of these methods must keep in mind that almost all patients require multiple surgical interventions and that the risks associated with overly aggressive resection and resultant scar are not worthwhile. Surgical treatment of distal airway papilloma is required to maintain or recreate distal airway patency where possible. Distal spread, however, is considered an indication for the initiation of adjuvant medical therapy.

10.2.4.2 Adjuvant Therapy

In patients with tracheobronchial extension, adjuvant therapy is considered. There is no single adjuvant therapy that has proven to be effective across patients or disease processes. These therapies include intralesional and systemic antivirals (interferon, ribavirin, acyclovir, and cidofovir), photodynamic therapy, dietary supplements (indole-3-carbinol), celecoxib, retinoids, vaccines (mumps and HPV), as well as aggressive anti-reflux regimens (Derkay and Wiatrak 2008). Radiation therapy has also been used. Each of these therapies has proven some benefit in select patients but also forces the patient and caregiver to contend with some untoward side effects. Most patients with aggressive disease have been trialed on one or more of these therapies. Interferon has historically been the most commonly used adjuvant treatment. The introduction of the vaccinations against HPV has opened a new opportunity with a very low side effect profile. Some have shown a good response with increased interval between surgical treatments and even induced remission in some (Hallmo and Naess 1991). Most recently, there have been reports of good response to intralesional bevacizumab (Rogers et al. 2013) and a handful of patients treated with systemic bevacizumab (Mohr et al. 2014; Zur and Fox 2016) with very promising results.

Despite multiple small studies showing promise for intralesional and systemic cidofovir, the only blinded randomized trial by McMurray et al. was unable to show any significant improvement in outcomes with cidofovir, although administered at a

low dose (McMurray et al. 2008). Additionally, concern has been raised about the potential for malignant transformation of RRP lesions in patients who have undergone treatment with cidofovir (Wemer et al. 2005).

10.3 Malignant Transformation

Recurrent respiratory papillomatosis (RRP) is generally considered a benign disease of viral etiology. Caused by human papillomavirus (HPV) subtypes 6 and 11, RRP has long been known to follow a different natural history than infection with high-risk subtypes 16 and 18. Unfortunately, dysplasia and carcinoma can occur in RRP, both adult onset and juvenile onset. Rates of dysplasia in adult-onset RRP range from 13 to 55% and juvenile onset 0–10% (Karatayli-Ozgursoy et al. 2016). The wide range likely reflects the rarity of the disease, differing definitions of pathologic changes, inter-rater variability among diagnosing pathologists (Fleskens et al. 2011), coinfection with high-risk subtypes (Sanchez et al. 2013), or other confounding behavioral or environmental contributions.

In patients with RRP, dysplasia is uncommon. Even less common but far more difficult to treat is invasive carcinoma. The progression of high-risk HPV types (HPV 16 and 18) from dysplastic epithelium to invasive carcinoma has been well described in both the cervical epithelium and the oropharyngeal epithelium (Doorbar et al. 2012). Due to the variability in malignancy in patients with known recurrent respiratory papillomatosis, it is not clear that malignancy arising in patients with RRP necessarily follows the well-described pathogenesis of its high-risk HPV counterparts.

10.3.1 Pathophysiology of Malignant Transformation

Human papillomavirus initially infects the basal layer of epithelia through minor abrasions. The acquisition of HPV-related RRP is either through vertical transmission in juvenile-onset RRP (Sajan et al. 2010; Lee and Smith 2005; Venkatesan et al. 2012; Byrne et al. 1987; Gerein et al. 2007), or in adult-onset RRP, through mucosal-mucosal contact or reactivation of latent viral infection (Sajan et al. 2010; Lee and Smith 2005; Venkatesan et al. 2012).

In the upper layers of squamous epithelia, virions are produced, which are freed through normal desquamation processes, causing inflammation. The virus produces E6 and E7 proteins which are recognized as oncoproteins. These proteins inactivate interferon regulatory factor allowing HPV infection to remain persistent and asymptomatic. Viral genomes can replicate in an episomal or integrated manner. When viral genomes replicate episomally, as do most cases of HPV types 6 and 11, they show relatively low levels of E6 and E7 gene expression. In most cases with low levels of E6 and E7, infection resolves spontaneously by an effective immune

system. However, when viral DNA is introduced into the host genome, in most cases, it often displays a strong expression of E6 and E7 genes. In these cases, carcinogenic transformation progresses rapidly. The E7 protein promotes cell division by binding pRb, while virus protein E6 binds and inhibits p53 protein which is active in repressing the cell cycle in case of DNA damage. This leads to prevention of apoptosis and cell cycle dysfunction (Mirghani et al. 2014; Lele et al. 2002). That increased expression of oncoproteins E6 and E7 is likely to occur in the progression of RRP to carcinoma is well understood. There are two mechanisms by which this could occur: (1) duplication of the upstream regulatory region in episomally active HPV which will result in increased expression of E6 and E7 (DiLorenzo et al. 1992) or (2) mutation in the upstream regulatory region or integration of HPV into the host cell genome with resultant increased expression of E6 and E7 oncoproteins (Kitasato et al. 1994).

Viral oncoproteins E6 and E7 have reduced transforming capacity but still carry biologic function to drive cellular proliferation. Alterations in the regulation of E6 or E7, its mechanism for duplication or its qualitative ability to affect the regulation of p53, pRb, and p21 proteins, can all lead to progression to carcinoma. Few studies have actually looked at HPV type, oncoproteins, or tumor suppressor genes in lesions across the malignant spectrum in the same patient. One study was able to demonstrate the presence of HPV 11 in all lesions comprising the morphologic spectrum of RRP progressing to carcinoma (Lele et al. 2002).

10.3.2 Epidemiology and Risk Factors for Malignant Conversion

The rate of malignancy in adult patients with RRP ranges from 2% to 4% (Lee et al. 2008) but was not well described in patients with juvenile-onset RRP until recently. By examining a cohort of 159 adult and juvenile patients, Karatayli-Ozgursoy et al. described a significant difference in the rates of dysplasia and invasive carcinoma between those with adult-onset RRP (AORRP) versus juvenile-onset RRP (JORRP). Of the patients with AORRP, 10% were diagnosed with dysplasia or CIS, while 5% were diagnosed with invasive carcinoma-ex-papillomatosis. In those patients with JORRP, no pathologic diagnoses of dysplasia or carcinoma in situ were described, with 5% of patients diagnosed with invasive pulmonary carcinoma-ex-papillomatosis.

The patients with adult-onset RRP who were also diagnosed with dysplasia or invasive carcinoma were more likely to be male, underwent significantly fewer procedures, and were diagnosed with AORRP at significantly older age than those with benign papilloma. Of these features, what was only noted to be statistically significant is the older age at diagnosis, as gender and number of procedures were not statistically significant. In patients with JORRP, the patients who developed invasive carcinoma were diagnosed with RRP at a significantly younger age. Additionally, all of the patients in this series diagnosed with carcinoma-ex-papillomatosis had tracheal and pulmonary disease (Karatayli-Ozgursoy et al. 2016).

In patients with aggressive laryngeal disease or tracheobronchial extension, the use of adjuvant therapy, especially cidofovir, has shown to be one of the most promising therapies. Cidofovir is an acyclic nucleotide phosphonate antiviral medication that is FDA-approved for treatment of cytomegalovirus (CMV) retinitis in patients with human immunodeficiency virus (HIV). It is a drug that has been used both locally with intralesional injections as well as systemic for disease not adequately treated locally. Unfortunately, cidofovir is a known carcinogen (Inglis 2005), and there have been case reports of malignant degeneration in patients undergoing treatment with intralesional cidofovir (Wemer et al. 2005).

Typical risk factors for development of aerodigestive tract malignancies do not necessarily apply to patients with malignant degeneration of RRP. Specifically, the use of tobacco products has not panned out as an independent risk factor for malignant degeneration. This is perhaps not surprising, as patients with HPV-related oropharyngeal carcinoma do not consistently demonstrate this risk factor (Ang et al. 2010).

10.3.3 Diagnosis and Treatment of Malignancy

The rarity of invasive carcinoma in patients with RRP makes it difficult to study in a systematic way. There have been fewer than 100 reports of carcinoma arising from recurrent respiratory papillomatosis in the literature. A number of these are only identified on histopathologic examination of the aerodigestive tract, particularly the lung, at autopsy (Cook et al. 2000). Diagnosis of dysplasia or invasive malignancy is based on biopsy and pathologic diagnosis. Pathologic diagnosis of pulmonary papillomatosis requires identification of squamous epithelium with underlying nests of squamous cells within alveolar spaces, distinguishable from invasive carcinoma by the presence of intact alveolar septa, low-grade cytology, a pushing border, and the absence of desmoplasia. Invasive carcinoma, by contrast, consists of irregular, invasive tongues of keratinizing squamous cells with moderate to severe cytologic atypia, with surrounding desmoplastic reaction and invasive destruction of surrounding alveolar parenchyma (Cook et al. 2000).

Dysplasia and even carcinoma that arises in the larynx, as is most common in patients with adult-onset RRP, can be managed similar to non-RRP-related laryngeal squamous cell carcinoma. For many patients, this ultimately requires salvage laryngectomy (Karatayli-Ozgursoy et al. 2016).

In patients with juvenile-onset RRP, dysplasia has not been described, but invasive carcinoma has almost exclusively affected those with pulmonary parenchymal involvement (Karatayli-Ozgursoy et al. 2016; Cook et al. 2000). There are no treatment strategies clearly efficacious for these patients. No current therapies are consistently effective in treating squamous cell carcinoma arising from pulmonary

papillomatosis, especially since these patients also suffer widespread parenchymal disease apart from the malignancy. The use of systemic bevacizumab to treat benign pulmonary papillomatosis may portend its use in patients who suffer pulmonary carcinoma. In addition, there seems to be hope that the prevention of RRP by the vaccines against HPV will decrease the overall incidence of the associated complications.

10.4 Conclusion

Though it is well understood that most recurrent respiratory papillomatosis arises from infection by low-risk viral subtypes of human papillomavirus, there is little consensus with regard to the mechanism by which more serious complications of this disease occur. It is clear that juvenile-onset RRP tends to be more aggressive with regard to tracheobronchial and pulmonary extension, but malignancy can occur in either cohort. Patients who require tracheotomy are more likely to have distal spread, and there are hypotheses regarding the pathology of this; however, causality is not proven. Viral subtype HPV 11 is almost exclusively implicated as the low-risk type associated with malignant progression. There is speculation regarding other factors that lead to malignant degeneration, including mutations in the virus or the host immune system, environmental factors, or coinfection by high-risk viral subtypes. Surgery remains the mainstay of treatment for RRP even when there is tracheobronchial extension or malignant degeneration. In these complicated scenarios, adjuvant therapies are considered; however, there is little consistency in which therapies prove to be beneficial for which patients. Historically, the addition of intralesional or systemic cidofovir and systemic alpha-interferon and standard chemotherapy for SCCA have been used. There is promise for systemic administration as well as intralesional injection of bevacizumab, the monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A. The effects of the HPV vaccines will likely be realized in the coming decade. It is conceivable that the rarity that makes studying these complications difficult will only increase.

The rarity of these complications and the interpatient variability make it exceedingly difficult to come to definitive conclusions regarding the risk factors, pathophysiology, or treatment of these complications of RRP. After all, we know that the number of people exposed to HPV far exceeds the number of patients diagnosed with laryngeal RRP; and the number of patients who live with RRP far exceeds the number of patients who suffer the life-threatening complications of tracheobronchial extension or malignant conversion. The need for ongoing investigation into these complications is apparent, if we are to achieve improved long-term outcomes for these patients.

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Chapter 11
Human Papillomavirus and Head and Neck Cancer

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11.1 Etiological Role of HPV and Mucosal Head and Neck Squamous Cell Carcinoma

Tobacco use and alcohol consumption are the traditional etiological factors for mucosal head and neck squamous cell carcinoma (HNSCC). In addition, areca nut chewing and poor dental hygiene have been linked to oral cavity cancer, while Epstein-Barr virus (EBV) (Chua et al. 2016) is the major carcinogenic agent for nasopharyngeal cancer. In recent decades, high-risk human papillomavirus (HPV) infection has been recognized as an etiological factor for an increasing proportion of HNSCC (Gillison et al. 2000).

The etiological role of high-risk HPV in the HNSCC carcinogenesis process was proposed as early as 1983 (Syrjanen et al. 1983). In 1989, Brandsma and Abramson

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(Brandsma and Abramson 1989) first confirmed the presence of HPV 16 DNA in SCC of the tonsil. A year later, Ishibashi et al. (Ishibashi et al. 1990) reported the detection of HPV 16 DNA in both tonsillar SCC and two lymph node metastases, suggesting a direct role for HPV infection in the development of SCC. In 2000, Gillison et al. (Gillison et al. 2000) confirmed a causal association between HPV and a subset of OPSCC in their epidemiological and molecular study. In 2007, the World Health Organization (WHO) first acknowledged the carcinogenicity of HPV in the oropharynx and oral cavity (World Health Organization 2007).

HPV infection is the most common sexually transmitted viral disease in North America. The prevalence of oral HPV infection is less common compared to genital infection and higher in men than women (Gillison et al. 2012). Oral-genital contact is believed to be the main route of HPV transmission (D'Souza et al. 2007). Vertical transmission (mother-to-child) may also be possible (Hahn et al. 2013; Park et al. 2012; Syrjanen 2010). In fact, mother-to-infant viral vertical transmission during vaginal labor is believed to be the major route of HPV transmission for recurrent respiratory papillomatosis (RRP) in children (Larson and Derkay 2010). Whether HPV can be transmitted via mouth-to-mouth (kissing) is debatable (Touyz 2014; Pickard et al. 2012; D'Souza et al. 2009; Antonsson et al. 2014). Increasing numbers of sexual partners, oral sex practice, and marijuana exposure increase the risk of HPV transmission but tobacco smoking, alcohol drinking, and poor oral hygiene do not (Gillison et al. 2008). An epidemiological study has shown that HPV+ HNSCC was independently associated with high-risk sexual behavior (higher numbers of sexual partners, greater frequency of oral sex partners) and exposure to marijuana, but not with tobacco exposure. Interestingly, HPV+ HNSCC patients are predominantly male with higher social-economic status and less tobacco exposure (D'Souza et al. 2007; D'Souza et al. 2010). The predominant male phenomenon is attributable to a higher total number of sexual partners and a higher rate of oral HPV prevalence per sexual partner in men compared to women (Nyitray et al. 2014). Higher viral load in the cervix mucosa compared to penile mucosa and a weaker immune response to HPV infection in men are potential contributing factors to the high prevalence of HPV+ OPC in men (Beachler et al. 2016).

Although oral HPV infection is common, most infections can be cleared in 1 year (Kreimer et al. 2013a). Persistent high-risk HPV infection can cause cancer. The carcinogenesis process of high-risk HPV in HNSCC is depicted in Fig. 11.1. Persistent infection of high-risk HPV allows the virus to insert its DNA fragments into the host cell genome with consequent overexpression of the E6 and E7 oncogenes. The E6 oncogene disrupts the tumor p53 suppressor gene pathway, and the E7 oncogene disrupts the retinoblastoma gene (pRb) pathway, which results in uncontrolled cell proliferation and eventually cancer. The inhibition of the pRb pathway results in downstream p16 overexpression, which contrasts with p16 deletion in smoking-related HNSCC. Therefore, p16 overexpression can conveniently be used as a surrogate marker for HPV+ OPC.

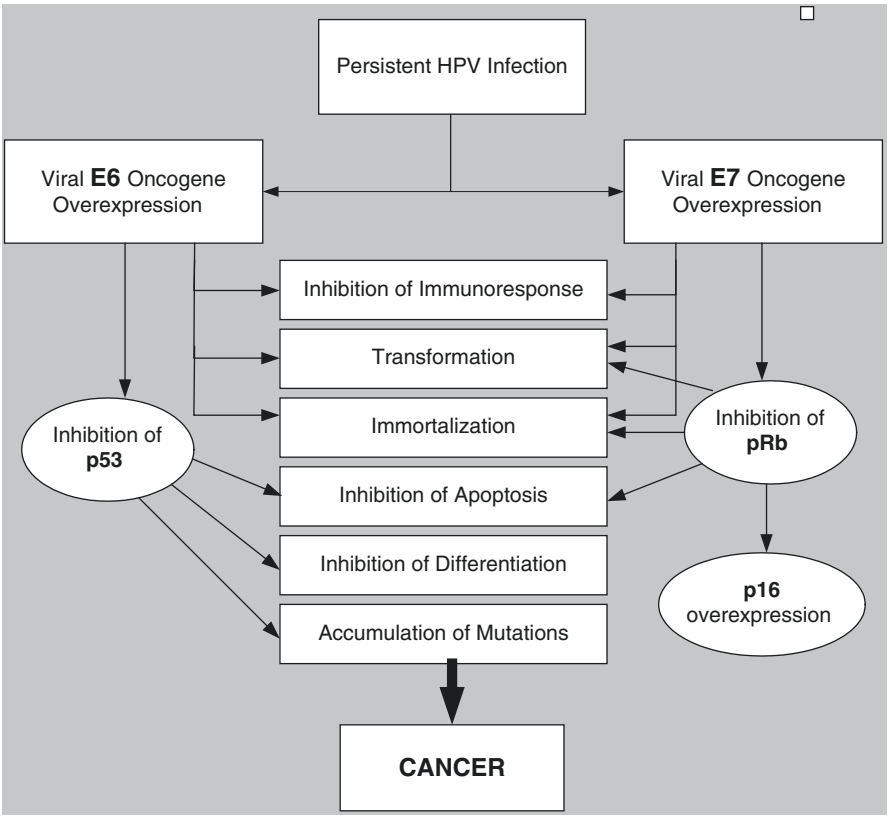

Fig. 11.1 HPV carcinogenesis process

11.2 HPV+ HNSCC Burden

Based on GLOBOCAN 2012 (Ferlay et al. 2015), head and neck cancer accounted for 4.8% of the 14.1 million new cancer cases worldwide in 2012, a slight decrease from 5.0% in 2008, attributable to smoking cessation programs. However, recent epidemiological data showed that there is a dramatic increase in the incidence of oropharyngeal cancer (OPC) in many western countries, in contrast to a decreasing trend in other HNSCC (Gillison et al. 2014; Chaturvedi 2012). The rapid increase of OPC is attributable to the emergence of HPV+ OPC. The global incidence of OPC was 85,000 new cases in 2012, of which 26% were HPV+ (~22,100 new cases per year) globally, and the prevalence of HPV+ OPC is much higher (50%) in developed countries (e.g., North America, Japan, and Australia) (Gillison et al. 2014; Giuliano et al. 2015). In fact, HPV+ OPC now comprises the majority of HNSCC

referrals in North America. If current trends continue, it is projected that the incidence of HPV+ OPC will overtake that of HPV-related cervical cancer by the year 2020 (Chaturvedi et al. 2011).

11.3 Site of HPV-Related HNSCC

Although WHO initially included both the oral cavity and oropharynx as potential sites of HPV-driven HNSCC, convincing evidence exists that HPV-related (HPV+) HNSCCs mainly occur in the oropharynx (predominantly in the tonsil and tongue base), while the prevalence of HPV-driven oral cavity SCC or other non-oropharynx sites is much lower than previously reported (Castellsague et al. 2016; Zafereo et al. 2016). A systematic review of published literature regarding the presence of HPV by PCR in non-oropharyngeal sites (oral cavity, larynx, nasal cavity, nasopharynx, and sinonasal SCC) reported a rate exceeding 20%. However, it is now evident that PCR-based HPV detection has overestimated oncologic-relevant HPV infection. In fact, the presence of high-risk HPV in the tumor does not necessarily indicate that HPV is a "driver" of the tumor but could be a "bystander" indicating an HPV coinfection at time of tumor detection. A study with large data on HPV DNA detection by PCR and p16 expression in HNSCC biopsies suggests that the probability of a cancer of the oral cavity, larynx, and hypopharynx being attributable to HPV is at least fivefold lower than that for oropharyngeal cancer (Combes and Franceschi 2014). A recent comprehensive analysis (Castellsague et al. 2016) of HPV biomarkers in 3680 HNSCC patients, using more robust HPV testing methods to differentiate HPV-driven tumor from coexisting HPV infection in tumor, has demonstrated that the prevalence of HPV+ tumor is less than 5% in the oral cavity, larynx, hypopharynx, and nasopharynx. A potential etiological role for HPV in a small proportion of sinonasal tumors is also suggested but confirmation is needed (Bishop et al. 2013; Syrjanen and Syrjanen 2013).

In addition, some benign lesions of the head and neck are also associated with HPV infection. For example, recurrent respiratory papillomatosis (RRP) has been confirmed as an HPV-related disease in both children and adults linked to low-risk subtypes 6 and 11 (Larson and Derkay 2010; Can et al. 2015). Malignant transformation may occur in a very small proportion of RRP with HPV subtype 11. Another potential HPV-related benign head and neck lesion is sinonasal inverted papilloma (SNIP), a locally aggressive neoplasm arising in sinonasal mucosa (Lisan et al. 2016). A growing number of molecular epidemiological studies have suggested an association between HPV infection and SNIP. Both low-risk and high-risk HPV subtypes have been detected in SNIP, but whether the presence of HPV is a "driver" or a "passenger" is yet to be fully elucidated (Lisan et al. 2016; Strojan et al. 2012; Thavaraj 2016). Studies have linked low-risk and/or high-risk HPV infection with SNIP (Buchwald et al. 1995; Hasegawa et al. 2012; Lin et al. 2016; Zhao et al. 2016; Mendenhall et al. 2007) and reported that about 5% of SNIPs could convert to invasive SCC, especially those infected with high-risk HPV subtypes.

In summary, high-risk HPV is a confirmed carcinogenic agent in oropharyngeal cancer (OPC) and may also be responsible for a small proportion of SCC beyond

the oropharynx and specifically in the oral cavity, larynx, hypopharynx, nasopharynx, and sinonasal mucosa. Low-risk HPV infection is associated with head and neck benign lesions including laryngeal papillomatosis and papilloma in the sinonasal mucosa. A small proportion of the latter might experience malignant transformation, especially those infected by HPV 11 or several high-risk HPV subtypes.

11.4 HPV Subtype and HNSCC

HPV is a non-enveloped double-stranded DNA virus from the papillomavirus family which affects human. HPV subtypes are commonly grouped as either cutaneous or mucosal, depending on the type of tissue of prediliction. More than 170 different HPV subtypes have been identified so far, of which more than 40 are mucosal subtypes (de Villiers 2013). Based on its oncogenic (cancer-causing) ability, it can be divided into low-risk (subtypes 6, 11, 42, 43, 44, 45) and high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and undetermined subtypes (Kumar et al. 2015). HPV genotyping analysis has shown that more than 90% of HPV+ OPC is caused by the HPV 16 subtype and the remainder are caused by other HPV subtypes (e.g., HPV 18, 33, and 35) (Gillison et al. 2014; Castellsague et al. 2016; Kreimer et al. 2005) (see Chap. 1). A greater diversity of high-risk HPV subtypes, such as 31, 33, 35, and 49, exist in non-oropharyngeal mucosa. The genotyping variation seems to be associated with prognostic significance in disease outcomes. Recent studies suggest that HPV+ HNSCC caused by the HPV 16 subtype seems to be associated with better outcomes compared to those caused by non-HPV 16 subtypes (Bratman et al. 2016; Goodman et al. 2015). This may partially explain why HPV+/p16+ non-OPC fare less well compared to HPV+/p16+ OPC (Chung et al. 2014).

Laryngeal papillomatosis is mostly caused by HPV 6 and 11 and rarely by HPV 16 or 18 (Larson and Derkay 2010). Malignant transformation is rare. A recent analyses of 35 adult RRP patients showed the HPV was present in all patients (80% were positive for HPV 6, 8% for HPV 11, and 1% for HPV 16). Another study on RRP showed that 95% of cases were HPV positive, of which 69% were caused by HPV 6, 27% by HPV 11, and 8% by HPV 16. HPV 11-related RRP seems to behave more aggressively compared to those caused by HPV 6. Both low-risk (6 and 11) and high-risk HPV (16, 18, 33, 57, etc.) were detected in SNIP (Zhao et al. 2016), and there was a strong association of HPV 16 and 18 with malignant SNIPs (Zhao et al. 2016).

11.5 Screening and Prevention of HPV+ OPC

Since HPV+ HNSCC occurs predominantly in the oropharynx and the natural history and clinical behavior are much less understood in non-oropharyngeal cancer, the discussion that follows will be confined to screening, diagnosis, staging, and treatment issues in the OPC setting.

Unlike cervical cancer, HPV+ OPC often lacks a visible precancerous lesion which poses a challenge in screening (Kreimer 2014). The French "Split" trial showed that tonsil "brushing" appeared to be less reliable in detecting HPV (Franceschi et al. 2015) compared to an oral rinse method (Gillison et al. 2012), but both are not OPC specific. Recently it was shown that serum HPV16 E6 antibody was detectable in >90% HPV+ OPC patients 2–10 years prior to their cancer diagnosis (Kreimer et al. 2013b). HPV16 antibodies with at least one early protein (E1, E2, E4, E5, E6, or E7) were detected in the sera of 90.6% of HPV+ OPC cases, 0% of partners, and 7.4% of healthy volunteers (Anderson et al. 2015). The detectable E6 antibody seropositive rate is very high (approaching 100%) in HPV+ OPC patients and much lower in non-OPC (oral cavity, larynx) and genital HPV+ cancers (e.g., cervix, vagina, vulva, and penis), except in anal cancer (Kreimer et al. 2013b); it is also rarely detected in healthy individuals (Lang Kuhs et al. 2015). For this reason, it is promising to use this biomarker to design a screening algorithm for HPV+ OPC and anal cancer (Brotherton et al. 2016). However, the choice of study end point and monitoring method in seropositive patients is a dilemma since there is no visible precancerous lesion to screen, even though severe dysplasia can exist. Bilateral tonsillectomy is not an ideal follow-up procedure for E6 seropositive patients as it is invasive and associated with a 50% chance of missing HPV+ OPC in the base of tongue.

Prevention of HPV+ OPC is potentially possible by modifying sexual behavior and HPV vaccination. Tonsillectomy does not prevent HPV+ base of tongue cancer although it might reduce the risk of HPV+ tonsillar cancer. A recent study has shown that previous tonsillectomy modifies the odds of both tonsil and BOT cancer, with decreased odds of tonsil cancer and increased odds of BOT cancer (Zevallos et al. 2016).

11.6 HPV+ OPC: Clinical Presentation and Diagnosis

Since there is no screening tool to facilitate early diagnosis, HPV+ OPC diagnosis largely relies on traditional clinical processes: symptom/signs prompt patients to visit medical professionals, biopsies confirm the primary tumor location, and HPV testing confirms the role of HPV.

Confirming an HPV+ OPC diagnosis can be challenging due to its unique clinical presentation and/or occasionally idiosyncratic patient behavior. Delay in diagnosis could occur when a patient fails to recognize the onset of symptoms or is in denial of a potential cancer diagnosis since many of such individuals are previously healthy without typical risk factors for traditional HNSCC. It could also occur due to clinician-related factors, such as unfamiliarity with potential initial presentations of HPV+ OPC, resulting in delayed referral from the family doctor to otolaryngologists and/or technical challenges in obtaining tissue or misdiagnosis by otolaryngologist (Lee et al. 2015; Truong Lam et al. 2016; Yu et al. 2008). Many HPV+ OPC patients present

as "unknown primary" with cervical lymph node metastasis without visible mucosal lesions. An asymptomatic neck mass (typically at level 2) is the most common initial clinical presentation for about two-thirds of patients with HPV+ OPC and is often the first sign prompting medical referral (Truong Lam et al. 2016; McIlwain et al. 2014). Local symptoms, such as dysphagia or odynophagia, are much less frequent and often mild, even in the presence of a large primary compared to HPV– cases (Truong Lam et al. 2016). An HPV+ nodal mass is often of cystic appearance (Goldenberg et al. 2008; Morani et al. 2013) (Fig. 11.2) and could be mistaken for a "branchial cleft cyst." They often have a "spongy" feeling on palpation that could be mistaken for a "lymphoma." Cervical lymph node involvement occurs earlier in the course of HPV+ OPC development, even with small (T1–T2) primaries, likely attributable to the anatomic structure of tonsillar crypt epithelium, which has a discontinuous basement membrane and contains numerous small blood vessels (Lewis and Chernock 2014). Table 11.1 summarizes typical clinical presentations of HPV+ OPC.

Small primaries arising "deep" to the basal cell layer of crypts with minimal mucosal changes coupled with a paucity of local symptoms and cystic lymph node(s) present a technical challenge in confirming the diagnosis for this patient population. This is particularly true if there is lack of awareness that the clinical presentation of this disease is different from "classic" HNSCC caused by smoking/alcohol. For example, several cases with small but visible mucosal changes in the tongue base still require repeated biopsies to yield a diagnosis which likely occurs because the initial biopsy attempt was insufficiently "deep." Initial lack of success

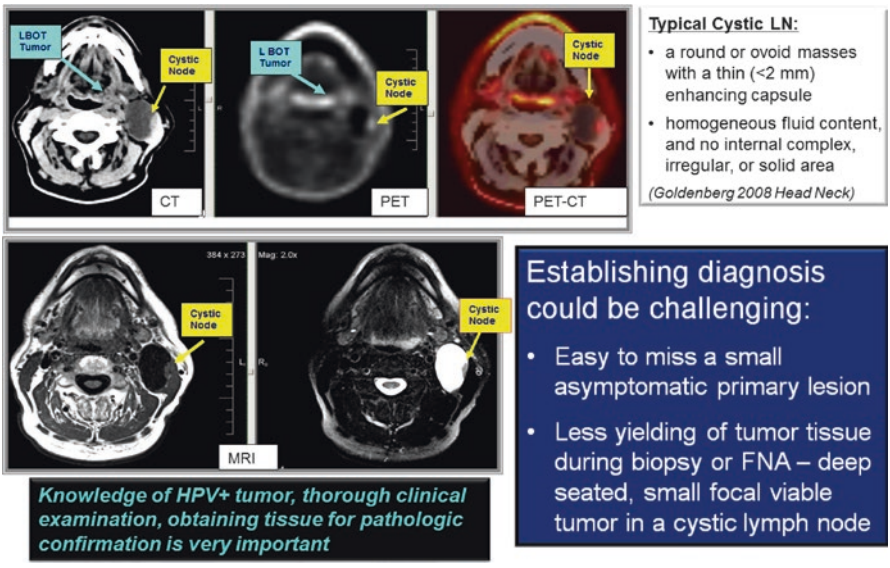

Fig. 11.2 An HPV+ base of tongue primary with a typical cystic lymph node

Table 11.1 Clinical presentation for HPV-positive oropharyngeal carcinomas

Natural history		HPV positive
Presentation	Local	Likely discreet small primary lesion (mostly T1–T2); soft or "rubbery" feeling in palpation Predominantly in tonsil or base of tongue Paucity of local symptoms, even in those with larger primary tumor Multicentric synchronous primaries may occur in a small proportion of patients (e.g., contralateral tonsil or other head and neck region outside of oropharynx)
	Regional	About 2/3 present with an asymptomatic neck mass without an obvious oropharyngeal primary ("unknown primary") Gross lymph node involvement is frequent, even in small (T1–T2) primary lesions Often the first sign for patients to seek medical attention Cystic lymph nodes are frequent and present in ~50% of cases
	Metastatic	~0.5% present with metastatic lesions, mainly in the lung; may also present in other organs, such as the liver, bone Long-term survival is possible for selected patients with single-organ metastasis

in establishing a diagnosis could also be explained by difficulty in acquiring representative tissue in small HPV+ primary tumors. The presence of a cystic lymph node is also challenging in yielding positive cytology when only a small focus of solid tumor exists in the wall of the cystic lymph node.

For the specialist facing an "unknown primary" with cervical lymph node involvement fitting the correct patient profile, especially when the lymph nodes are soft or "spongy" on palpation or with a cystic component on CT and or MRI, the likelihood of HPV(+) tonsil or BOT primary should be high on the potential list of diagnoses. Obtaining tissue (e.g., core lymph node biopsy) for p16 staining would be more reliable due to established limitations of p16 staining on FNA specimens (Bishop et al. 2015). P16 positivity would highly suggest tonsil or BOT origin. PET CT may also identify a potential primary and should preferably be undertaken prior to invasive procedures to avoid false positivity arising from biopsy artifact (Huang et al. 2015a). Tonsillectomy may identify a tonsil primary more successfully compared to tonsil biopsy. Emerging evidence suggests that trans-oral robotic surgery (TORS) is a useful diagnostic tool to detect an "unknown" primary arising from the tonsil or base of tongue and is a promising therapeutic option for small tonsil/BOT primary with low-volume neck disease (Kang et al. 2015; Mehta et al. 2013). Notably, multicentric synchronous primaries may occur in a small proportion of HPV+ patients (e.g., contralateral tonsil or other head and neck regions outside the oropharynx) (Huang et al. 2012; Joseph et al. 2013; Roeser et al. 2010; Rasband-Lindquist et al. 2016; McGovern et al.

2010). Adequate pretreatment workup including clinical, endoscopic, and radiological exam is important to identify potential sites of cancer (e.g., contralateral tonsil, tongue base, supraglottic larynx). It has been reported that some HPV+ synchronous head and neck lesions may not be obvious with routine CT/MRI and fiberoptic examination and may only be successful during examination under anesthesia (Huang et al. 2012).

11.7 Histology and Confirmation of HPV+ OPC

Histological confirmation of HPV-driven OPC is important since HPV+ and HPV– OPC have different prognoses, and staging and treatment might also differ (see discussion below) in the foreseeable future. Although HPV+ tumors are SCC, they are often poorly differentiated of nonkeratinizing or basaloid morphology.

To determine whether a tumor is HPV driven, specific HPV testing is required (Boscolo-Rizzo et al. 2016). Many HPV testing methods exist including assays for HPV E6 and E7 DNA or mRNA by PCR or in situ hybridization (ISH). Currently there is no consensus regarding optimal tumor HPV testing. Table 11.2

Table 11.2 Commonly used HPV testing method

Type of tumor sample	Tumor markers	Comments
Tumor tissue (formalin-fixed paraffin-embedded, or fresh frozen)	HPV DNA (e.g., viral E6 and E7) by polymerase chain reaction (PCR) or in situ hybridization (ISH)	High sensitivity The presence of HPV DNA in tumor may not always indicate the tumor is driven by HPV
	HPV RNA (e.g., viral E6 and E7 mRNA) by PCR or ISH	Generally considered to be the gold standard of HPV detection High sensitivity and specificity: definitive evidence of viral integration
	p16 overexpression by immunohistochemistry staining	Commonly used as a surrogate marker HPV-driven OPC Less costly, easy to conduct High sensitivity but low specificity Some rare tumor histologies, such as neuroendocrine tumor, can also result in p16 overexpression
Cell blocks from fine needle aspiration (FNA)	p16 overexpression by immunohistochemistry staining	Requires enough tumor cells Less reliable than p16 staining on FFPE

p16 staining as surrogate marker, preferably performed on tissue blocks over FNA
For equivocal p16 staining, confirmation with PCR or ISH is recommended

summarizes HPV testing methods which can be used for the detection of HPV-positive tumors, of which p16 staining is generally accepted as a reliable surrogate marker for HPV-driven OPC, if appropriately scored and interpreted. Strong and diffuse p16 immunohistochemistry staining indicates an HPV+ OPC and does not require further confirmation, while patchy or weak p16 staining requires further HPV testing (El-Naggar and Westra 2012; Thomas and Primeaux 2012; Shi et al. 2009).

Although p16 is an acceptable surrogate marker for HPV-driven OPC, it is not a reliable marker for non-OPC cases (Zafereo et al. 2016; Chung et al. 2014; Maxwell et al. 2010). Confirming the presence of oncologically relevant HPV E6/E7 DNA in tumor is required for HPV-driven tumor in non-OPC (Bishop et al. 2015; Young et al. 2015).

11.8 Staging of HPV+ OPC

Although HPV+ and HPV– OPC are two different diseases, presently they are still classified by the same TNM staging system (UICC/AJCC 7th edition TNM). Convincing evidence exists that the current TNM staging system (7th edition) (Dahlstrom et al. 2013; Huang et al. 2015b; Keane et al. 2016; O'Sullivan et al. 2016) is not adequate for HPV+ OPC. An HPV+ OPC-specific new TNM stage classification has been proposed (Huang et al. 2015b) and refined and validated in a multicenter dataset (O'Sullivan et al. 2016) which combined N1-N2b into N1 category and collapsed T4a and T4b into only a T4 category. Table 11.3 presents the TNM classification for HPV+ OPC introduced by the UICC/AJCC 8th edition TNM.

Table 11.3 TNM classification for HPV+ OPC introduced in the 8th edition UICC/AJCC TNM

HPV(+) OPC stage			
Stage I	T1, T2	N0, N1	M0
Stage II	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: N-category in the proposed TNM for HPV+ OPC: • N0: no involved lymph node • N1 (7th edition N1, N2a, N2b): unilateral neck lymph node(s), all <6 cm • N2 (7th edition N2c): bilateral or contralateral neck lymph node(s), all <6 cm • N3: >6 cm lymph node(s)

11.9 Treatment of HPV+ OPC

HPV+ OPC patients have much better outcomes compared to their HPV– counterparts. However, current treatment guidelines do not differentiate HPV+ OPC from HPV– OPC. Since the majority (>90%) of HPV+ OPC patient present with lymph node metastasis, they are typically treated with chemoradiotherapy. Although treatment outcomes are exemplary for HPV+ OPC with this approach, it carries significant cost. Too often, patients suffer severe sequelae from anatomic dysfunction in the head and neck regions, in additional to potential other relevant consequences, including renal, hearing, hematological, and neurocognitive impairment.

Since HPV+ OPC patients are younger with expected long-term survival, current clinical trials are exploring treatment deintensification for low-risk patients, while novel approaches are warranted for high-risk patients (Bhatia and Burtness 2015). These deintensification strategies include reducing radiotherapy dose and volume, reducing or omitting chemotherapy, and integrating minimally invasive surgery, such as trans-oral robotic surgery (TORS) or trans-oral laser microsurgery (TLM) into treatment algorithms for T1–T2 disease (Nichols et al. 2013; Wierzbicka et al. 2015; Masterson et al. 2014; Mirghani et al. 2015). For high-risk patients, novel intensive treatment approaches, such as immunotherapy, are being considered.

11.10 Counseling HPV+ Patient and Family

HPV+ OPC is a fast rising disease entity. Due to unfamiliarity and lack of knowledge, there are many stigmata and myths that surround this disease. Healthcare professionals must be sensitive, knowledgeable, and honest when discussing the diagnosis of this disease with patients and his/her family members. Fakhry et al. (Fakhry and D'Souza 2013) have provided useful answers to some frequently asked questions.

When a patient is given a diagnosis of HPV+ OPC, he/she could face many psychosocial stresses and anxiety. Patient often feels guilty, is concerned about infecting others, and is afraid of being blamed for infidelity. It is important to let patients know that trans-oral HPV infection is common and often acquired many years previously. Oral sex is also not the only means of contacting HPV infection. Although trans-oral HPV infection is a sexually transmitted disease (STD), HPV+ OPC is not an STD since HPV+ OPC patients are not contagious. This is because HPV DNA integration into host cells often occurs many years prior to diagnosis and can take decades to develop cancer after initial infection. Therefore, active HPV infection at the time of tumor diagnosis is unlikely. This is supported by evidence that partners of HPV+ OPC patients do not have a higher incidence of oral HPV infection com-

pared to the general population (D'Souza et al. 2014). This observation should also ease putative concerns of increased occupational exposure to HPV infection when otolaryngologists are examining HPV+ OPC patients.

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Chapter 12
Advocacy for Recurrent Respiratory Papillomatosis

Bill Stern and Susan Woo

A dictionary definition of an advocate is "a person who works for a cause or group," and advocacy is "active support, especially for a cause." The following key paragraph excerpted from the RRPF mission statement provides a more focused definition as it pertains to RRP: "The Recurrent Respiratory Papillomatosis Foundation (RRPF) was created to provide patient/family support, serve as an information resource for patients and practitioners, promote public awareness, and aid in the prevention, cure and treatment of RRP by encouraging and participating in promising RRP research studies." It is this statement which has served as a basis for RRP advocacy since 1992 when the RRP Foundation was founded.

Before delving into the details of specific advocacy efforts, it seems reasonable to discuss the motivation for the existence of an RRP advocacy organization. As with most rare diseases, the patient and family of RRP patients experience overwhelmingly difficult situations trying to find knowledgeable medical personnel familiar with the care and treatment of the disease. Breathing symptoms, which are typically part of early-age diagnosis of juvenile-onset RRP (JORRP), are often not immediately recognized as a sign of RRP so as to delay a proper diagnosis. (We have heard this from many RRP parents and certainly this was our personal experience.) The problem is that RRP is sufficiently rare that most pediatricians have never seen a case, so they will assume the breathing issues are being caused by croup, bronchitis, or asthma. Finally, after ruling out those possibilities, the pediatrician hopefully refers the case to an otolaryngologist, who hopefully can identify the airway obstruction as RRP. The family is typically shocked to learn that their child

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has a disease that they never heard of and don't know anyone else with this disease. For adult-onset RRP (AORRP), the diagnosis process differs, since voice hoarseness is typically the main symptom, and quickly ruling out cold-related laryngitis should allow for a more timely diagnosis by an otolaryngologist. However, the shock of learning that you have this rare disease is similar for the AORRP patient – both are left with a feeling of having to face RRP alone. It is a somewhat better situation if the diagnosing otolaryngologist is associated with a major medical center with experience in treating RRP, but there still is this need to interact with others who are dealing with similar situations. They want to share disease experiences, i.e., find out how RRP is affecting the lives of others and learn how and where other patients and families are being treated. It was this unfilled need that motivated the founding of the RRP Foundation in 1992.

In late 1992, in an effort to reach out to RRP families, hard copies of the *RRP Newsletter* premier issue (Stern and Stern 1992) were disseminated via regular mail (internet and email were just starting to be used but at that time very rarely by the medical community) to a number of otolaryngology departments at major medical centers around the country, requesting that they distribute copies to their RRP patients. The initial advocacy efforts of the RRP Foundation are outlined in these paragraphs excerpted from this RRP Newsletter issue:

> … Our desire to learn about the experience of others who are coping with similar situations, has motivated us to initiate this newsletter. We hope this will serve to bring into mutual contact, families who have had their lives affected by this very difficult disease (i.e., a support network).
>
> There are two main objectives in this first issue. First, to compile a list of names, addresses, telephone numbers, electronic mail addresses, etc. This list would be made available *only* to those names on the list. The second objective is to get an idea of how this disease has progressed and how it is affecting the lives of the patients and families involved. In this regard we have included a questionnaire. If you wish to remain anonymous just omit your names and addresses. All information relating disease specifics and patient names will remain confidential, i.e., any published information based on this questionnaire will *not* include names ….

What started as a support network of RRP families has evolved into an organization that advocates over a wide range of RRP principles and issues. Although getting RRP patients and families "talking" with one another is very important from an emotional support perspective, the RRPF realized that providing informational support to the RRP community was equally important. Patients and parents had many questions. Some of the more frequently asked are "How did I (my child) get this disease?" "How many surgeries will I (my child) have to endure?" "Will this disease ever end?" "Will my (my child's) voice ever be normal?" "Where are the best places to get treated for RRP?" "Are there nonsurgical and natural treatments for this disease?" "Where can I get help with some of the expenses related to this disease?" If one is fortunate enough to be located near a major medical center that treats a number of RRP patients, they may be able to get some answers based on the center's experiences treating their own patients. Unfortunately, many RRP patients are treated by local otolaryngologists who may have only seen a few RRP patients in

their entire career and are not familiar enough with the disease to provide the answers to most of these questions. What started as a very simple survey to help connect RRP families and get an overview of how they were being affected by this disease has evolved into a rather comprehensive questionnaire that attempts to detail the epidemiology as well as some of the quality of life impacts of RRP.

The survey design consists of four parts:

1. Patient history and current disease status
2. Surgical/adjuvant treatment history
3. Voice outcomes
4. Complications/costs/social/economic issues

Some statistics compiled from questionnaires completed by patients and parents are shown in Tables 12.1, 12.2, 12.3, 12.4, and 12.5. Tables 12.1 and 12.2 present some statistics associated with the symptomatic and epidemiological presentation of RRP. Many RRP patients and parents inquire about nonsurgical approaches that may put this disease in remission or at least allow for fewer surgical procedures.

Table 12.1 Disease symptoms

Hoarseness	590 (80.2%)
Breathing disorder	266 (36.1%)
Swallowing disorder	130 (17.7%)
Voice abnormality	541 (73.5%)
Breathing abnormality during exercise	308 (41.8%)
Breathing abnormality at rest	234 (31.8%)
Active papilloma growth	544 (73.9%)

Table 12.2 Sites of involvement

Above the vocal cords	295 (40.1%)
At the level of vocal cords	597 (81.1%)
Trachea	136 (18.5%)
Bronchi	59 (8.0%)
Lung	32 (4.3%)
Oral cavity	7 (1.0%)
Other head/neck regions	2 (0.3%)

Table 12.3 Adjuvant therapy outcomes – changes in voice quality

Adjuvant therapy	No. of patients	0–12 months pre-start of adjuvant therapy	0–12 months post-start adjuvant therapy	12–24 months post-start adjuvant therapy
DIM	59	59 Good 10 (16.9%) Fair 23 (39.0%) Poor 26 (44.1%)	53 Good 18 (34.0%) Fair 19 (35.8%) Poor 16 (30.2%)	38 Good 13 (34.2%) Fair 16 (42.1%) Poor 9 (23.7%)
Cidofovir	97	97 Good 15 (15.5%) Fair 34 (35.1%) Poor 48 (49.5%)	82 Good 26 (31.7%) Fair 31 (37.8%) Poor 25 (30.5%)	74 Good 22 (29.7%) Fair 28 (37.8%) Poor 24 (32.4%)

Table 12.4 VQOL: parents of children < 12 years old

Question	1	2	3	4	5(worst)
My child has trouble speaking loudly or being heard in noisy situations	4	3	8	12	11
My child runs out of air and needs to take frequent breaths when talking	11	11	7	7	2
My child sometimes does not know what will come out when he/she begins speaking	13	9	11	3	1
My child is sometimes anxious or frustrated (because of his/her voice)	8	7	6	10	7
My child sometimes gets depressed (because of his/her voice)	16	10	5	3	4
My child has trouble using the telephone or speaking with friends in person (because of his/her voice)	8	7	10	5	6
My child has trouble doing his/her job or schoolwork (because of his/her voice)	17	8	6	4	2
My child avoids going out socially (because of his/her voice)	24	4	5	1	3
My child has to repeat himself/herself to be understood	4	5	6	10	13
My child has become less outgoing (because of his/her voice)	19	6	5	3	4

Table 12.5 VQOL: patients > 17 years old

Question	1	2	3	4	5(worst)
I have trouble speaking loudly or being heard in noisy situations	10	9	11	27	29
I run out of air and need to take frequent breaths when talking	24	20	17	17	6
I sometimes do not know what will come out when I begin speaking	20	14	19	18	13
I am sometimes anxious or frustrated (because of my voice)	12	13	19	19	22
I sometimes get depressed (because of my voice)	20	18	16	16	15
I have trouble using the telephone or speaking with friends in person (because of my voice)	18	15	17	20	16
I have trouble doing my job or practicing my profession (because of my voice)	17	9	22	19	18
I avoid going out socially (because of my voice)	32	15	14	13	10
I have to repeat myself to be understood	14	17	16	24	15
I have become less outgoing (because of my voice)	23	19	13	18	12

Statistics from one of the survey questions addresses this by asking for an assessment of voice quality before and after trying various RRP adjunctive therapies. In Table 12.3, voice quality assessment statistics are presented for two adjuvant RRP treatments that are quite different, yet the voice outcome statistics are fairly close, i.e., both DIM and cidofovir show similar significant percentage increases in "good" voice quality as well as similar percentage decreases in "poor" voice quality. So armed with this information, the RRP patient advocate is able to have an intelligent conversation with their treating physician about the possibility of trying DIM, which

is a much more benign and easy to administer treatment than the potent antiviral cidofovir. With voice impairment being the most common symptom of RRP, it is possible to use voice quality assessments as an indicator of how this disease is impacting a patient's quality of life. In 2012, Dr. Hartnick and Dr. Rodgers [personal communication] developed a voice quality of life (VQOL) survey for RRP that was originally designed by Boseley et al. (2006), for more general pediatric voice disorders. This RRP VQOL survey was adapted for and included as part of the RRPF patient questionnaire to get a sense of how much impact RRP is having on a patient's ability to pursue a "normal" life. Tables 12.4 and 12.5 show a compilation of responses to the VQOL section of the RRPF patient questionnaire for pediatric patients (parents' responses) and adult patients, respectively. It is interesting to note that for most of the VQOL questions, the responses appear statistically similar. However, there are apparent differences in the distribution of responses for two questions, i.e., there is more depression among adult RRP patients than juvenile, and adults with RRP appear to have more difficulty doing their jobs than juvenile patients have doing their school work. In summary, the RRPF patient questionnaire has helped to understand how this disease is impacting RRP patients and families from medical, social, occupational, and emotional perspectives.

So, if the disease appears to be controlled, i.e., the papilloma tumors remain in the upper respiratory area, then patient advocacy is focused on referring RRP families/patients to otolaryngologists with significant RRP experience/expertise and directing patients to alternative approaches that potentially offer improved disease management. These adjunct therapies may serve to augment the patient's existing standard treatment of papilloma tumor removal procedures. Often the RRP patients find that these alternatives therapies have helped to stall the disease progression and to ameliorate the symptoms (see Fig. 12.1 RRP Foundation Home Page "RRP Patients link").

A key starting point for developing an RRP doctor referral database was to include those practitioners who are members of the RRP Task Force (Armstrong et al. 1999). In order to provide RRP families with additional RRP practitioner contact information, the database has been expanded via referrals from several sources including:

1. RRPF medical advisors
2. RRP practitioners themselves contacting the RRPF via the RRPF website practitioner survey and email
3. RRP patients/families providing referrals for others with RRP via the RRPF email LISTSERV and RRPF Facebook page.

Fear and frustration are common emotions that the RRP patient and caretakers' face. As the patient and his family gains knowledge of this disease, there are the emotional/psychological dimensions, which warrant more attention. In this regard, Jennifer Woo, former RRPF President, carried out a special advocacy project to explore the psychosocial impact of RRP. During the summer of 2005, she spent several months traveling coast to coast across the United States, interviewing patients and families in their homes, and, as Jennifer Woo stated in 2006, "immersing myself

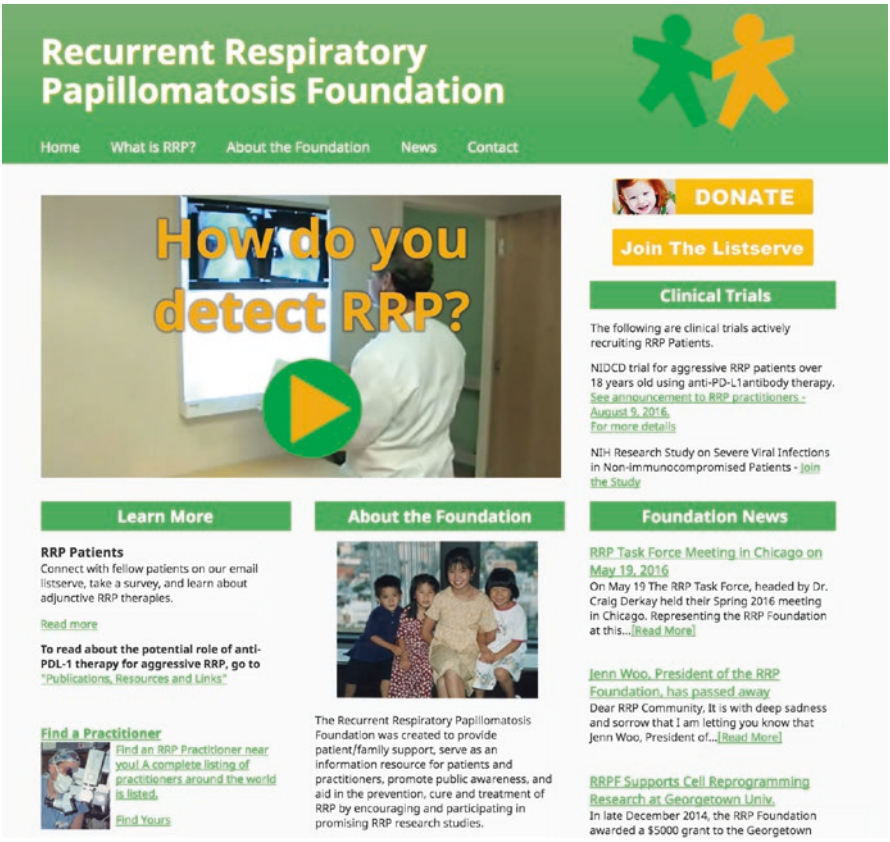

Fig. 12.1 RRPF website home page

in the lives of these individuals as a participant-observer." Additionally, Jennifer met with several clinicians and researchers in their clinical settings in order to provide an "ethnography of the RRP patient, research and care provider community".

An issue that often arises on the various RRP-related Internet platforms is "how did I get this disease" or "how did my child get this disease." Indeed there is some social stigma associated with this disease. There is a shame factor that cannot be ignored. Since HPV is acquired sexually, the etiology of the disease may affect the patients and their primary caretakers' view of the disease and how vocal they are in explaining this condition to their friends and families and ultimately to how they may react to the medical treatments offered by their physicians. There is the perception that if RRP is juvenile-onset, then the patient is an innocent victim of the disease or a victim of an accident in contracting this disease, while in adult-onset cases, it may have been acquired through oral sexual contact. There is a huge shame factor involved when discussing sexually transmitted diseases. The way the patients and primary caretakers' perceive their role in disease acquisition may play a large part in how proactive they are in seeking further knowledge about RRP

and ultimately making better medical treatment choices in allaying its progression. In light of innate prejudices toward sexually transmitted diseases, it is even more important that advocacy organizations be more visible and more involved in the public discussion in all aspects of this disease. Greater awareness will bring greater public understanding of the need for prevention such as promoting HPV vaccination in children before they become sexually active. If there is any doubt as to the negative attitude toward sexually transmitted diseases, one can only be astounded at the wide public objection to the HPV vaccine when it was presented several years ago as a necessary addition to the panel of childhood vaccines. Despite all these HPV acquisition issues, as an advocacy organization, it is most important to remind RRP families that the focus should be on "defeating the enemy," i.e., the HPV virus, and not necessarily the derivation.

Perhaps one of the most difficult RRP advocacy situations is providing support and guidance for those patients with deep respiratory involvement, particularly those who have papilloma in the lungs. With upper respiratory RRP, vigilant surveillance of the disease through removal of the papilloma tumors from the airway typically controls the disease. However, once the disease progresses into the pulmonary area, surgery to remove papillomas is often not a viable option, presenting significant challenges to both the patient and their practitioner. At this point, the focus changes from surgical and medical removal of the papilloma tumors to vigilant surveillance in order to monitor further progression and possible transformation of the disease. This ongoing assessment of the disease progression might require further medical expertise from a new set of medical experts, i.e., interventional radiologists, interventional pulmonologists, thoracic surgeons, or even oncologists, if the disease has transformed into cancer. Hence, advocating for the RRP patient diagnosed with papilloma in the lungs presents the challenge of finding experienced physicians willing to treat and accommodate the special needs of these pulmonary RRP patients.

In 2009 an effort was launched by the RRP Foundation (spearheaded by Jennifer Woo) to improve advocacy for these most afflicted RRP patients (pulmonary involvement occurs in perhaps 5% of RRP patients but represents at least 95% of the mortality associated with this disease). It was targeted to solving the greatest RRP research challenge, i.e., new treatment approaches for pulmonary RRP (see Woo and Stern 2009). This "Pulmonary Papilloma Research Initiative (PPRI)" was designed with two major goals:

1. To foster research into pulmonary papillomatosis by providing funds to young investigators in the field of pulmonology, otolaryngology, and thoracic surgery
2. To fund a pilot project which may lead to long-term research support from other granting agencies

Since the 2009 PPRI initiative, a significant grant was awarded in late 2011 to study the development of a therapeutic vaccine for RRP, and additional funding support has been provided for RRP/HPV cell reprogramming research in late 2014.

A current overview of advocacy efforts for RRP patients is depicted in Fig. 12.2, i.e., the front page of the RRP Foundation brochure. The full two-page brochure is

Fig. 12.2 RRPF brochure overview of RRP advocacy efforts

available as a link from the RRPF website "publications and resources" section at http://rrpf.org/publications-and-resources/. The brochure lists a number of links that provide up-to-date information about RRP, including surgical treatment approaches, adjunctive therapies, clinical trials, new RRP research directions, and an RRP educational/awareness video. Additionally, the RRPF email LISTSERV has been a key forum for RRP patients and families to share disease information and express their concerns. The LISTSERV has also served to network patients with RRP physicians and researchers, as a number of RRP professionals are LISTSERV subscribers.

It is the goal of advocates to address all the needs of patients. As an advocacy organization, the RRPF has strived to do so. However, there is still significant work to be done, particularly for those patients with very aggressive disease and those with deep respiratory involvement. In an effort to find better treatment options for these (any other) RRP patients, the RRPF is continuing the PPRI, originally launched in 2009, by encouraging new research efforts. In addition, the RRPF is forming a pulmonary papilloma working group, with the stated mission as, "To find medical treatment and, ultimately, a cure for pulmonary RRP, by aggressively working across government, private and not-for-profit organizations, while providing support for pulmonary RRP patients and families." Among a number of objectives is to develop and manage a registry of physicians who have had significant experience in treating pulmonary RRP. In addition, by working with other groups associated with HPV of the head/neck and lungs, we can make the public more aware that

RRP is another disease associated with HPV. It is our hope that with heightened public awareness of RRP and other HPV-related disease, there will be much greater compliance in vaccinating children to prevent HPV, which could eventually eliminate RRP in future generations.

Acknowledgments We would like to dedicate this chapter to the former president of the RRPF, Dr. Jennifer Woo, who passed away at the age of 31 after battling pulmonary RRP. In addition to being an RRP patient herself, she devoted much of her short life to advocating for other RRP patients.

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