Family Practice Oncology CME Day
November 18, 2017, Vancouver, BC

BC Cancer Agency
CARE + RESEARCH
*An agency of the Provincial Health Services Authority*

# HPV-RELATED CANCERS: ENCOURAGING EARLY DIAGNOSIS

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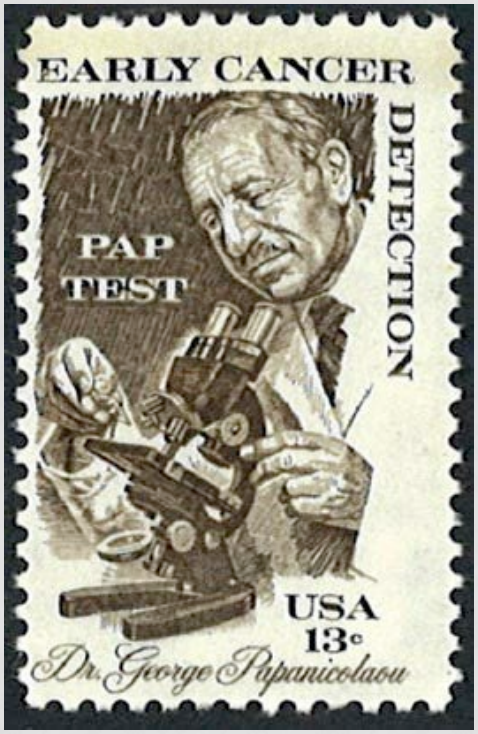
Radiation Oncologist

# OUTLINE

- Overview
- Epidemiology
- Risk Factors
- Biology & Carcinogenesis
- Early Diagnosis: approach to patients
- Frequently asked questions

# OVERVIEW: CERVICAL CANCER SCREENING

- George Nicholas Papanicolaou (1883-1962)
  - Immigrant from Greece, early work in human physiology as a lab technician at Cornell University Medical College
    - 1920s – focussed on cytopathology of human reproductive system
      - Found that malignant and normal cervical cells could be discerned from viewing a swab on microscopic slides
    - 1943 – collaberation with Dr. Herbert Traut, a gynecologic pathologist at New York Hospital resulted in publication of "Diagnosis of Uterine Cancer by the Vaginal Smear"
      - Described what is now the gold-standard screening test, the Pap smear
        - Simple, economical, effective
    - 1962 – died of myocardial infarction within 3 months of arriving at Miami Cancer Institute
      - Renamed Papinicolaou Cancer Research Institute
    - 1978 – honoured with commemorative postage stamp by US postal service



# OVERVIEW: CERVICAL CANCER SCREENING

- Canadian Task Force on Preventative Health:

| Age | Recommendation | Explanation | Grading of Recommendations* |
|---|---|---|---|
| 19 or younger | Do not routinely screen | Even without screening, the incidence of invasive cervical cancer is very rare (0.3 per 100,000 per year). If screened, 10% of women in this age group will have an abnormal Pap test, resulting in additional unnecessary tests (e.g. colposcopy, biopsy). | Strong recommendation; high quality evidence |
| 20-24 | Do not routinely screen | Even without screening, the incidence of invasive cervical cancer is about 3 per 100,000 per year. If screened, 10% of women in this age group will have an abnormal Pap test, resulting in additional unnecessary tests (e.g. colposcopy, biopsy). | Weak recommendation; moderate quality evidence |
| 25-29 | Routine screening every 3 years | The incidence of invasive cervical cancer increases after age 25. Without screening, the incidence is about 9 per 100,000 per year. Benefits of screening may begin to outweigh the harms (i.e. additional unnecessary tests, such as colposcopy and biopsy). | Weak recommendation; moderate quality evidence |
| 30-69 | Routine screening every 3 years | After age 30, the incidence of invasive cervical cancer increases significantly up to 35 per 100,000 per year without screening, while rates of abnormal Pap tests decline. Benefits of screening outweigh the harms (i.e. additional unnecessary tests, such as colposcopy and biopsy). | Strong recommendation; high quality evidence |
| 70 or older | Cease routine screening only if the last 3 Pap tests in the last 10 years were negative | There appears to be minimal additional benefit of continuing screening if Pap test results have been consistently negative. | Weak recommendation; low quality evidence |

*Recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. For more information on GRADE, visit the CTFPHC website: www.canadiantaskforce.ca

# OVERVIEW: CERVICAL CANCER SCREENING

- ACOG recommendations for management of abnormal pap smears:

| | *Ages 21–24* | *Ages 25–29* | *Ages 30 and Older* | |
|---|---|---|---|---|
| | | | *HPV Negative* | *HPV Positive* |
| Normal Pap test results | Routine screening: Pap test every 3 years | Routine screening: Pap test every 3 years | Routine screening: Preferred— Co-testing* every 5 years<br>Acceptable— Pap test alone every 3 years | Acceptable— Co-testing* in 12 months<br>Acceptable— HPV typing† |
| ASC-US | Preferred— Repeat Pap test in 12 months<br>Acceptable— Reflex HPV test‡ | Preferred— Reflex HPV test‡<br>Acceptable— Repeat Pap test in 12 months | Repeat co-testing* in 3 years | Colposcopy |
| LSIL | Repeat Pap test in 12 months | Colposcopy | Preferred— Repeat Pap test in 12 months<br>Acceptable— Colposcopy | Colposcopy |
| ASC-H | Colposcopy | Colposcopy | Colposcopy | Colposcopy |
| HSIL | Colposcopy | Immediate excisional treatment or colposcopy | Immediate excisional treatment or colposcopy | Immediate excisional treatment or colposcopy |
| AGC | AGC has several subcategories. The type of follow-up tests that are recommended depend on the AGC subcategory. Tests performed for follow-up include colposcopy, endocervical sampling, and endometrial sampling. | | | |

Abbreviations: ASC-H = atypical squamous cells, cannot rule out HSIL; ASC-US = atypical squamous cells of undetermined significance; AGC = atypical glandular cells; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

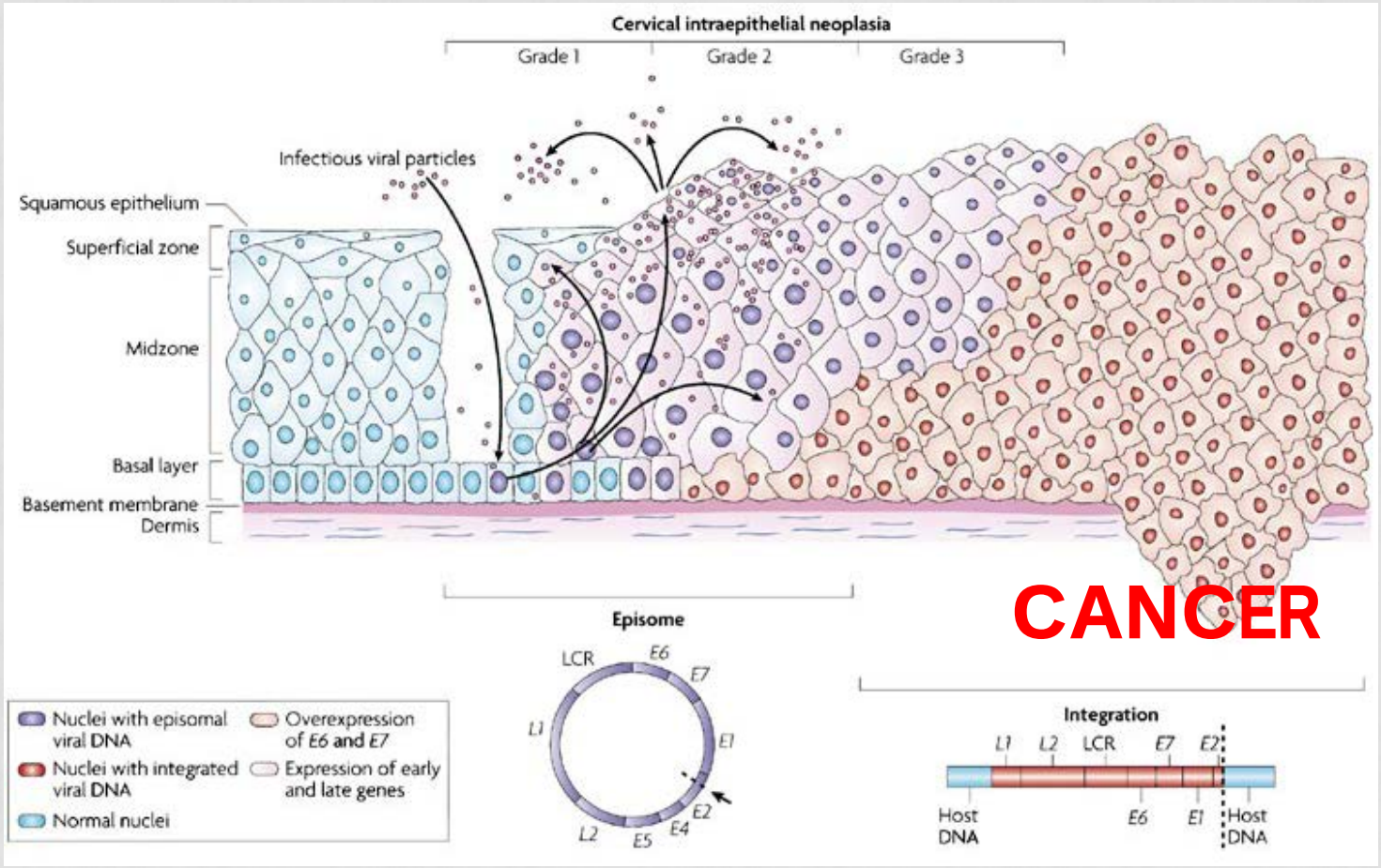
*Co-testing: Combined Pap test and HPV test

†HPV typing: A test for the presence of HPV type 16 and HPV type 18

‡Reflex HPV test: A test for the presence of high-risk HPV types using the sample used for a Pap test

# OVERVIEW OF HPV-ASSOCIATED CANCERS

- Discovery: Harold zur Hausen, Nobel Prize in Physiology or Medicine 2008
  - demonstrated in 1983 that cervical cancer in humans is caused by certain types of papilloma viruses (wart viruses), the genes from which are incorporated into the host cells' DNA




Nature reviews, 2007

# OVERVIEW OF HPV-ASSOCIATED CANCERS

- Cervical Cancer:
  - 4th most common cancer among women
    - HPV-16: 50% cases
    - HPV-18: 20%
    - Other serotypes: 19%
- Vulvar & Vaginal Cancer:
  - Uncommon globally
    - Estimated 60-80% are HPV-16 or -18 associated
- Penile Cancer:
  - Uncommon globally
    - Estimated 70-80% are HPV-16 or -18 associated
- Anal Cancer:
  - Relatively uncommon
    - Estimated 90% associated HPV-16 or -18 associated
- Oropharyngeal Cancer:
  - Increasing incidence…

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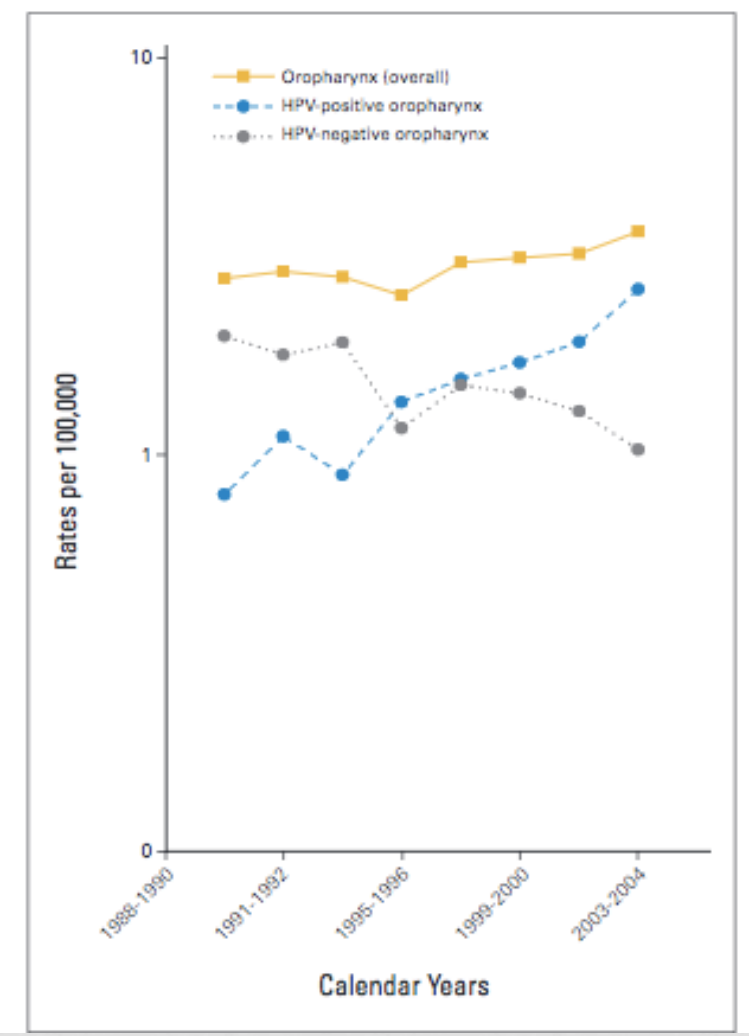
# EPIDEMIOLOGY OF HPV+ OROPHARYNGEAL CANCER

**Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States**

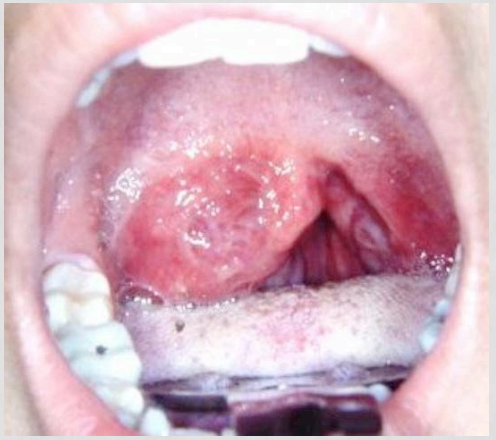
*Anil K. Chaturvedi, Eric A. Engels, Ruth M. Pfeiffer, Brenda Y. Hernandez, Weihong Xiao, Esther Kim, Bo Jiang, Marc T. Goodman, Maria Sibug-Saber, Wendy Cozen, Lihua Liu, Charles F. Lynch, Nicolas Wentzensen, Richard C. Jordan, Sean Altekruse, William F. Anderson, Philip S. Rosenberg, and Maura L. Gillison*

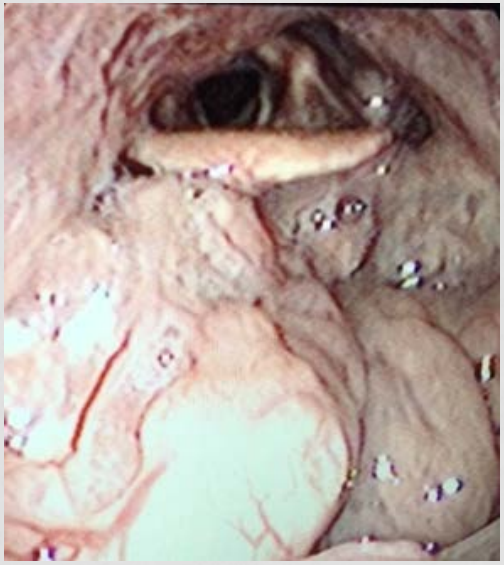
- Incidence is rising:
  - Increased by 28% 1988-2004
    - Largely because of increase in HPV-associated disease (up 225%)
    - HPV-unassociated oropharyngeal cancer is down 50% over same time period



# EPIDEMIOLOGY OF HPV+ OROPHARYNGEAL CANCER

- Gender distribution
  - M:F 3:1
- Higher socioeconomic status
- Age:
  - Bimodal, peaks ~ 30 & 55 yoa (5-10 years younger than HPV-)
- Anatomic location:
  - HPV-associated, usually arise at the Base of tongue/Tonsils
  - Easy access for infection



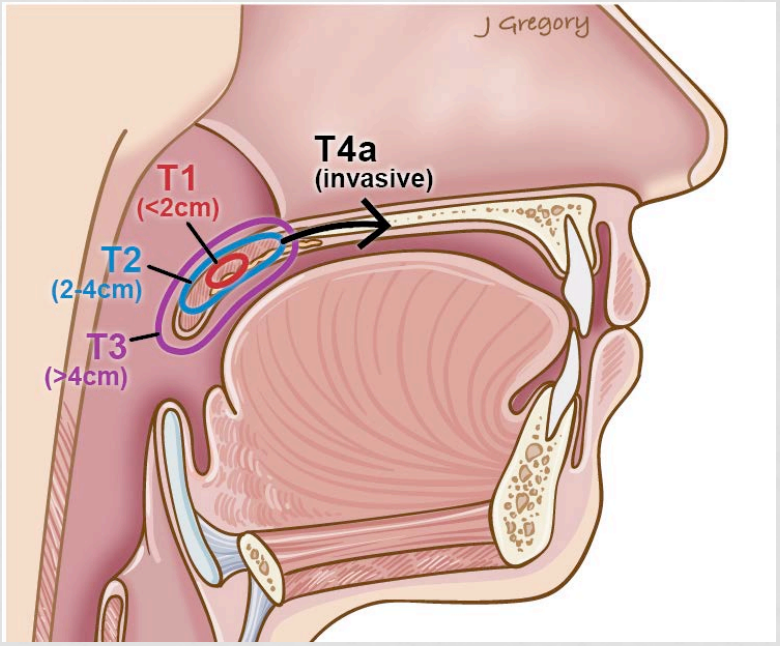


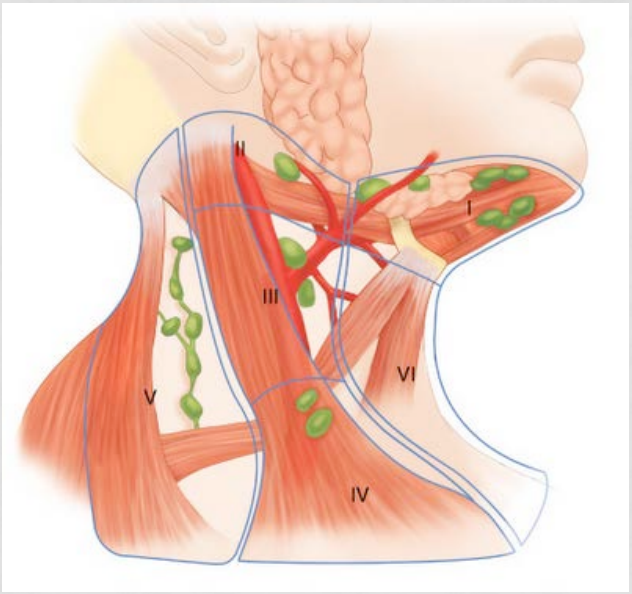
- BY 2020…
  - The annual number of HPV-positive OPSCCs (approximately 8,700 patients) will surpass the annual number of cervical cancers (approximately 7,700 patients) with the majority occurring among men (approximately 7,400).
- By 2030…
  - OPSCC will likely constitute a majority (47%) of all head and neck cancers.

Chaturvedi A K et al. JCO 2011

# EPIDEMIOLOGY OF HPV+ OROPHARYNGEAL CANCER

- Stage at presentation:
  - More likely early (T1-2)
  - Greater risk for more advanced disease in neck (N2-3)



# HPV & CANCER

**Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers**

*Maura L. Gillison, Wayne M. Koch, Randolph B. Capone, Michael Spafford, William H. Westra, Li Wu, Marianna L. Zahurak, Richard W. Daniel, Michael Viglione, David E. Symer, Keerti V. Shah, David Sidransky*

2000: Cancer tissues from 253 H&N Squamous cell cancers were analyzed for the presence of HPV by several methods

25% were HPV+: mostly oropharyngeal sites, less likely to be smokers/drinkers, with better prognosis

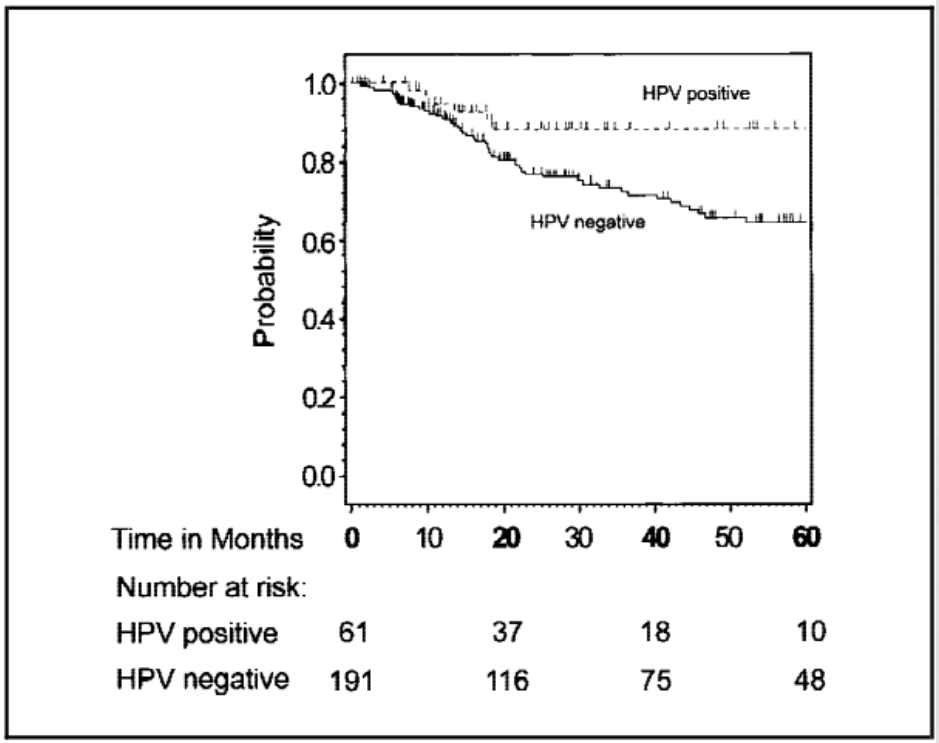



**Fig. 3.** Kaplan–Meier plot of disease-specific survival for head and neck squamous cell carcinoma patients with human papillomavirus (HPV)-positive and HPV-negative tumors. **Vertical ticks** represent censored events. Patients with HPV-positive tumors had significantly improved disease-specific survival when compared with patients with HPV-negative tumors (log-rank, chi-squared$_{(1\ df)}$ = 5.33; $P$ = .02).

# HPV & CANCER

The NEW ENGLAND JOURNAL of MEDICINE

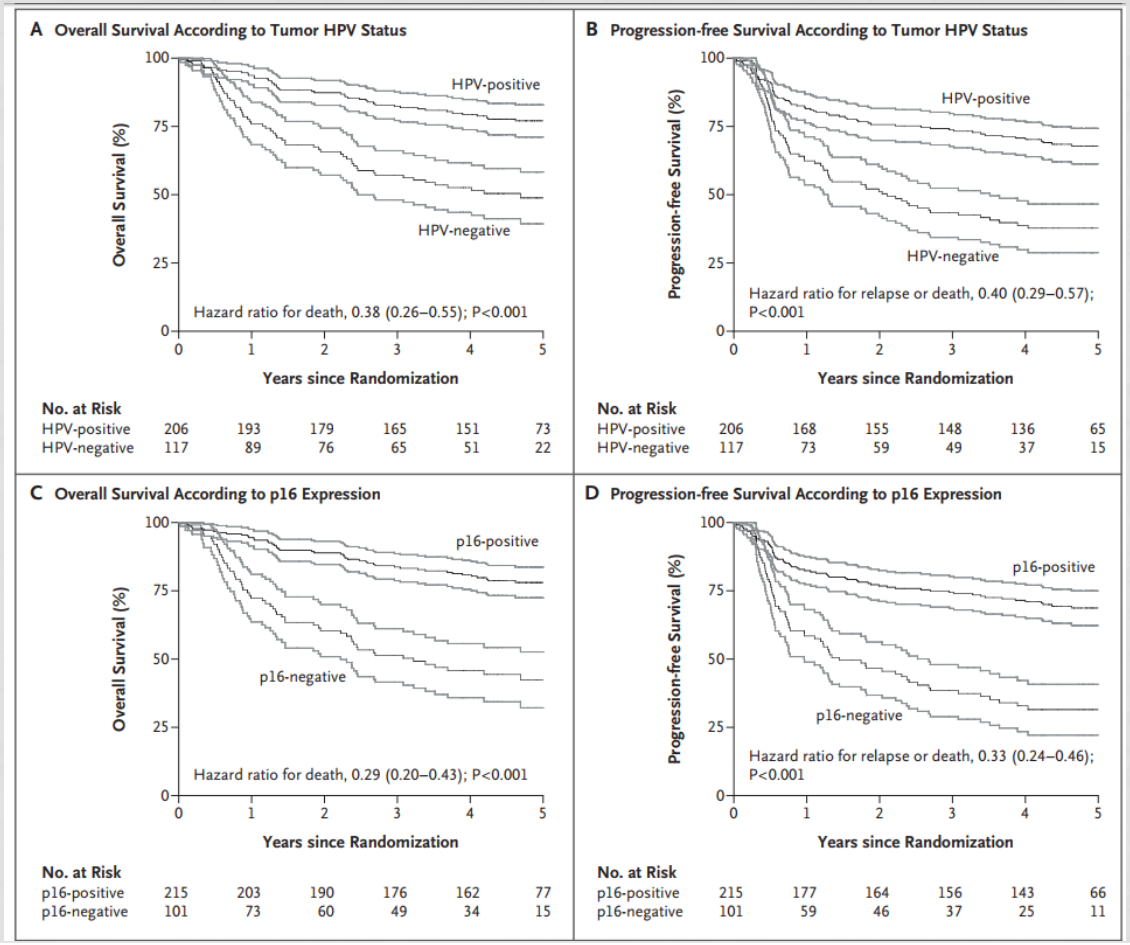
ORIGINAL ARTICLE

## Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

2010: Compared 2 radiotherapy schedules with concurrent chemotherapy, 323/433 patients had HPV+ oropharyngeal cancer

HPV+ OPC associated with several favourable prognostic factors: nonsmokers, younger age, better performance, smaller primary tumors



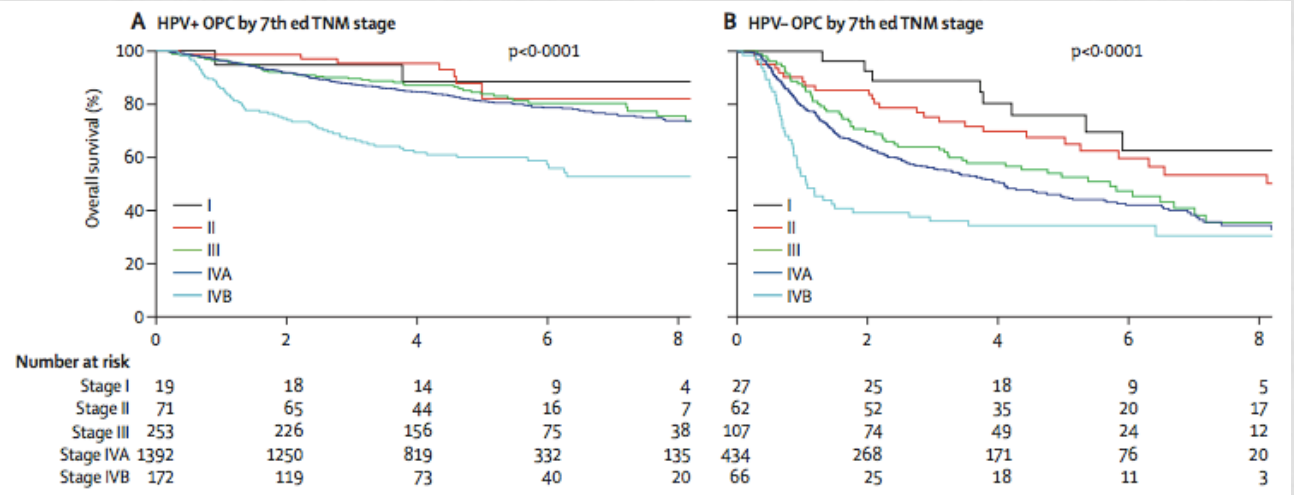
# HPV & CANCER

**Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study**

*Brian O'Sullivan, Shao Hui Huang, Jie Su, Adam S Garden, Erich M Sturgis, Kristina Dahlstrom, Nancy Lee, Nadeem Riaz, Xin Pei, Shlomo A Koyfman, David Adelstein, Brian B Burkey, Jeppe Friborg, Claus A Kristensen, Anita B Gothelf, Frank Hoebers, Bernd Kremer, Ernst-Jan Speel, Daniel W Bowles, David Raben, Sana D Karam, Eugene Yu, Wei Xu*

| ICON-S stage classification | T1 | T2 | T3 | T4 |
|---|---|---|---|---|
| N0 | I | I | II | III |
| N1 | I | I | II | III |
| N2 | II | II | II | III |
| N3 | III | III | III | III |

| Stage (7th Ed.) | HPV+ 5y OS | HPV- 5y OS |
|---|---|---|
| I | 88% | 76% |
| II | 82% | 68% |
| III | 84% | 53% |
| IVA<br>IVB | 81%<br>60% | 45%<br>34% |



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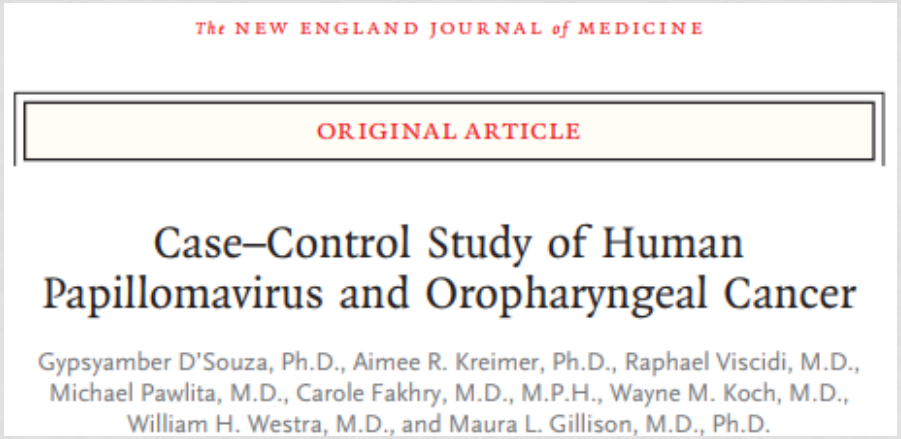
# RISK FACTORS



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

- Associated with sexual behaviours:
  - High number vaginal/oral sex partners
  - Infrequent condom use
  - Engagement in casual sex
  - Early age of first intercourse
- Other Risk Factors:
  - 80% without a smoking history
  - increased risk if coinfected with HIV

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# BIOLOGY & CARCINOGENESIS

- ds circular DNA virus
- High & Low-risk types:
  - Serotypes 16 & 18 most common in cancer
    - 2-4x risk of cancer with infection
  - HPV 16 = most common associate
    - present in >90% HPV-related oropharyngeal cancer (OPC)
      - 14-fold increase risk with infection
- latency of onset
  - probably >10 years from HPV exposure to development of OPC
  - most infections resolve in 6-12 months
  - can enter a latent stage

# HPV TRANSMISSION

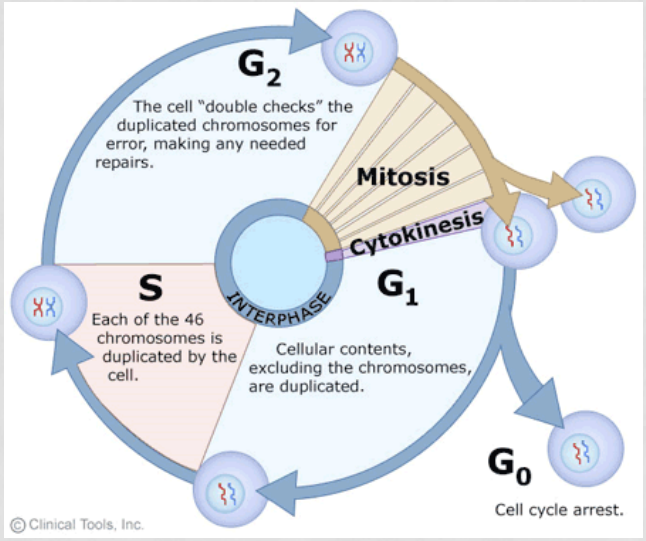
- 70-80% of sexually active adults infected during life time
- 10-30% active infection in young adults
- HPV infects by direct contact (mucosa)
  - Not airborne or bloodborne
  - Virus infects keratinocyte stem cells of basal layers
  - Thought to infect by entering microabrasions
  - Responsible for most cervix cancers, anal, vulvar and penile cancers

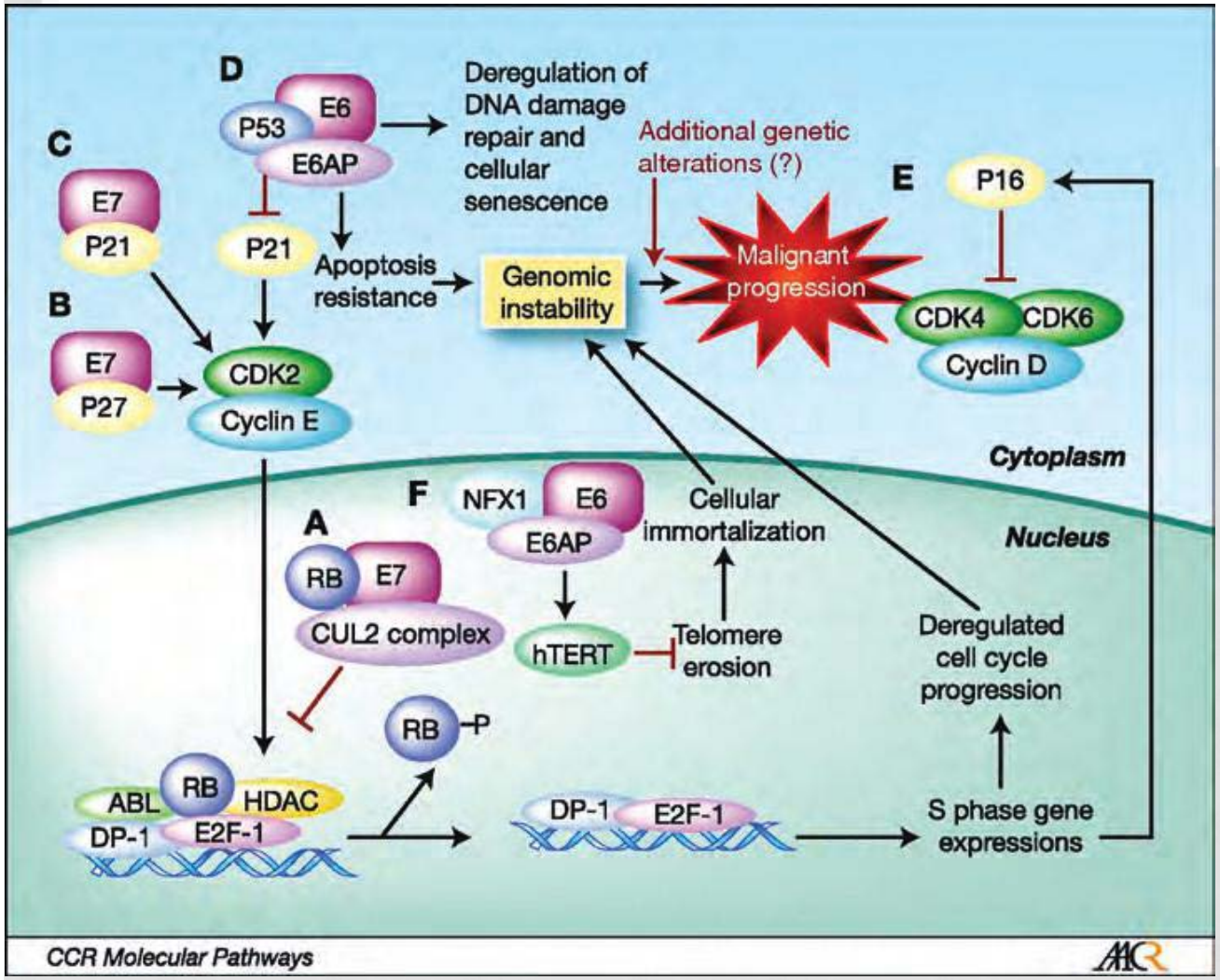
# BIOLOGY & CARCINOGENESIS

- HPV: early & late genes
  - early proteins
    - E1-5: nonstructural proteins involved in replication, transcription
    - E6-7: host cell tumoral transformation
  - late proteins L1-2
    - structural capsid
- Host: Tumor Suppressors
  - Retinoblastoma protein, Rb
  - P16

# BIOLOGY & CARCINOGENESIS

- Oncogenesis mediated primarily by E6 & E7
  - E6 complexes with other proteins & is involved in destruction of p53
    - Dysregulation of G1/S & G2/M checkpoints
  - E7 complex acts on Rb protein
    - Loss of G1/S checkpoint control
  - E6/7 driver oncoproteins but not sufficient on their own
    - Likely others are involved



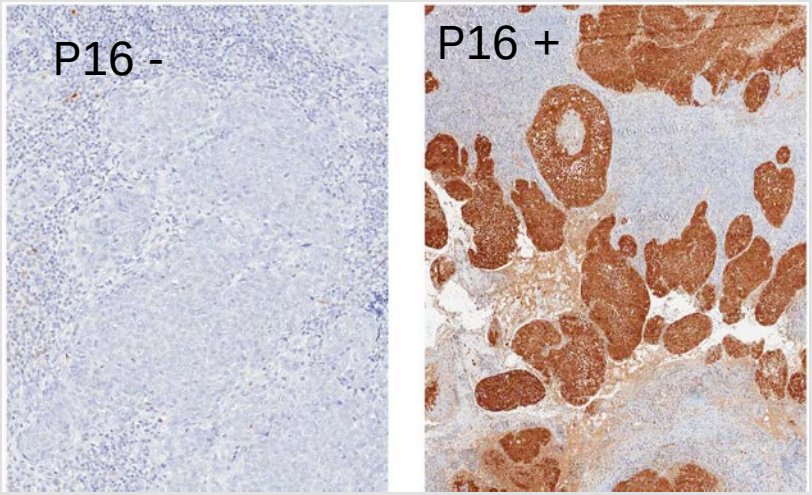



## P16 Tumor Suppressor:

- HPV+
  - *up-regulated via feedback mechanism*
- HPV-
  - *loss via genetic deletion, hypermethylation, or gene mutation*

# BIOLOGY & CARCINOGENESIS

- DNA testing (PCR)
  - Serotype by in situ hybridization
- Immunohistochemistry (P16)
  - Commonly used surrogate marker of HPV



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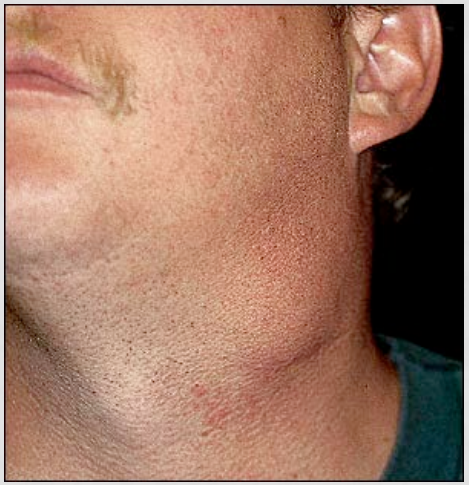
# EARLY DIAGNOSIS: AN APPROACH TO PATIENTS

- (1) Painless neck mass



  - Are there findings suspicious of cancer?
    - Persistent/non-resolving nodes
    - Dysphagia
    - Voice changes
    - Otalgia
    - Pharyngeal bleeding
    - Throat pain
  - If yes, arrange further workup:
    - Referral to otolaryngologist (don't delay for imaging!)
    - Imaging:
      - CT H&N, or
      - MRI of nasopharynx & oropharynx
  - If no, treat symptomatically & if ineffective, consider workup as outlined above

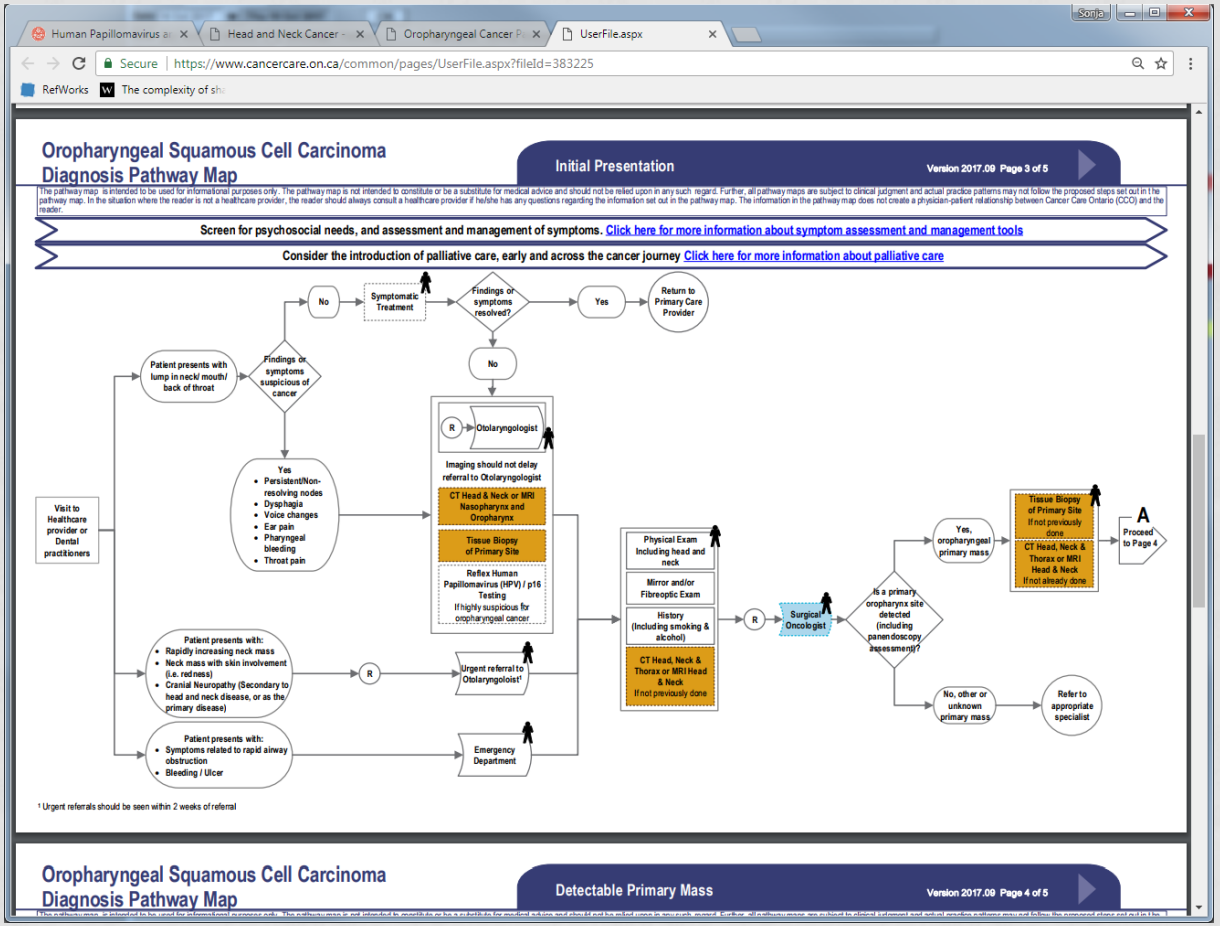
# EARLY DIAGNOSIS: AN APPROACH TO PATIENTS

- (2) Rapidly increasing neck mass, possibly with cranial neuropathy or skin involvement (eg. redness)
  - Urgent referral to otolaryngologist
    - should be seen <2 weeks

# EARLY DIAGNOSIS: AN APPROACH TO PATIENTS

- (3) symptoms related to rapid airway obstruction, or bleeding/ulceration
  - Emergency department

# APPROACH TO PATIENTS: DETAILS AVAILABLE AT WWW.CANCERCARE.ON.CA



# EARLY DIAGNOSIS: AN APPROACH TO PATIENTS

- Primary treatment options:
  - Radiation alone
    - For early stage disease (I, II), or if unfit for chemotherapy
  - Combined chemotherapy & radiation
    - Preferred modality for advanced disease (III, IV)
  - Surgery “TORS” = trans oral robotic surgery
    - May be considered for early disease, T1-2
    - Adjuvant treatment may be recommended

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# FREQUENTLY ASKED QUESTIONS

- How common is HPV?
  - Very common, up to 75% of sexually active Canadians may be infected with HPV at least once in their lives

# FREQUENTLY ASKED QUESTIONS

- How are people infected with HPV?
  - sexually transmitted infection
  - direct contact via genitalia/oral mucosa

# FREQUENTLY ASKED QUESTIONS

- What are the symptoms of HPV infection?
  - Most are asymptomatic
  - Many clear the infection on their own within 6-12 months
  - Those who have not cleared the infection may be at increased risk for certain cancers

# FREQUENTLY ASKED QUESTIONS

- How do I know if I have an HPV infection?
  - For women, testing may be done as a part of pap smear screening for cervical cancer
  - There are no screening tests to check for HPV infection in the mouth or throat

# FREQUENTLY ASKED QUESTIONS

- How can I protect myself from infection?
  - Regular checkups and Pap tests as recommended
  - Practice safe sex
  - Talk to your doctor about HPV vaccination

# FREQUENTLY ASKED QUESTIONS

**If a patient has HPV(+) head and neck cancer, are their partners at risk?**

- Study analyzing oral rinse samples for presence of HPV
  - 164 patients with oropharynx cancer (65% with HPV identified)
  - N=93 partners
  - 4% have HPV infection
  - Only 1 had oncogenic HPV16
  - Most partners effectively clear any active infection to which they are exposed

# ACKNOWLEDGEMENTS


- Dr. Sonja Murchison (PGY3 Radiation Oncology)
  - Helped with preparation of material/slides

And THANK YOU for listening!

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