

HPV Infection and associated cancer and disease

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Objectives

1. Understand HPV transmission and the burden of infection
2. Demonstrate knowledge of HPV related cancer and disease
3. Understand screening for and detecting HPV infection and disease.

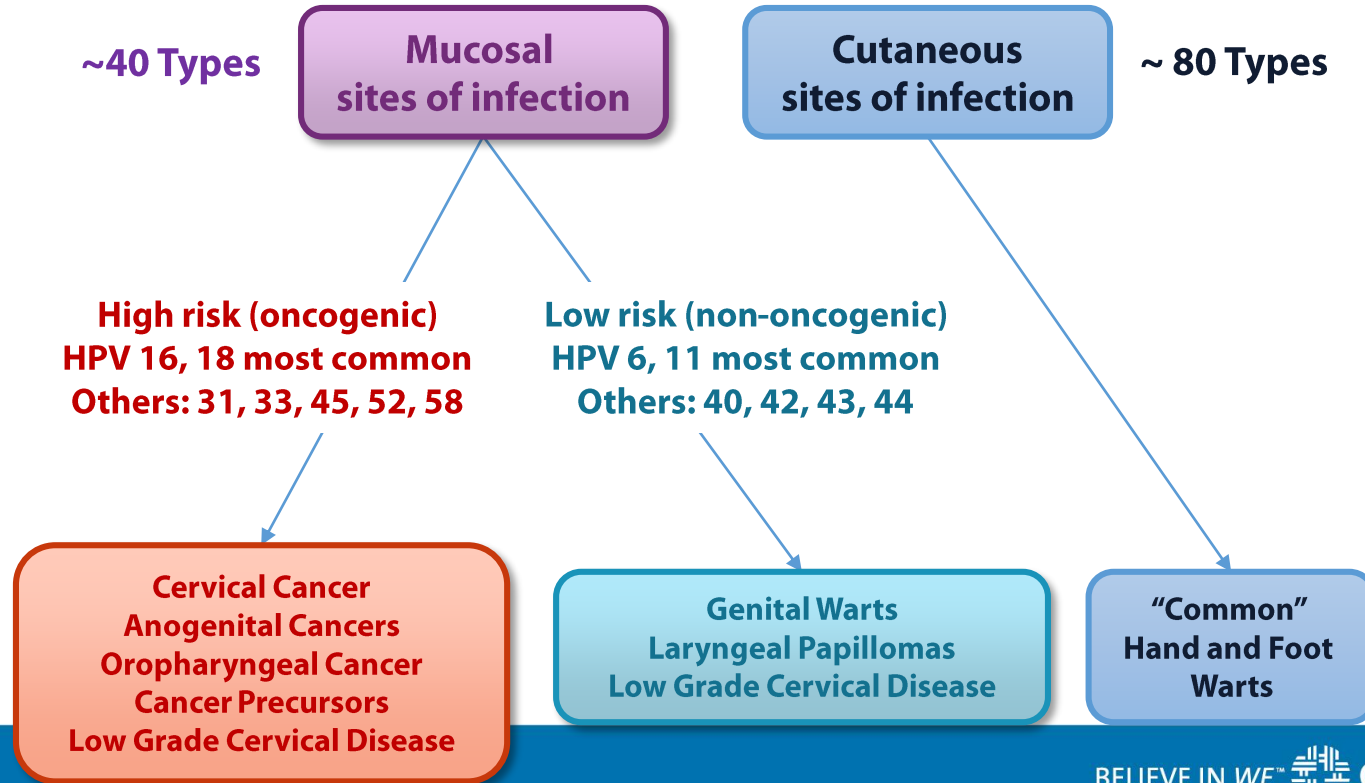
HPV transmission and infection

HPV -- Human papillomavirus

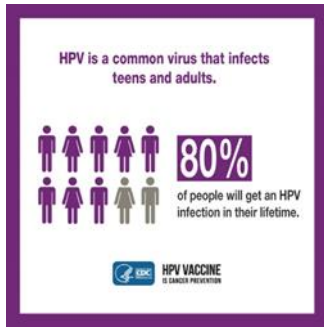
Nonenveloped double-stranded DNA virus



HPV Types Differ in Disease Associations



HPV infection

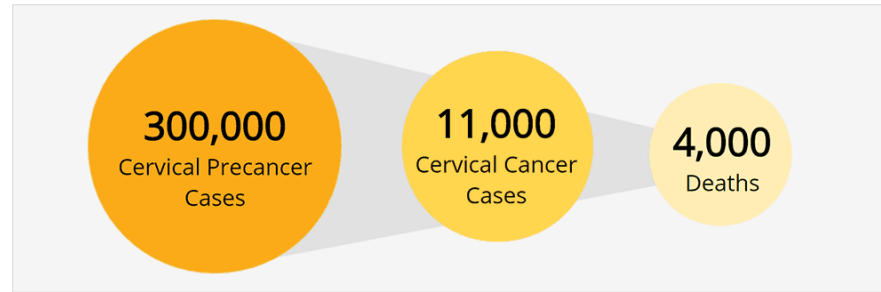
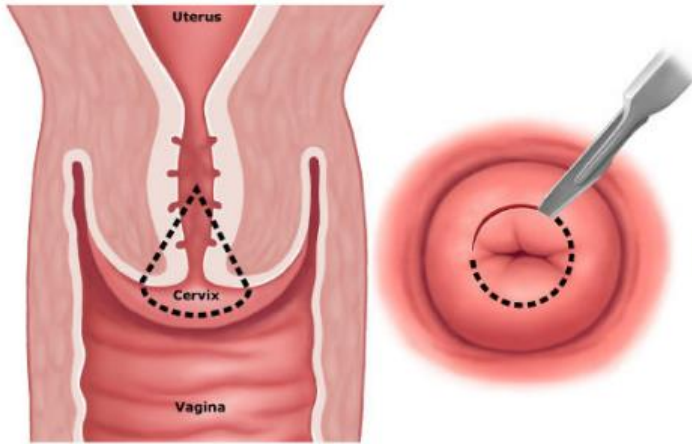


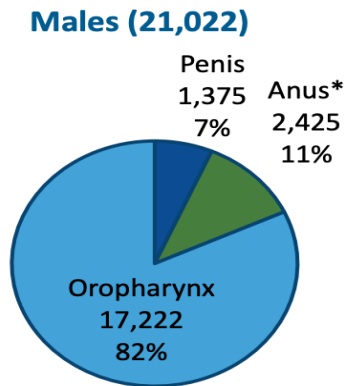
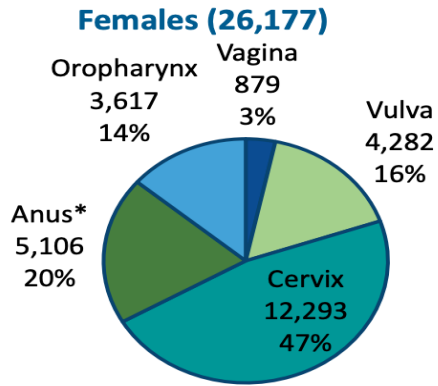
- High risk HPV infection is asymptomatic
- Can occur with any intimate sexual contact
- Almost ALL (80%+) will be infected with at least 1 type HPV
- ~79 million Americans currently infected (~1/4 are currently infected)

- No commercially available test for Men
- Male partners of women with CIN:
 - High risk HPV infection 58%
 - Penile intraepithelial neoplasia 9-33%
- Routine condom use = increased:
 - Regression of CIN lesion: 53% vs 35%
 - Clearance of hrHPV 23% vs 4%

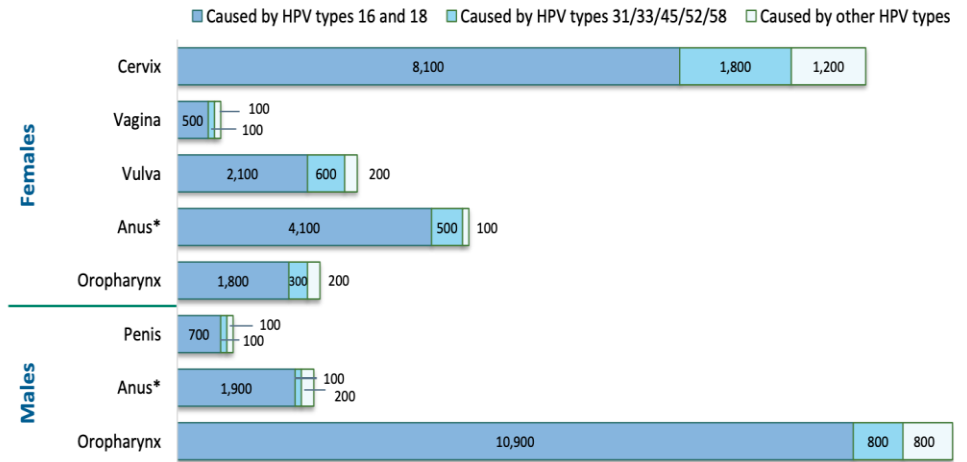
Cervical Precancer in the United States

~196,000 high grade cervical lesions every year





Estimated Annual Number of Cancer Cases Attributable to HPV by Sex, Cancer Type, and HPV type



Centers for Disease Control and Prevention. *Cancers associated with human papillomavirus, United States—2015–2019* USCS Data Brief, no.31. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2022.

Number of HPV-Attributable Cancer Cases per Year

Cancer site	Average number of cancers per year	Percentage probably caused by any HPV type	Estimated number probably caused by any HPV type
Cervix	12,293	91%	11,100
Vagina	879	75%	700
Vulva	4,282	69%	2,900
Penis	1,375	63%	900
Anus	7,531	91%	6,900
Female	5,106	93%	4,700
Male	2,425	89%	2,200
Oropharynx	20,839	70%	14,800
Female	3,617	63%	2,300
Male	17,222	72%	12,500
TOTAL	47,199	79%	37,300
Female	26,177	83%	21,700
Male	21,022	74%	15,600

Data source: National Program of Cancer Registries SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic file 1998–2018. United States Department of Health and Human Services, Centers for Disease Control and Prevention. Released June 2021, based on the 2020 submission. From: <https://www.cdc.gov/cancer/hpv/statistics/cases.htm>. accessed 12/3/22.

HPV is linked with:

91%

of cervical
and anal
cancers

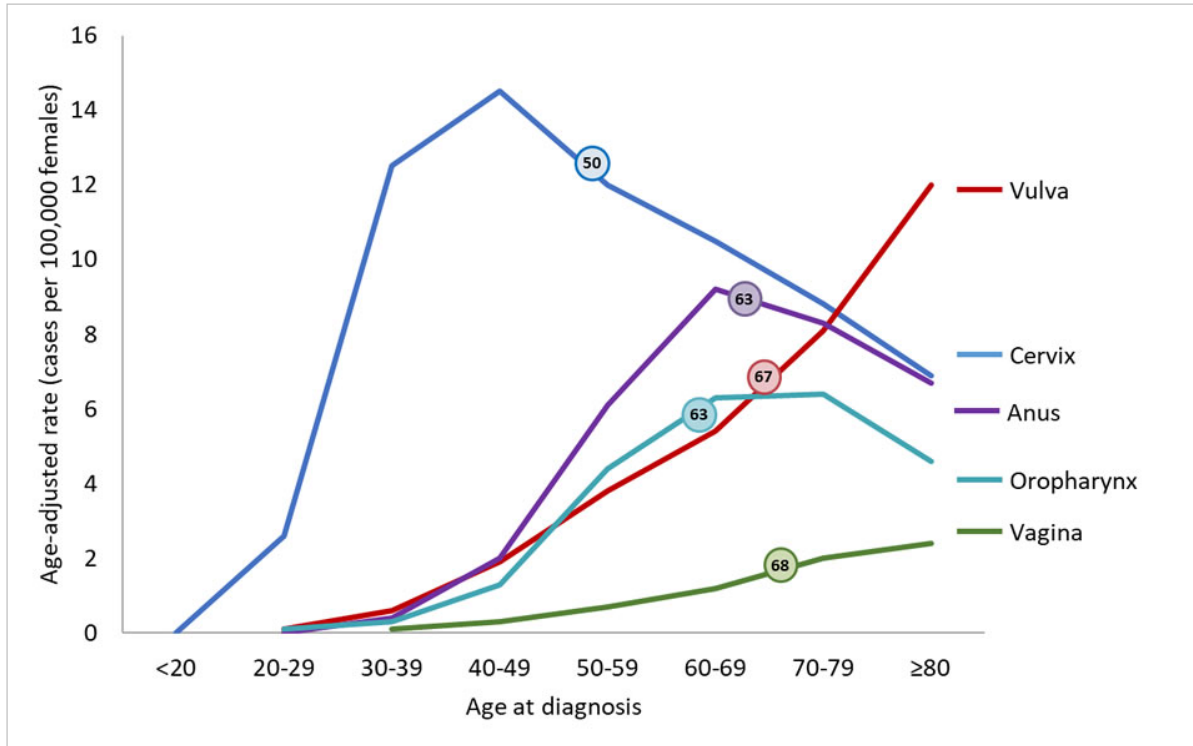
70%

of oropharyngeal
cancers

63%

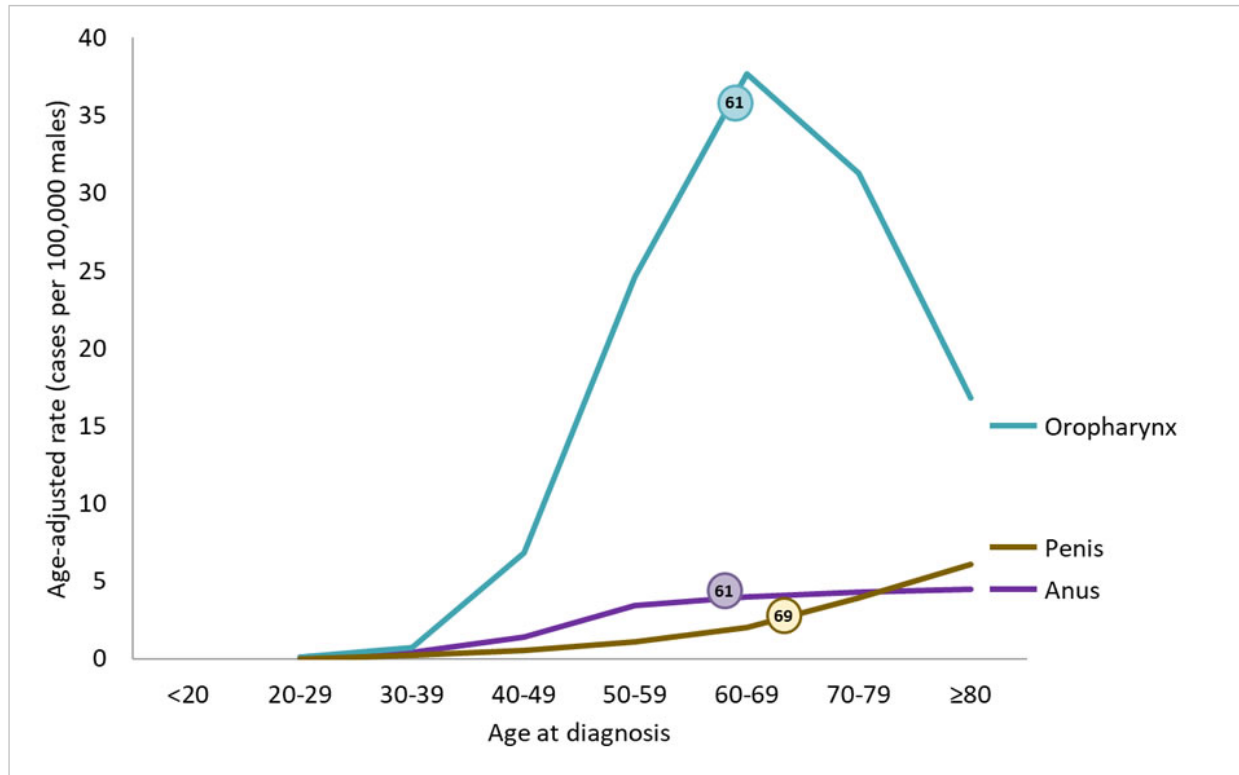
of penile cancers

Rates of HPV-Associated Cancers and Age at Diagnosis Among Women in the United States per Year, 2015–2019



The chart above shows rates by age group for HPV-associated cancers in the United States during 2015–2019. The rates shown are the number of women in each age group who were diagnosed with HPV-associated cancer for every 100,000 women. Rates were not shown for some cancer sites and age groups because there were fewer than 16 cases.

Rates of HPV-Associated Cancers and Age at Diagnosis Among Men in the United States per Year, 2015–2019

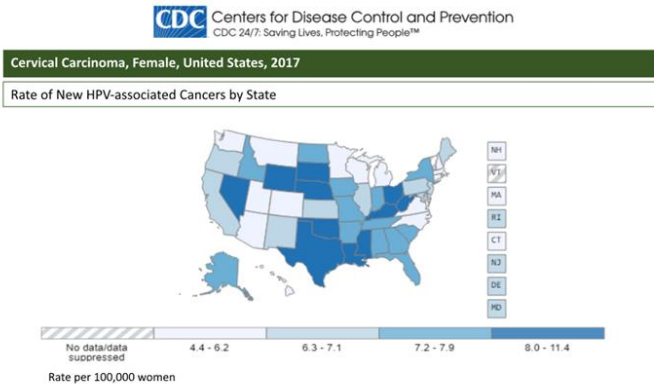


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Cervical Cancer

Epidemiology and Risk Factors

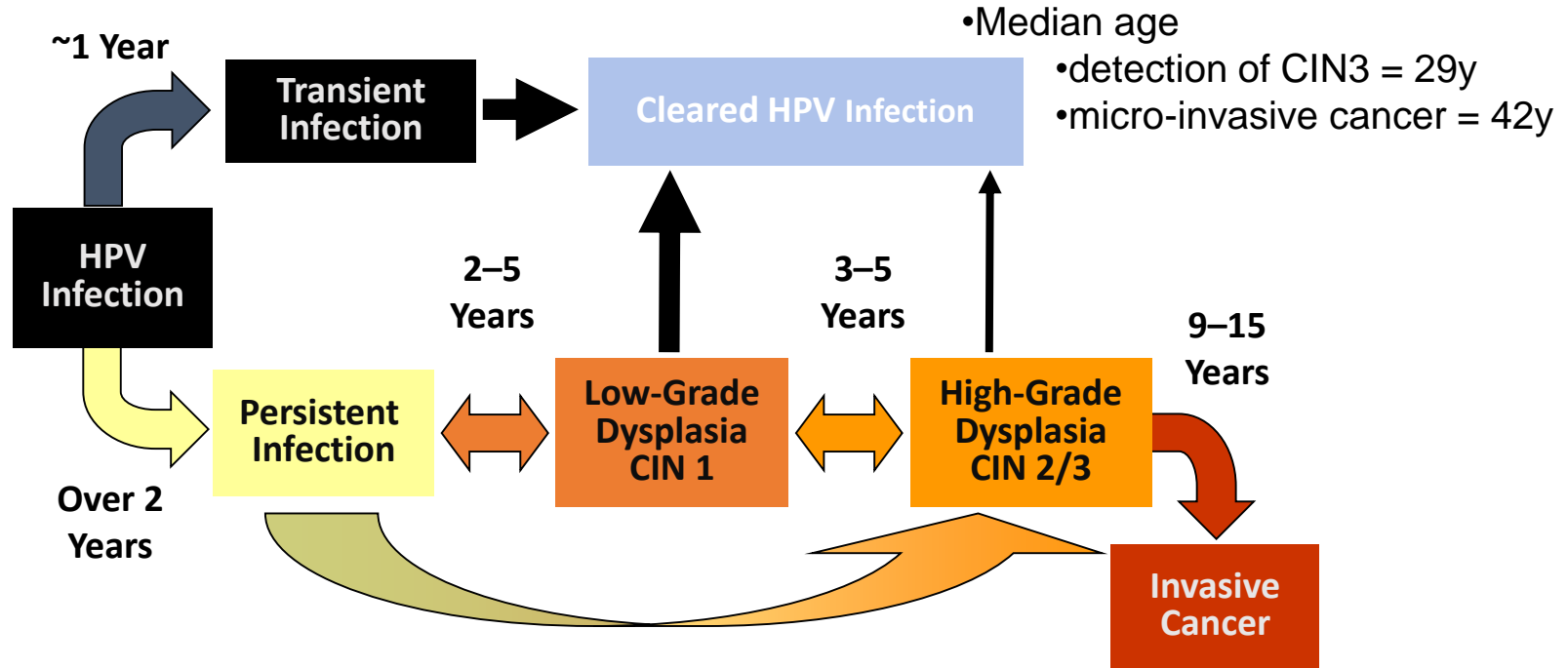
- US
 - 14,500 new cases
 - 4300 deaths
- Race: increased black and Hispanic

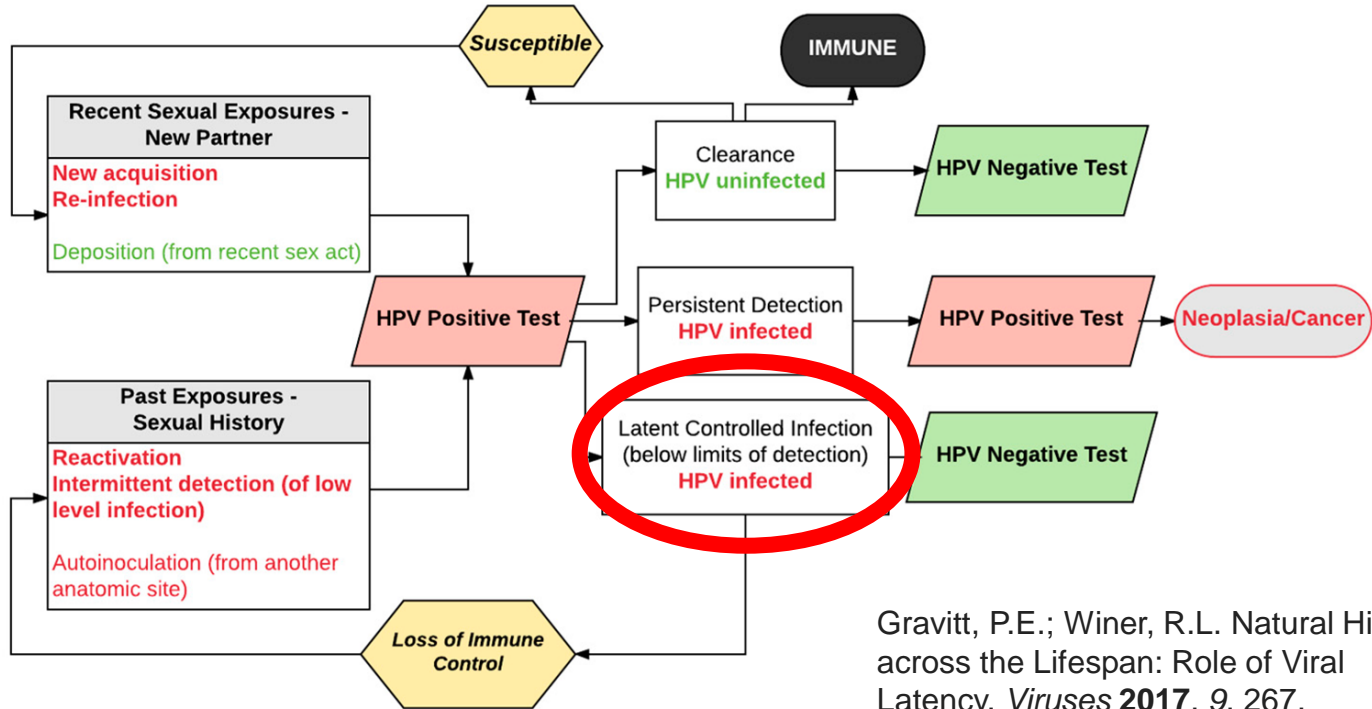


Data source – U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2019 submission data (1999-2017); U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; <https://www.cdc.gov/cancer/dataviz/>, June 2020.

- HPV related
 - Related to increased exposure
 - Multiple/High Risk partners
 - Early onset of sexual activity
 - History of other STI
 - Non-circumcised partner
 - Immunosuppression
- Non-HPV risk factors
 - Low SES (limited access to health care and screening)
 - Smoking (Squamous cell)
 - ?genetic

Natural History of Cervical High-Risk HPV





Gravitt, P.E.; Winer, R.L. Natural History of HPV Infection across the Lifespan: Role of Viral Latency. *Viruses* **2017**, *9*, 267. <https://doi.org/10.3390/v9100267>

Three testing modalities for cervical cancer screening or surveillance

- Primary HPV screening
- Co-testing: HPV and cytology used together
- Cytology alone

ASCCP 2019: cytology alone ONLY acceptable if HPV testing not feasible

- HPV annually = cytology q6m
- HPV q3years = cytology annually

HPV tests used for cervical cancer screening and surveillance [1,2]

Approved indication	Commercial name	Assay target*	DNA/RNA
Cotest or reflex testing (use only in combination with cervical cytology)	Aptima [¶]	Pooled detection of 14 high-risk HPV subtypes ^Δ	RNA
	Aptima HPV 16 and 18/45 [¶]	Specifically reports on the presence or absence of HPV 16 and 18/45	
	Cervista HPV HR [¶]	Pooled detection of 14 high-risk HPV subtypes ^Δ	DNA
	Cervista HPV 16/18 [¶]	Pooled detection of 14 high-risk HPV subtypes ^Δ and specifically reports on the presence or absence of HPV 16 and 18	
Hybrid Capture 2 (HC2) [¶]	Pooled detection of 13 high-risk HPV subtypes [◊]		
Primary test (use without concurrent cervical cytology)	Cobas HPV [¶]	Pooled detection of 12 high-risk HPV subtypes [§] and specifically reports on the presence or absence of HPV 16 and 18	DNA
	BD Onclarity [¶]	Specifically reports on the presence or absence of 14 high-risk HPV subtypes ^Δ (individual results for 6 HPV subtypes [16, 18, 31, 45, 51, and 52] and grouped results for the remaining subtypes [33/58, 35/39/68, and 56/59/66])	
	Cepheid Xpert HPV [‡]	Pooled detection of 11 high-risk HPV subtypes [‡] and specifically reports on the presence or absence of HPV 16 and 18/45	
	Qiagen careHPV [‡]	Pooled detection of 14 high-risk HPV subtypes ^Δ	

HPV: human papillomavirus; HR: high-risk.

* A positive pooled result indicates that at least one high-risk HPV subtype was detected. The test cannot identify the HPV subtype or whether one or more HPV subtypes are present, unless otherwise indicated.

¶ US Food and Drug Administration approval.

Δ The 14 high-risk HPV subtypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

◊ The 13 high-risk HPV subtypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

§ The 12 high-risk HPV subtypes include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

‡ World Health Organization prequalified.

‡ The 11 high-risk HPV subtypes include 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and 68.

References:

1. Integrating HPV testing in cervical cancer screening program: a manual for program managers, Pan American Health Organization 2016.
2. Fontham ET, Wolf AM, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020.

Average Risk Patient Screening

- Asymptomatic
- Immunocompetent
- All normal cervical cancer screening results in the past, exceptions
 - Age <25 with ASCUS, HPV negative
 - Age <25 with LSIL or HPV+ ASCUS followed by two consecutive negative cytology
 - Age >25 with LSIL, HPV+ ASCUS, or HPV+ NIML → colpo no CIN2+ → three consecutive negative co-testing
- Age 21-29 (USPSTF 2018)
 - Cytology every 3 years
- Age ≥30 (USPSTF 2018)
 - Primary HPV testing q5 years
 - Co-testing (pap and HPV) q5 years
 - Pap test q3 years
- Age ≥25 (ACS 2020)
 - Primary HPV testing q5 years
 - Co-testing (pap and HPV) q5 years
 - Pap test q3 years

HPV based preferred

Higher Risk Patients -- immunosuppressed

- HIV positive patients
- Solid Organ Transplant
- Allogenic hematopoietic stem cell transplant
- System Lupus erythematosus
- Inflammatory bowel disease requiring **current** immunosuppressive treatment
- Rheumatologic disease requiring **current** immunosuppressive treatment

Higher Risk Patient Screening

- Initial Screening

- HIV (or immunosuppression)
<21: initiate 1 year after sexual activity or age 21
- <30yo: cytology along
- ≥25-30yo: **co-testing** or cytology
- Screening colposcopy with exam of vulva, vagina, anus

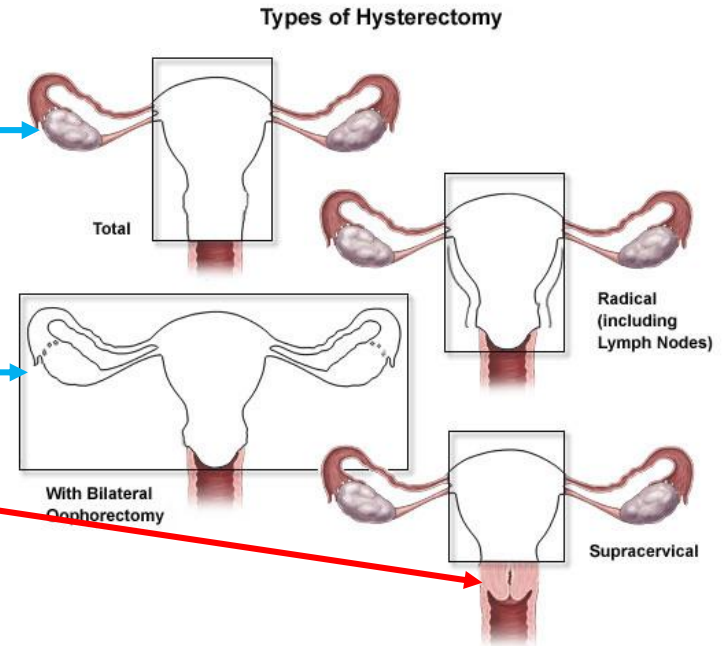
- Subsequent screening

- Cytology
 - Q12m x 3 years
 - Then q3 years
- **Co-testing (≥25-30)**
 - Q3 year screening (do not need yearly x 3)

****Co-testing preferred****

Post-Hysterectomy Screening

- Total hysterectomy (with removal of cervix) **with no history of cervical cancer or CIN** → stop screening
- Sub-total hysterectomy or supra-cervical → **cervix is present** → keep screening!
- Unsure: need exam to check

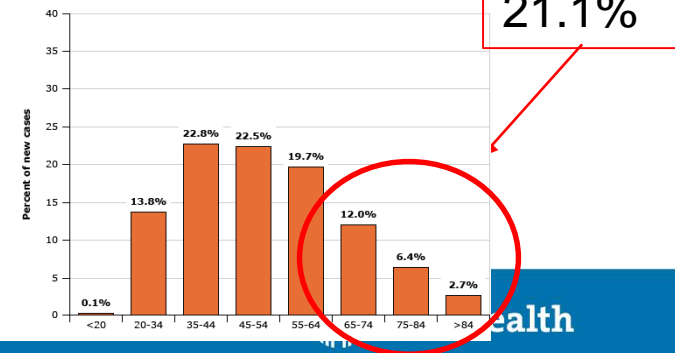


When to stop cervical cancer screening

- Consider at age 65 if:
 - No history of CIN 2+ for 25 years
 - Adequate prior screening
 - Two consecutive negative HPV tests in last 10 years, one within 5 years
 - Two consecutive negative co-tests in last 10 years, one within 5 years
 - Three consecutive negative pap tests in last 10 years
 - No new partners

- Continue if:
 - No adequate screening
 - New partners
 - h/o CIN 2+
- Recommend to continue if life expectancy >10 years

Percent of new cases by age group: Cervical cancer*



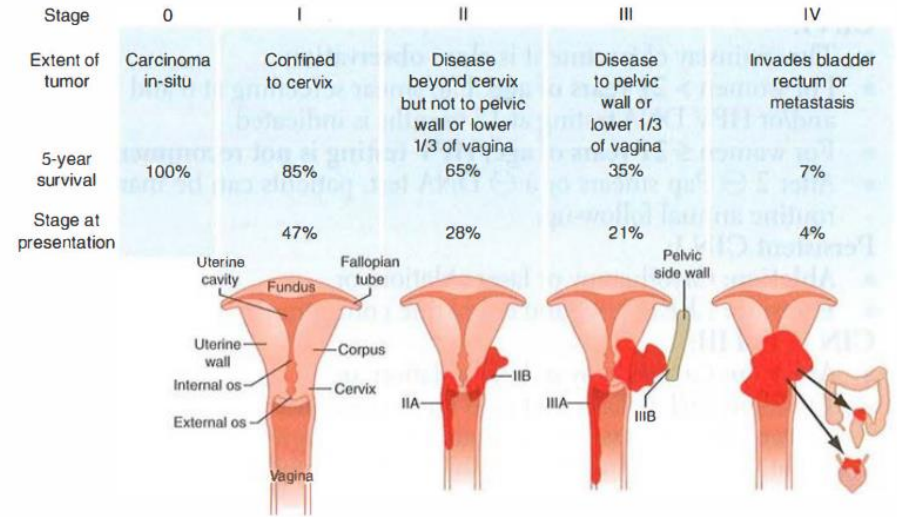
Reproduced from: SEER Cancer Stat Facts: Cervical cancer. National Cancer Institute. Available at: <https://seer.cancer.gov/statfacts/html/cervix.html> (Accessed on August 28, 2020)

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Health

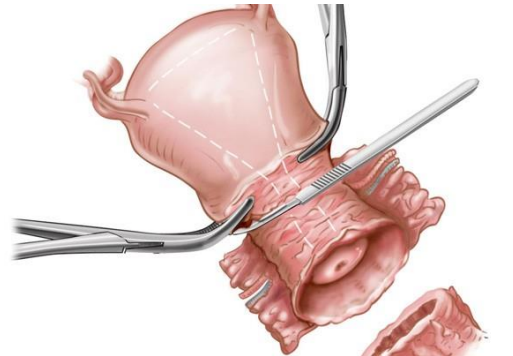
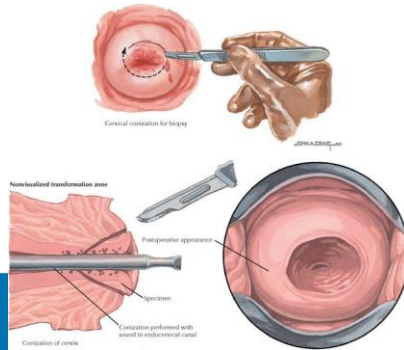
Diagnosis

- Asymptomatic in early stages
 - screening testing pap/hpv
 - Colposcopy and biopsy after abnormal screening test
- Endocervical tumors and those below the epithelium care impossible to visualize on exam
- Pap test: 50% false negative in symptomatic patients
- **BIOPSY ESSENTIAL** for any lesion or abnormal cervix



Treatment

- Cervical lesion <4 cm
 - Radical hysterectomy with lymph node dissection
 - **<2cm: fertility preservation possible with conization or trachelectomy**
- Cervical lesion > 4cm
 - Primary chemotherapy/radiation vs surgery
- Positive lymph nodes/locally advanced disease
 - Primary chemotherapy/radiation
- Metastatic disease
 - Chemotherapy/immunotherapy
 - Other targeted agents

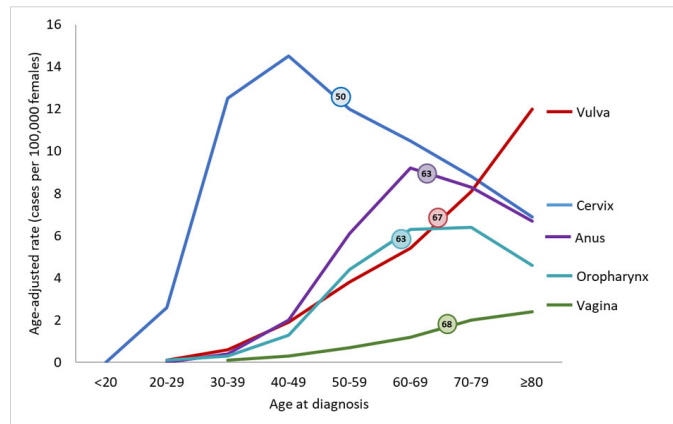


Vulvar cancer

Vulvar cancer

- US Incidence
 - 6330 new cases
 - 1560 deaths
- Risk Factors
 - History of cervical dysplasia/cancer (HPV)
 - Cigarette smoking
 - Lichen sclerosus
 - Immunosuppression
- Etiology
 - HPV
 - Chronic inflammation: vulvar dystrophy (Lichen sclerosus)

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- Squamous cell carcinoma most common (75%)
- Less common histology: basal cell carcinoma, Bartholin gland adenocarcinoma, sarcoma, and Paget disease

Diagnosis and Survival

- Symptoms
 - Itching or burning
 - Pain
 - Bleeding
- Delay in diagnosis is common
- Exam and biopsy essential
- Stage at diagnosis
 - Local: 59%
 - Regional: 30%
 - Distant: 6%

Survival by FIGO stage for patients with vulvar cancer 1999 to 2001 FIGO statistics

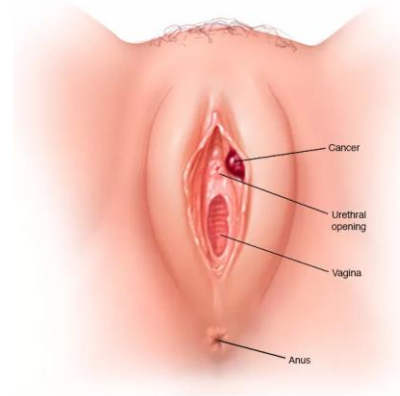
FIGO stage	Number of patients	Overall survival (percent)		
		One year	Two years	Five years
I	286	96.4	90.4	78.5
II	266	87.6	73.2	58.8
III	216	74.7	53.8	43.2
IV	71	35.3	16.9	13.0

FIGO: International Federation of Gynecology and Obstetrics.

Original table modified for this publication. From: Beller U, Quinn MA, Benedet JL, et al. Carcinoma of the vulva. Int J Gynaecol Obstet 2006; 95:S7. Table used with the permission of Elsevier Inc. All rights reserved.

Treatment

- Vulvar mass amenable to resection: Surgical excision with lymph node evaluation
 - Adjuvant radiation
- Unresectable: Primary radiation with chemotherapy
- Metastatic/recurrent disease: Palliative chemotherapy and/or immunotherapy



Vaginal cancer

Vaginal cancer

- Incidence
 - New cases:1,368
 - Deaths: 431
- Risk factors
 - Previous cervical, vulvar, anal dysplasia/cancer
 - Smoking
 - Immunosuppression
- Etiology
 - HPV infection
- Symptoms
 - Asymptomatic (can be detected via pap/hpv)
 - Vaginal bleeding
 - Pain, urinary symptoms
- Diagnosis
 - Exam and biopsy
 - CT unlikely to detect vaginal lesions (useful for staging)
- Treatment
 - Surgery (small lesions)
 - Radiation
 - Chemotherapy/immunotherapy

Anal and Rectal squamous cell carcinoma

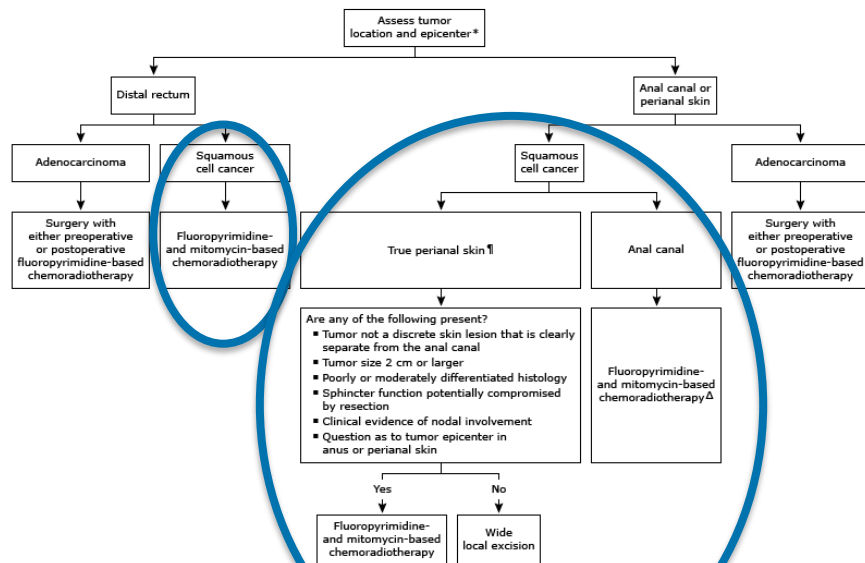
Anal cancer

- Incidence
 - New cases: 9,440
 - Deaths: 1,670
- Etiology
 - HPV infection (90+%)
- Symptoms
 - Bleeding : 40%
 - Rectal mass: 30%
 - No symptom: 20%
- Risk factors
 - MSM
 - History of cervical dysplasia or malignancy
 - History of anorectal condyloma (30-50% vs 1-2% general population)
 - HPV infection
 - Smoking
 - Immunosuppression

Anal dysplasia and cancer screening

- High risk groups to consider screening
 - HIV positive people
 - People who have penile anal intercourse (MSM)
 - Immunosuppression (Transplant patients, long term steroid use)
 - People with history of high grade cervical, vaginal, vulvar dysplasia
 - History of anal warts
- Similar to cervical screening....
 - Anal cytology
 - High resolution anoscopy
- Referral to colorectal surgery or a group that does anoscopy!!

Algorithmic approach to initial treatment for localized tumors of the anus, based on tumor location and histology



* Determination of the anatomic site of origin of carcinomas that overlap the anorectal junction can be problematic. For staging purposes, such tumors are classified as rectal cancers if their epicenter is located more than 2 cm proximal to the dentate line or proximal to the anorectal ring on digital examination, and as anal canal cancers if their epicenter is 2 cm or less from the dentate line. The majority of rectal squamous cell cancers represent anal squamous cell cancers that have extended into the distal rectum.

† Tumors that arise within the skin at or distal to the squamous mucocutaneous junction that can be seen in their entirety with gentle traction placed on the buttocks and are within 5 cm of the anus are classified as perianal skin cancers.

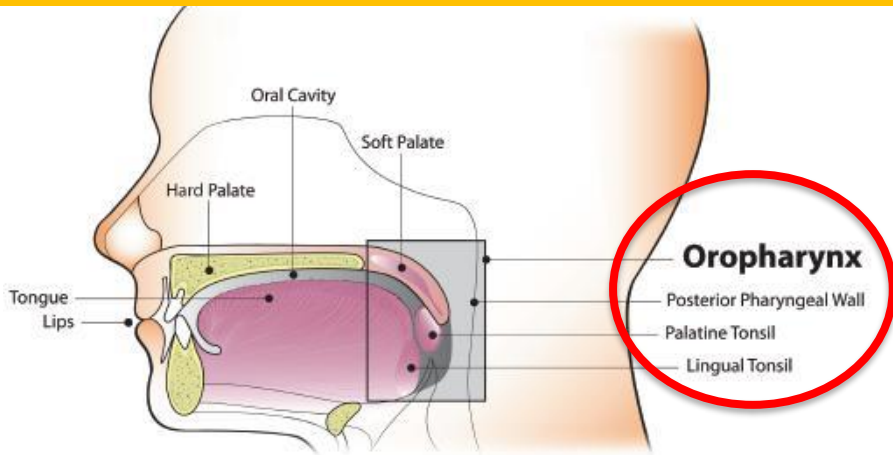
Δ Local excision may be an option for carefully selected patients with very favorable, superficially invasive tumors that are completely excised and have ≤3 mm of basement membrane invasion and a maximal horizontal spread of ≤7 mm. For the extremely aged population with T1N0 tumors or those with significant comorbidities, elimination of mitomycin and administration of fluorouracil alone during radiation therapy could be considered.

	5-year survival
T2N0	82%
T3N0	74%
T4N0	57%
T2N+	70%
T3N+	57%
T4N+	42%

Welton ML, Steele SR, Goodman KA, et al. Anus. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.275.

Oropharyngeal cancer – HPV related

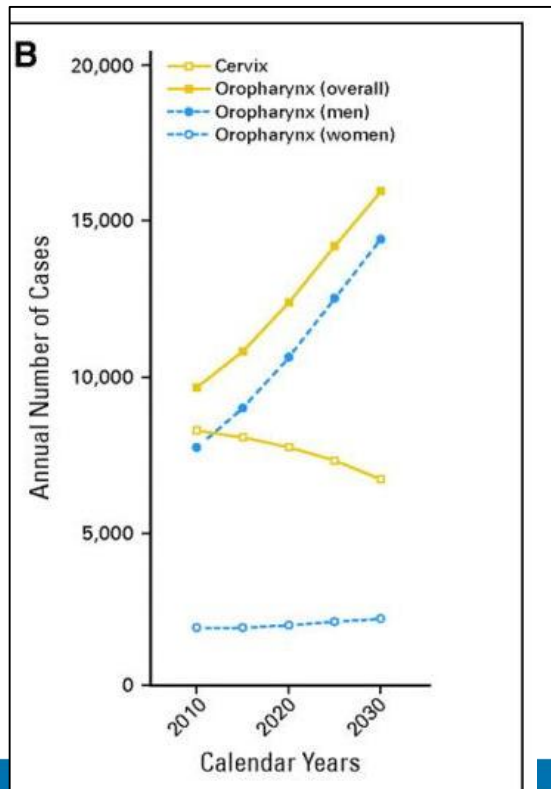
Oropharyngeal cancer is the most common HPV related cancer among males



There is **no** effective screening tool for oropharyngeal cancer.

HPV is not considered a cause of cancers in the mouth, larynx, lip, nose, or salivary glands.

Rates of oropharyngeal and cervical cancers



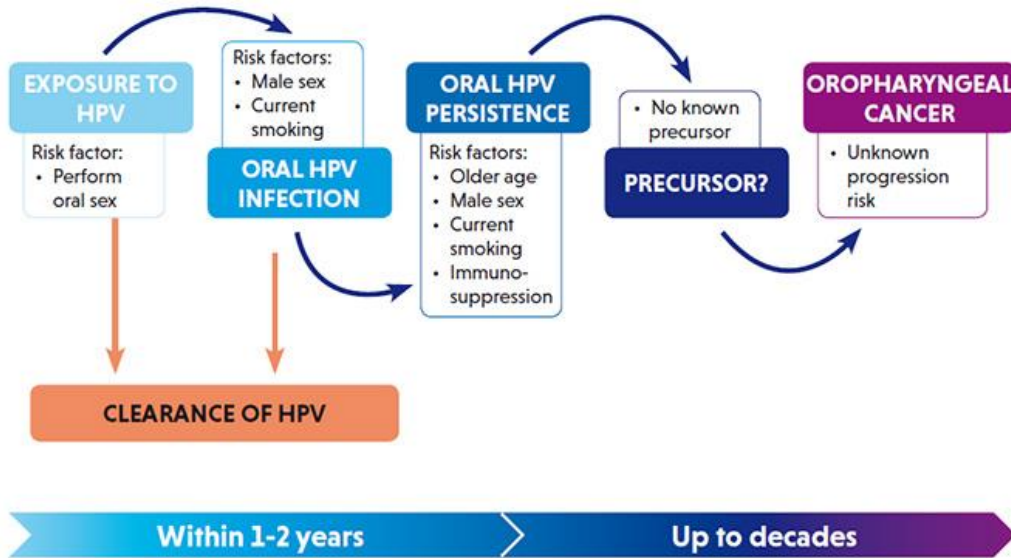
Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011 Nov 10;29(32):4294-301.

HPV associated oropharyngeal cancer

- Incidence
 - New cases ~20k
 - Deaths
- Risk factors
 - HPV 16 (and other HR)
 - Smoking
 - Immunosuppression
- Presentation
 - Neck mass
 - Less likely to have classic symptoms of odynophagia and otalgia
- Diagnosis
 - Examination
 - Laryngoscopy
 - Biopsy/FNA of neck mass
- Treatment
 - Radiation and chemotherapy

Figure 1

Natural history of HPV-related oropharyngeal cancer: knowns and unknowns.



- Potential biomarkers identified
 - systemic HPV antibodies
 - oral HPV DNA
- Screening limited by several factors
 - No known precursor lesion
 - Inability to detect early malignancy
 - no proven risk-mitigation strategies for the prevention of cancer

Treatment

- T1/T2: small tumor – surgical excision with negative margins
 - Adjuvant RT in select patients
- Locally advanced disease: primary chemotherapy/radiation
- Metastatic disease: palliative chemotherapy or immunotherapy or other targeted agents

Final Reminder.....

HPV is linked with:

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63%

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