

# **RRP Medical Reference Service**

**An RRP Foundation Publication**

**edited by**

**Dave Wunrow and Bill Stern**

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## Preface

The *RRP Medical Reference Service* is intended to be of potential interest to RRP patients/families seeking treatment, practitioners providing care, micro biological researchers as well as others interested in developing a comprehensive understanding of recurrent respiratory papillomatosis.

This issue focuses on a selection of references with abstracts from recent (2004 and later) RRP related publications. These listings are sorted in approximate reverse chronological order as indicated by the "PMID" numbers. Each listing is formatted as follows:

Journal or reference  
Title  
Language (if it is not specified assume article is in English)  
Author(s)  
Primary affiliation (when specified)  
Abstract  
PMID (PubMed ID)

If copies of complete articles are desired, we suggest that you request a reprint from one of the authors. If you need assistance in this regard or if you have any other questions or comments please feel free to contact:

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## RRPF Selected Articles and Abstracts

*Laryngoscope. 2004 Nov;114(11, PART 2):1-23.*

### **Recurrent Respiratory Papillomatosis: A Longitudinal Study Comparing Severity Associated With Human Papilloma Viral Types 6 and 11 and Other Risk Factors in a Large Pediatric Population.**

Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L.

From the Department of Pediatric Otolaryngology (b.j.w., l.l.), Children's Hospital of Alabama, and the Department of Biochemistry and Molecular Genetics (t.r.b.), University of Alabama at Birmingham, Birmingham, Alabama, U.S.A.

**OBJECTIVES/HYPOTHESIS::** A database was developed for prospective, longitudinal study of recurrent respiratory papillomatosis (RRP) in a large population of pediatric patients. Data recorded for each patient included epidemiological factors, human papilloma virus (HPV) type, clinical course, staged severity of disease at each surgical intervention, and frequency of surgical intervention. The study hypothesizes that patients with HPV type 11 (HPV-11) and patients younger than 3 years of age at diagnosis are at risk for more aggressive and extensive disease. **STUDY DESIGN::** The 10-year prospective epidemiological study used disease staging for each patient with an original scoring system. Severity scores were updated at each surgical procedure. **METHODS::** Parents of children with RRP referred to the authors' hospital completed a detailed epidemiological questionnaire at the initial visit or at the first return visit after the study began. At the first endoscopic debridement after study enrollment, tissue was obtained and submitted for HPV typing using polymerase chain reaction techniques and in situ hybridization. Staging of disease severity was performed in real time at each endoscopic procedure using an RRP scoring system developed by one of the authors (B.J.W.). The frequency of endoscopic operative debridement was recorded for each patient. Information in the database was analyzed to identify statistically significant relationships between extent of disease and/or HPV type, patient age at diagnosis, and selected epidemiological factors. **RESULTS::** The study may represent the first longitudinal prospective analysis of a large pediatric RRP population. Fifty-eight of the 73 patients in the study underwent HPV typing. Patients infected 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, patients with HPV-11 RRP were significantly more likely to develop tracheal disease, to require tracheotomy, and to develop pulmonary disease. Patients receiving a diagnosis of RRP before 3 years of age had significantly higher severity scores, higher frequencies of surgical intervention, and greater likelihood of requiring adjuvant medical therapy. Patients with Medicaid insurance had significantly higher severity scores and required more frequent surgical debridement. Birth by cesarean section appeared to be a significant risk factor for

more severe disease and necessity of more frequent surgical intervention. CONCLUSION:: Statistical analysis of the relationships among epidemiological factors, HPV type, and clinical course revealed that patients with HPV-11 and patients younger than 3 years of age at RRP diagnosis are prone to develop more aggressive disease as represented by higher severity scores at endoscopic debridement, more frequent operative debridement procedures per year, a greater requirement for adjuvant therapy, and greater likelihood of tracheal disease with tracheotomy.

PMID: 15514560

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*Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2002 Mar;16(3):109-10.*

### **[Evaluating the impact of human papilloma virus infection on prognosis of juvenile laryngeal papilloma]**

[Article in Chinese]

Chen X, Tan Y, Li Z, Wu J.

Department of Otolaryngology, First Affiliated Hospital, Wenzhou Medical College, Wenzhou 325000.

OBJECTIVE: To evaluate the relationship between human papilloma virus (HPV) and pathological characteristics of juvenile laryngeal papillomas (JLP). METHOD: Using polymerase chain reaction protocol, we analyzed paraffin embedded tissue in 25 cases of juvenile laryngeal papilloma and determined the HPV type. RESULT: A total HPV infection positive rate was 96%, and HPV11 positive rate was 56%, HPV6 positive rate was 40%. None of all was positive for HPV16, 18, 33, 71% of patients need tracheotomy in HPV11 infection group, and 30% of patients need tracheotomy in HPV6 infecting group. The post-operation relapse rate in HPV11-positive group was 86% ,and in HPV6-positive group was 40%. CONCLUSION: Juvenile laryngeal papilloma is associated with HPV11, HPV6 infection and we considered that HPV11 infection may be the important guideline of the evaluation of disease prognosis.

PMID: 15510659

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*Can Respir J. 2004 Sep;11(6):443-6.*

### **Interferon treatment of multiple pulmonary malignancies associated with papilloma virus.**

Aaron S, Wong E, Tyrrell D, Duggan M, Vallieres E, Jewell L, Romanowski B, Doe PJ.

University of Alberta, Edmonton, Canada.

Over a period of four years, beginning in spring 1988, a previously healthy man developed a primary squamous cell carcinoma of the tonsil, treated with radiotherapy, followed by 10 distinct, primary bronchial squamous cell carcinomas. Four of the cancers were surgically resected, all of which were positive by hybridization for human papilloma virus (type 16). Following the institution of alpha interferon, three smaller lesions disappeared and a larger one shrank in size, facilitating surgical resection. Over the following seven years no new ones have appeared. The finding of papilloma virus in malignancies should prompt consideration of antiviral therapy.

PMID: 15510252

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*Laryngoscope. 2004 Nov;114(11):1906-1909.*

### **Integration of Human Papillomavirus Type 11 in Recurrent Respiratory Papilloma-Associated Cancer.**

Reidy PM, Dedo HH, Rabah R, Field JB, Mathog RH, Gregoire L, Lancaster WD.

From the Department of Otolaryngology (p.m.r., r.h.m.), Wayne State University, Detroit, MI; the Department of Otolaryngology (h.h.d.), University of California San Francisco, San Francisco, CA; the Department of Pathology (r.r.), Wayne State University, Detroit, MI; the Center for Molecular Medicine and Genetics (j.b.f.), Wayne State University, Detroit, MI; and the Department of Immunology/Microbiology (l.g.), Wayne State University, Detroit, MI, U.S.A.

**OBJECTIVES/HYPOTHESIS::** The main objective was to demonstrate that human papillomavirus (HPV) type 11 is an aggressive virus that plays a significant role in the development of laryngeal cancer in patients with a history of recurrent respiratory papillomatosis (RRP). We have done so by preliminary investigation into the molecular mechanism underlying the malignant transformation of RRP to invasive squamous cell carcinoma. **STUDY DESIGN::** An experimental, nonrandomized, retrospective study using tissue specimens from nine patients with a history of RRP that progressed to laryngeal or bronchogenic cancer was performed. **METHODS::** DNA and RNA were extracted from 20 formalin-fixed, paraffin-embedded specimens from six patients with a history of early onset RRP and laryngeal cancer and from three patients with early onset RRP and bronchogenic

cancer. Polymerase chain reaction (PCR) was performed on DNA to determine the HPV type in each specimen. Reverse-transcriptase PCR specific for virus transcripts was performed on RNA to determine whether the viral genome was integrated into the host genome.

**RESULTS::** HPV-11 but not HPV-6, 16, or 18 was found in all of the laryngeal and bronchogenic cancers in patients with a history of early onset RRP in this study. RNA, sufficiently intact for examination, was obtained from seven patients. Analysis of HPV 11 transcripts revealed integration of the viral genome in three of seven patients.

**CONCLUSIONS::** HPV type 6 and 11 are considered "low-risk" viruses and are not associated with genital cancers, as are HPV types 16 and 18. However, our data suggests that HPV type 11 is an aggressive virus in laryngeal papilloma that should be monitored in patients with RRP.

PMID: 15510012

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*Rev Assoc Med Bras. 2004 Jul-Sep;50(3):252-6. Epub 2004 Oct 21.*

### **[Human papillomavirus (HPV) infection and its relation with squamous cell carcinoma of the mouth and oropharynx]**

[Article in Portuguese]

Tinoco JA, Silva AF, Oliveira CA, Rapoport A, Fava AS, Souza RP.

Departamento de Cirurgia de Cabeça, Pescoco, e Otorrinolaringologia, Hospital Heliópolis, São Paulo, SP.

**OBJECTIVE:** To establish a connection between infection by the human papilloma virus (HPV) and development of malignant (squamous cell carcinoma) and benign lesions (epithelial hyperplasia papillomatosis and papilloma) of the oral cavity and oropharynx.

**METHOD:** A retrospective study of 66 blades and paraffin blocks with biopsy tissue fixed with formalin. This material, collected in 2002, refers to a group of 44 men (66.7%) and 22 women (33.3%) with ages ranging from 11 to 100 years, with confirmed diagnoses of squamous cell carcinoma in 38 cases, of epithelial hyperplasia papillomatosis in 20 cases and of papillomas in 8 cases. This material was analyzed by immunohistochemistry and the presence of viral DNA in the biopsy samples was determined. **RESULTS:** Presence of the viral DNA (HPV) in 16 of the 38 cases of carcinoma (42.5%), 19 in 20 cases of hyperplasia (95%) and 8 in 8 cases of papilloma (100%) was detected. **CONCLUSION:** The samples in this study show the predominant incidence of the HPV in the epithelial hyperplasia papillomatosis and papilloma in relation to squamous cell carcinoma. This last lesion, on the other hand, did not show statistical correlation to the HPV.

PMID: 15499474

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*Expert Rev Anti Infect Ther.* 2003 Jun;1(1):21-43.

## **Potential of acyclic nucleoside phosphonates in the treatment of DNA virus and retrovirus infections.**

De Clercq E.

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The acyclic nucleoside phosphonates [HPMPC: cidofovir, Vistide; PMEAs: adefovir dipivoxil, Hepsera; and PMPA: tenofovir, Viread] have proven to be effective in vitro (cell culture systems) and in vivo (animal models and clinical studies) against a wide variety of DNA virus and retrovirus infections, for example, cidofovir against herpesvirus [herpes simplex virus type 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus type 6, 7 and 8], polyoma-, papilloma-, adeno- and poxvirus (variola virus, cowpox virus, vaccinia virus, molluscum contagiosum virus and orf) infections; adefovir against herpesvirus, hepadnavirus [human hepatitis B virus] and retrovirus [HIV type-1 and 2, simian immunodeficiency virus and feline immunodeficiency virus] infections; and tenofovir against both hepadna- and retrovirus infections. Cidofovir has been officially approved for the treatment of cytomegalovirus retinitis in AIDS patients, tenofovir disoproxil fumarate (Viread) for the treatment of HIV infections (i.e., AIDS) and adefovir dipivoxil for the treatment of chronic hepatitis B.

PMID: 15482100

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*Rev Laryngol Otol Rhinol (Bord).* 2004;125(2):107-12.

## **[Laryngeal papillomatosis in adults: report on 4 cases]**

[Article in French]

Lazrak A, Nazih N, Filali AA, Kzdri M.

Hopital des Specialites, Instituts, Service ORL, BP 6220, Rabat, Maroc. lazna56@yahoo.fr

Laryngeal papillomatosis is well-known as one part of benign lesions of the larynx in children under 15 years. Cases of papillomatosis are extremely rare in adults. OBJECTIVES: To report our experience about 4 cases. MATERIAL AND METHOD: It concerns 3 females and 1 male, who are in good health and without any disease in relation of upper respiratory tract or viruses. For all patients there is no familiar viral disease (especially cutaneous or genital). The age of patients is between 28 and 72 years. All clinical signs at the diagnosis aren't specific and are observed in other laryngeal diseases. Direct micro-laryngoscopy is

mandatory in order to establish the right diagnosis and to perform the first stage of local treatment. Micro-instruments are used to remove these benign nipple-like without CO2 laser or local medicines or injections. RESULTS: Our study mentions a frequent association of gastro-oesophageal reflux (3 cases). The average follow-up is 5 years and half and in this period, there is no malignant evolution. CONCLUSION: The authors also review the literature and in particular the potential cause of laryngeal papillomatosis and new ideas on treatment of this unusual condition.

PMID: 15462170

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*Cornea. 2004 Oct;23(7):726-9.*

### **Adjunctive treatment with interferon alpha-2b may decrease the risk of papilloma-associated conjunctival intraepithelial neoplasm recurrence.**

Chen HC, Chang SW, Huang SF.

Department of Ophthalmology, Chang-Gung Memorial Hospital, Taoyuan, Taiwan.

PURPOSE: To report a case of bilateral papilloma virus-positive conjunctival intraepithelial neoplasm and the treatment results of using adjunctive interferon alpha-2b. METHODS: Case report and literature review. RESULTS: A 73-year-old man underwent subtotal excisional biopsy of the 270-degree gelatinous limbal lesion of the right eye to avoid creating a limbal deficiency and cicatricial change. Total excisional biopsy of the temporal elevated leukoplakic limbal lesion was performed on his left eye. Histology examination showed bilateral intraepithelial neoplasia, and human papilloma virus-16 and -18 were detected by polymerase chain reaction in both lesions. Two supplemental perilesional injections of interferon alpha-2b in the right eye were given, and the residual mass decreased in size gradually and completed clinical resolution 7 weeks following initial surgery. Although no recurrence was noticed in the right eye, recurrence of the conjunctival intraepithelial neoplasm lesion was noticed in the left eye. CONCLUSION: Adjunctive therapy might lower CIN recurrence rate, especially in extensive lesions, when surgical excision cannot ensure a tumor-free margin. Our bilateral case provided a good control example for the recurrence with or without adjunctive therapy.

PMID: 15448502

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*Arch Otolaryngol Head Neck Surg. 2004 Sep;130(9):1043-5.*

### **STAT3 activation in recurrent respiratory papillomatosis.**

Patel NJ, Hansen A, Merati AL, Kerschner JE.

Division of Laryngology, Department of Otolaryngology and Communication Sciences,

Medical College of Wisconsin, Milwaukee, USA. napatel@mcw.edu

**BACKGROUND:** The activation of signal transducer and activator of transduction (STAT) protein is thought to lead to the genesis of neoplasia by promoting cellular growth and preventing apoptosis, and by immune system modulation; STAT3 protein has also been implicated in tumor survival and propagation in recurrent respiratory papillomatosis (RRP). **OBJECTIVES:** To investigate the presence and activation of STAT3 protein in papilloma specimens from subjects with RRP and compare findings with those obtained from control subjects' tissue. **DESIGN:** Laryngeal papilloma samples were collected from 8 nonselected consecutive patients undergoing surgery for RRP, and control samples of anterior tonsillar pillar mucosa were collected from 8 patients undergoing adenotonsillectomy. After extraction, we applied gel shifting to the nuclear protein using an electromobility shifting assay kit. Quantitative analysis of the gel shifts was performed, and levels of activated STAT3 protein in RRP specimens and tissue from controls were compared. **RESULTS:** There was STAT3 protein activation in the nuclear extracts of all (100%) RRP specimens, which was significantly more frequent than in normal epithelial tissue from controls ( $P < .03$ ). **CONCLUSIONS:** We conclude that STAT3 protein activation is present in RRP. However, further study is needed to determine if STAT3 protein activation is an important pathway through which human papillomavirus results in the propagation and persistence of RRP.

PMID: 15381590

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*Arch Otolaryngol Head Neck Surg.* 2004 Sep;130(9):1039-42.

### **American Society of Pediatric Otolaryngology members' experience with recurrent respiratory papillomatosis and the use of adjuvant therapy.**

Schraff S, Derkay CS, Burke B, Lawson L.

Eastern Virginia Medical School and the Children's Hospital of the King's Daughters, Norfolk, VA 23507-1914, USA.

**OBJECTIVE:** To evaluate how evolving treatment technologies have affected our management of recurrent respiratory papilloma (RRP) since the last comprehensive survey of pediatric otolaryngologists in 1998. **DESIGN:** Web-based survey of all American Society of Pediatric Otolaryngology members residing in the United States, Canada, Europe, and Australia. **RESULTS:** Evaluable survey results were tabulated from 74 practitioners in 62 separate practices managing 700 current children with RRP. A total of 150 (21%) of these patients presently receive adjuvant medical therapies with cidofovir and interferon, accounting for more than two thirds of the total. Sixty-one percent of patients treated with cidofovir have experienced a beneficial response. Distal spread of RRP has occurred in 94 (13%) of the 700 patients. Half of the practices surveyed have experienced a death from RRP, with 89% of deaths directly related to RRP. The laryngeal microdebrider (53%) has supplanted the carbon dioxide laser (42%) as the preferred means of surgically removing

papilloma from the larynx in children. Spontaneous, apneic, and jet ventilation (88%) anesthesia techniques have replaced the use of laser-safe endotracheal tubes (10%) as the preferred anesthetic management. Routine human papillomavirus subtyping is practiced by 45% of respondents while 15% treat all their patients with antireflux medications. Half of respondents send lesions for histologic examination only if there is a change in growth pattern while one third send lesions with every surgery. CONCLUSIONS: Recurrent respiratory papilloma continues to be a frustrating disease to treat and is associated with significant morbidity and mortality. There has been an evolution in the past decade toward the increased use of antiviral adjuvant therapy and the use of microdebrider techniques for surgical management.

PMID: 15381589

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*Otolaryngol Head Neck Surg.* 2004 Sep;131(3):327-9.

### **Recurrent laryngeal papillomas in identical twins.**

Pearson SE, Choi SS.

Children's National Medical Center, Washington, DC, USA. [spearson@cnmc.org](mailto:spearson@cnmc.org)

No abstract available.

PMID: 15365556

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*Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2004 Jun;18(6):353-4.

### **[Malignant change of laryngeal papilloma in adults]**

[Article in Chinese]

Wang M, Teng Q, Yao C, Zheng Z.

Department of Otolaryngology, the Third Affiliated Hospital of Xinxiang Medical College, Henan Province, Xinxiang, 453003, China.

OBJECTIVE: To explore the canceration of laryngeal papilloma in adults, especially its pathological figures, clinical characters and long-term therapeutic efficacy. METHOD: Among 17 cases of laryngeal papilloma with malignant changes, total laryngectomy and single functional neck dissection were performed for 4 cases (glottis type T3 N1 M0 1, Supraglottic type T4 N0 M0 1, Subglottis type T4 N1 M0 2), partial laryngectomy were performed for other 13 cases. All patients received appropriate radiotherapy whose dose is

45-55 Gy. RESULT: Tracheal cannulas of all patients (17 cases) were pull out one year after operation. The rate of extubation is 100%. All patient were follow-up more than 5 years. Among 4 cases of total laryngectomy, one patient died from tumor recurrence 2 years after operation, one patient died from distant metastasis 3 years and 4 months after operation, two patients still alive without tumor 8 years after operation and voicing by using esophagus. Among 13 cases of partial laryngectomy, 12 patients still alive and 1 patient loss follow-up 3 years after operation; 11 patients still alive and 1 patient died from distant metastasis 5 years after operation. CONCLUSION: It is important that repeatedly biopsies to avoid fail to report the malignant change of laryngeal papilloma. The key to cure is complete resection of tumor.

PMID: 15354780

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*Nippon Jibiinkoka Gakkai Kaiho. 2004 Jul;107(7):690-4.*

### **[Congenital laryngeal stridor]**

[Article in Japanese]

Morimoto N, Kawashiro N, Tsuchihashi N, Taiji H.

Department of Otolaryngology, National Center for Child Health and Development, Tokyo.

We reviewed the diagnosis, complications and treatment of congenital laryngeal stridor (CLS), in 97 patients who consulted our clinic between 1991 and 2001. The 97 patients were diagnosed with laryngeal malacia (32%), vocal cord paralysis and laryngeal stenosis (22%), a neoplastic disease like hemangioma and papilloma (11%), or cystic disease (7%). The cases with vocal cord paralysis, laryngeal stenosis or laryngeal cysts were usually diagnosed within 2 months of birth based on severe dyspnea. Two of the 31 cases of laryngeal malacia and 2 of the 22 cases of vocal cord paralysis were associated with neuromuscular disorders. Three patients suffered from vocal cord paralysis complicated by laryngeal stenosis. Thirty-three of the 97 cases required a tracheostomy; these 33 cases included the one case of laryngeal papilloma (100%), 9 of the 10 cases of hemangioma (90%), and 18 of the 24 cases of laryngeal stenosis (75%). Since any disorders of the upper airway can potentially induce stridor, establishing an accurate diagnosis is sometimes difficult when stridor is the only presenting symptom. Hence, information on associated symptoms and the past history of the subject is particularly important for an accurate diagnosis. In addition, decisions regarding the course of treatment course require adequate consideration of possible complications.

PMID: 15346896

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*Hum Immunol.* 2004 Aug;65(8):773-82.

**HLA alleles, IFN-gamma responses to HPV-11 E6, and disease severity in patients with recurrent respiratory papillomatosis.**

Bonagura VR, Vambutas A, DeVoti JA, Rosenthal DW, Steinberg BM, Abramson AL, Shikowitz MJ, Gjertson DW, Reed EF.

Division of Allergy and Immunology, North Shore-Long Island Jewish Research Institute, Department of Pediatrics, Long Island Jewish Medical Center, New Hyde Park, New York, USA. bonagura@lij.edu

Recurrent respiratory papillomatosis (RRP) remains an immunologic enigma. Human papillomavirus (HPV) types 6 and 11 are the predominant HPV viruses that cause papilloma development. However, it is unclear why only a very small fraction of HPV-exposed individuals develop RRP. We performed high-resolution HLA class I and II genotyping on 70 randomly selected patients (56 Caucasians and 14 African-Americans) with RRP. We report, for the first time, an increased frequency of HLA-DRB1\*0102 in Caucasian patients with RRP, suggesting that this allele predisposes individuals to RRP. Additionally, HLA-DRB1\*0301, DQB1\*0201, and DQB1\*0202 alleles were selectively enriched in Caucasians with severe disease, suggesting that these alleles may regulate disease severity. In contrast, HLA-DQB1\*0602 was more frequent in controls than in Caucasians with severe disease, suggesting a severity-sparing effect of this allele. Furthermore, both DQB1\*0201 and DQB1\*0202 were enriched, whereas DQB1\*0602 was absent, in African-Americans. Interestingly, HLA-DRB1\*0301 and DQB1\*0201 correlated with reduced interferon-gamma expression in patients with RRP. Larger studies are needed to identify other class II major histocompatibility complex alleles that may influence disease predisposition, disease severity, or both, especially in African-American patients, to ultimately illuminate the regulatory effects of these alleles in the predisposition and severity of RRP.

PMID: 15336778

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*Otolaryngol Head Neck Surg.* 2004 Jul;131(1):44-9.

**Preliminary report of endolaryngeal and endotracheal laser surgery of juvenile-onset recurrent respiratory papillomatosis by Nd:YAG laser and a new fiber guidance instrument.**

Janda P, Leunig A, Sroka R, Betz CS, Rasp G.

Department of Otorhinolaryngology, Ludwig-Maximilians University, Munich, Germany.  
philip.janda@gmx.de

**OBJECTIVES:** Recurrent respiratory papillomatosis (RRP) caused by human papilloma virus (type 6 and 11) is the most common benign neoplasm of the larynx in children. Despite being a benign disease, treatment is very difficult and is characterized by frequent recurrence, spread throughout the respiratory tract, and malignant degeneration. Besides surgical resection and the established CO<sub>2</sub> laser treatment, laser surgery by fiber-guided Nd:YAG laser light promises to be a bloodless and effective treatment procedure. To improve this new method, a novel fiber guidance instrument has been developed to aid in endolaryngeal laser surgery of RRP. **Study design and setting** The method described uses a specially designed instrument for fiber guidance that is equipped with a bendable distal tip to move the fiber end precisely. Moreover, the instrument includes an additional channel for the suction of smoke and pyrolysis products. Up to now, 5 patients (aged 4 to 8 years) with RRP were treated by Nd:YAG laser light ( $\lambda = 1064 \text{ nm}$ ; power, 10 W; irradiance, 3.5 kW/cm<sup>2</sup>, continuous wave) with a prototype version of the new instrument and were followed up for 12 months each. **RESULTS:** Because of the adequate length and the bendable distal tip with a range of -5 degrees up to 45 degrees to the optical axis of the fiber and less than 10% light loss at maximal deflection, RRP can be treated by Nd:YAG laser light easily and precisely. The continuous suctioning ensured an optimum view of the operating field and a minimal load of potential infectious laser plume and toxic pyrolysis products for the patient as well as for the physician. The laser treatment of RRP with the new fiber guidance instrument was only minimally traumatic. During 1-year follow-up visits, all Nd:YAG laser light-treated patients, showed a regression of the disease. **CONCLUSIONS:** The new fiber guidance instrument enables a precise and easy treatment of the RRP with fiber-guided laser systems (eg, Nd:YAG-, diode-, and KTP-lasers) and an effective removal of infectious laser plume as well as toxic pyrolysis products. A follow-up period of 1 year revealed that Nd:YAG laser surgery seems to prevent a rapid recurrence of juvenile respiratory papillomatosis in the treated patients.

PMID: 15243556

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*J Natl Cancer Inst. 2004 Jul 7;96(13):998-1006.*

### **Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus.**

Braakhuis BJ, Snijders PJ, Keune WJ, Meijer CJ, Ruijter-Schippers HJ, Leemans CR, Brakenhoff RH.

Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands. [bjm.braakhuis@vumc.nl](mailto:bjm.braakhuis@vumc.nl)

**BACKGROUND:** Transcriptionally active high-risk human papilloma viruses (HPVs), particularly HPV type 16 (HPV16), are found in a subset of head and neck squamous-cell carcinomas (HNSCCs). HPV16-associated carcinogenesis is mediated by expression of the viral E6 and E7 oncoproteins, which cause deregulation of the cell cycle by inactivating p53

and pRb, respectively. We tested the hypothesis that HPV-associated HNSCCs display a pattern of genetic alterations different from those of HNSCCs without HPV DNA.

**METHODS:** Polymerase chain reaction-based assays were used to examine 143 consecutive HNSCCs (106 of the oral cavity and 37 of the oropharynx) for the presence of HPV DNA and for viral E6 and/or E7 messenger RNA (mRNA) expression. The HPV DNA- and E6 and E7 mRNA-positive HNSCCs and an equal number of HPV DNA-negative HNSCCs were further analyzed for mutations in TP53, the gene encoding p53, and for allelic loss of 28 microsatellite markers at chromosome arms 3p, 6q, 8p, 9p, 13q, 17p, and 18q, including markers located in regions of chromosome arms 9p and 17p that harbor genes involved in the p53 and pRb pathways. All statistical tests were two-sided. **RESULTS:** Twenty-four (16.7%) of the 143 HNSCCs were positive for HPV16 DNA, and 12 of these HNSCCs (8.4% of total number) expressed E6 and E7 mRNAs. None of the HPV DNA- and E6/E7 mRNA-positive tumors had TP53 gene mutations, whereas nine (75%) of the 12 HPV DNA-negative tumors had such mutations ( $P < .001$ ). Compared with the HPV DNA-negative HNSCCs, the E6/E7 mRNA-positive HNSCCs had statistically significantly lower levels of allelic loss for 13 of the 15 markers on 3p, 9p, and 17p. **CONCLUSIONS:** HNSCCs with transcriptionally active HPV16 DNA are characterized by occasional chromosomal loss, whereas HNSCCs lacking HPV DNA are characterized by gross deletions that involve whole or large parts of chromosomal arms and that already occur early in HNSCC development. These distinct patterns of genetic alterations suggest that HPV16 infection is an early event in HNSCC development.

PMID: 15240783

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*Am J Otolaryngol.* 2004 Jul-Aug;25(4):282-4.

### **Respiratory epithelial adenomatoid hamartoma associated with nasal polyposis.**

Delbrouck C, Fernandez Aguilar S, Choufani G, Hassid S.

Department of ENT, Hopital Erasme, Universite Libre de Bruxelles, Brussels, Belgium.

Hamartoma is a rare, non-neoplastic tumor characterized by an abnormal mixture of tissues, which are indigenous to the region. They are rare in the nasal cavity. We report a 79-year-old woman with an adenomatoid hamartoma in the left nasal cavity associated with nasal polyposis. This association supports the hypothesis that inflammation is one of the factors that induce the development of a hamartoma. Functional endoscopic sinus surgery was performed to completely remove it, and this lesion was found to have arisen from the lateral nasal wall. It is an unusual localization because the most common site in the nasal cavity is the nasal septum, particularly the posterior aspect. Limited but complete surgical resection is the treatment of choice. Although adenomatoid hamartoma arising from the sinonasal tract is very rare, head and neck surgeons should be aware of this pathological entity as a differential diagnosis for inverted papilloma and adenocarcinoma. Misinterpretation of these lesions as a

true neoplasm may result in unnecessarily aggressive surgery for this benign lesion.

PMID: 15239039

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*Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2004 Mar;18(3):154-6.*

**[Expression of human papillomavirus and pRb in head and neck squamous cell carcinoma]**

[Article in Chinese]

Chen B.

Department of Otolaryngology, the Second Hospital of Shandong University, Jinan, 250033, China.

**OBJECTIVE:** The purpose of this study was to examine the interrelationship between human papilloma virus (HPV) and retinoblastoma protein (pRb) in patients with squamous cell carcinoma of the head and neck (SCCHN). **METHOD:** Archival material from 33 oropharynx, 40 oral cavity was selected for study based on the availability of tissue from the primary tumors prior to surgery. HPV detection was done using general primer GP5 (+)GP6(+) mediated PCR enzyme immunoassay (PCR-EIA) and typed with type-specific probes. Monoclonal antibodies specific for pRb was used for immunohistochemical detection of Rb protein in these primary tumors. **RESULT:** HPV DNA was detected in 12.3% of tumors. All were HPV 16 DNA. When stratified, 18.0% of oropharyngeal cancers was positive compared with 7.5% of oral cavity tumors; pRb negative was 12.3%. HPV positive patients tended to present with a higher stage and lymph node metastasis. In spite of the higher stage at presentation, survival in patients with HPV positive and pRb negative SCCHN was significantly longer than that of HPV-negative patients. **CONCLUSION:** Patients with HPV-positive tumors may have a survival advantage relative to patients with HPV-negative tumors. This indicates that HPV-positive and pRb-negative tumors are sensitive to radiotherapy.

PMID: 15222267

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*Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2004 Mar;18(3):152-4.*

**[Clinical application of laryngeal endoscopy in the minimally invasive surgery of laryngeal diseases]**

[Article in Chinese]

Zou Y, Huang J, Zhang X, Liu Q, Li W, Peng S, Zhan S, Zeng Q.

Department of Otorhinolaryngology-Head and Neck Surgery, Guangdong Province 177 Hospital, Guangzhou, 510317, China.

**OBJECTIVE:** To study the value of laryngeal endoscopic system in the treatment of laryngeal diseases with minimally invasive surgery. **METHOD:** This paper was to summarized retrospectively the clinical experience of 34 cases suffered from laryngeal diseases treated by minimally invasive surgery with laryngeal endoscopic system. The remain tumor and hemorrhage were treated by microwave machine. The malignant tumors were treated by radiotherapy with  $^{60}\text{Co}$  in 40 Gy, postoperatively. **RESULT:** The tumors were totally resected and no serious complications were revealed. Followed-up these 34 cases, 26 cases with benign pathological changes who had hoarseness preoperatively recovered to normal 1-month after operation. In 2 cases with vocal cord carcinoma at the early stage, the functions and construction of throat were retained and no recurrence was founded after 6-12 month postoperatively. **CONCLUSION:** The laryngeal endoscopic system is valuable in treating laryngeal pathological regions and early stage carcinoma for its minimally invasion, wide operative field, good illuminative degree and normal construction and function reserved.

PMID: 15222266

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*Arch Otolaryngol Head Neck Surg.* 2004 Jun;130(6):711-6.

### **Clinical course of recurrent respiratory papillomatosis in Danish children.**

Silverberg MJ, Thorsen P, Lindeberg H, Ahdieh-Grant L, Shah KV.

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**OBJECTIVE:** To evaluate the clinical course of juvenile-onset recurrent respiratory papillomatosis (RP) with respect to age, disease duration, and maternal condylomas. **DESIGN:** Inception cohort study. **SETTING:** All ear, nose, and throat departments in public Danish hospitals. **PATIENTS:** Fifty-seven Danish children diagnosed with RP and born between 1974 and 1993 were observed for an average of 14 years after diagnosis. **MAIN OUTCOME MEASURE:** Removal of respiratory papillomas by knife biopsy, laser surgery, or cryotherapy. **RESULTS:** Children younger than 5 years diagnosed with RP underwent an average of 4.1 surgeries in the first year of disease, the highest rate among all our patients. The overall surgery rate decreased over time after initial diagnosis but remained significantly higher for children with a younger age of onset for the first 4 years of disease ( $P < .001$ ) and for children with a maternal history of condylomas in pregnancy for years 4 to 10 of the disease ( $P < .001$ ). We also observed an independent and statistically significant ( $P < .001$ ) decreasing surgery rate with increasing age and time from initial diagnosis. The trend for children with recurrent disease was a decreasing rate of surgical procedures (28 of 42 patients with recurrent disease); however, a third of patients (14/42) demonstrated a constant or

increasing rate of surgical procedures over time. CONCLUSIONS: The clinical course of RP is characterized by a high frequency of surgeries soon after diagnosis that diminishes over time and with increasing age. Additional studies are warranted to identify factors associated with cases that do not conform to the usual disease course.

PMID: 15210551

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*Curr Opin Mol Ther.* 2004 Apr;6(2):206-11.

### **Technology evaluation: HPV vaccine (quadrivalent), Aventis Pasteur MSD/CSL.**

Reinis M.

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CSL, licensee of UniQuest's HPV technology, and Aventis Pasteur MSD (a joint venture between Merck & Co and Aventis) are jointly developing a vaccine for the potential prophylaxis of genital warts and cervical cancer caused by human papilloma virus infection. Enrollment for a phase III trial has been completed.

PMID: 15195933

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*Ann Thorac Surg.* 2004 Jun;77(6):2201-2.

### **Human papillomavirus and squamous cell carcinoma in a solitary tracheal papilloma.**

Lam CW, Talbot AR, Yeh KT, Lin SC, Hsieh CE, Fang HY.

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We report the case of a 52-year-old woman suffering from breathlessness on exertion. A chest radiograph identified a lesion in the intrathoracic trachea. A tumor 0.4 x 0.5 x 0.7 cm in size causing an approximately 80% reduction in the cross-sectional area of the trachea 3 cm above the carina was removed, and histology showed moderately differentiated squamous cell carcinoma. Intrathoracic resection of the tumor and anastomosis was performed through a right lateral thoracotomy. The final histology examination showed atypical papilloma. Polymerase chain reaction-restriction fragment length polymorphism confirmed human papillomavirus-6b in the tumor. The patient remained well 18 months after surgical intervention without recurrence.

PMID: 15172304

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*West Afr J Med. 2004 Jan-Mar;23(1):91-3.*

**Recurrent respiratory papillomatosis mimicking retropharyngeal abscess in a Nigerian child.**

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Recurrent respiratory papillomatosis (RRP) is not an uncommon disease of the aero-digestive tract, usually involving points of narrowing. Involvement of the oropharynx, particularly when florid, may be easily confused with a retropharyngeal abscess. **STUDY DESIGN:** Case report of a 1 1/2 year-old child with florid pharyngeal RRP. **RESULTS:** The clinical presentation and features on radiography of this patient mimicked retropharyngeal abscess. The patient successfully had a preoperative tracheostomy and excision of the RRP. **CONCLUSION:** There was a diagnostic dilemma in this patient because of the identical features of the two conditions. A high index of suspicion and painstaking, careful clinical and radiological evaluation is the key to diagnosis and prompt definitive management.

PMID: 15171539

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*Curr Opin Otolaryngol Head Neck Surg. 2004 Jun;12(3):157-9.*

**Current treatment for laryngeal papillomatosis.**

Kendall KA.

No abstract available.

PMID: 15167022

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*Vestn Otorinolaringol. 2004(3):29-33.*

**[Prevalence of human papilloma virus types and their influence on the course of the disease in children suffering from recurrent respiratory**

**papillomatosis]**

[Article in Russian]

[No authors listed]

The type of human papilloma virus (HPV) was determined in 26 children aged between 1 year 10 months to 15 years 5 months suffering from recurrent respiratory papillomatosis (RRP). Polymerase chain reaction identified DNA of HPV type 6, 11, 16 and 18. HPV DNA was detected in all the patients including fifteen patients infected with HPV type 11; seven patients infected with HPV type 6; four children infected with HPV type 6 and 11. Types 16 and 18 of HPV were not detected. The analysis of RRP course has found that laryngeal papillomatosis runs a more aggressive course in cases with HPV type 11 infection than in those with HPV type 6.

PMID: 15159735

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*Cancer Gene Ther.* 2004 Jun;11(6):457-64.

**DNA vaccines against the human papillomavirus type 16 E6 or E7 oncoproteins.**

Wlazlo AP, Deng H, Giles-Davis W, Ertl HC.

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DNA vaccines expressing the E6 or E7 oncoproteins of human papilloma virus type 16 (HPV-16) in either their wild-type form or fused to sequences that affect intracellular trafficking were tested for induction of protective immunity against tumor cell challenge in two models based on BALB/c and C57Bl/6 mice. The DNA vaccines to E7 gave uniformly disappointing results, while the DNA vaccine that expressed E6 linked to a viral leader sequence protected BALB/c mice against tumor cell challenge given before or after vaccination. The efficacy of this vaccine could be enhanced by a DNA vector prime/viral vector boost regimen. In contrast, priming of mice with the DNA vaccines to E7 reduced the efficacy of a viral vector expressing the same antigen. Copyright 2004 Nature Publishing Group

PMID: 15118761

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*Ann Otol Rhinol Laryngol.* 2004 Apr;113(4):265-76.

**Office-based treatment of glottal dysplasia and papillomatosis with the 585-nm pulsed dye laser and local anesthesia.**

Zeitels SM, Franco RA Jr, Dailey SH, Burns JA, Hillman RE, Anderson RR.

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Treatment of glottal papillomatosis and dysplasia was mirror-guided and performed in surgeons' offices in the 19th century. It migrated to the operating room in the 20th century to accommodate direct laryngoscopic surgery, which required assistants to administer anesthesia and procedural support. Presently, the primary treatment goals, which are disease regression and voice restoration or maintenance, are tempered by the morbidity of general anesthesia and potential treatment-induced vocal deterioration. In fact, general anesthesia has been appropriately considered to be an acceptable source of morbidity for the promise of a precise procedure, which usually ensures airway safety and an optimal vocal outcome. However, patients with recurrent glottal papillomatosis and keratosis with dysplasia are typically monitored with various degrees of watchful waiting until there is a subjective judgment (on the part of the patient and surgeon) that the disease is more of a liability than is the procedure to treat it. Innovations in the 585-nm pulsed dye laser delivery system have allowed for its use in the clinic with local anesthesia through the working channel of a flexible fiberoptic laryngoscope. A prospective assessment was done on 51 patients in 82 cases of recurrent glottal papillomatosis (30) and dysplasia (52). All individuals had previously undergone microlaryngoscopic management with histopathologic evaluation. Five procedures could not be completed because of impaired exposure (2) or discomfort (3). Of those patients who could be treated, there was at least a 50% disease involution in 68 of 77 cases (88%) and 25% to 50% disease regression in the remaining 9 (12%). Patient self-assessment of the voice revealed that 34 of 77 were improved, 39 were unchanged, 4 were slightly worse, and none were substantially worse. These data confirm that diseased mucosa can be normalized without resection or substantial loss of vocal function. The putative mechanisms, which vary according to the fluence (energy) delivered by the laser, are photoangiolysis of sublesional microcirculation, denaturing of epithelial basement membrane linking proteins, and cellular destruction. Furthermore, this relatively safe, effective technique allowed for treatment of many patients (in a clinic setting) in whom classic surgery-related morbidity would have often delayed intervention.

PMID: 15112968

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*Otolaryngol Pol.* 2004;58(1):211-5.

**Human papillomavirus DNA presence of the upper respiratory tract mucosa of healthy children.**

Szydlowski J, Durzynski L, Myga M, Grzegorowski M, Gozdicka-Jozefiak A.

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The papillomaviruses are a group of small DNA (8 kbp) viruses which induce papillomas in human and animals. Most of them can also transform epithelial cells of human and other vertebrates. Examinations of children with Recurrent Respiratory Papillomatosis (RRP), using PCR method with specific primers, revealed HPV type 6 or/and 11 in 98%-100% tissue samples. Little is known about HPV infection in upper respiratory tract of healthy children. The group of 201 healthy children (from 3 to 10 years old) was laryngologically examined. The smears from noses and throats were studied for the presence of HPV viruses DNA. PCR was performed as described by Tucker et al. 28.8% of children from the study group were HPV positive. The presence of HPV in respiratory tract in children is relatively high. "High risk" HPV are not observed in the respiratory tract in children. The Human Papillomavirus in children may be transmitted by direct contacts.

PMID: 15101283

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*Int J Pediatr Otorhinolaryngol.* 2004 May;68(5):529-36.

### **Voice quality of prepubescent children with quiescent recurrent respiratory papillomatosis.**

Lindman JP, Gibbons MD, Morlier R, Wiatrak BJ.

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**OBJECTIVE:** The purpose of this study was to assess the long-term impact of recurrent respiratory papillomatosis (RRP) and its treatment on voice quality in prepubescent children. **STUDY DESIGN:** Case-control study. **METHODS:** Prepubescent children with RRP in remission for at least 12 [according to MM section] months were asked to participate. Remission was documented by absence of papillomas on fiberoptic flexible laryngoscopy. An age- and sex-matched control was selected for each patient enrolled. Voice was evaluated using the voice-related quality of life (V-RQOL) questionnaire, perceptual evaluations of voice quality by speech-language pathologists using the GRBAS (grade of hoarseness, roughness, breathiness, asthenia, strain) scale, and acoustic analysis (fundamental frequency, maximal phonation time, and relative average perturbation) using the Visi-Pitch II 3300. **RESULTS:** Medical records of 84 patients were reviewed and 15 met study criteria. Five agreed to participate but one was excluded due to the presence of papillomas. The four study patients and four matched controls were between 9- and 11-years old. On the V-RQOL questionnaire, each control rated V-RQOL as normal (10/50) and the average patient group score was within the normal range (11.5/50). On perceptual evaluations, the patient's voices were more hoarse, breathy, and rough compared to controls'. Acoustic analysis showed that

patients' voices had a lower average fundamental frequency (F(0)) (200 Hz compared to 243 Hz for controls) and a higher relative average perturbation (RAP) (1.10 compared to 0.77), although only one patient's voice actually had elevated RAP (2.89), which had a large impact on raising the average score for the patient group. The average maximal phonation times were similar for the two groups (7.8s for patients and 7.4s for controls) but lower than average normal scores reported in the literature. CONCLUSIONS: Although children with RRP do not perceive their voice quality to have a negative impact on V-RQOL, speech-language pathologist evaluations and acoustic measurements show objective differences between the voices of children with quiescent RRP and those of normal, healthy controls.

PMID: 15081224

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*Otolaryngol Pol. 2003;57(6):823-7.*

### **[The interaction of stilbazolium merocyanines with hyperproliferative laryngeal papilloma cells--preliminary study]**

[Article in Polish]

Szydlowski J, Cofta J, Wiktorowicz K, Grzegorowski M.

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Recently increasing interest focused in possible clinical application on photodynamic therapy was observed. Many scientists are looking for new chemical compounds effective in therapy and giving no side effects. Stilbazolium merocyanines belong to lipophilic dyes, binding to cell membranes. The aim of this study was to estimate the usefulness of the selected stilbazolium merocyanines to treatment on human recurrent respiratory papillomatosis. A patients group consisted of seven children, ages 10 months to 18 years, with moderate to severe recurrent disease. The patients were treated surgically. Tissue samples were analyzed for presence of Human papillomavirus (HPV). The incorporation of the dye into papillomas cells membranes was measured by flow cytometry. As a measure of fluorescence intensity the value "mean channel" was used. The hyperplastic tissue showed the highest fluorescence intensity than normal epithelium. Obtained results showed that continue to this preliminary studies is necessary.

PMID: 15049182

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*Zhonghua Er Bi Yan Hou Ke Za Zhi. 2003 Dec;38(6):421-5.*

**[Diagnosis and treatment of juvenile recurrent laryngeal papillomatosis]**

[Article in Chinese]

Wang HG, Lin XQ.

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**OBJECTIVE:** To evaluate some perplexing problems in the diagnosis and treatment of juvenil recurrent laryngeal papillomatosis (JRLP) and the relationship between juvenile onset recurrent respiratory papillomatosis(JORRP) and infantile laryngeal condyloma accuminatum (ILCA). **METHODS:** A group of 44 cases with JRLP were analyzed retrospectively from March, 1994 to March, 2002 in the light of literature review. **RESULTS:** The average age of first visit was 1.6 years. Average 5.3 operations had been performed per patient. There was an interval of average 2.4 months between two surgical excisions. Of 233 operations, the total incidence rate of all the complications was 3.9%. At present, the laryngeal lesion of 18 cases have withered away for over 1 year. 11 cases have being followed up. 10 cases have lost follow-up and 5 cases have died (11.4%). Combined laryngeal lesion excision with tracheotomy aiming at prolonging operative interval or Chinese traditional medicine has received more satisfactory effect than other therapies. There is an extensive similarity between JORRP and ILCA. **CONCLUSIONS:** To demondrate further whether JORRP and ILCA are the same identical disease has important significance in both theoretical study and clinic practice. The treatment for JRLP is still difficult. The tracheotomy for laryngeal obstruction resulted from the laryngeal lesion of JRLP should be avoided as far as possible. Combined laryngeal lesion excision with tracheotomy aiming at prolonging opertive interval or Chinese traditional medicine shows optimistic prospect.

PMID: 15040102

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*Med Wieku Rozwoj. 2003 Oct-Dec;7(4 Pt 1):495-502.*

**Mucosal immune response to Human Papilloma Virus (HPV) infection in HIV positive women.**

Agarossi A, Casolati E, Valieri M, Ferrazzi E, Maffeis G, Trabattoni D, Clerici M.

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Mucosal immunity plays a central role in the control of genital human papilloma virus (HPV) infection. HIV infection is associated with higher risks of HPV-induced neoplasias. Prevalence, incidence and evolution of genital HPV lesions are correlated with the level of immunodepression. Several changes of the local immune response in the genital tract of HIV

infected women have been demonstrated. The influence of HIV on the production of some immunoregulatory cytokines appears of particular interest. The shift from the helper T cells type 1 (Th1) to the helper T cells type 2 (Th2) immune response, which determines the downregulation of the cell-mediated immunity, may explain the frequent loss of immunologic control of HPV and its oncological complications

PMID: 15010560

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*Braz J Med Biol Res. 2004 Jan;37(1):83-8. Epub 2003 Dec 18.*

### **Estrogen and progesterone receptors in human papilloma virus-related cervical neoplasia.**

Coelho FR, Prado JC, Pereira Sobrinho JS, Hamada G, Landman G, Pinto CA, Nonogaki S, Villa LL.

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Estrogen (ER) and progesterone (PR) receptors in the normal uterine cervix, cervical intraepithelial neoplasia and invasive carcinoma were studied in consecutive samples from Hospital do Cancer, Sao Paulo, between 1996 and 1997. Tissue was collected by removing a fragment of the tumoral area using a 5-mm diameter biopsy punch, followed by removal of a macroscopically normal area as close as possible from the tumor. Histopathological confirmation was obtained for all specimens analyzed. A total of 24 normal tissues, 17 cases of cervical intraepithelial neoplasia and 7 of invasive carcinomas were studied. The ER/PR ratio was determined by immunohistochemistry using monoclonal antibodies specific for each receptor. Adjacent tissue slides were submitted to generic PCR for human papillomavirus (HPV) DNA detection followed by typing by dot blot hybridization. About half (45.8%) of the tumors were HPV DNA positive while 29.1% of the patients were also HPV positive in their respective normal tissue. ER was negative in the tumoral epithelium of 11 HPV-positive patients ( $P=0.04$ ). There was a trend in the ER distribution in normal tissue that was opposite to that from lesions, but it was not statistically significant ( $P=0.069$ ). No difference in ER distribution in stromal tissues was observed between HPV-positive and HPV-negative tissues. PR staining was negative in the epithelium of all cases studied. The results obtained from this small number of cases cannot be considered to be conclusive but do suggest that factors related to viral infection affect the expression of these ER/PR cervix receptors.

PMID: 14689048

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