Diversity of Oral Cancer

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Lecture Goals

- Understand the role of gender, race, age, and habits in oral cancer
- What is the etiology of oral cancer in non smokers?
- How is HPV implicated in oral and oropharyngeal cancer
- Role of HPV vaccine

University of Maryland OMS Oncology February 1991-June 2011.

- Total Patients 3,291
- Cancer Patients 2,032 (61.4%)
- Oral/Jaw Cancer 1,842 (89% of cancers)

Pathologic Variants

- **Cancer Oral Cavity/Jaws**
- Epidermoid carcinoma 79.6%
- Salivary (intra-oral) 11.7%
- Sarcomas 2.8%
- Lymphomas 2.6%
- Metastatic 2.3%
- Others 1.0%

- Oral cancer is a disease of elderly men who abuse tobacco and alcohol and usually present with advanced disease

Demographic Changes

- Gender
- Habits
- Race
- Age

Gender

Sex Ratio for Oral Cancer

	Male : Female
1930	10 : 1
1950	6 : 1
2000	3 : 2

- “For almost every smoking/alcohol category the risks are higher for women then men.”

- “Among women increased risks were observed for all levels of smoking and alcohol intake.”

- Muscat et al. Cancer Research Nov. 1996

Gender differences in smoking and risk for Oral Cancer

- There is a significantly higher trend in the ORs for women than men for both the cumulative tar measure and pack year measure (adjusted for alcohol and other variables). >40 pack-years smoking increases risk of oral cancer 2-fold in men and 5-fold in women.
- Muscat et al 1996

- “Women may be more vulnerable than men to alcohol-induced carcinogenesis.”

- Talamini et al J. of Nat. Cancer Instit. Dec 1998

Talamini et al J. of Nat. Cancer Instit. Dec 1998

- Drinkers > than 35 drinks/week compared
- to nondrinkers showed OR of 2.4 in men and OR 14.4 in women, CI 95%. These risk estimates were not statistically heterogenous.

Alcohol and Tobacco consumption in cancer of the mouth , pharynx and larynx: A study of 316 female patients

	Males		Females	
	n	%	n	%
Mouth	759	**29.9**	169	**53.9**
• Hypopharynx	366	**14.4**	14	**4.4**
• Larynx	466	**18.4**	29	**9.2**
• Epilarynx	217	**21.7**	11	**3.5**

- Controlled for age, alcohol, tobacco
- Luce et al Laryngoscope 1988

Habits

Patients without risk factors for oral cancer

Non-smokers

Non-drinkers

Non-Smokers

- Disproportionate number of women, oral cavity (especially tongue), and very young or old individuals (46 patients)

- Koch et al. Laryngoscope 109:1999

Non-Smokers

- The proportion of female patients amongst nonsmokers with HNSCC is significantly higher than among smokers.

- Hodge et al Cancer 1985
- Wynder et al Cancer 1957

Non-Smokers

- Male Smokers
  - Tongue Ca 57%
  - Floor of Mouth 74%
- Female Smokers
  - Tongue Ca 53%
  - Floor of Mouth 75%
- Prevalence of smoking was lowest for tongue and highest for floor of mouth.
- Muscat et al Cancer Res 1996

Non-Smokers

- Nonsmokers
  - 54% tongue
  - 3.7% Floor of mouth.
- Koch et al Laryngoscope 1999

- Floor of mouth cancer
  - in smokers 37.8% and
  - in non smokers 6.6%.
- Schmidt et al J Oral Maxillo Fac Surg 2004

Non-Smokers
What is the etiology?

- **Cancer of the Oral Cavity and Pharynx in non-smokers who drink alcohol and in non-drinkers who smoke tobacco.**
- Talamini et al. J. Nat Cancer Inst 90:1998

- In nonsmokers:
  - OR not > by 35 drinks or less/week,
  - OR 5.0 for 35-55 dpw and
  - 5.3 > 56 dpw .
  - Confirmed statistically significant risk of O/PSCC with heavy alcohol intake in never smokers .

Non-Smokers
What is the etiology?

- Is alcohol responsible for more intra-oral cancer?
- Hindle et al. Oral Oncology 36:2000

- Population based study (OPCS mortality data) Lung cancer and liver cirrhosis used as surrogate markers for smoking and drinking.

Non-Smokers
What is the etiology?

- The strongest associations were in males aged 35-64 years.

- Negative correlation lung/OSCC -0.98 p0.01
- Positive correlation cirrhosis/OSCC 0.71 p0.01

- Suggests rising alcohol consumption since the 1950s more closely related to > incidence OSCC than smoking most notably amongst young males since the 1970s
- Hindle et al. Oral Oncology 36:2000
-

Non-Smokers
What is the etiology?

- OR for OED in smokers 4.1 (adjusted for alcohol). Risk increased with > levels of smoking .
- Patients drinking >7 drinks/week OR 2.4 for OED (controlled for smoking).
- Both smoking and alcohol risk factors for OED

- Morse et al Cancer Epi Bio Prev 1996

Non-Smokers
What is the etiology?

– Many non-smokers are non-drinkers or drink little alcohol.

-
- 84% non-smokers also non-drinkers.
- Koch et al

- 54% non-smokers also non-drinkers and 33% drank < 1 drink a day
- Ord RA

Non-Smokers
What is the etiology?

- Review of 7 case-control studies regarding mouthwash use and oral cancer.

- “Neither the data for the overall association nor the analysis in patients without other clinical risk factors support a link between mouthwash use and oral cancer.”
- Elmore and Horwitz OtoHNS 113:1995

Non-Smokers
What is the etiology?

- Review of 10 Case Controlled Studies on Mouthwash use and Oral Cancer.

- No epidemiological evidence to support a link between oral cancer and mouthwash.

- La Vecchia C. Oral Oncology 2009

Non-Smokers
What is the etiology?

- Studies of young patients (under 40) who are non-smokers showed over expression of p53 despite a lack of mutations.
- Sorenson et al. 1997; Lingen et al. 2000
-
- Young non-smokers with SCCHN show increased sensitivity to chromosomal damage upon exposure to mutagens.
- Schantz et al. JAMA 262:1989

Non-Smokers
What is the etiology?

- Tumors of nonsmokers harbor a lower frequency of common genetic changes than those of smokers. Fewer genetic alterations may be involved in malignant transformation in at least some of these tumors. Increased LOH at 6p in nonsmokers in this study did not reach statistical significance.

  Koch et al. Laryngoscope 109:1999

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Non-Smokers
What is the etiology?

- **<u>Oral Cancer the evidence for sexual transmission.</u>**

- Recent studies indicate HPV may be etiologically important in some OPC.
- Studies of OSCC have suggested possible sexual transmission of HPV.

- Scully C. Brit Dent J. 2005

Non-Smokers
What is the etiology?

- **HPV Prevalence (5,046 cases)**
- OSCC 23.5% HPV16 68.2%
- HPV18 34.1%

- OPSCC 35.6% HPV16 86.7%
- HPV18 2.8%

- Larynx 24.0% HPV16 69.2%
- HPV18 17.0%
- Kreimer et al Cancer Epidemiol Biomarkers Prev 2005

Age

Age in Oral Cancer

- Median Age for Oral Cancer 60-65 years
- Patients less than 40 Years 0-3%

Increase in Tongue Cancer in Young Adults

- Finland – 4% 1960's
- 7% 1980's
- Atula et al Arch OtoHNS 122:1996

- USA – 4% 1971
- 18% 1993
- Myers et al OtoHNS 122:2000

Review of NCI SEER Data 1973-1997

- 63,409 H+N Cancer Patient
- 3,339 less than 40 years.

- 1973-1984 compared to 1985-1997,
  - showed 60% increase in tongue cancer in patients under 40 years.

- Change affected birth cohorts between 1938-1948.

- Distinct disease process apparent in white not blacks.

- Schantz and Yu Arch OtoHNS 128:2002

Oral Cancer in Young Patients

1. What is the Etiology?

2. How does this cancer behave?

Etiology of Oral Cancer in Young Patients

- Initial studies focused on the percentage of non-smokers, non-drinkers, or that the duration of exposure may be too short in this population to induce tumorigenesis.

Etiology of Oral Cancer in Young Patients

1. Conflicting evidence regarding tobacco/alcohol
2. Meager information regarding occupation, familial risk, immune deficits, and virus infection
3. Predisposition to genetic instability?

- Llewellyn et al Oral Oncology 37:2001

Etiology of Oral Cancer in Young Patients

- “Most are exposed to traditional risk factors of tobacco smoking, alcohol, and low consumption of fruit and vegetables.”

- 109 patients 1981-1995 Scotland
- 38 returned questionnaires

- Mackenzie et al Oral Oncology 36:2000

Etiology of Oral Cancer in Young Patients

- 137 cases. <46 years from 2 case controlled studies in Italy and Switzerland
  - OR 20.77 >25 cigarettes/day,
  - OR 4.9 >10 drinks/day,
  - combination of tobacco+alcohol OR >48.
  - High coffee OR 0.25,
  - fresh vegetables OR 0.39,
  - fruit OR 0.73,
  - β-carotene OR 0.48

- Rodriguez et al Oral Oncology 2004

Etiology of Oral Cancer in Young Patients

- Tobacco accounted for 77% of all cancer cases in this population, alcohol for 52%, low vegetable consumption for 52% and the combination of all three for 85%.

- Rodriguez et al Oral Oncology 2004

Etiology of Oral Cancer in Young Patients

- 6 cases aged 19-38 years H+N cancer in marijuana smokers.

- Donald, PJ. Otolaryngol Head Neck Surg 1986

- Marijuana smoking as a possible cause of tongue cancer in young patients.

- Almadori et al J Laryngology Otol 1990

Etiology of Oral Cancer in Young Patients

- Lifetime prevalence of marijuana use was 49.9% among full-time college students, and 54.5% among young adults 19-28 years in 1998.

Etiology of Oral Cancer in Young Patients

- OR for marijuana smokers for head and neck cancer was 2.6 (173 cases) case controlled
- Zhang et al Cancer Epidemiol. Biomarkers Prev. 8:1999

- "Further epidemiological studies are necessary to confirm the association of marijuana with head and neck cancers."
- Hashibe et al J Clin Pharmacol 42:2002

- Mathematical models estimate 7-10 individual genetic alterations must occur for the development of cancer.

- This can involve activation of oncogenes and innactivation of tumor suppressor genes.

- Inactivation of p53 tumor suppressor gene common in SCCHN with approximately 50% of cancers having a mutant p53 protein.

- Field Eur J Cancer 28B:1992

- A strong correlation between mutation of p53 and chronic tobacco and alcohol use is documented.

- In non-smokers only 14-17% incidence of p53 mutations.

- Lingen et al Curr Opin Oncol 13:2001

- Absence of p53 mutation in SCC of the tongue in non-smoking and non-drinking patients younger than 40 years
- Sorensen et al Arch OtoHNS 123:1997

- Over expression of p53 in SCC of the tongue in young patients with no known risk factors is not associated with mutations in Exons 5-9.
- Lingen et al Head and Neck 22:2000

Etiology of Oral Cancer in Young Patients

- LOH at 3,9,and 17 p chromosomes in young adults no different to those found in older patients.
- Jin, Y-T Oral Oncology 35:1999

- No significant differences in the expression of p53, p21, Rb, and MDM2 proteins from tongue SCC in patients <35 years compared to patients >75 years.
- Regezi, JA Oral Oncology 35:1999

Etiology of Oral Cancer in Young Patients

- **Genetic Predisposition**
- Young adults with H+N Ca. > susceptibility to mutagen-induced chromosome damage.
- Schantz et al JAMA 1989
- Increased frequency of carcinogen-metabolising polymorphisms.
- Cheng et al Int J Cancer 1999
- Increased frequency of DNA repair gene polymorphisms.
- Sturgis et al Carcinogenesis 1999

Etiology of Oral Cancer in Young Patients

- Correlation of HPV and Oral Ca.

  Gillison et al. Curr Opin Oncol 1999

- 5x higher expression HPV in OSCC than normal oral mucosa.

  Miller et al. Oral Surg Oral Med Oral Path 2001

- HPV 16 + 18 carcinogenic correlate with p53 mutation.

  Shima et al. Brit J OMS 2000

Etiology of Oral Cancer in Young Patients

►HPV integration into oral epithelium cell genome leads to cellular immortalization and enhances chemical carcinogenesis.

- Li et al Carcinogenesis 1992

- It is not proven that HPV infection increases over time in young patients and that this increase is a responsible factor for increase in tongue cancer in young patients.
- Schantz SP, and Yu G-P Arch Otolaryngol HNS 2002

Behavior of Oral Cancer in Young Patients

- **Increased mortality in young patients in:**

- Europe : Levi et al, Eur J Cancer 1999
- Franchesci et al, Eur J Cancer 1994

- USA: Schantz and Yu, Arch Otolaryngol HNS 2002

- India: Gupta, PC. J Indian Med Assoc 1999

Behavior of Oral Cancer in Young Patients

- 27 patients
  - <40 Yale-New Haven MC
  - 1958-80 with oral/oropharyngeal CA.

- 3 year survival rate was 17%.

- Loco-regional recurrence was 91%.

Son Y and Kapp D, Cancer 1985

Behavior of Oral Cancer in Young Patients

- Review 14 reports (1968-1993) – 152 patients.

- 64% Stage I and II
- 57% Locoregional Failure
- 47% Died of Disease

Behavior of Oral Cancer in Young Patients

- Oral Tongue Cancer in Young Adults Less Than 40 Years of Age: Rationale for Aggressive Therapy.
- Sarkaria JN, Harari PM. Head and Neck 16:1994

Behavior of Oral Cancer in Young Patients

- Squamous Cell Carcinoma of the Tongue in Young Patients: A Matched-Pair Analysis.
- Friedlander et al Head and Neck 20:1998

- 36 patients under 40 matched to older population. There was no significant difference in disease free survival, local, regional or distant recurrence.
- There was a significant increase in loco-regional recurrence in the younger patients which did not translate into a survival difference.

Behavior of Oral Cancer in Young Patients

- A Matched Control Study of Treatment Outcome in Young Patients with SCC of the Head and Neck.
- Verschuur et al Laryngoscope 109:1999

- 185 cases HNSCC
  - <40 compared to control group
  - >40 selected randomly.
- 5 year cause specific survival no difference.
- Younger cases significantly better **overall** survival.

Behavior of Oral Cancer in Young Patients

- Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes.
- Myers et al Otolaryngol HNS 2000

- T stage, N stage, perineural and lymphatic invasion were all associated with decreased survival. Patients who received a neck dissection as part of primary treatment had better chance of survival.

Behavior of Oral Cancer in Young Patients

- 5 year survival 1985-97 (SEER)
  - 70.6% <40yr
  - 49.8% 40-64 yr,
  - 45.8% >65yr.

- 1973-97: 5 year survival increased in all age groups.
  - Absolute increase largest in <40yr 11.7%, p=.009.
  - Increase of 20% in young patients with regional or distant disease,
  - only 3% in localized disease.
- Schantz and Yu Arch Otolaryngol HNS 2002

Human Papilloma Virus

Human Papilloma Viruses
risk stratification

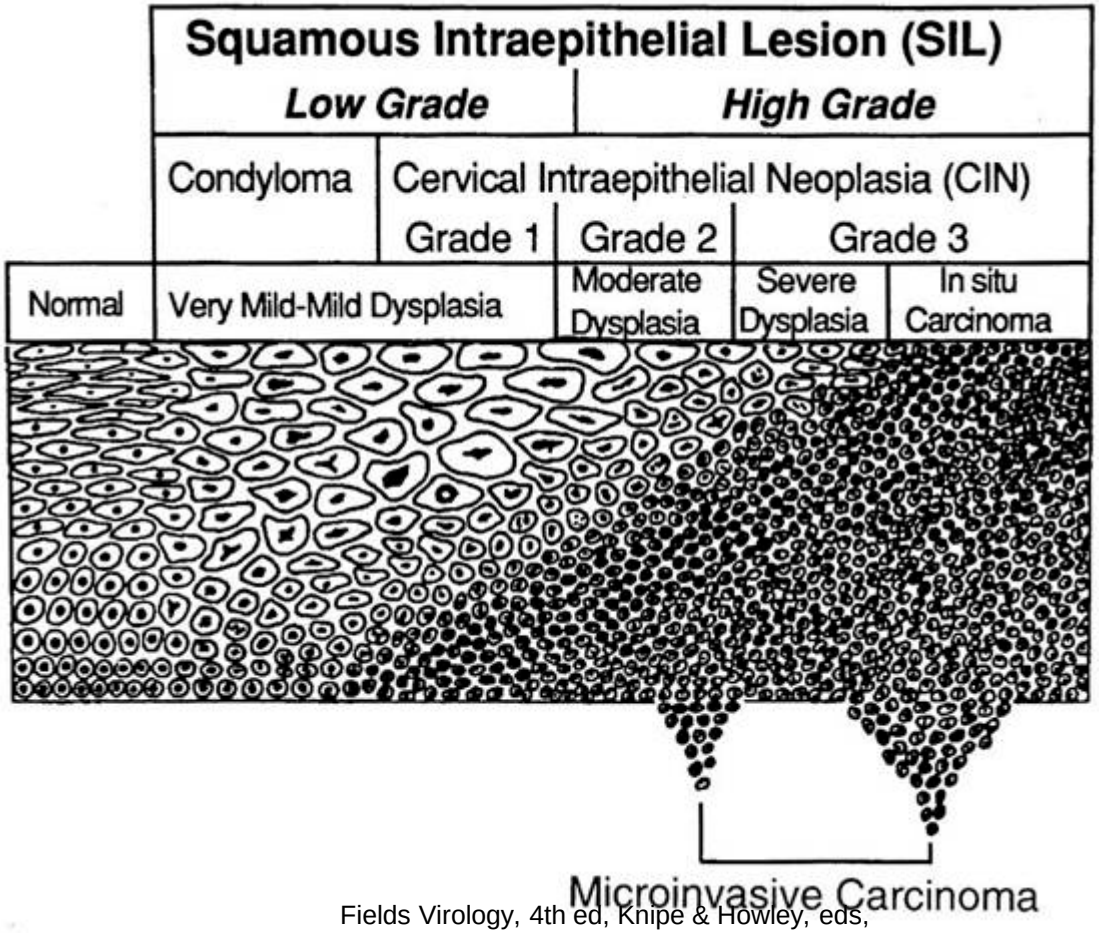
- LOW RISK TYPES
- Associated with benign proliferative growths
- (HPV 1, 2, 6,11)

- HIGH RISK TYPES
- Infection with high risk types is associated with both pre-malignant and malignant lesions
- (HPV 16, 18, 31, 33, 35, 39, 45)

Cervical Cancer and HPV

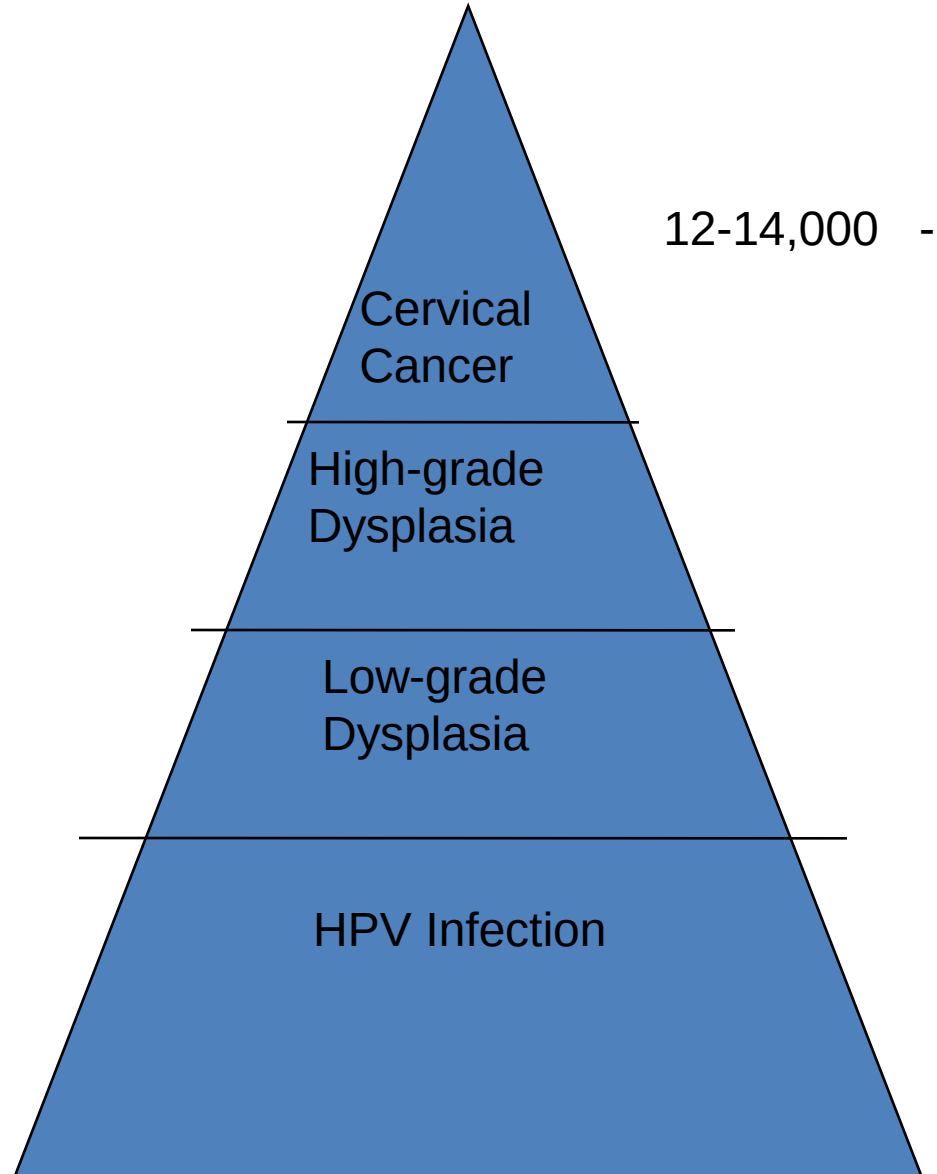
- HPV 16/18
  - 99.7% of cases of cervical cancer
- Increase risk 200X to develop cervical cancer
- 20,000,000 currently infected

Histologic Progression of Cervical Cancer



Fields Virology, 4th ed, Knipe & Howley, eds,

Histologic Progression of Cervical Cancer



12-14,000 - 4,000 deaths/year

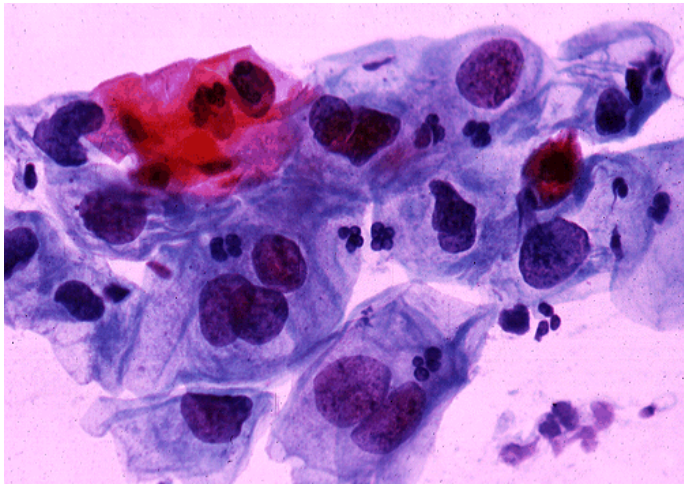
300,000

1,000,000

10,000,000-20,000,000

HPV Natural History

- Nearly ubiquitous
  - >90% sexually active adults have antibodies to L1 protein



- Transient
  - >90% of infections are cleared
  - No sequelae
- Dysplasia
  - May develop in low risk types/carriers
  - Persistent infection with high risk HPV
    - may lead to dysplasia [CIN 2,3] and cancer

HPV and Cervical Cancer

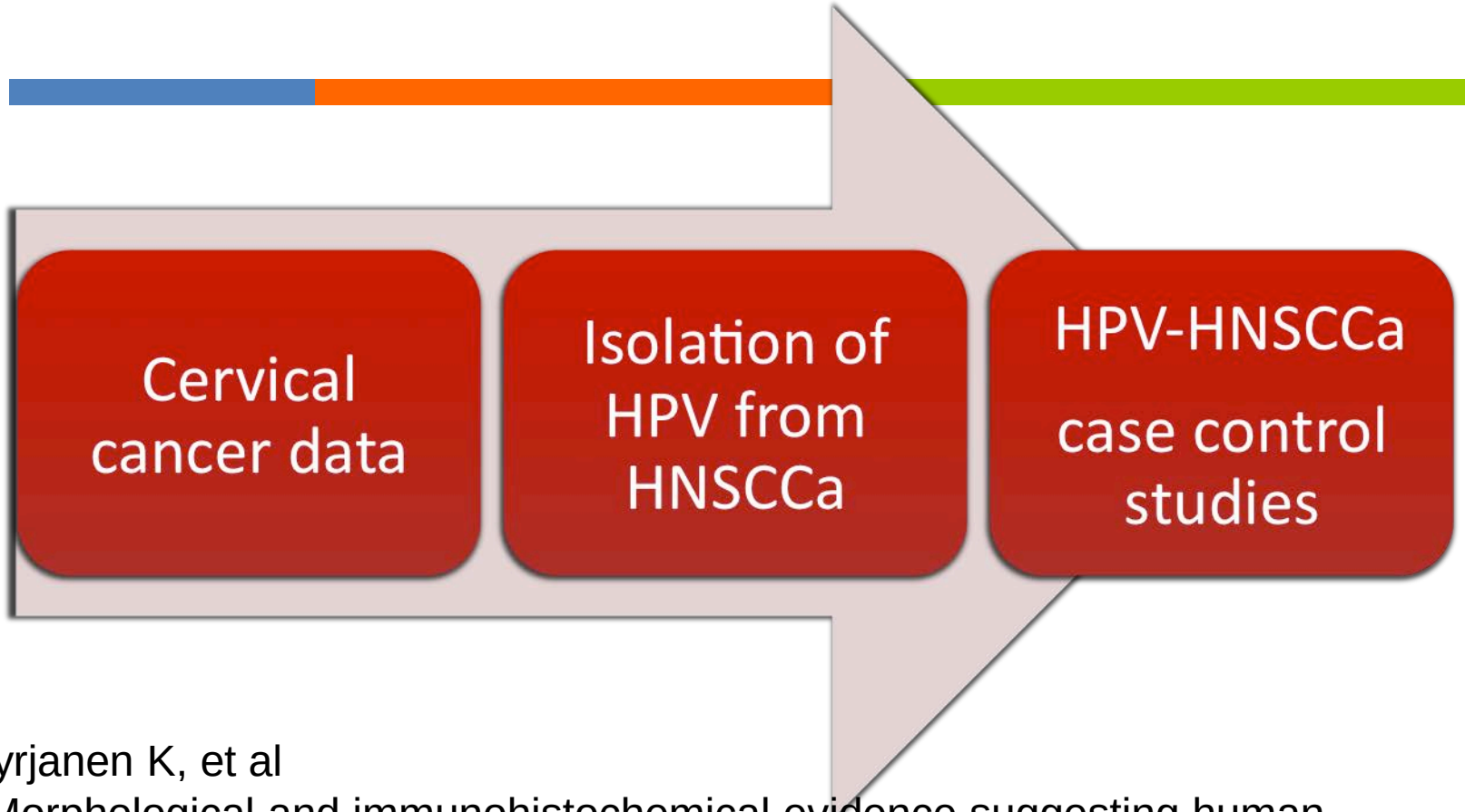
- CDC estimates of HPV infection
  - Lifetime risk ☞50% of sexually active females
  - 80% infected by age 50
  - 10% of population has active HPV infection

- WHO estimates of Cervical Cancer
  - 12,200 cases in 2003 in US
    - 4100 deaths in 2003 in US
  - 500,000 cases worldwide
    - 250,000 deaths each year worldwide
  - Second most common cancer in the world for women

Head and Neck Cancer

- 4% of all cancers
- 34,000 new cases each year in US
- 7,000 deaths each year
- 271,000 deaths annually worldwide
- Roughly 15-20% associated with HPV infection

Jemal, 2004; Mork, 2001

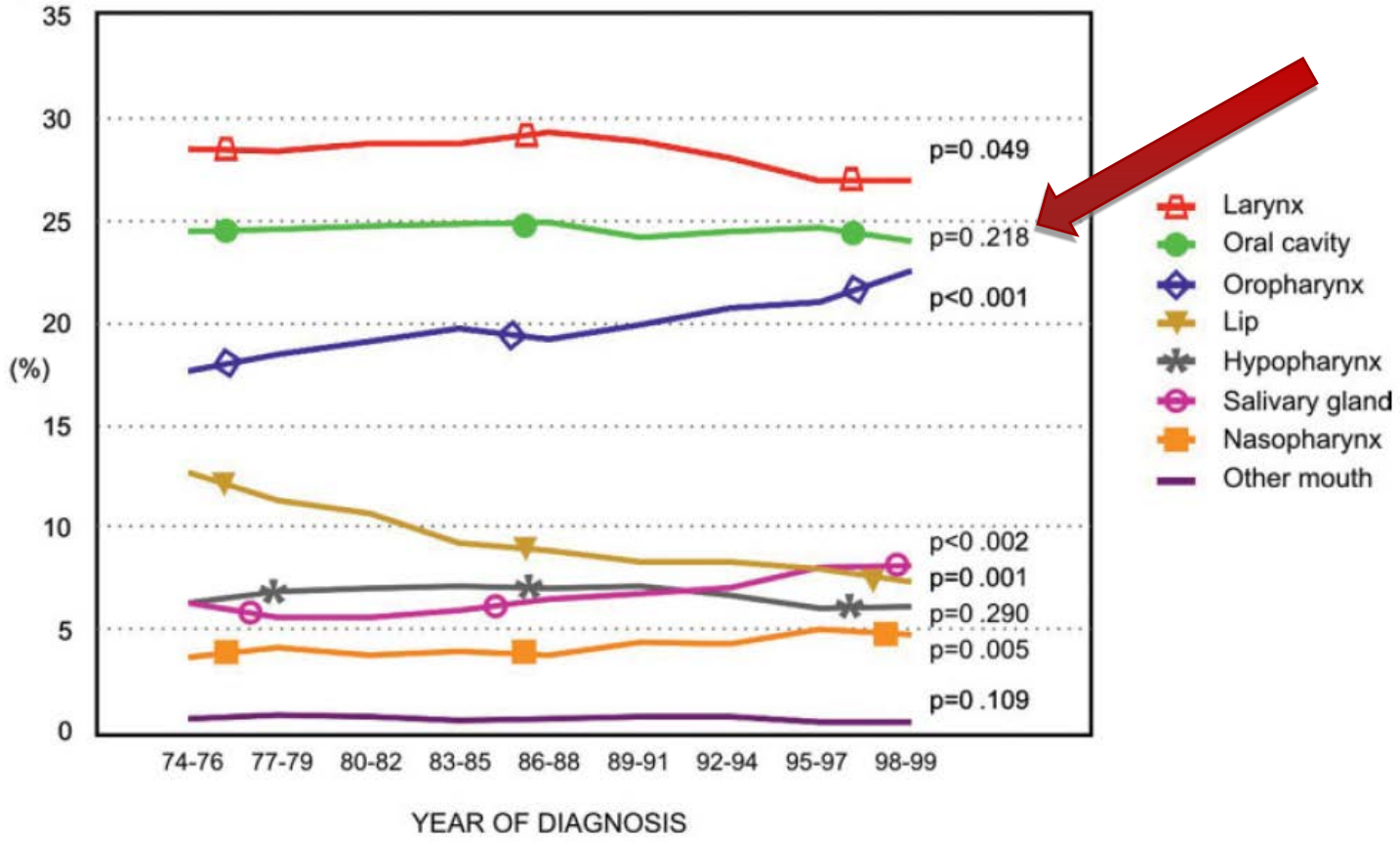


Syrjanen K, et al
“Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis
Int J Oral Surg. 1983

Park NH, Min BM, Li SL
“Immortalization of normal oral human keratinocytes with type 16 human papillomavirus”
Carcinogenesis 1991, 12:1627–1631

Trends in Head and Neck Cancer

rise in oropharyngeal cancer



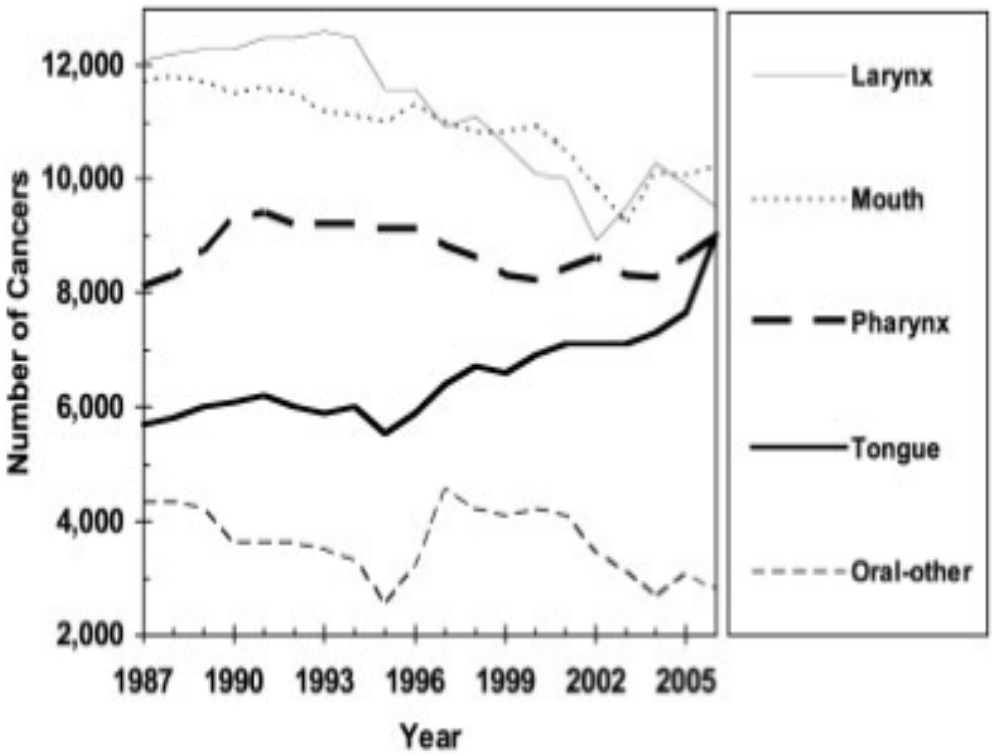
Carvalho A. Int J Cancer 2005

HPV and HNSCCa

- SEER Database
- Increased incidence of oropharynx cancer
  - 2.1% increase of base of tongue cancer
  - 3.9% increase of tonsil cancer
- Different demographic
  - increased among white men and women
  - increased for ages 20-44
  - 2-3% per year increase in tonsil cancer among men younger than 60 1975-1998
- More than doubled from 1975-2005

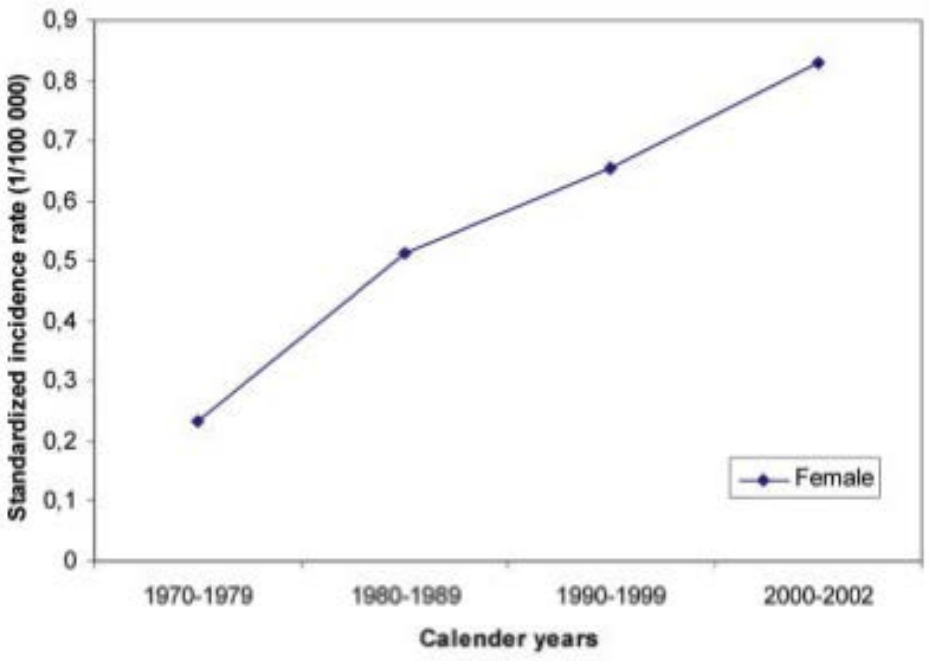
Head and Neck Cancer Trends

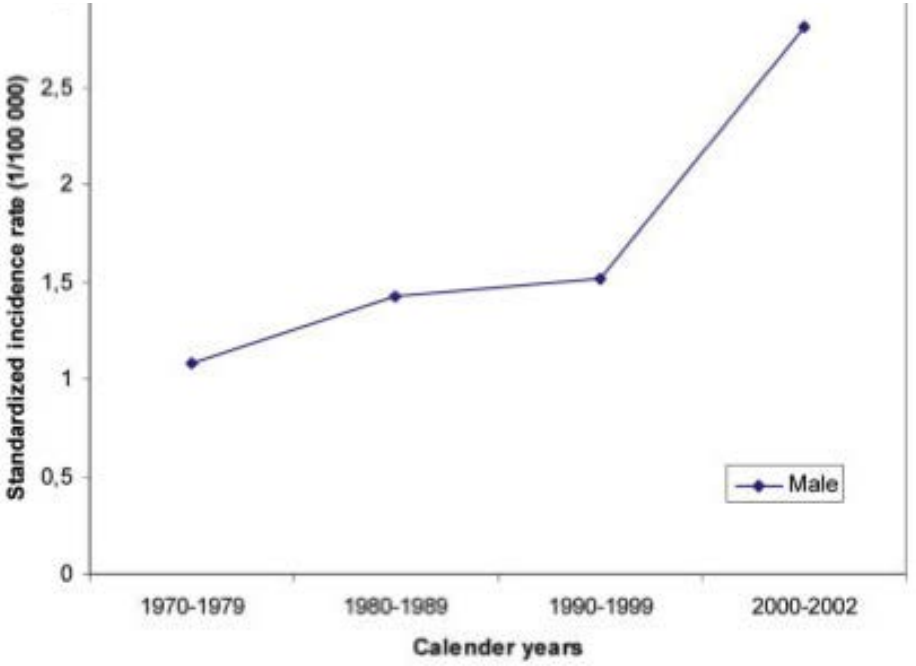
- US
  - BOT 1.27%/year
  - Tonsil 0.6%/year



Chaturvedi J. Clinical oncology 2008

Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer





- 1.3/100,000→3.6/100,000

Hammarstedt, Int J cancer, 2006

Estimates
HPV related Oropharyngeal Cancer

- World wide
  - 6000-33000/year
  - US 800-4600/year
- HPV Oropharyngeal related cancers (%)

North America	47%
Asia	46%
South/Central America	36%
Europe	26%

What did the initial studies show?

- High risk type HPV (16) is a cause of oropharyngeal cancer
- HPV related HNSCCa is a distinct disease from traditional HNSCCa

Risk Factors
HPV and Head and Neck Cancer

Variable	HPV-16–positive case subjects, % (n = 92)	Control subjects, % (n = 184)	Adjusted OR (95% CI)	P_{trend}
Total lifetime number of vaginal sex partners				
0–1	8	19	1.0 (referent)	<.001
2–10	38	53	2.5 (0.75 to 8.2)	
≥11	54	28	6.4 (1.9 to 22)	
Total lifetime number of oral sex partners				
0	8	20	1.0 (referent)	.004
1–5	47	54	2.1 (0.66 to 6.7)	
≥6	46	26	4.3 (1.4 to 14)	
History of casual sex				
No	40	61	1.0 (referent)	
Yes	60	39	2.9 (1.5 to 5.6)	
Age at first sexual intercourse, y				
≥19	30	45	1.0 (referent)	
<19	70	55	1.8 (0.96 to 3.3)	
Age at first oral sex, y				
≥21	48	64	1.0 (referent)	
<21	52	36	1.7 (0.90 to 3.1)	

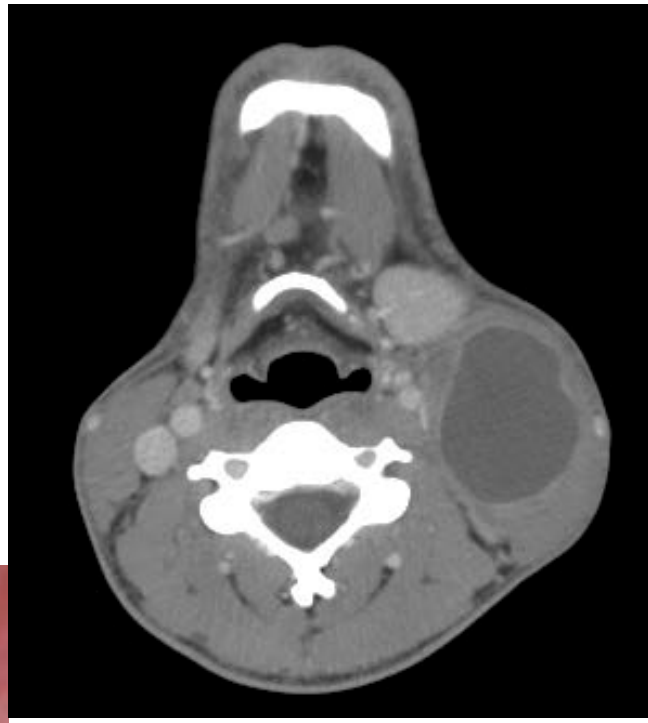
Risk Factors
HPV and Head and Neck Cancer

- Is Oropharyngeal cancer an STD?
  - Increased number of vaginal-sex partners
  - Increased number of oral-sex partners
  - Early age 1st intercourse
  - Anal sex
  - “One-night stands”
  - Rare condom use
  - History of STDs

Epidemiology of HPV+ HNSCCa

- Never smokers
- Mild alcohol use
- Intact dentition
- High oral sex exposure
- Age <45

Tonsillar Cancer



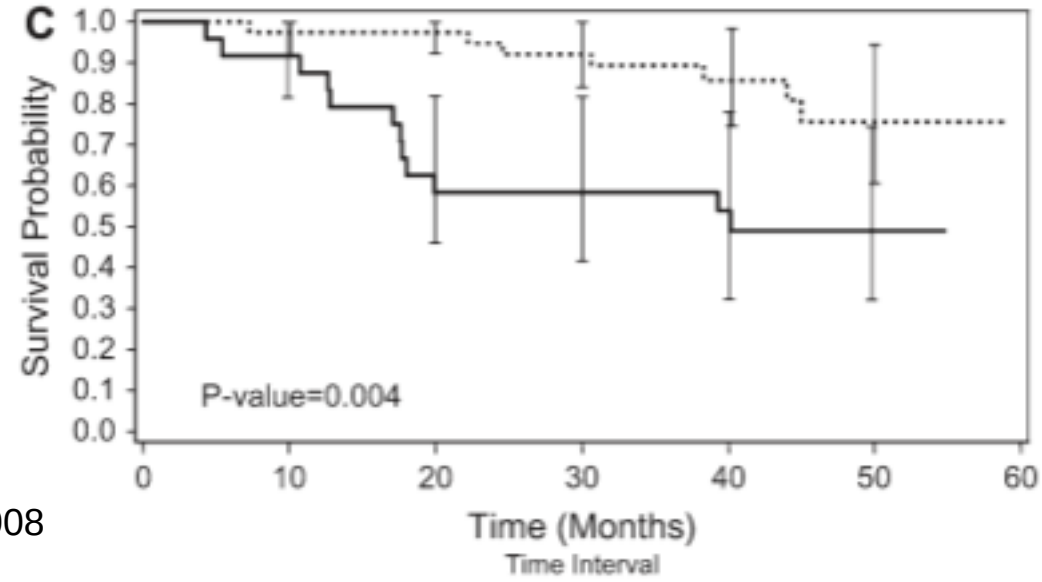
Outcomes
HPV+ versus HPV -

- Improved responses to induction chemotherapy
- Improved response to chemoradiotherapy
- Improved 2 year survival
- Improved performance status
- Lower risk of disease progression

Outcomes HPV+ versus HPV -

- Phase II ECOG trial
- Stage III/IV HPV +/-
- Induction chemo + concomitant chemo + standard regime XRT

Overall survival

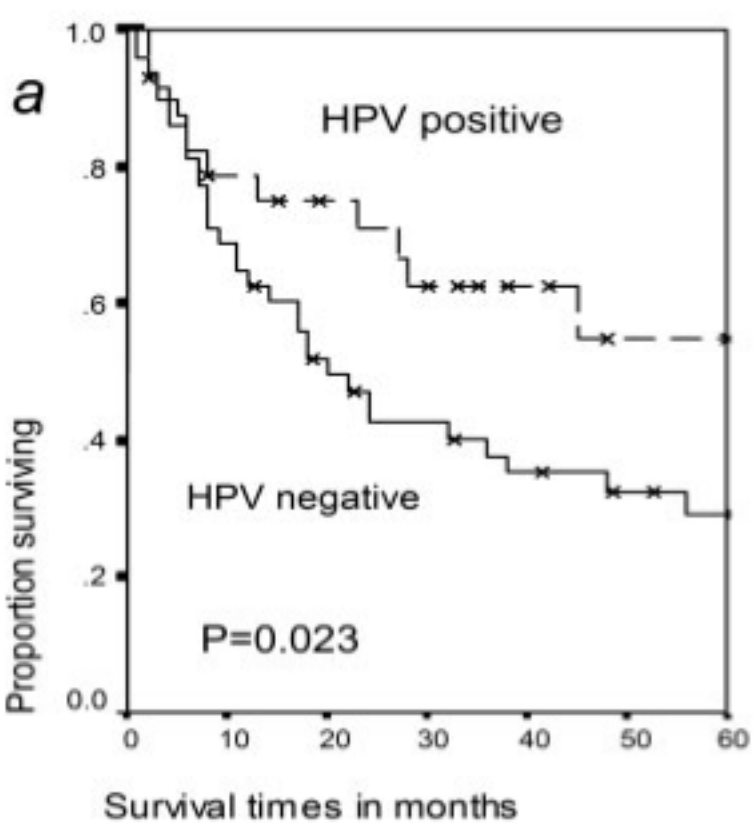


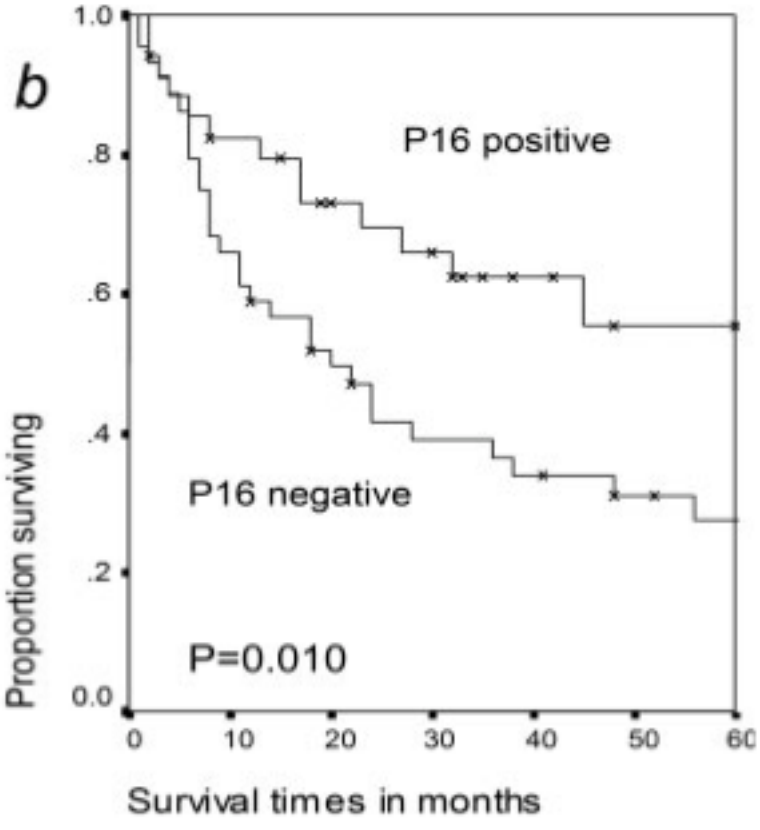
Fakhry et al. Journal National Cancer Inst, 2008

Outcomes HPV+ versus HPV -

- HPV +
  - Improved DSS
  - ↑ p16 levels
  - ↑ HPV integration
  - ↓ tobacco/etoh use
  - ↓Cellular differentiation
  - ↓Regional metastasis
  - ↓LR recurrence

Outcomes HPV+ versus HPV -





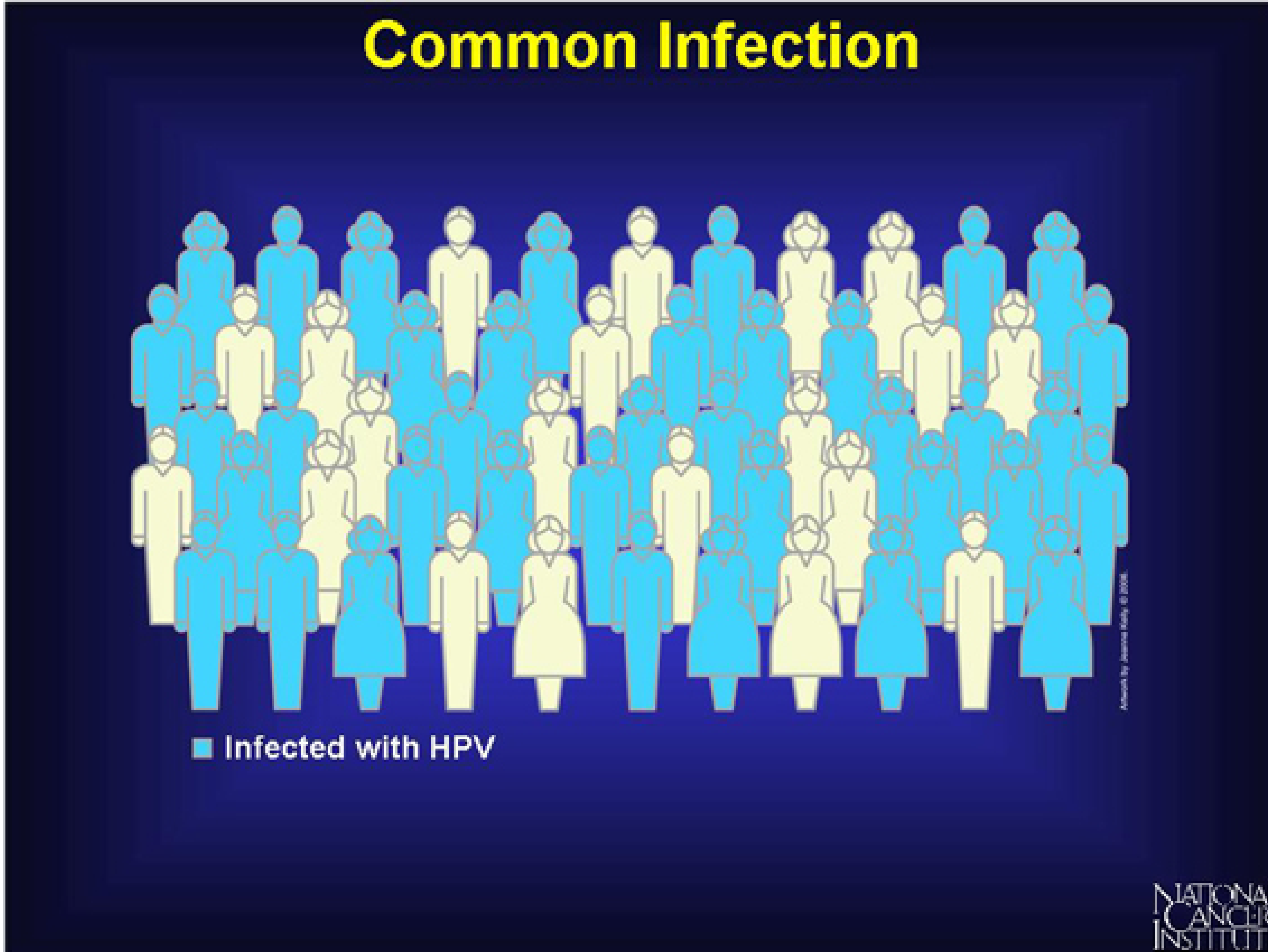
HafKamp et al. Int. Journal of Cancer, 2008

Links between cervical cancer and HNSCC

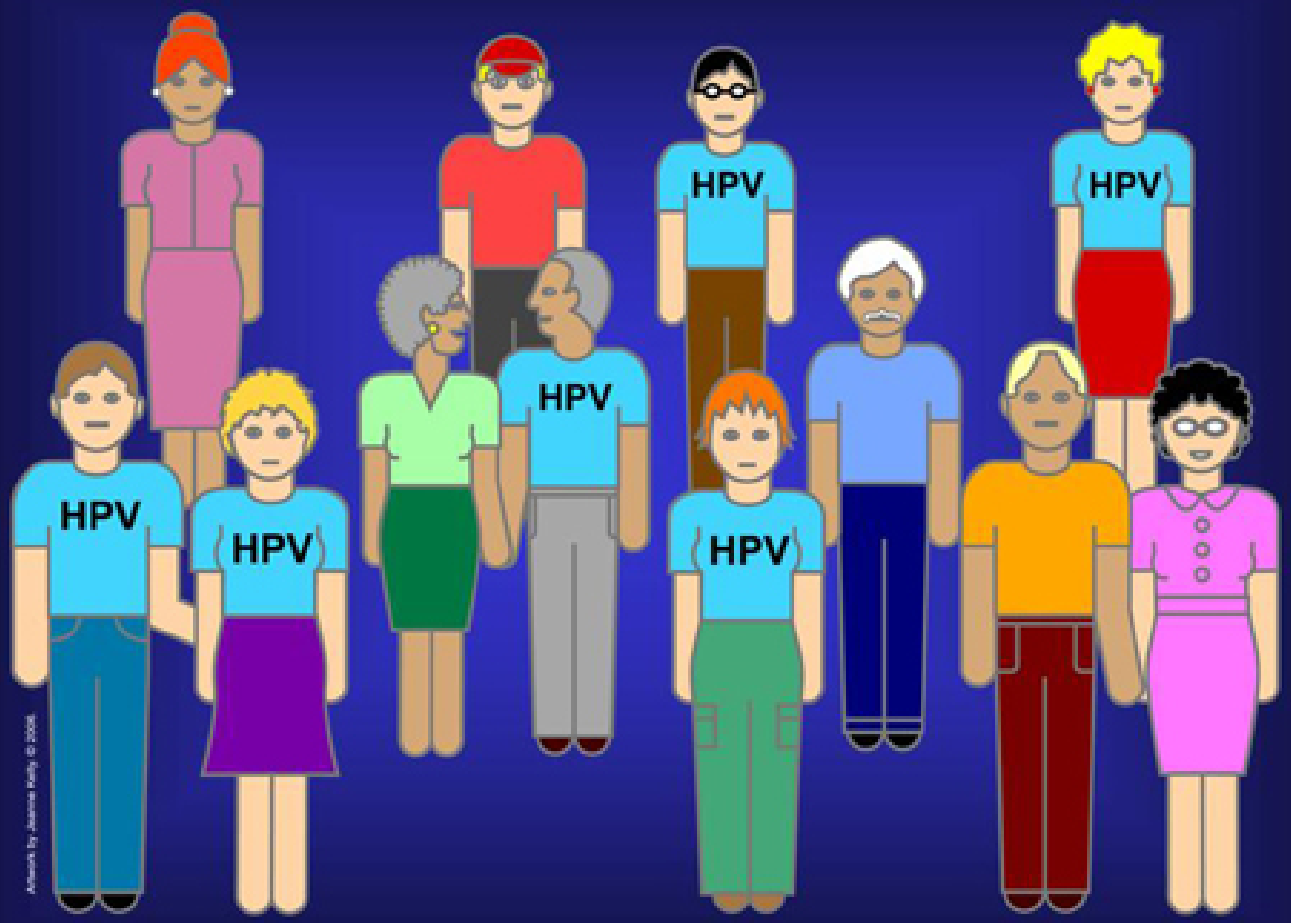
- Lifetime risk of second HNSCC in patients with cervical cancer SIR 1.7 (standardized incidence ratio) Rose et al Head Neck 2008

- Female patients with cervical CIS had SIR 1.68, and invasive cervical cancer SIR 2.45 and husbands also had an elevated SIR for HNSCC.
- Hemminiki et al Eur J cancer Prev 2000

HPV vaccine

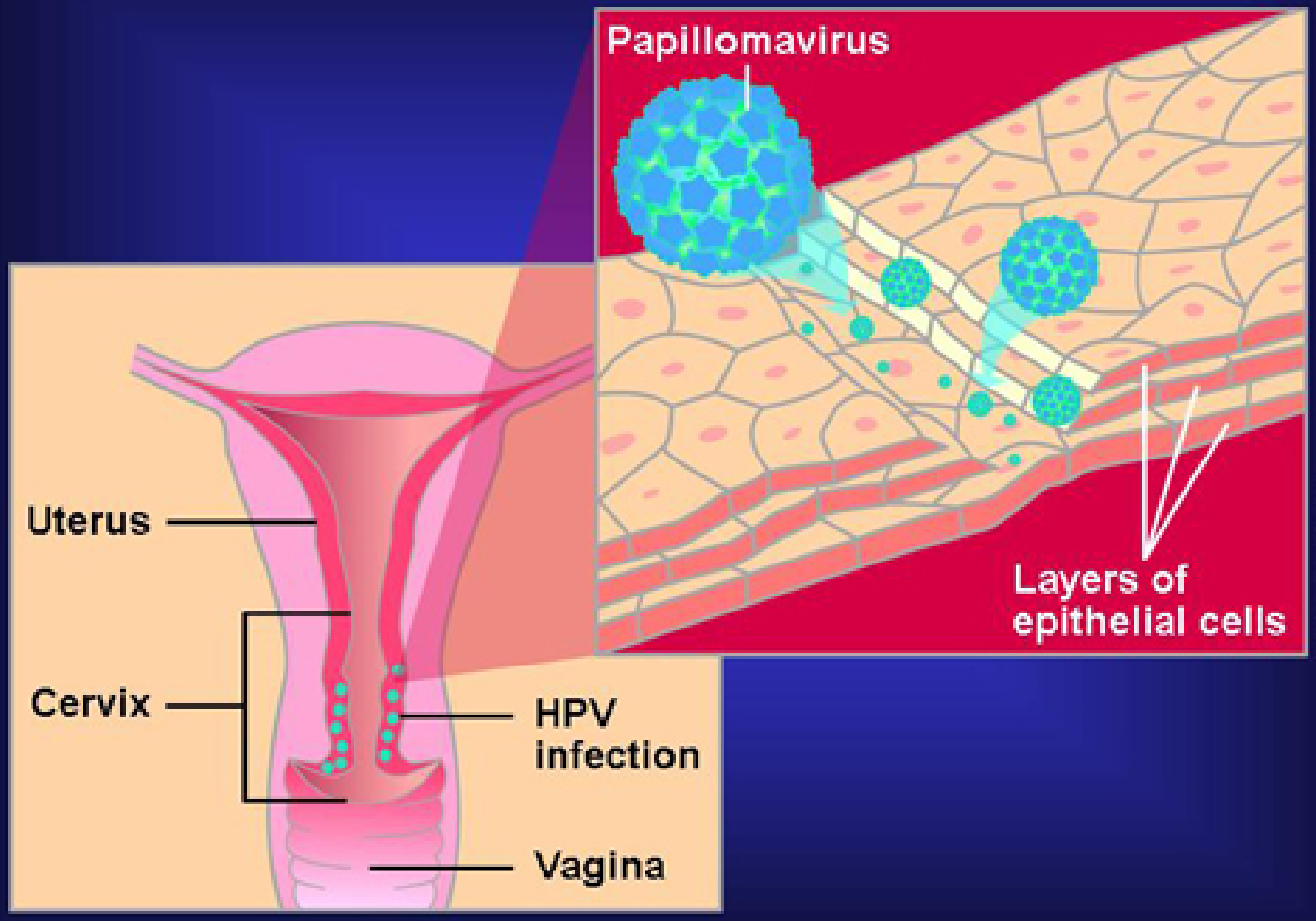

Common Infection
Infected with HPV
NATIONAL CANCER INSTITUTE

Infection Is Sexually Transmitted

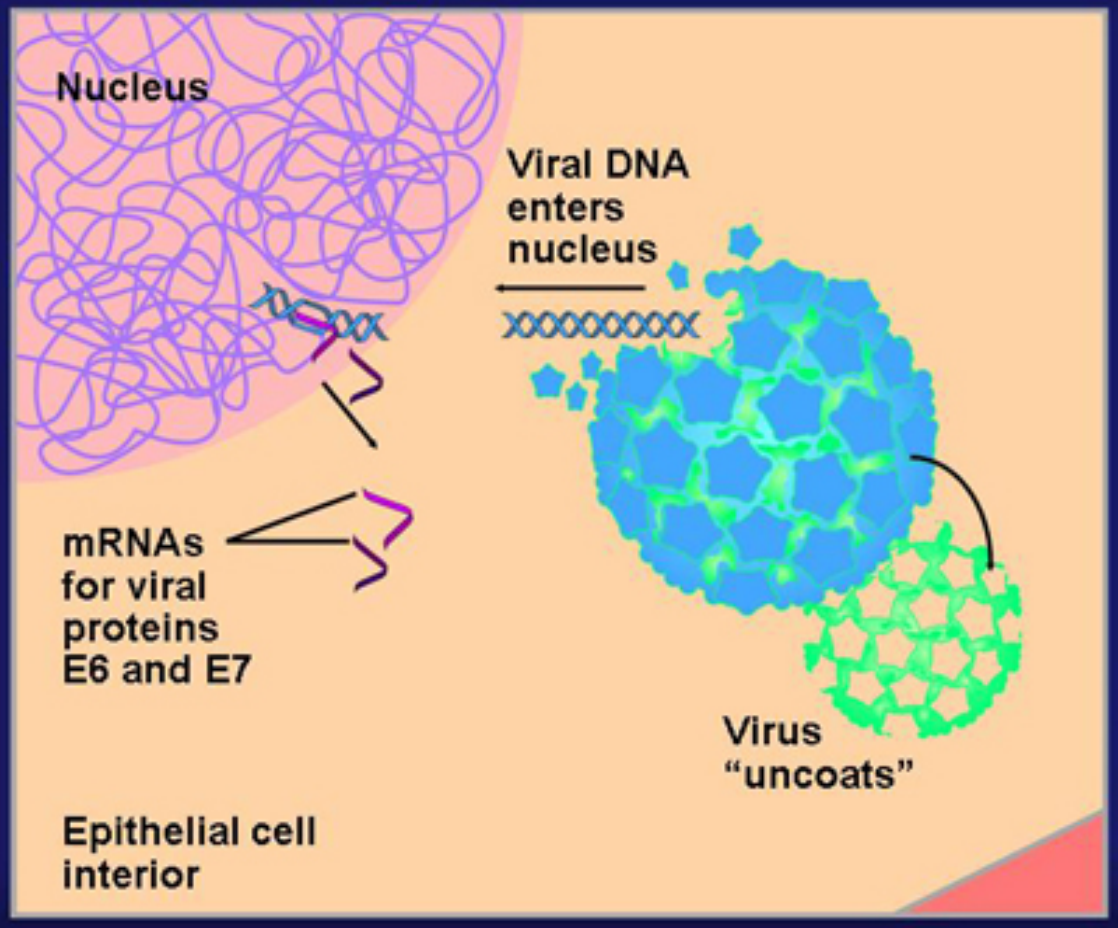


NATIONAL CANCER INSTITUTE

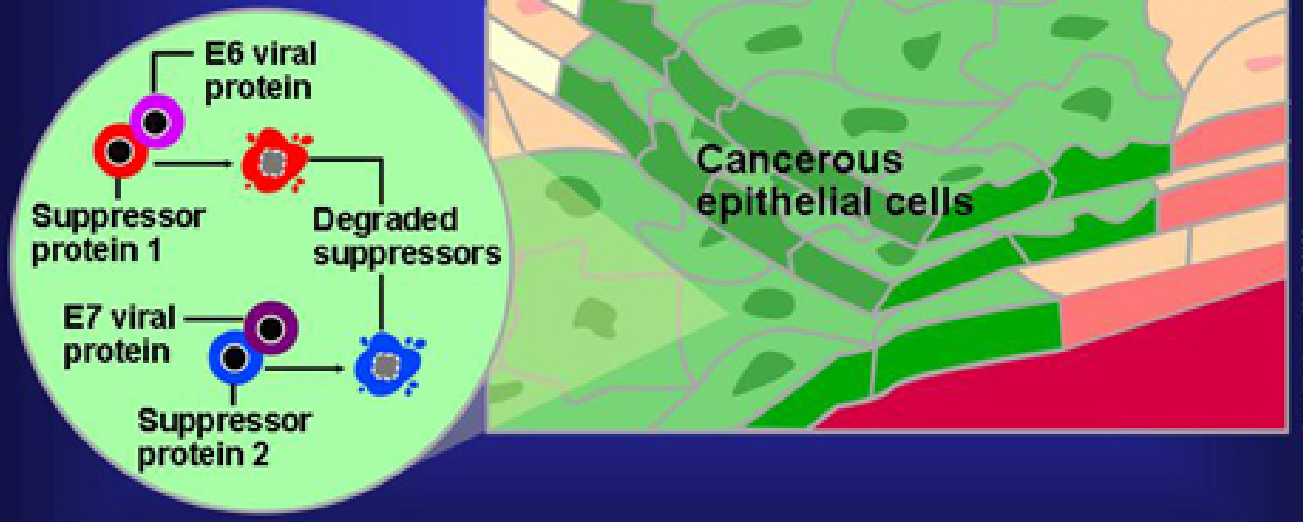
Virus Penetrates Cervix



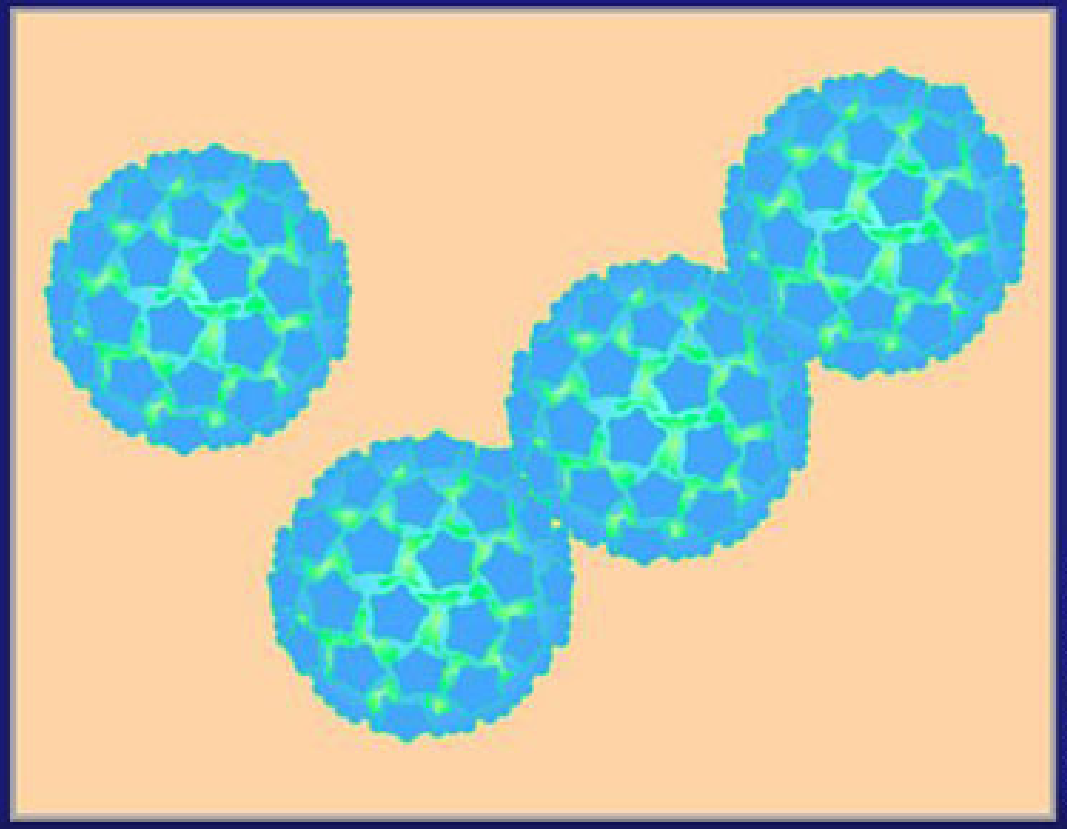
Virus Uncoats



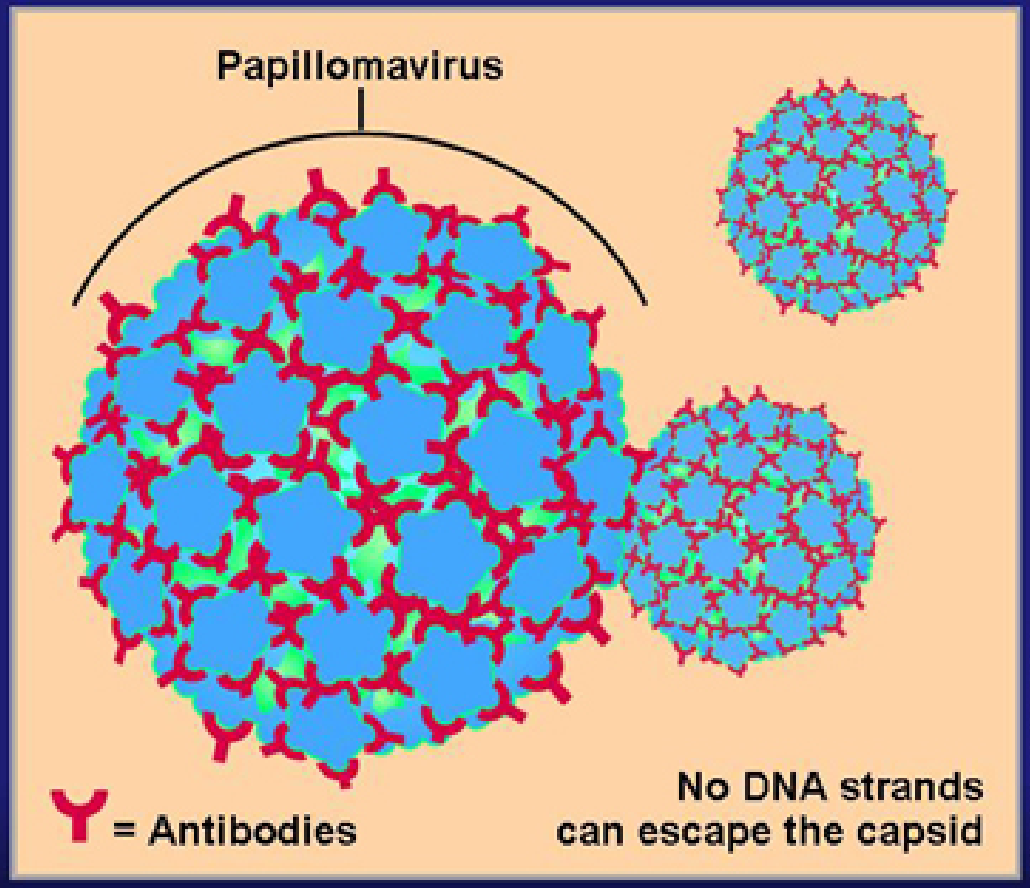
Virus Disables Suppressors



Virus-Like Particles



Antibodies Prevent Infection



NATIONAL CANCER INSTITUTE

Prophylactic HPV Vaccine ⃠acquisition/persistence⃠

- FDA approved
  - Cervarix
    - HPV 16,18,31,33,45
  - Gardasil
    - HPV 16,18,31
    - HPV 6,11 (venereal warts, papillomatosis)

Neither has been shown to prevent cancer

Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial

- Incidence and persistence of infection ↓90%
- Decrease CIN2/3 97.1%

Villa et al, Lancet Oncology, 2005

Vaccine Recommendations

Table 2. Current Guidelines and Recommendations for HPV Vaccine Use

Organization	Recommendation
Centers for Disease Control Advisory Committee on Immunization Practices[53]	Routine vaccination 11-12 years old; can start as young as 9 years old; catch-up vaccination at 13-26 years old
American College of Obstetricians and Gynecologists[54]	Routine vaccination of females aged 9-26 years old
American Cancer Society[55]	Routine vaccination of girls aged 11-12 years old; girls as young as 9 years old may get vaccinated; catch-up vaccination at 13-18 years old; inadequate information for vaccinating women 19-26 years old

Abbreviation: HPV, human papillomavirus.

Chan JK, Berek JS. JCO 2007

Vaccine for men

- 2009 approved for the prevention of genital warts in men 9-26 years.


THANK
YOU!