

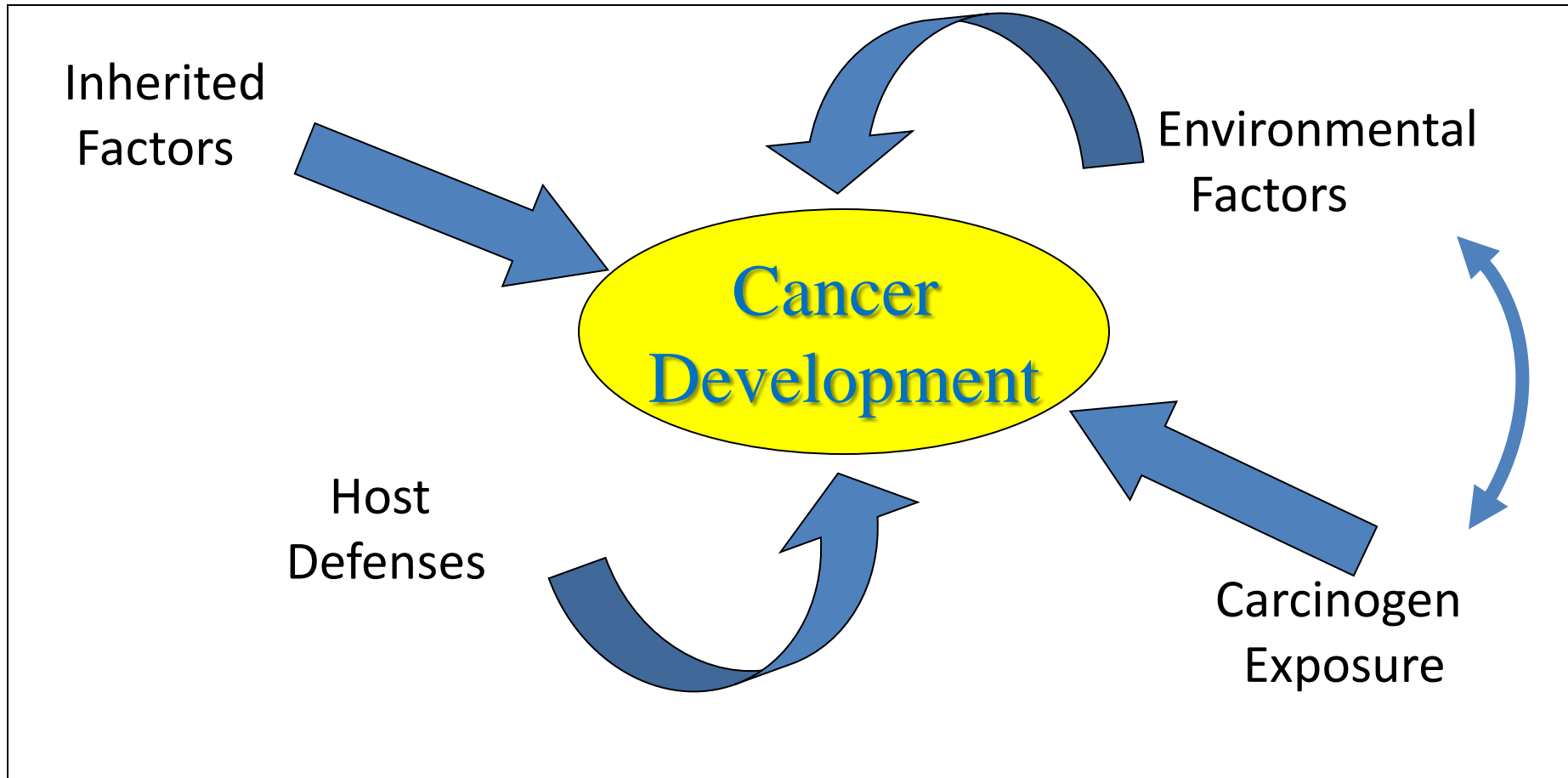
Head and neck cancer and Fanconi anemia

Bhuvanesh Singh, MD, PhD

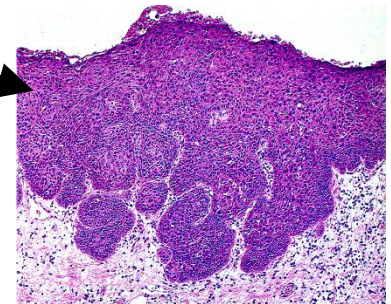
Associate Attending Surgeon

Memorial Sloan-Kettering Cancer Center

Factors promoting cancer development



Genetics- An overview

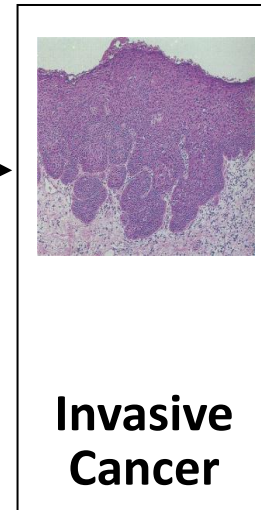
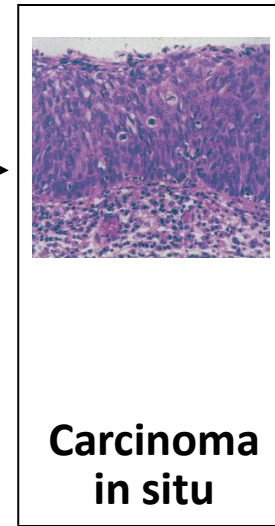
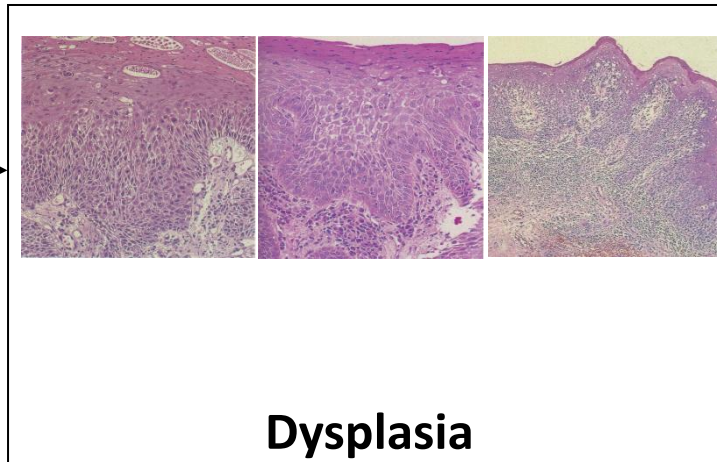
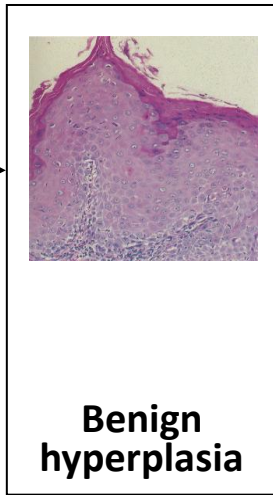
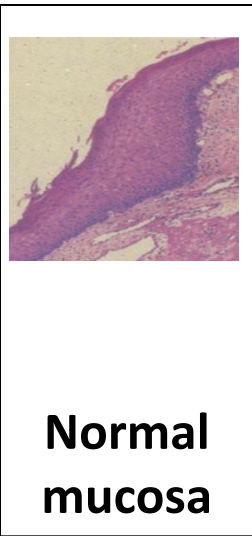


Head and neck cancer pathogenesis

Genomic instability

0

>10,000 mutations

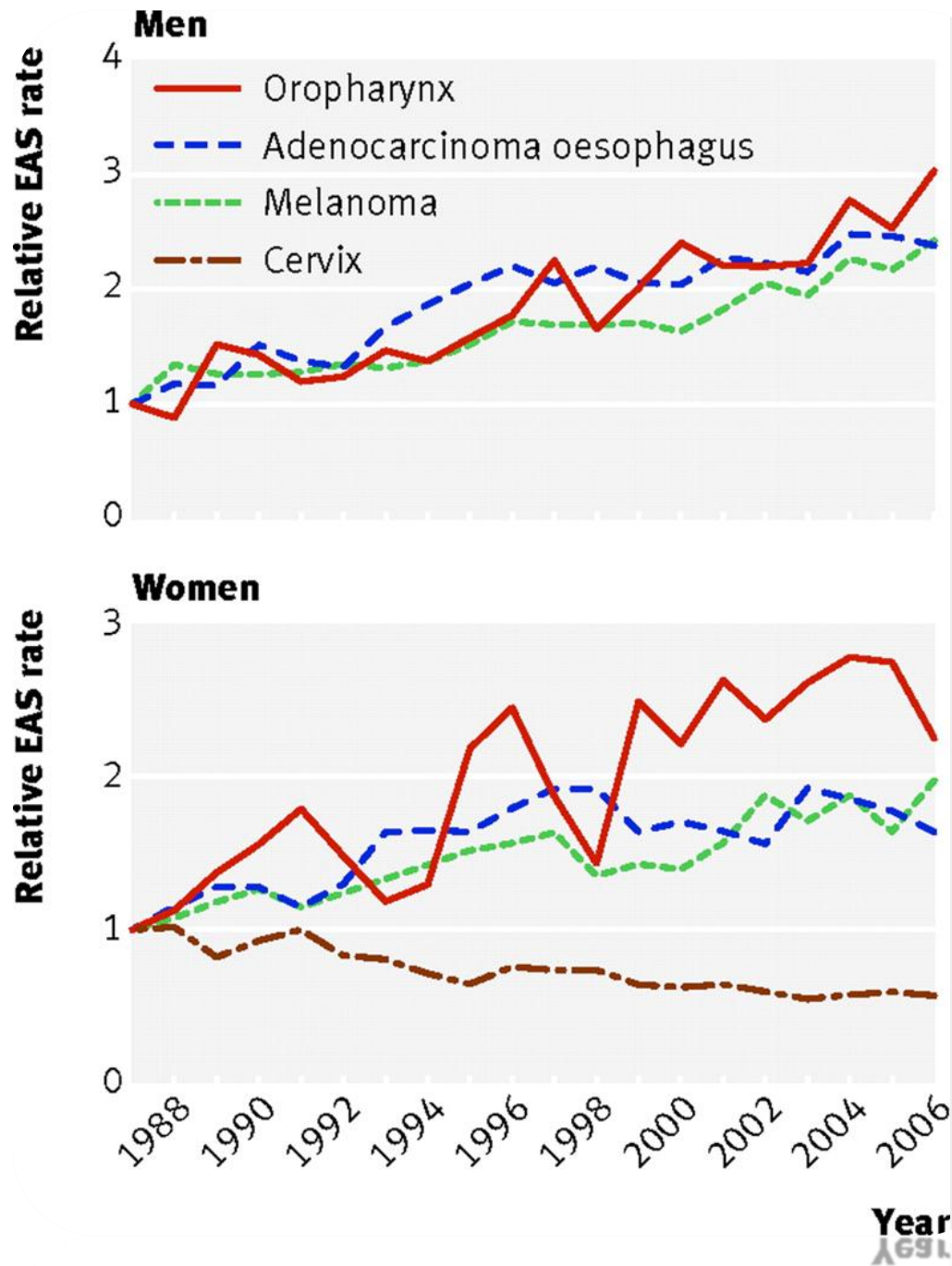


Factors predisposing to the accumulation of genetic events

- Carcinogen exposure
 - Tobacco
 - Alcohol
- Inherited factors

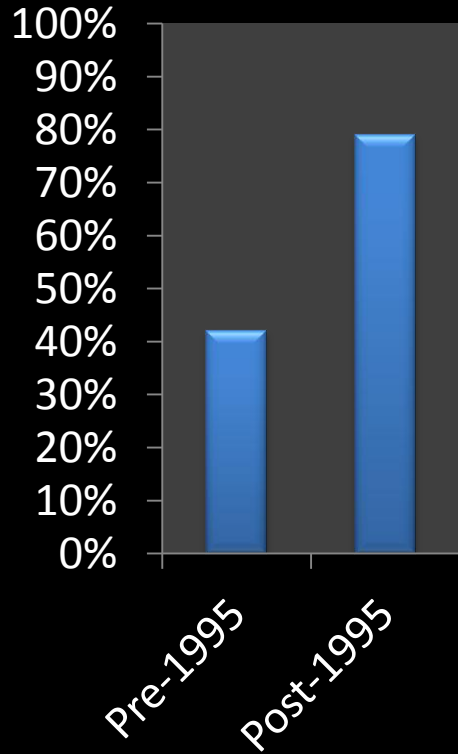
Familial HNSCC

- Susceptibility to carcinogens modified by many factors
 - First degree family members w/ 2-14 fold increase HNSCC risk—related to tobacco use
 - Non-smokers who get head and neck cancer
 - Issues of second hand smoke
- Activating carcinogens
 - Cytochrome p450 (CYP1- meta analysis)
- Clearing carcinogens (detoxifying enzymes)
 - *GSTM1*
- Repairing tobacco induced damage
 - XRCC1

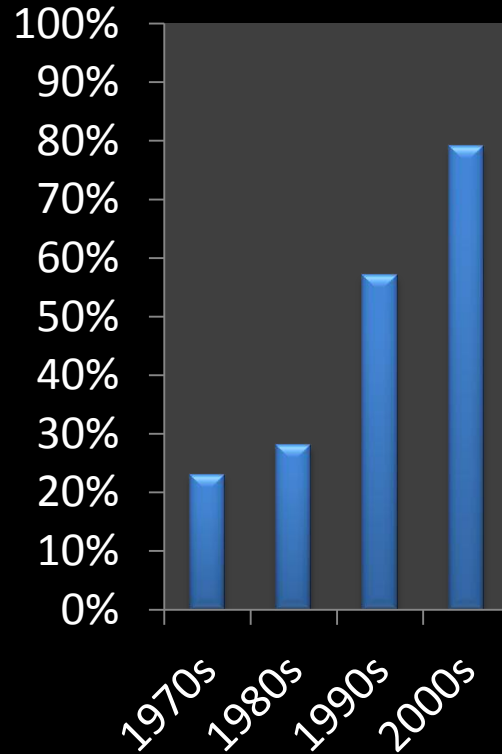


Rising prevalence of HPV+ oropharyngeal cancer

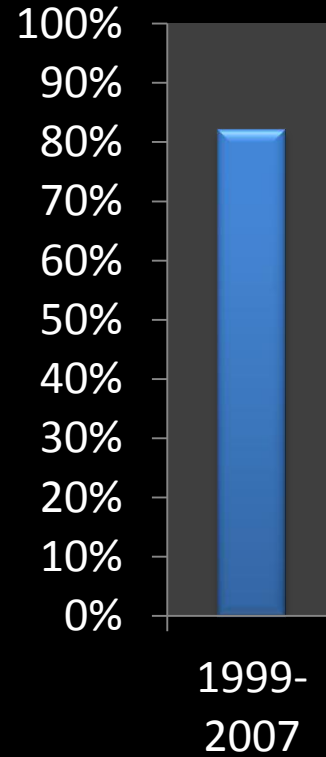
Colorado



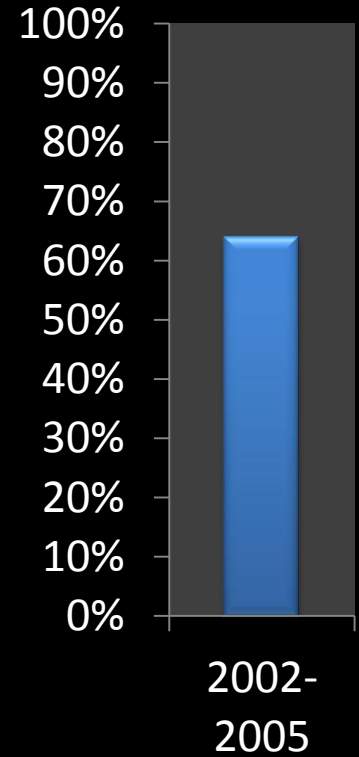
Sweden



Michigan



RTOG 0192



Ernster et al, Laryngoscope 2007
Nasman et al, Int J Cancer 2009
Maxwell et al, ClinCancer Res 2010
Ang et al, NEJM 2010

Emerging role of HPV

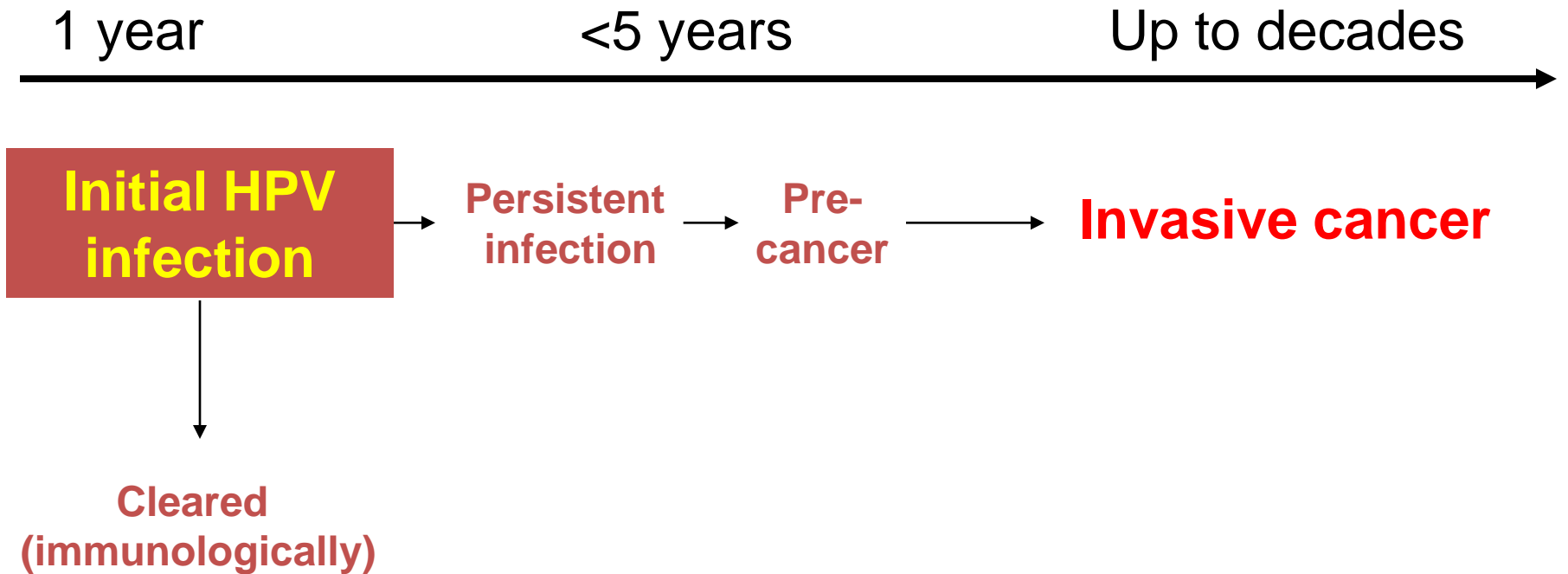
- Meta analysis-- 26% of HNSCC with HPV
 - >40-50% of oropharyngeal cancers (exp. tonsillar cancers)
- Related to sexual history
- Predilection for non-smokers
- Basaloid histology

Gillison. JNCI 2000

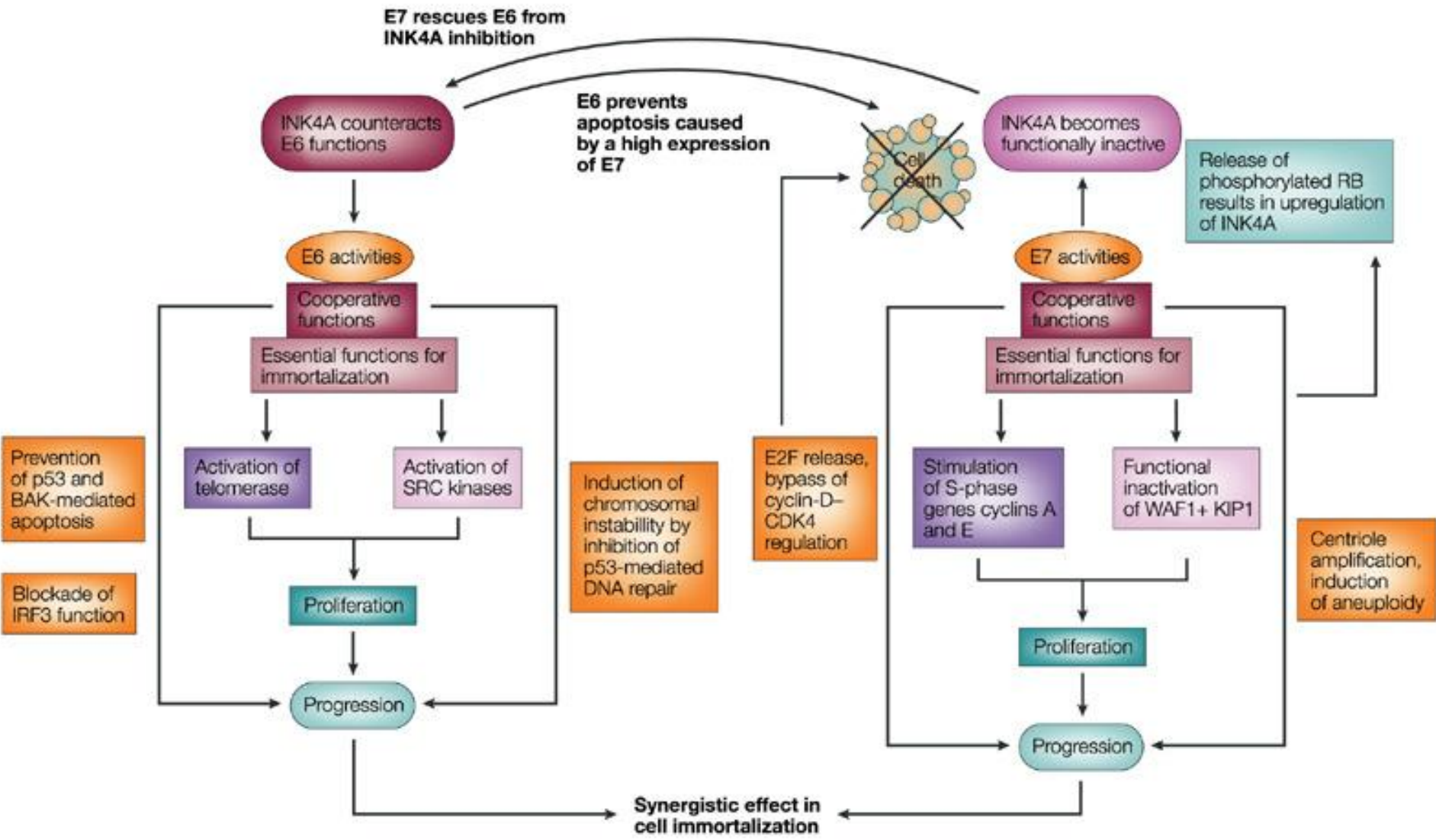
Weinberg. JCO 2006

Kutler...Singh JNCI 2004

Natural course of HPV infection



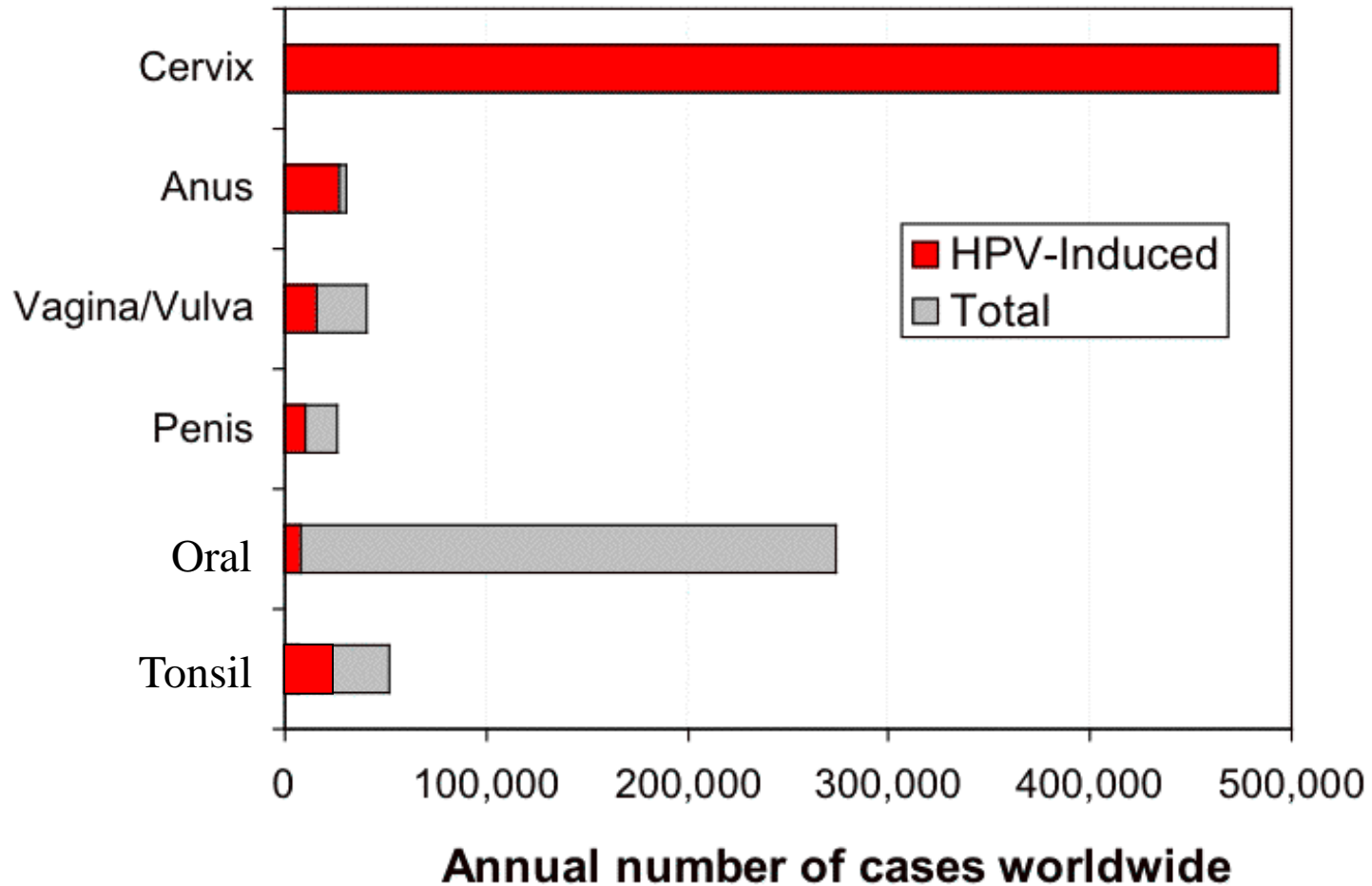
Mechanism of HPV induced oncogenesis



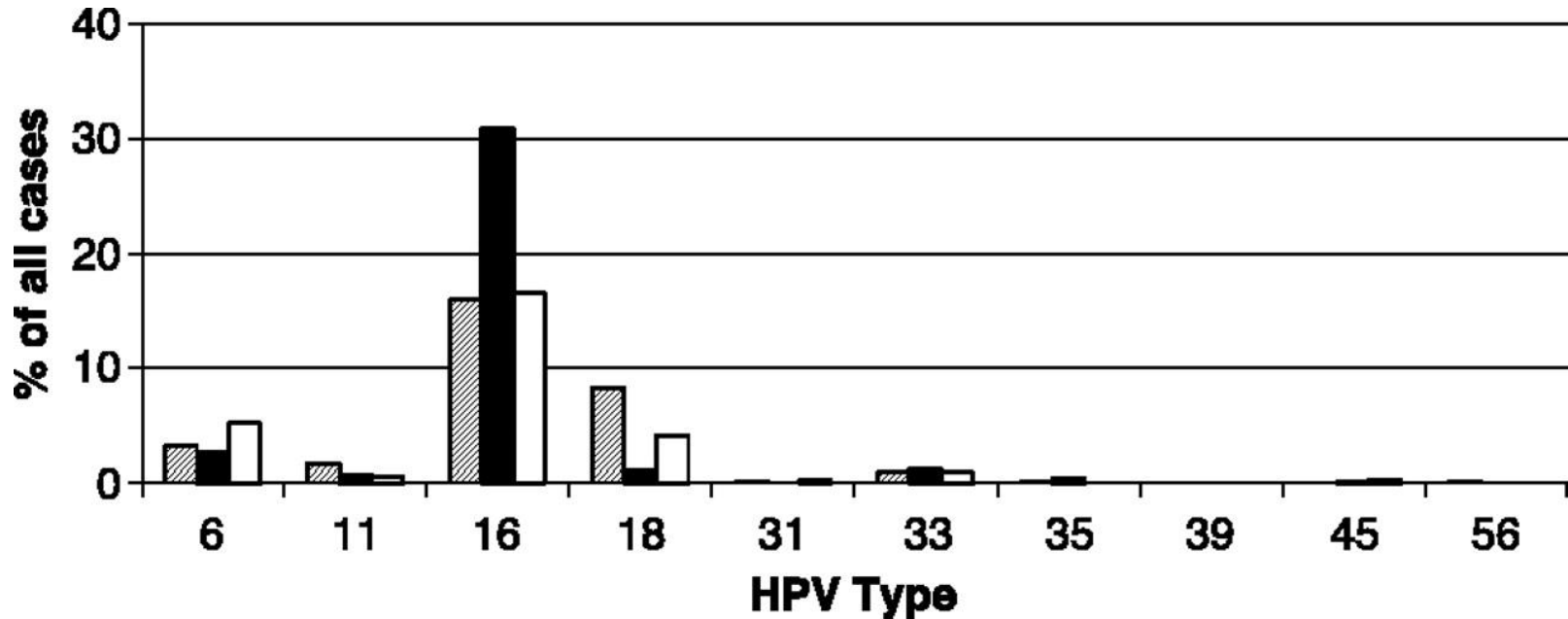
HPV

- More than 100 types
- 40 types infect mucosal tissues
 - High risk “oncogenic types”
 - 16, 18, 31, 33, 35, 45, 52,...
 - Low risk types
 - 6, 11, 42, 43, 44, ...

HPV associated cancer distribution

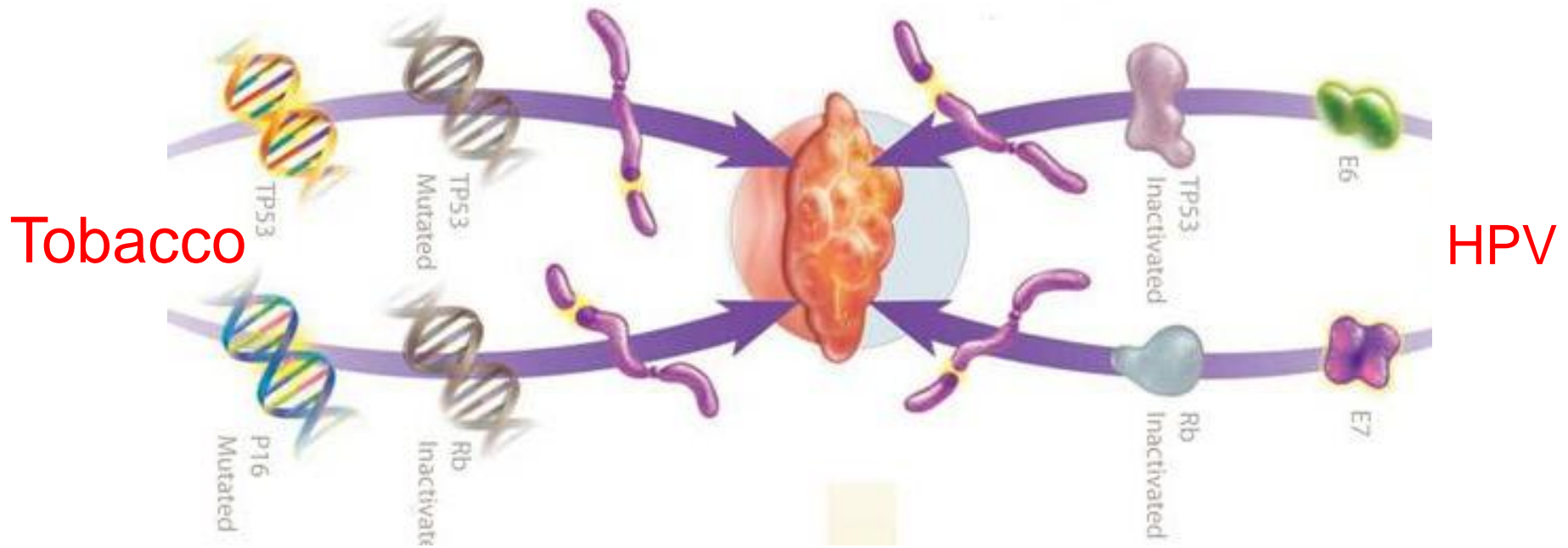


Distribution of HPV types in HNSCC

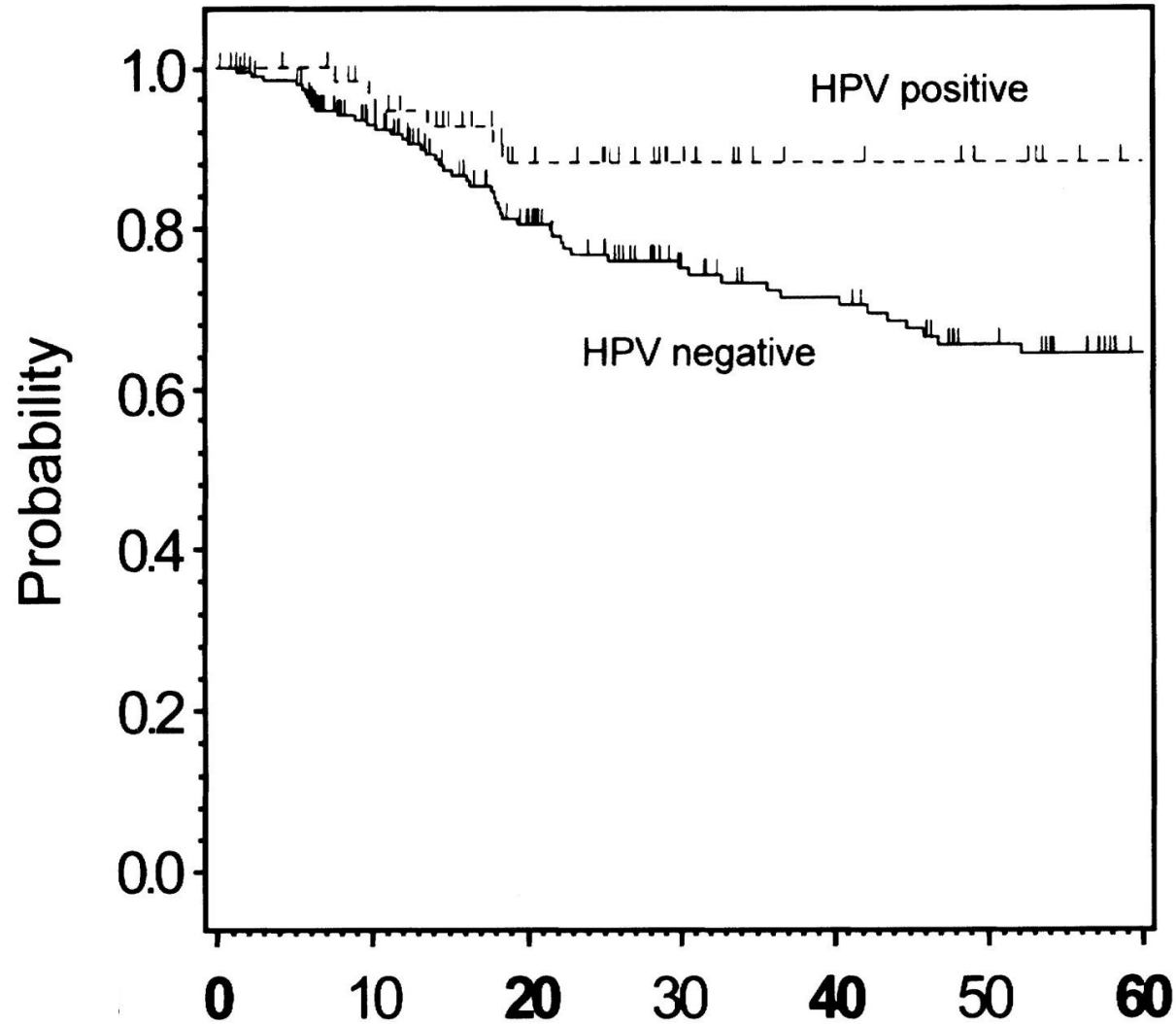


Increased prevalence in oropharynx

Different paths --same cancer?



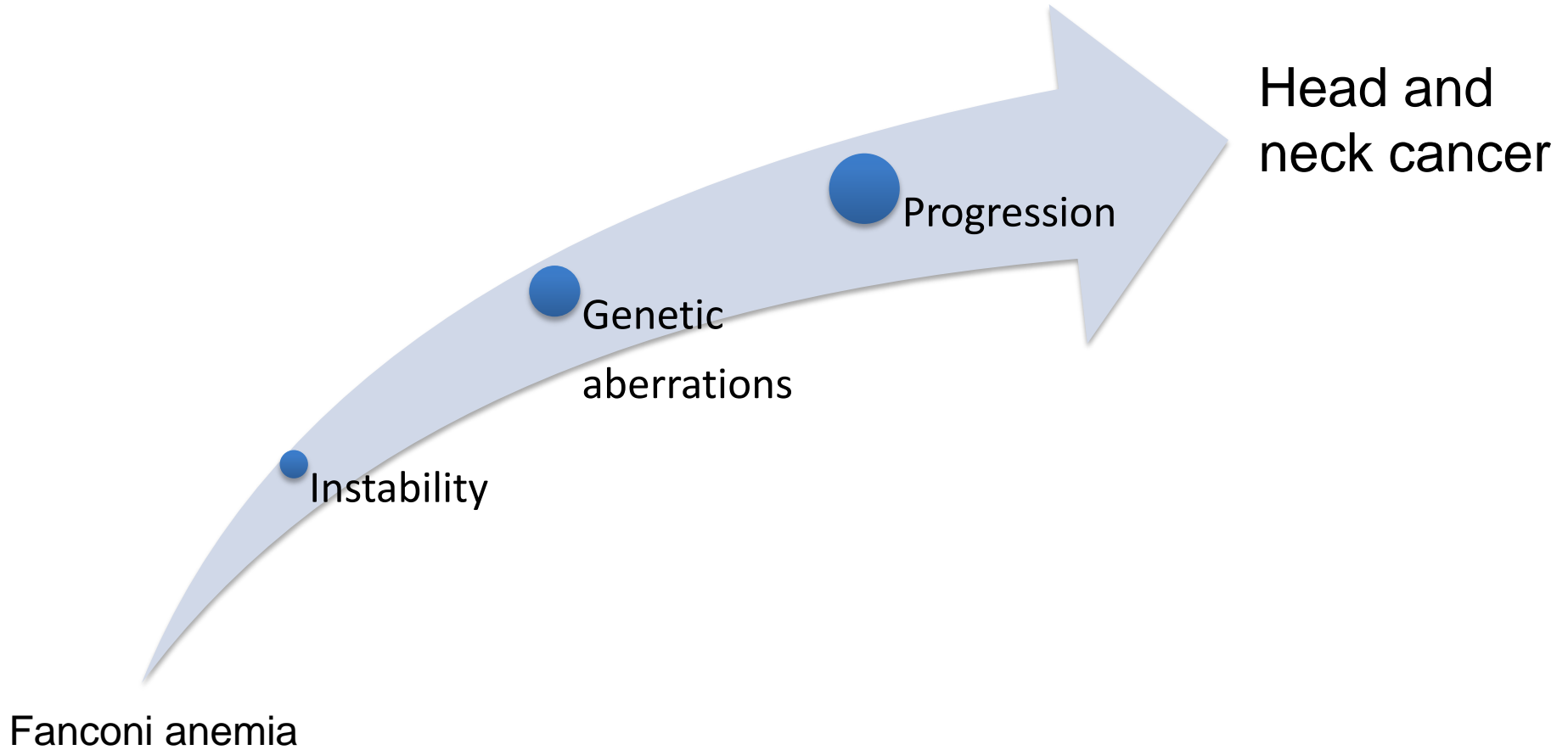
Survival in HPV-HNSCC



Clinical trials analysis

	HPV +	HPV-
Tax 324	79%	31%
ECOG 2399	95%	62%
RTOG 0129	82%	57%
RTOG 9003	60%	29%

Different path to HNSCC in FA?

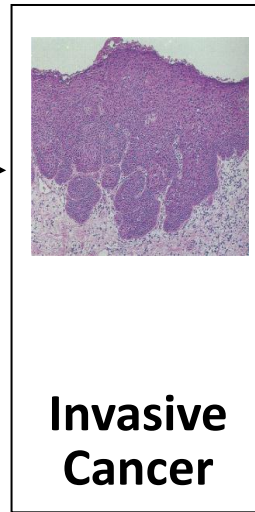
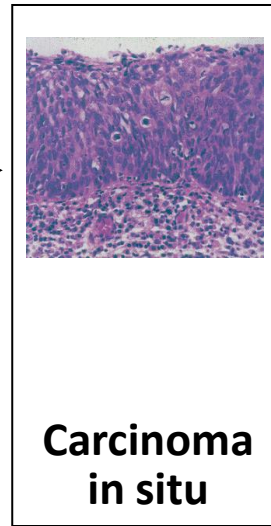
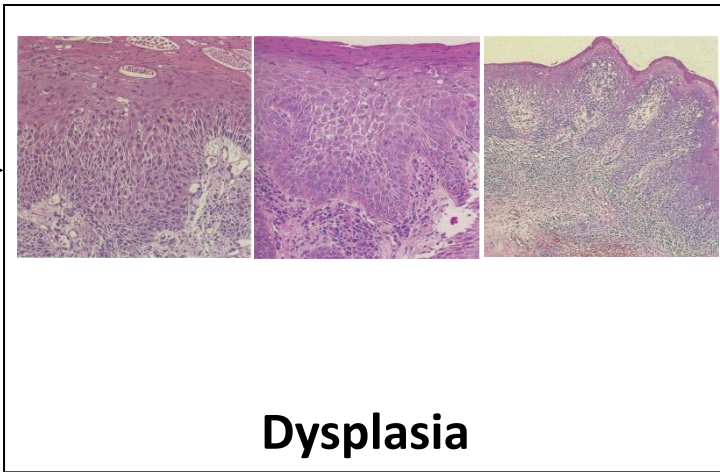
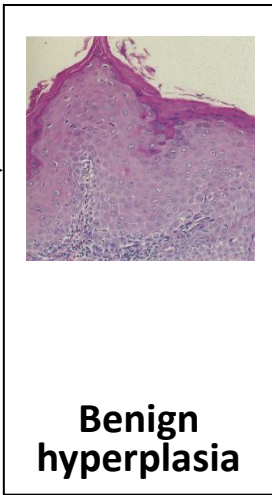
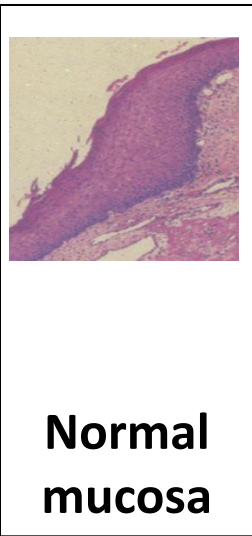


Effect of genetic factors

Genomic instability

0

>10,000 mutations



Genetic syndromes associated with HNSCC

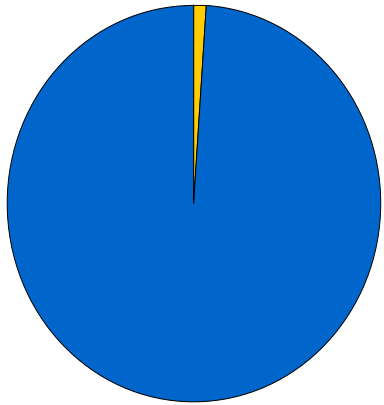
Syndrome	Gene	Other cancers	H & N Cancer
Fanconi	FANC family	Hematological	>500 fold
Dyskeratosis congenita	DKC1, hTR/TERC or TERC	AML, leukoplakia	Significant increase
Bloom	BLM (RecQ like helicase)	Hematological, Wilms tumor	Significant increase
Rothmund-Thompson	RECQL4 (RecQ like helicase)	Skin cancer	Oral tongue
Xeroderma pigmentosum	XP-A to XP-G	UV induced skin cancer	Rare
Ataxia telangiectasia	ATM	Leukemia, lymphoma	Rare
Li Fraumeni	p53	Lymphoma, sarcoma	Rare
Retinoblastoma	Rb	Rb, sarcomas	NC (32 fold)
N/A	p16	Melanoma	Rare
N/A	RNASEL	Prostate, cervix, breast	1.5 fold risk

Supporting events in progression to HNSCC

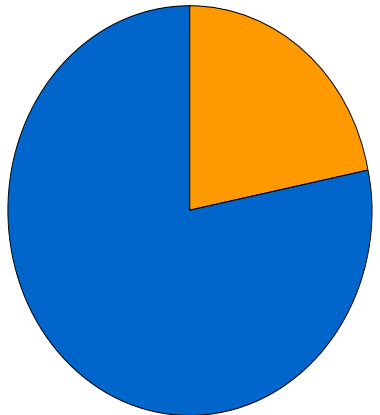
Syndrome	Gene	Association
Fanconi	FANC family	HPV?
N/A	RNASEL	HPV?
Bloom	Helicase	??
Xeroderma pigmentosum	XP-A to XP-G	HPV?
Ataxia telangiectasia	ATM	HPV?
	RNASEL	HPV
Retinoblastoma	RB	Radiation
XP	XP Family	UV

HNSSCC in FA: Increased frequency : Shorter latency

Standardized Incidence Ratio (SIR) =
500 (95% CI: 300-781, $p < 0.0001$).

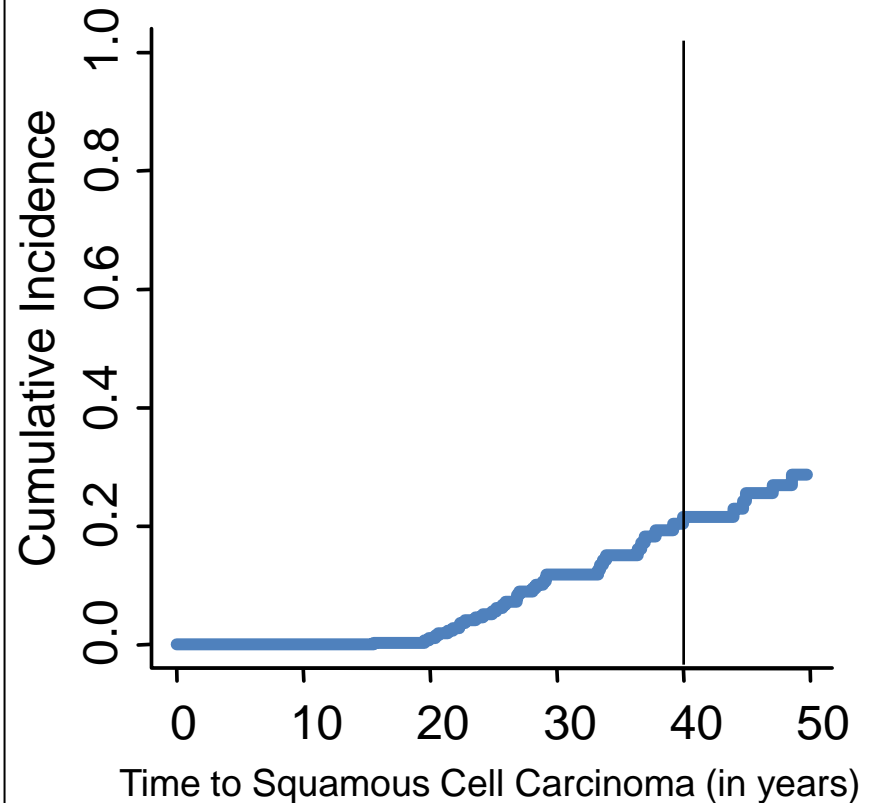


SEER population
Expected incidence: 0.038%



FA population
Cumulative incidence: 19%

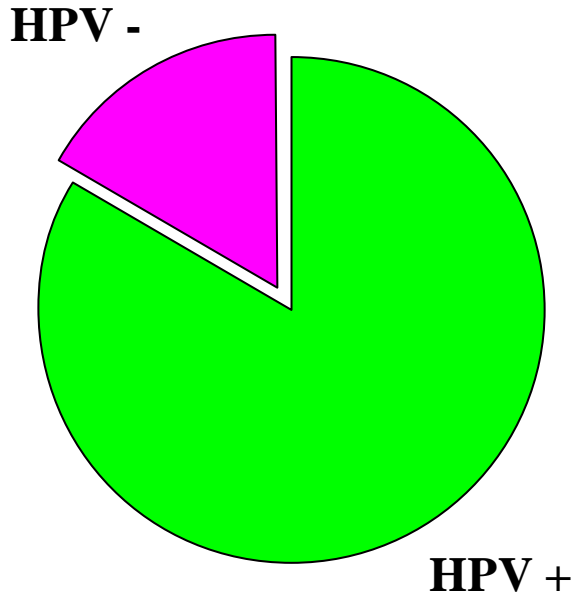
21% incidence by age 40



HPV positivity: Supporting events

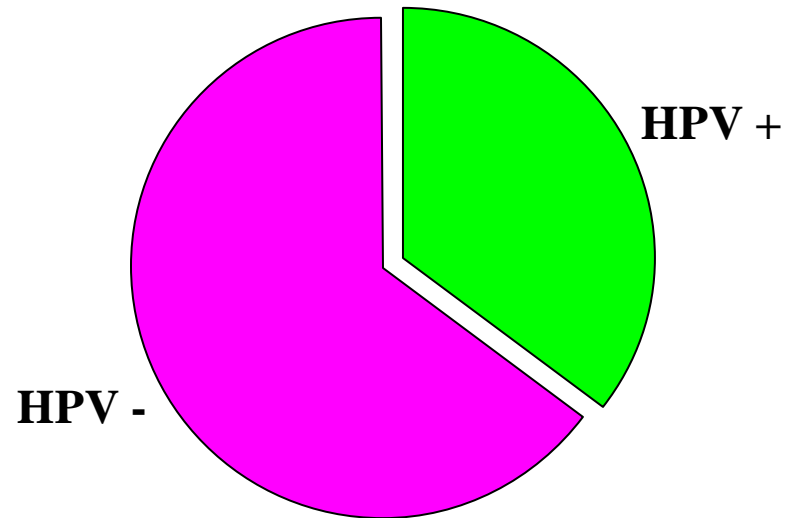
FA associated SCC vs. control SCC

FA-associated SCC



83% HPV Positive
N=25

Normal control SCC

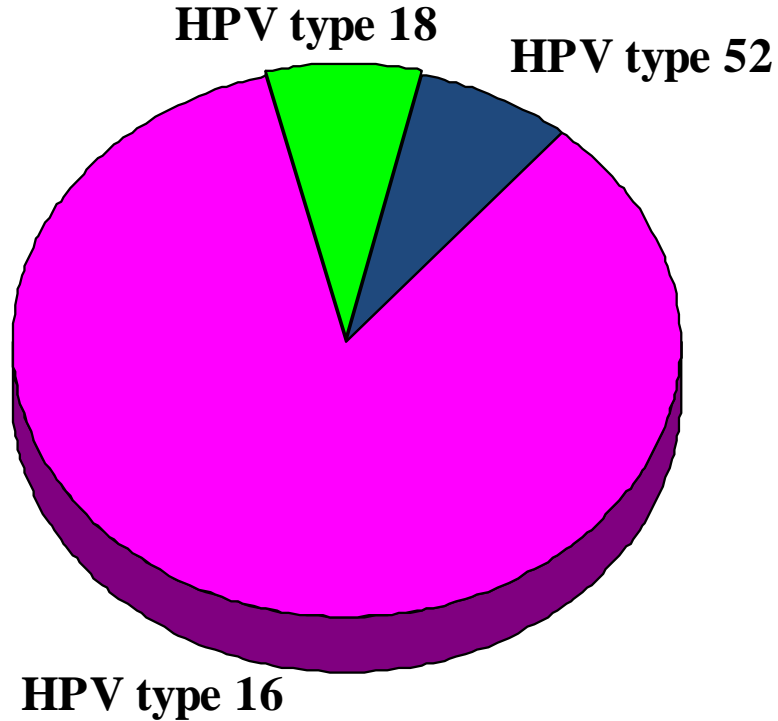


36% HPV Positive
N=50

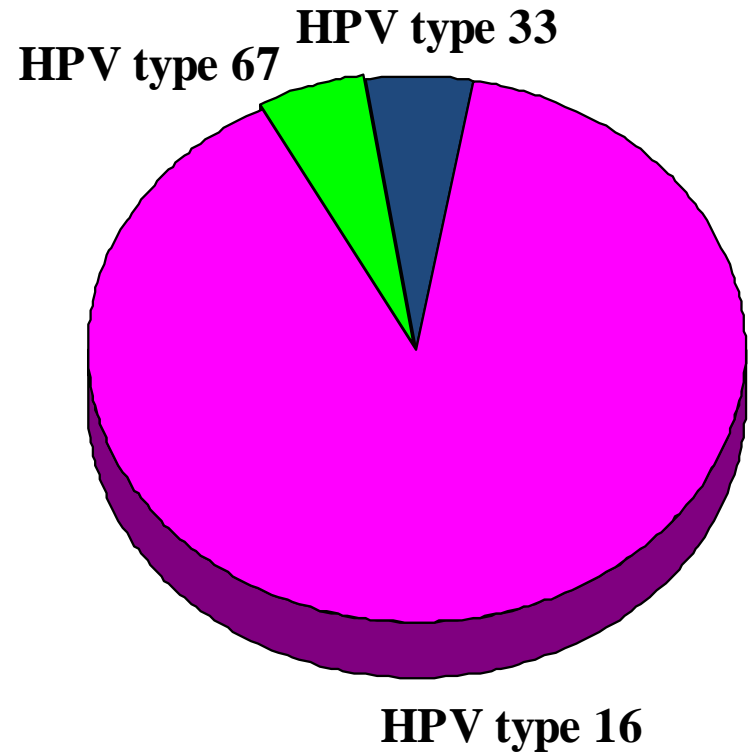
P<0.001

HPV Types in FA-associated HNSCC

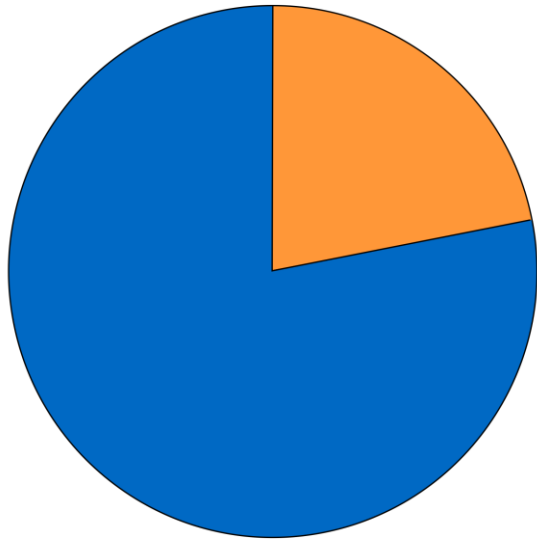
FA-Associated



Normal control SCC

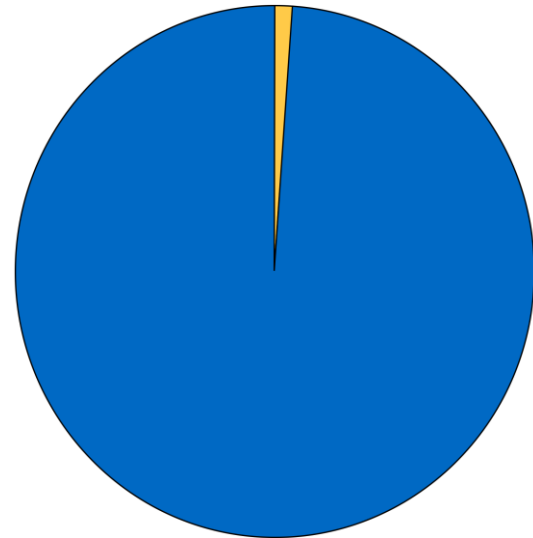


Is HPV a cause of HNSCC?



FA population

Cumulative incidence: 19%



SEER population

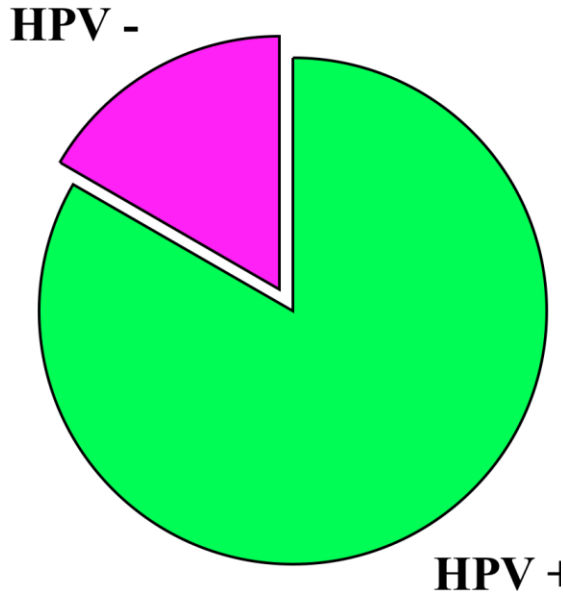
Expected incidence: 0.038%

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HPV positivity

FA associated SCC vs. control SCC

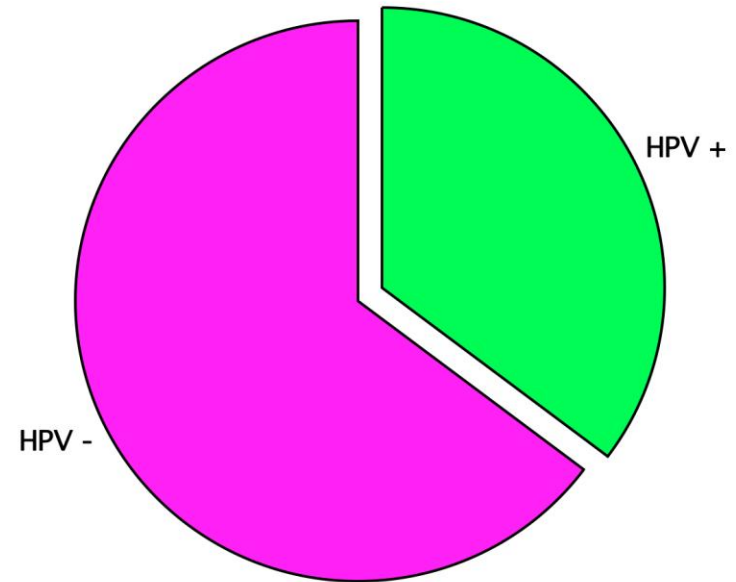
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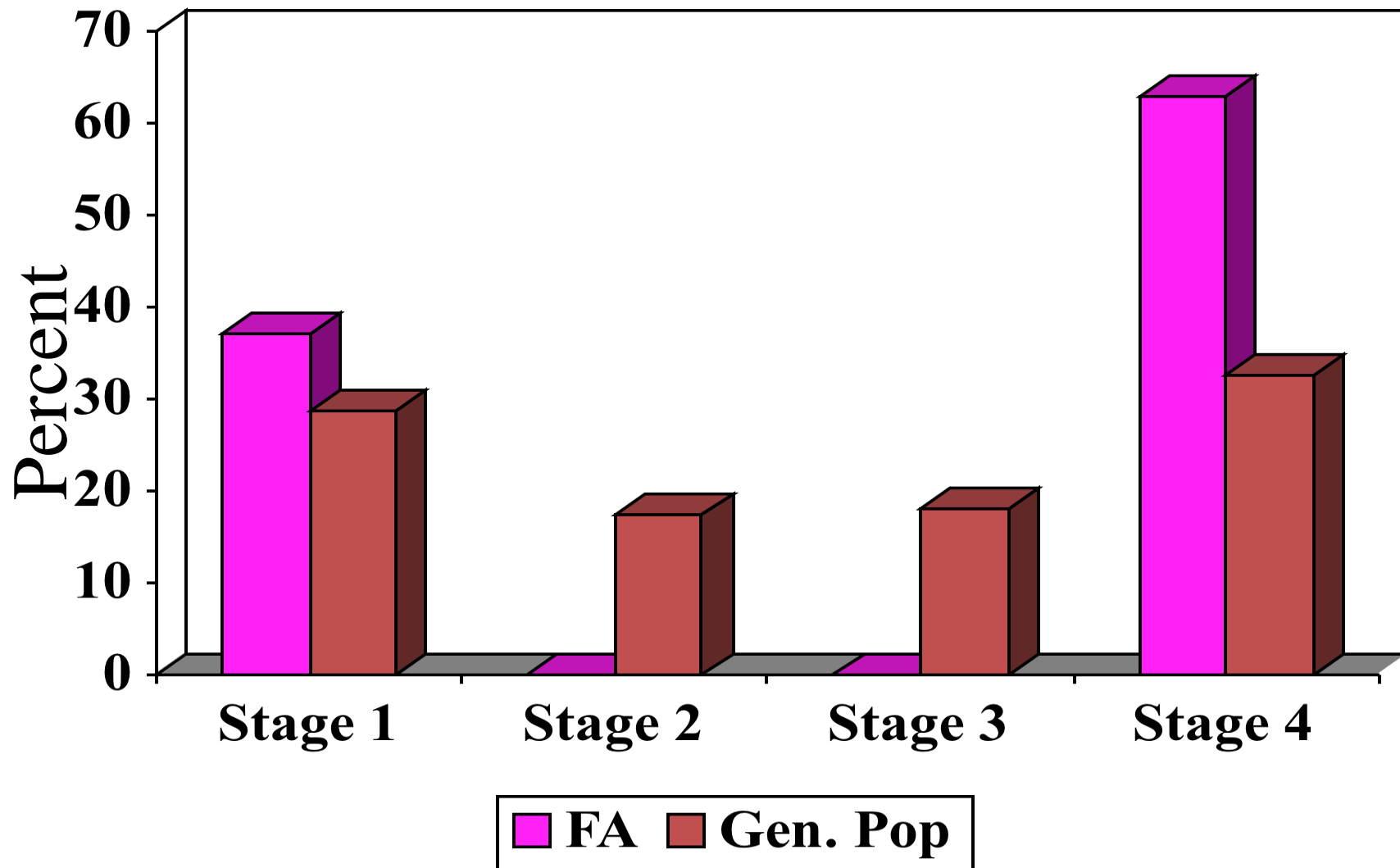
N=50

$P < 0.001$

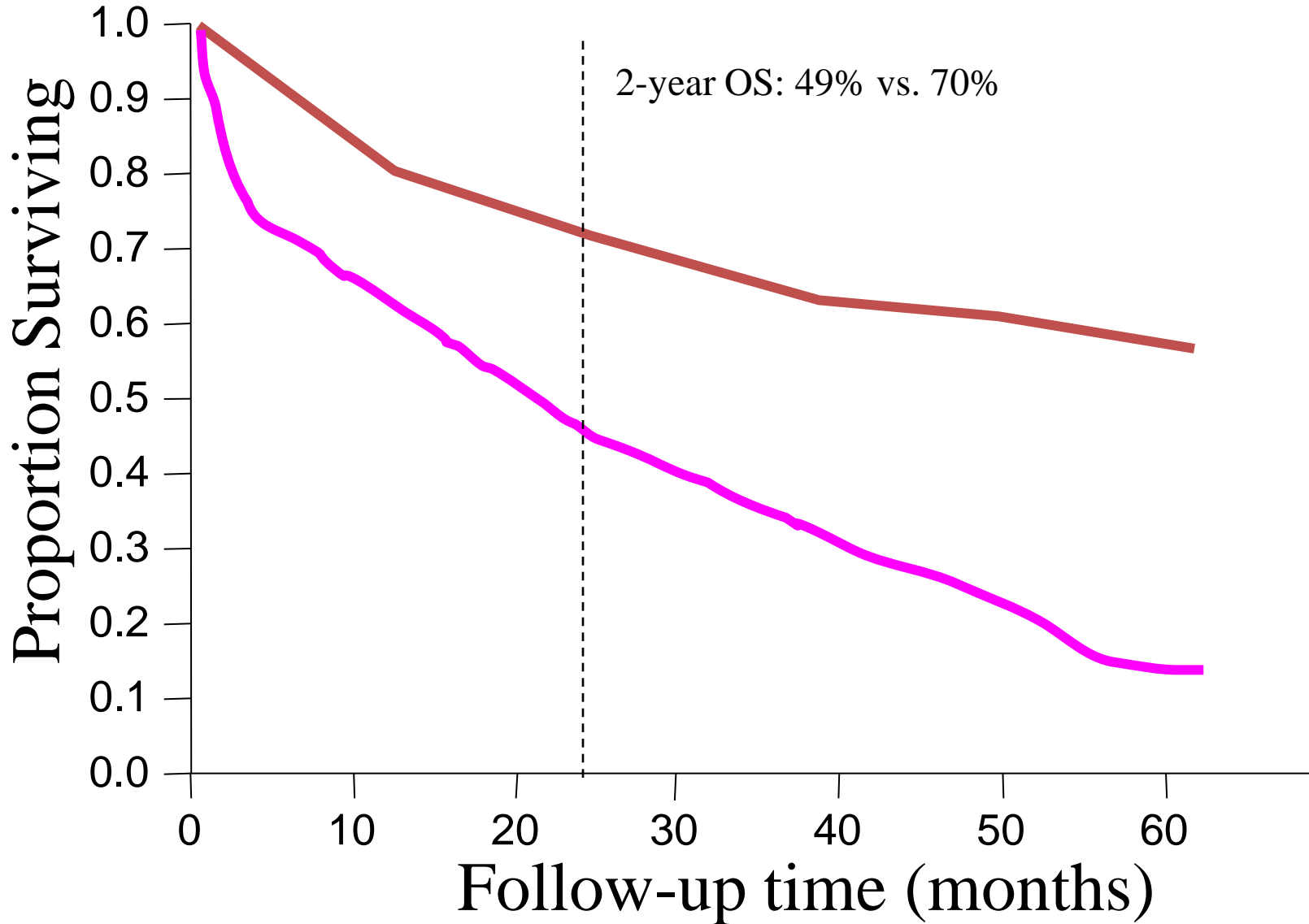


- Controversial
 - US vs. European data
- Factors in support
 - Ano-genital association
 - Anatomic distribution
 - Laboratory data
 - Human tumor analysis
 - “Hit and run” theory

TNM staging



Overall survival



Reasons for worse outcome

- Tumor biology
- Advanced stage at presentation
- Inadequate treatments
- Limitations in adjuvant treatment
 - 100% have adverse effects with Rtx
 - ~50% with severe toxicity
 - <50% can finish radiation

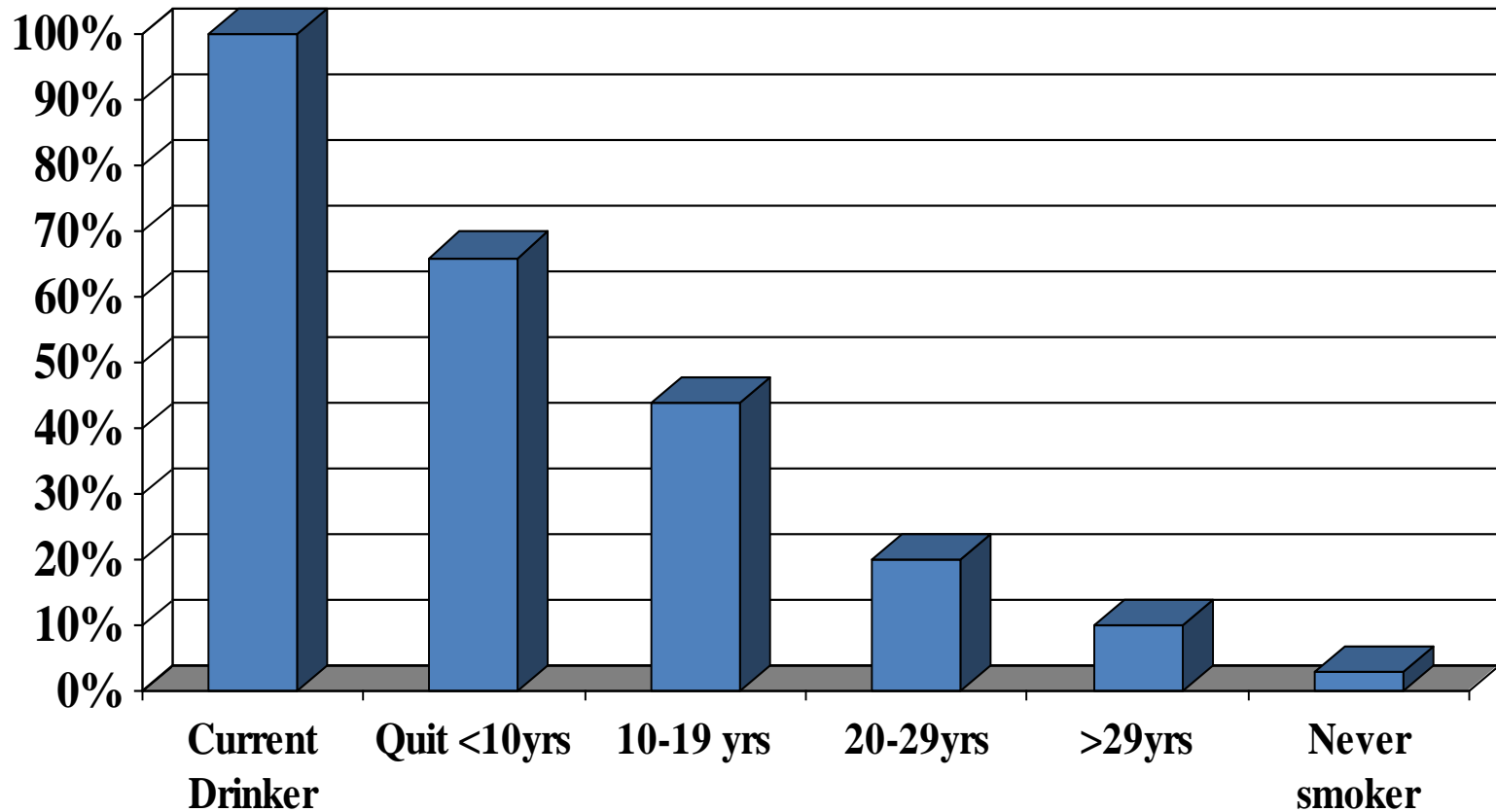
Treatment approach

- EARLY DETECTION
- Surgery is the preferred treatment
- Use radiation and chemotherapy with caution and in limited circumstances
- ? Need for modification of treatment (use non- DNA damaging chemotherapy modalities)
- Very close surveillance

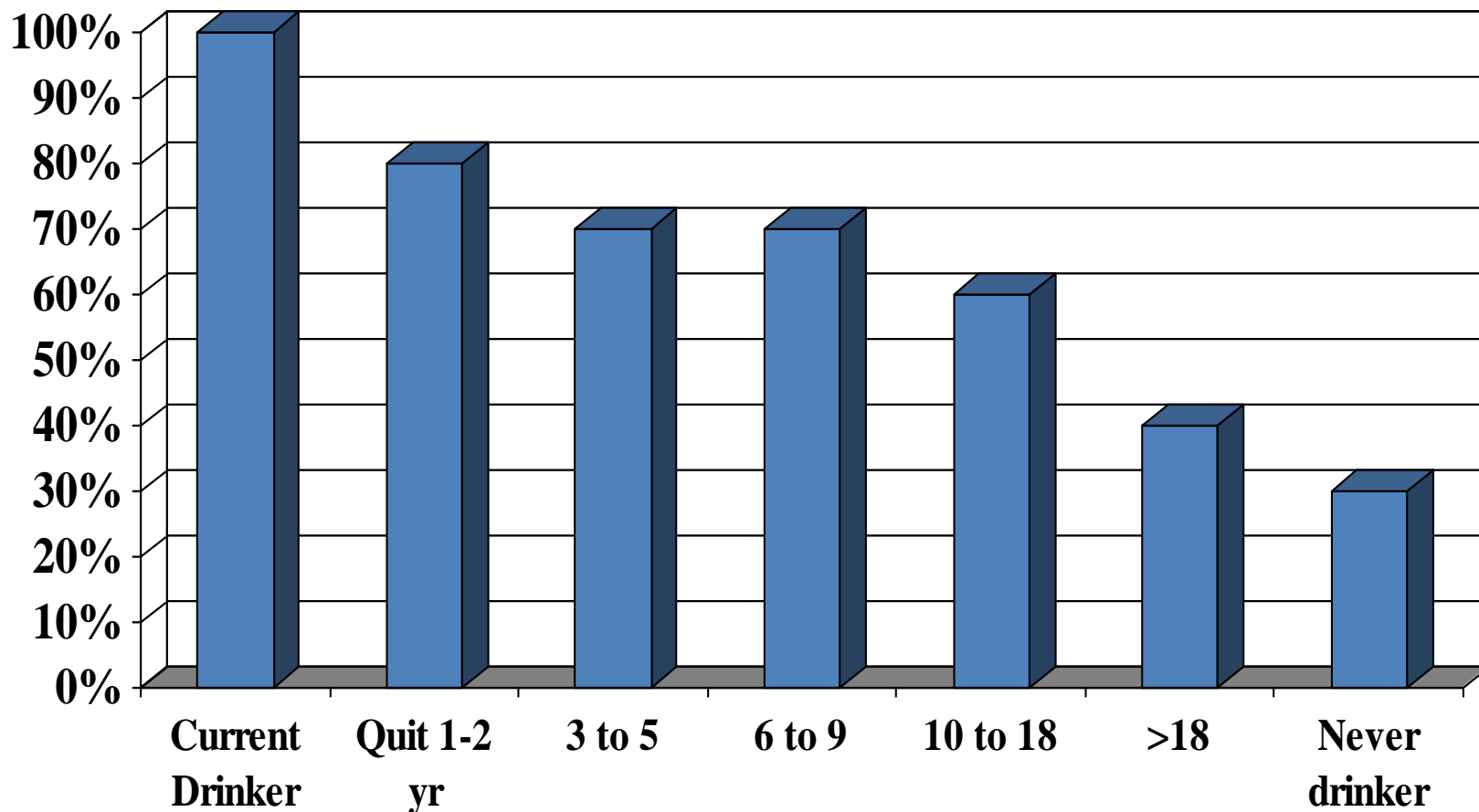
How can we prevent
head and neck cancer?

- Abstinence from tobacco and alcohol use
 - Avoidance of second hand smoke exposure
- Maintenance of oral hygiene
 - Avoid alcohol containing mouthwashes
- Aggressive monitoring and routine screening

Tobacco cessation and cancer risk



Alcohol cessation and cancer risk



Vaccine targeting

- HPV L1 capsid protein assembles into Viral like particles and provokes immune response
- Two types of vaccines available:
 - Quadravalent (Gardasil)– 6/11/16/18
 - Reduction in CIN reported (Future II. NEJM 2007)
 - Reduction of anogenital disease (Garland. NEJM 2007)
 - Bivalent (Cervarix)- 16/18
 - Reduction in CIN (Harper. Lancet 2006)
- Effects though to be optimal before HPV infection (prevention NOT therapy)

Routine screening

Start evaluation of head and neck at age 10 years

1. Head and neck exam by experienced professional
2. Flexible fiberoptic examination

Normal exam

Evaluate patient on a semi-annual basis

Lichen planus
Leukoplakia
Erythroplakia

Excisional biopsy

Increase surveillance timing to once every 2-3 months

Lesion suspicious for squamous cell carcinoma

Biopsy of lesion

Appropriate treatment, if positive

Close follow-up every 2-3 months

Who should do the screening?

- What should I do
- Type of health care professional
- What should be done

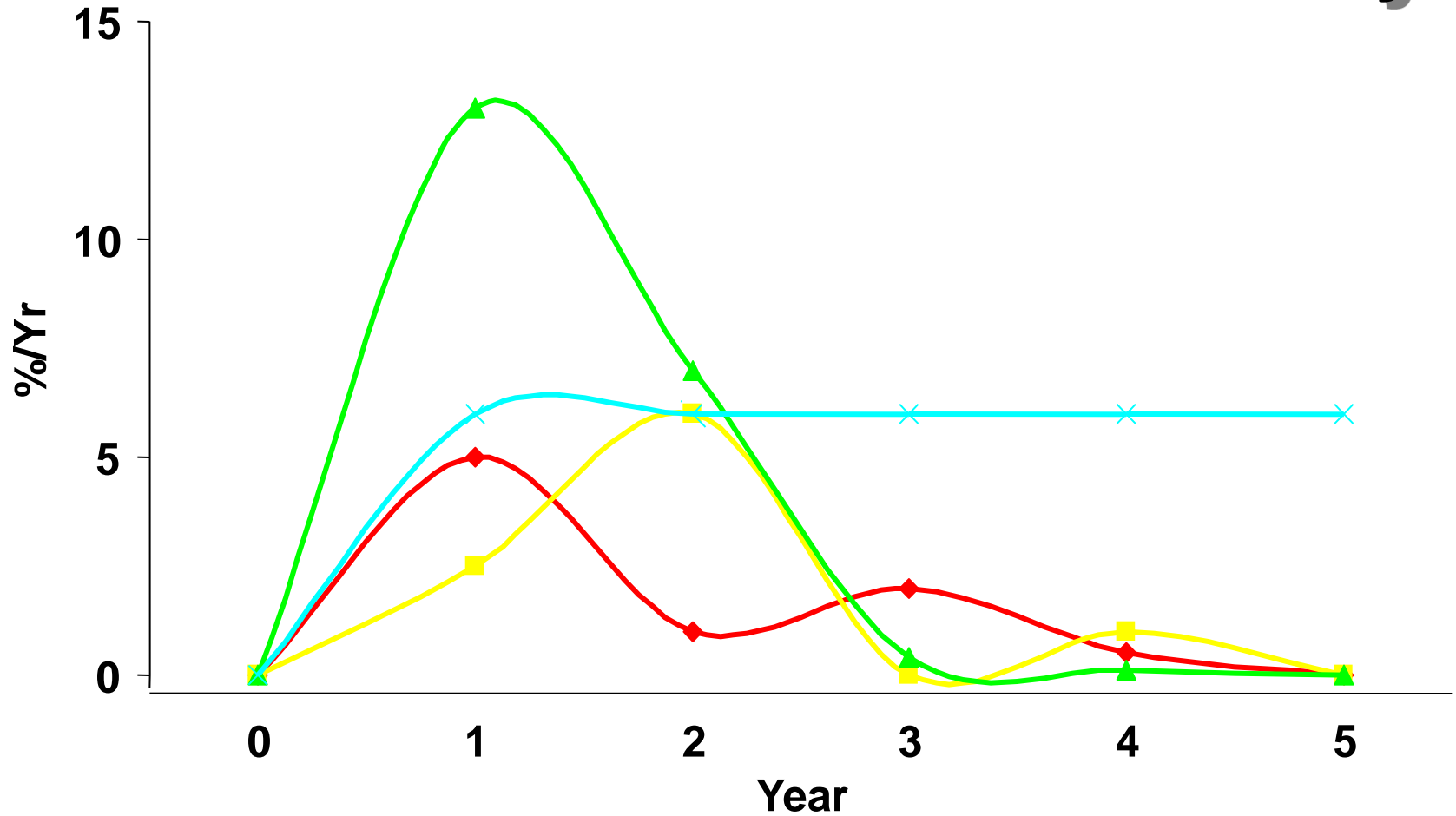
What should I do if I'm diagnosed with head and neck cancer?

- Treatment at major center with experienced treatment team
- Surgery is the main stay of treatment as much as possible
- Role of radiation and chemotherapy

Post-treatment surveillance after treatment for cancer

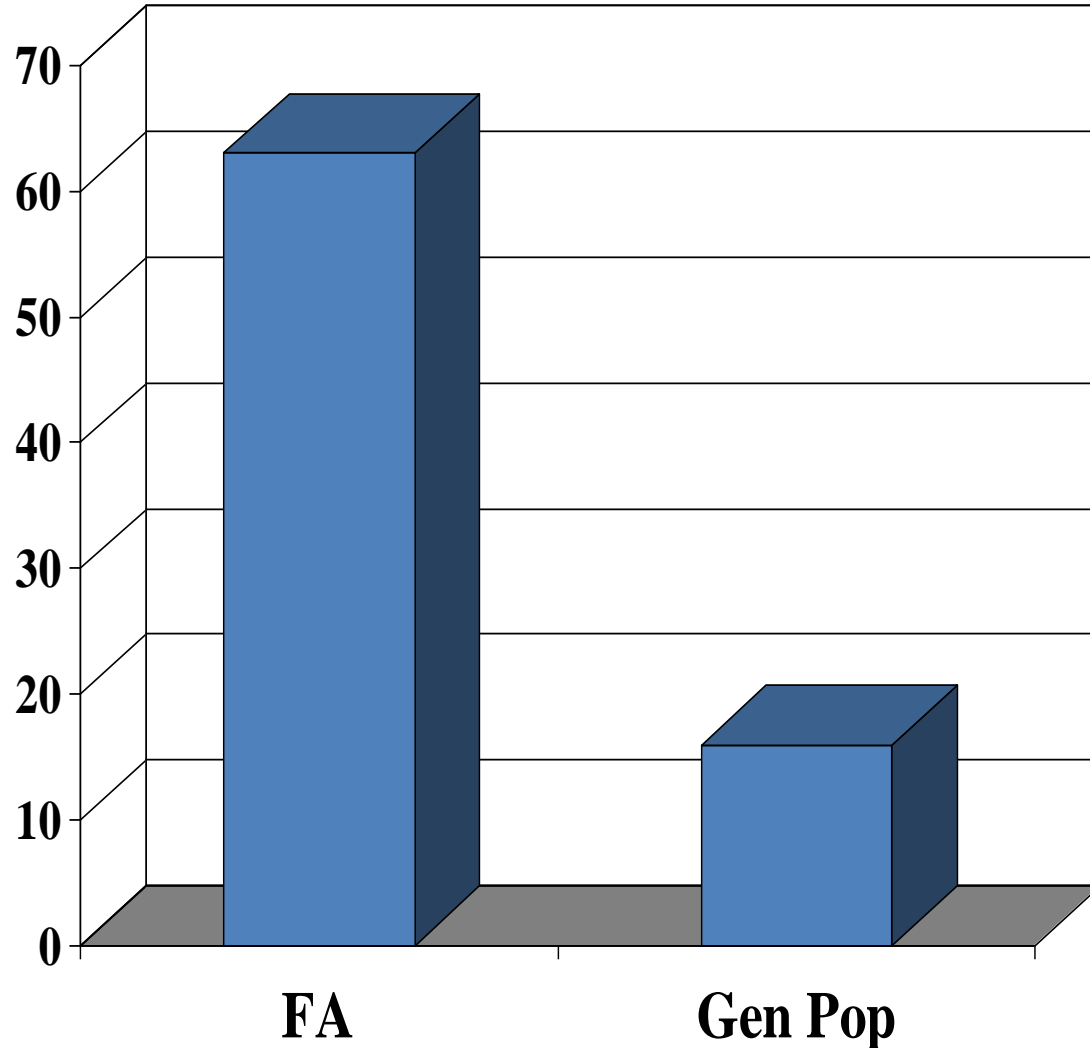
- Routine follow-up is mandatory (every 3 months or better)
 - Complete examination of upper aerodigestive tract mucosa
 - Chest X-ray annually
 - ? Use PET scan ?
- Screening to include gynecological exam in women

New Cancer Appearance after Treatment of H&N Primary



◆ Local Recurr ■ Neck Recurr ▲ Distant Mets × 2nd Primary

Second primary malignancies: Screening/prevention



- 12 of 19 (63%) developed multiple malignancies during their lifetime.
- 5 patients had >2 malignancies

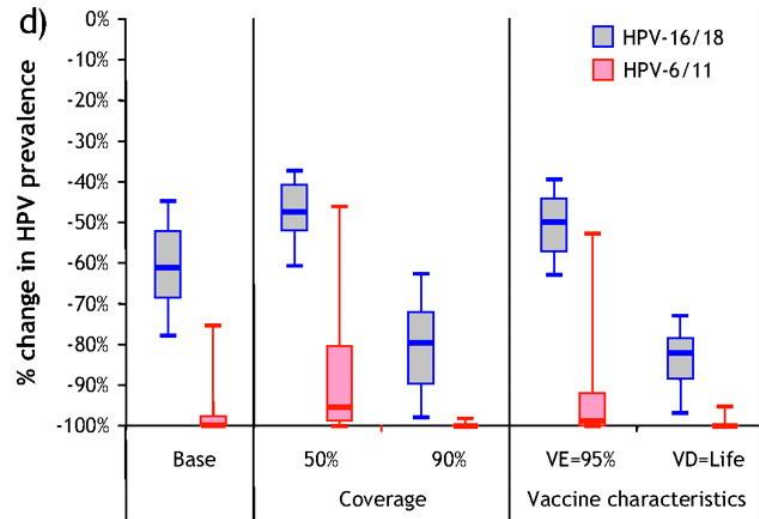
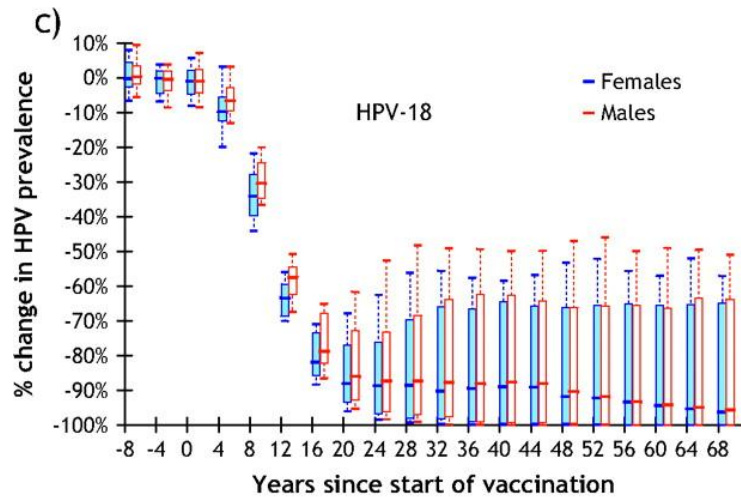
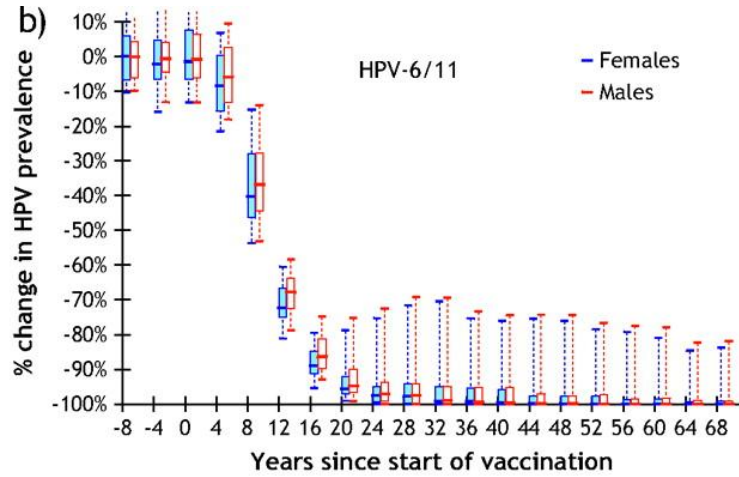
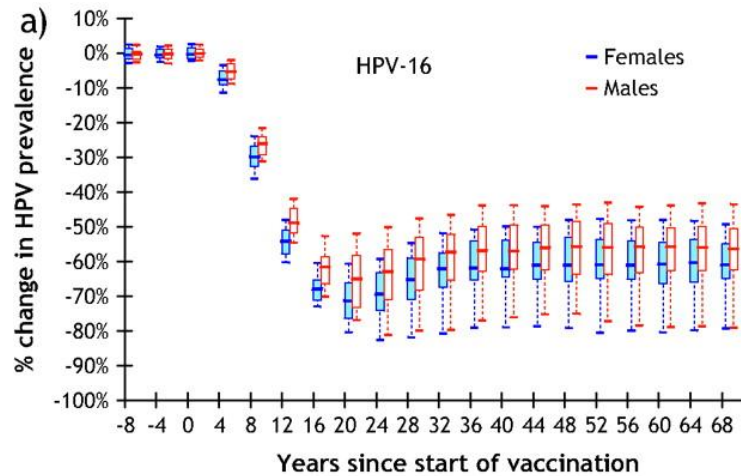
Surveillance recommendations for SCC in FA patients

- Routine head and neck screening
 - Role of qualified examiner
 - Age of onset (12-14 years)
 - Frequency- Biannual
- HPV vaccination

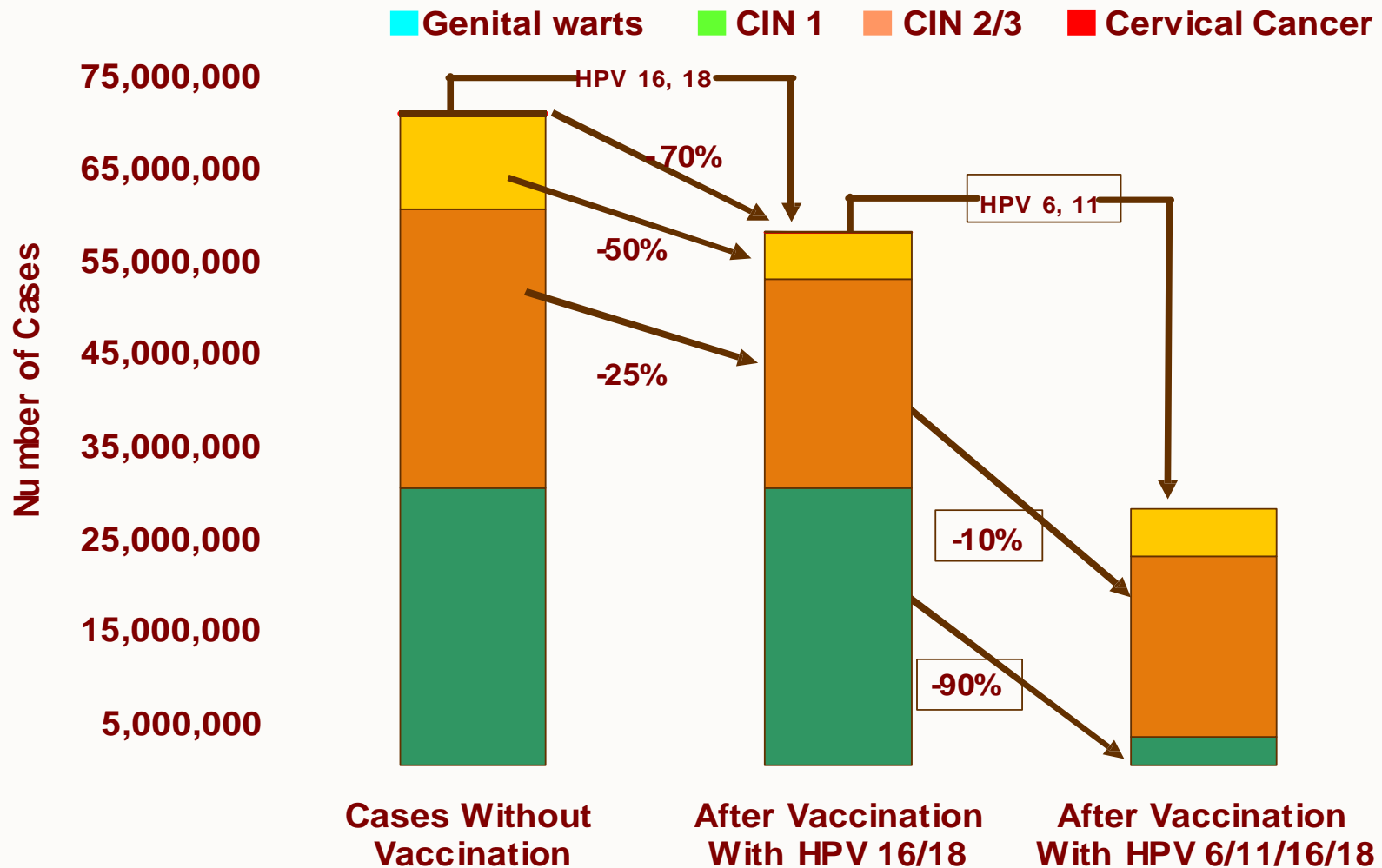
Vaccine targeting

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 - Bivalent (Cervarix)- 16/18
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Effect of vaccination on HPV prevalence



Effect of vaccination on HPV-diseases



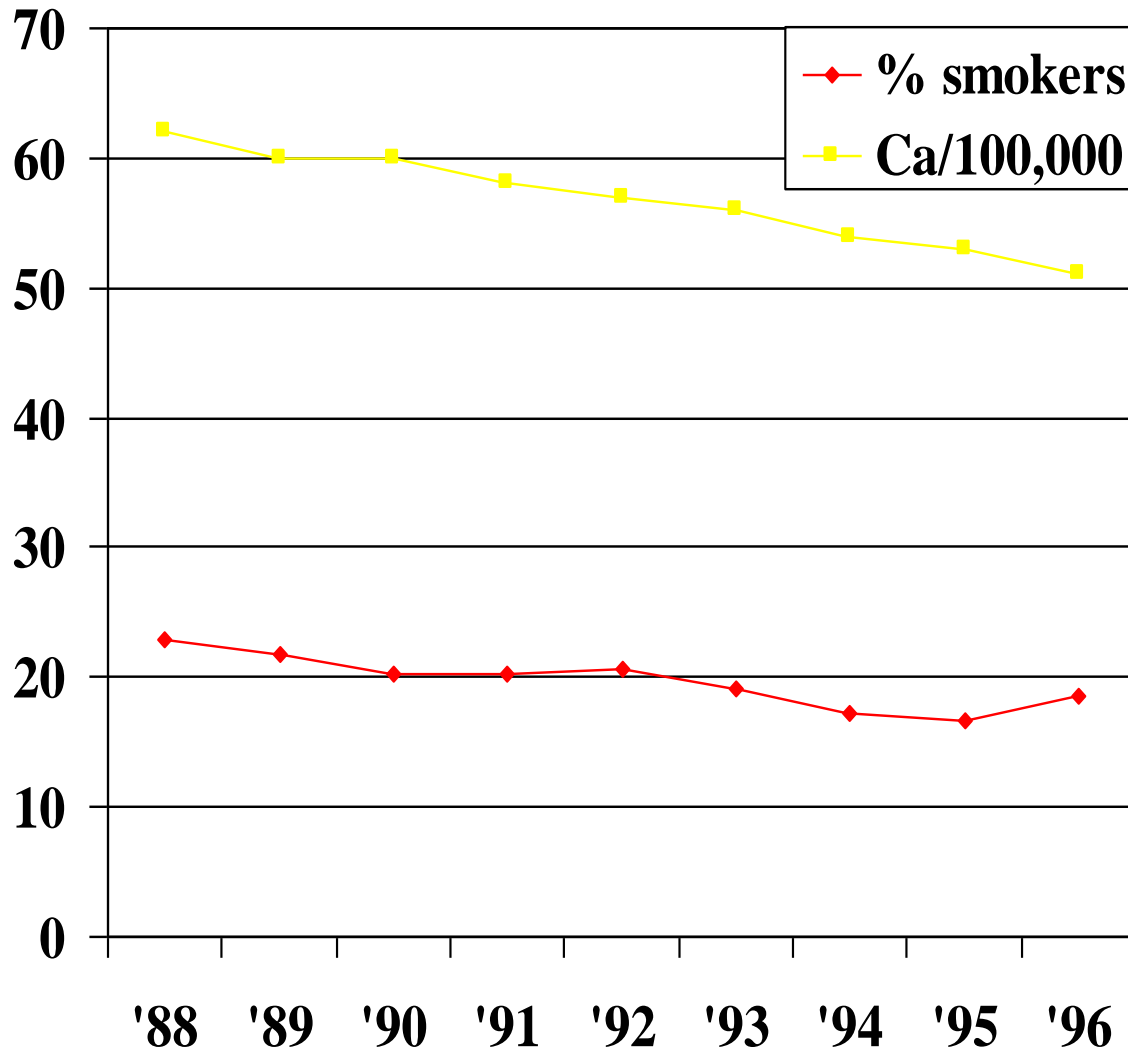
Vaccine specific recommendations

	Quadrivalent HPV L1 VLP Vaccine (MSD)	Bivalent HPV L1 VLP Vaccine (GSK)
HPV VLPs	HPV types 6, 11, 16, 18	HPV Types 16, 18
Schedule	0, 2, 6 months Flexibility up to 12 months	0, 1, 6 Months
Indication	<p>9 - 26 years <i>(Boys 9 – 15 yrs (some countries))</i> In US: Prevention of cervical, vulval , and vaginal cancers caused by HPV types 16/18; genital warts caused by HPV types 6/11; and CIN 1, CIN 2/3, AIS, VIN 2 and 3, or VaIN2 and 3 caused by HPV types 6/11/16/18</p>	<p>10 – 25 years Prevention of premalignant cervical lesions and cervical cancer causally related to HPV types 16/18</p>

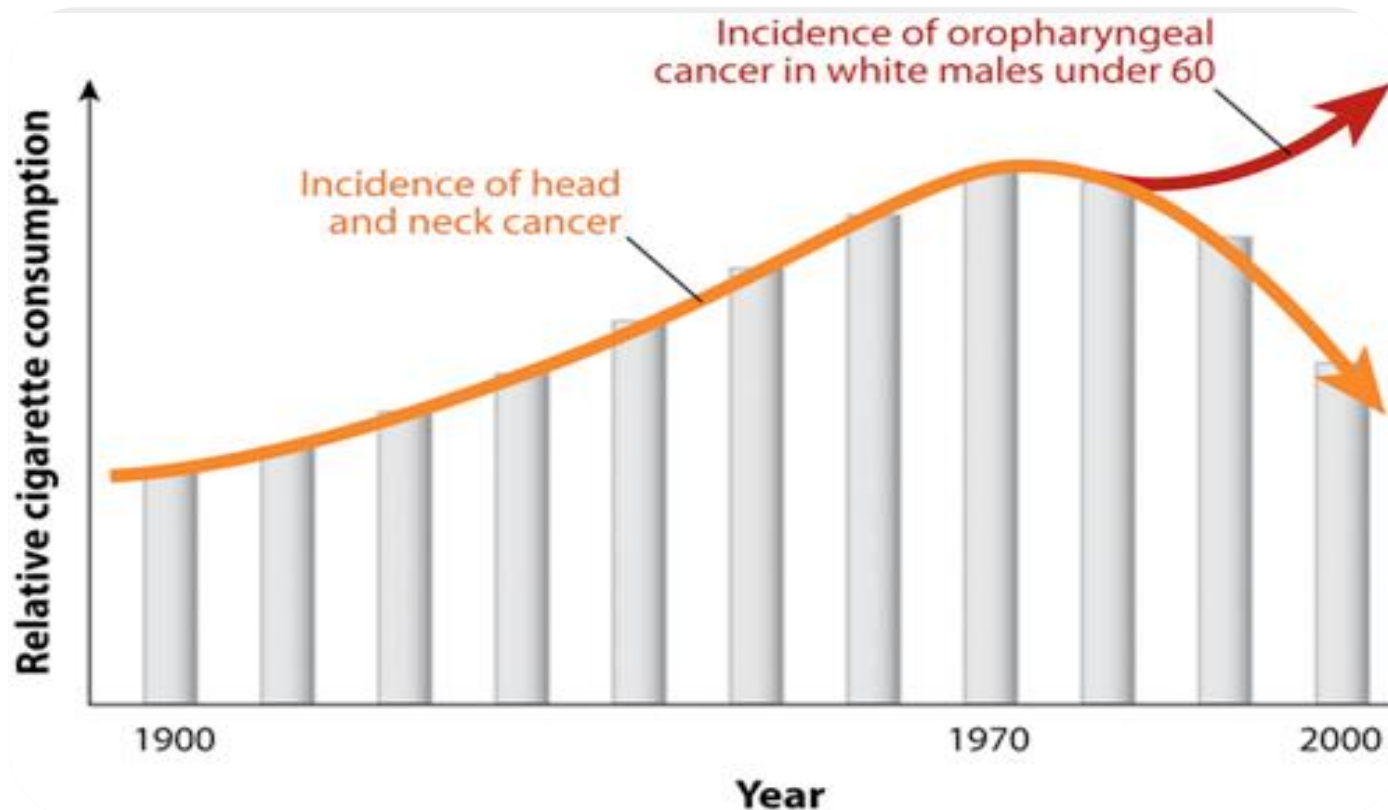
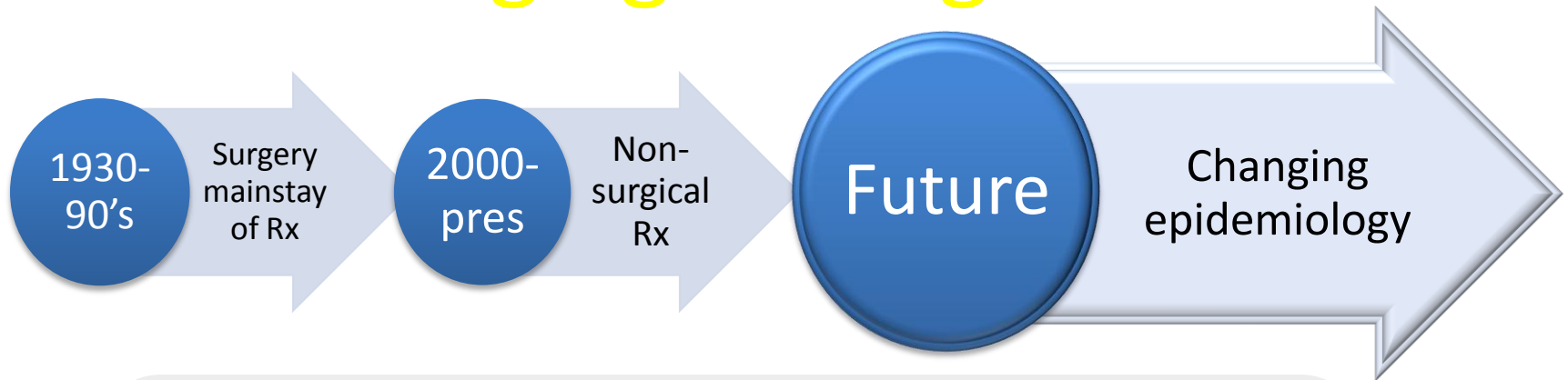
Questions--Contact

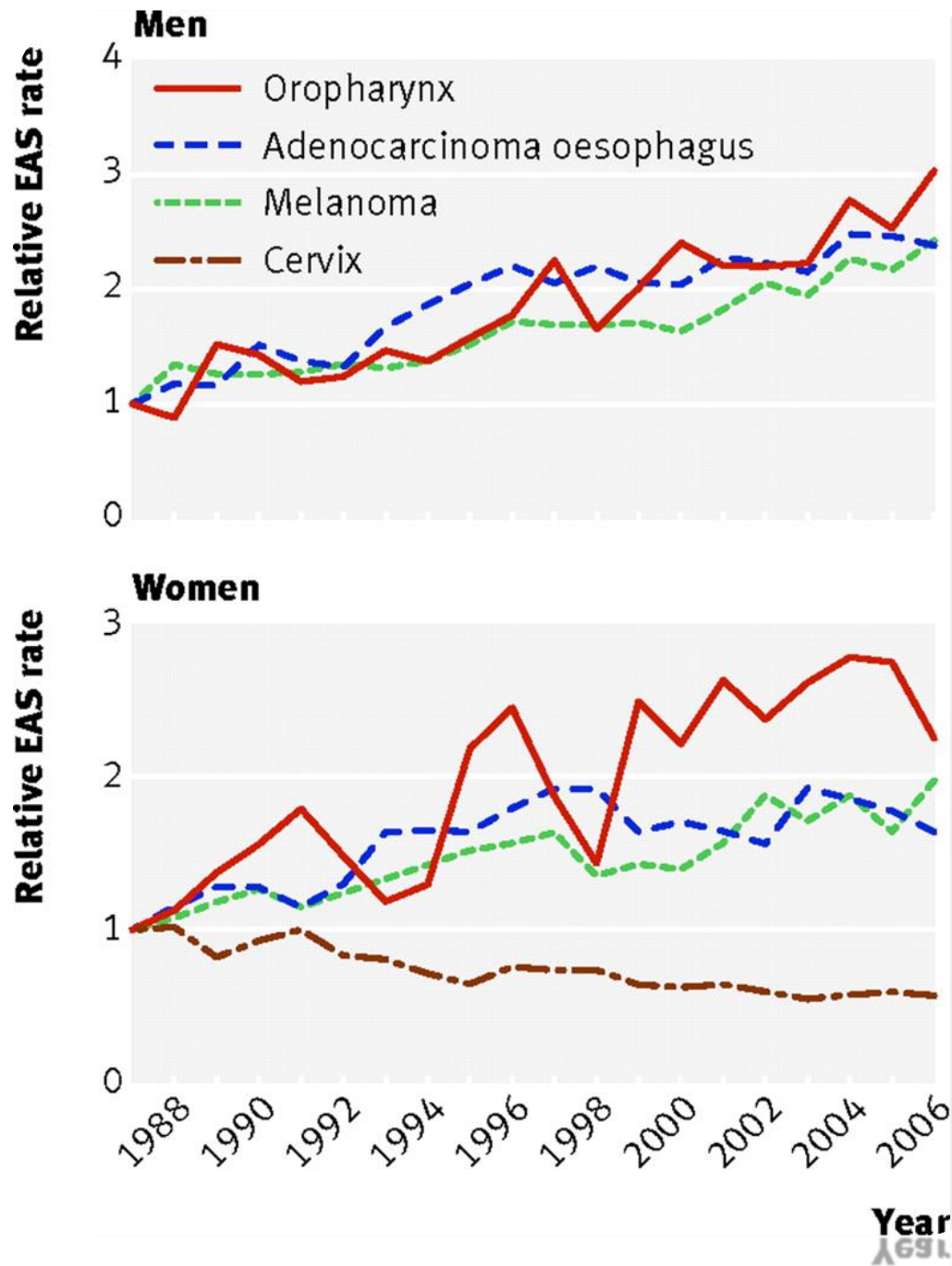
singhb@mskcc.org

Tobacco use and cancer rates in California

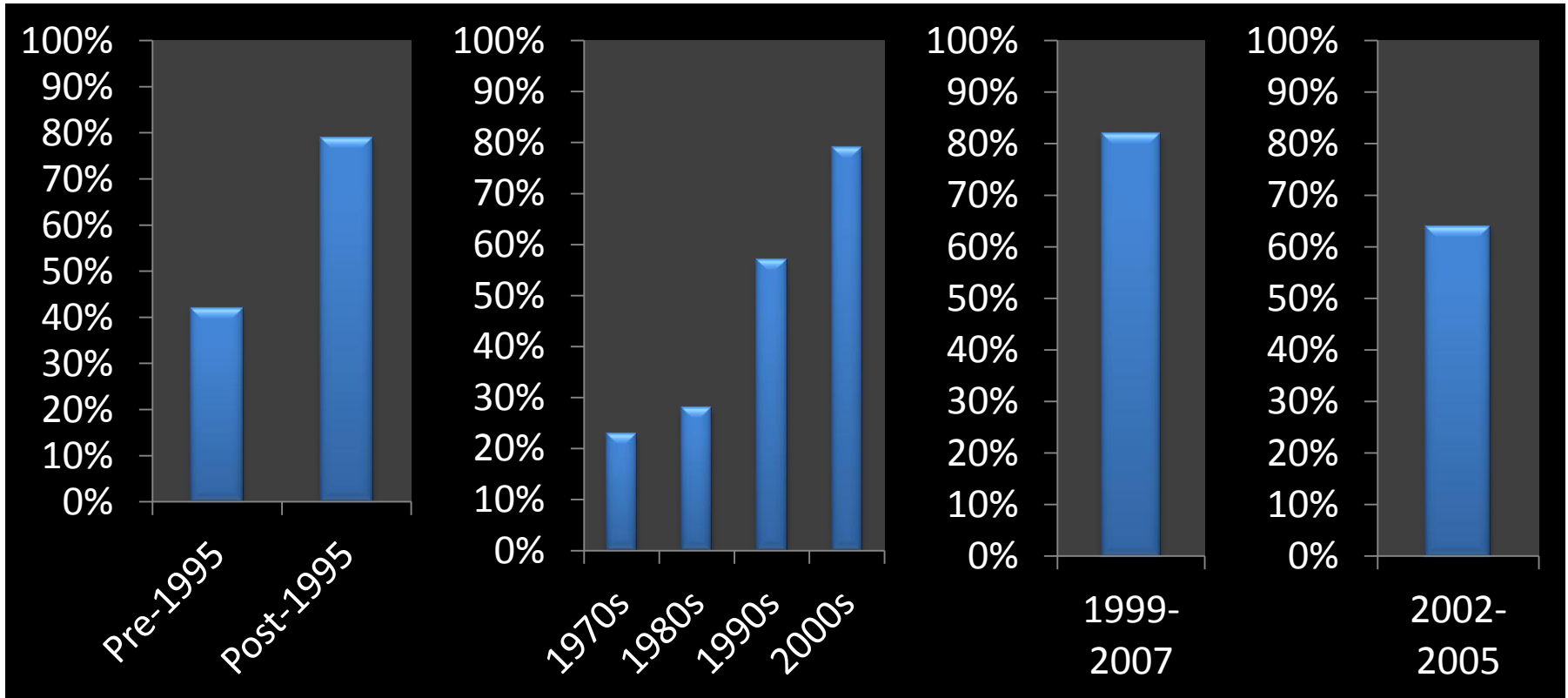


Changing management





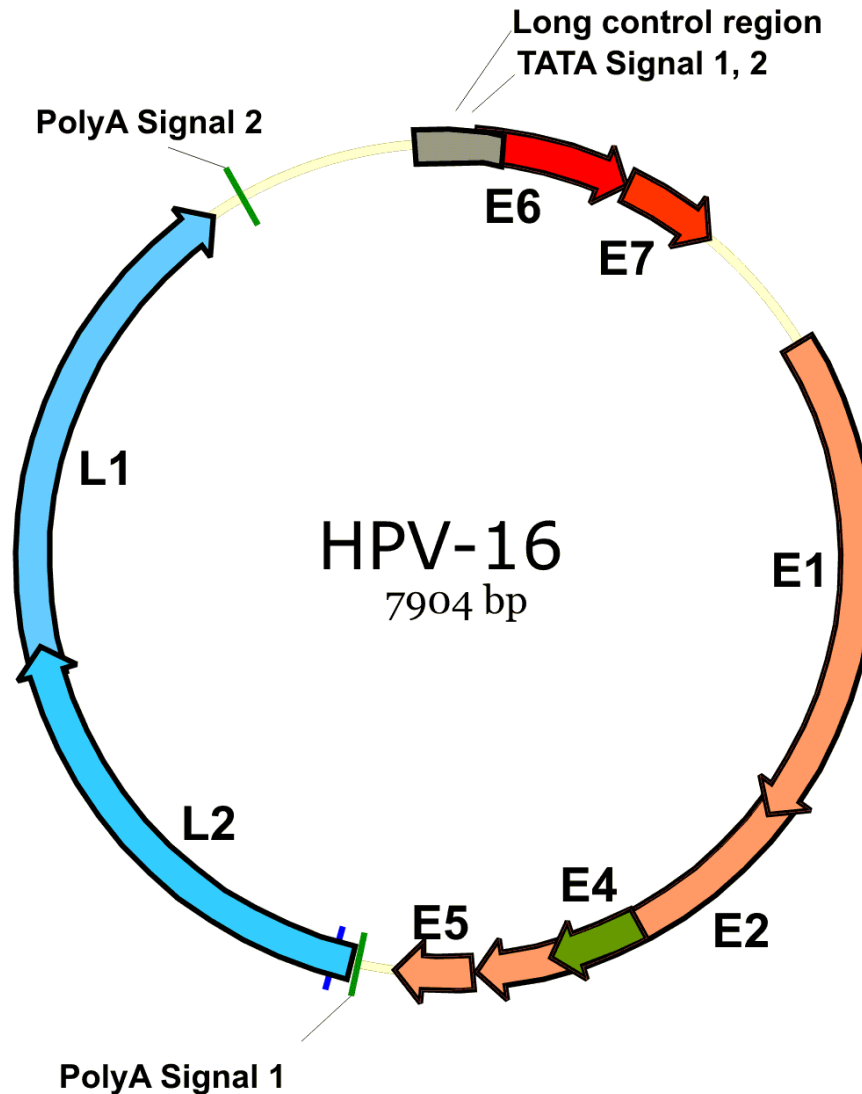
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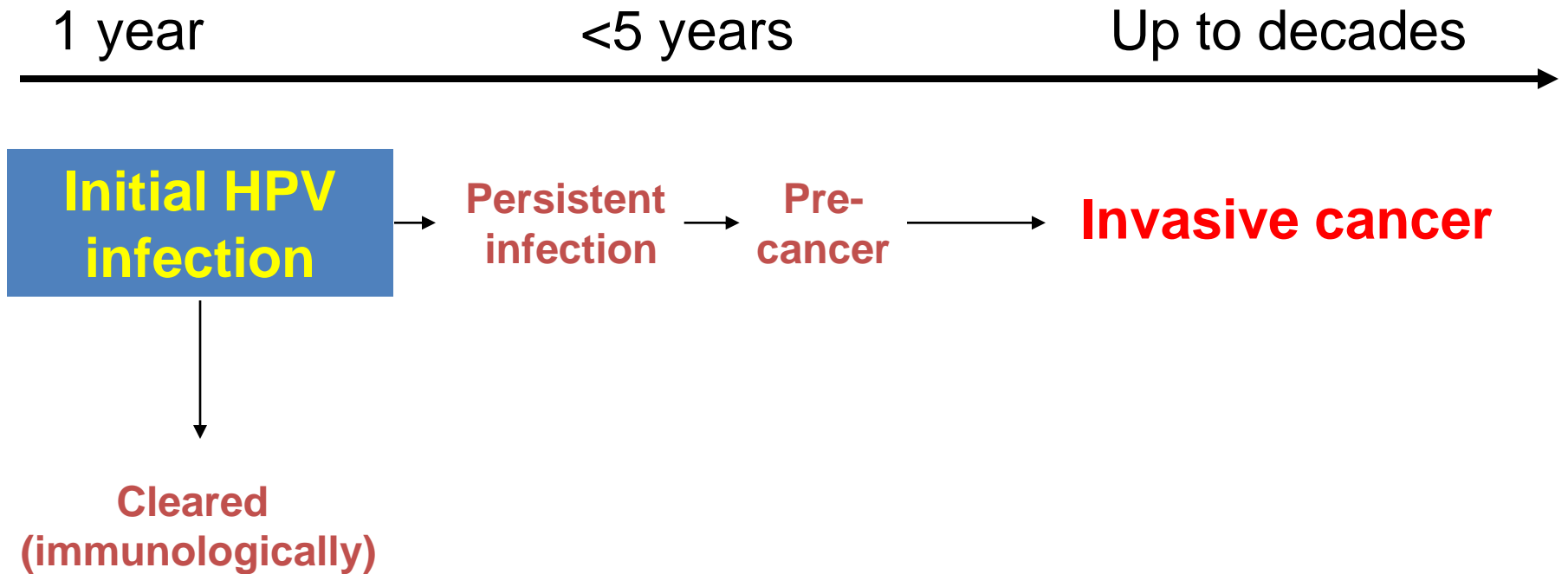
HPV

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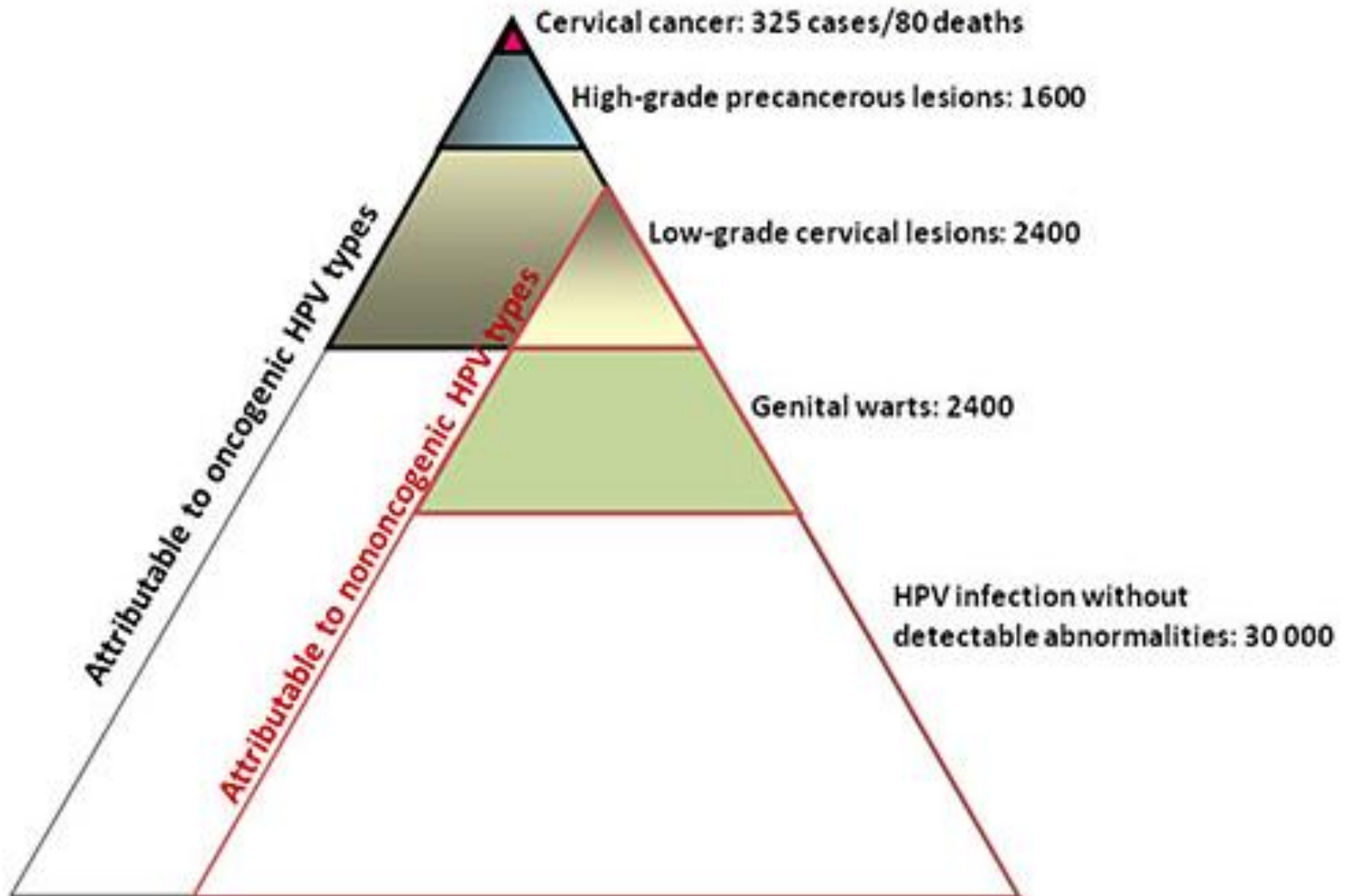
Mechanisms of HPV associated carcinogenesis



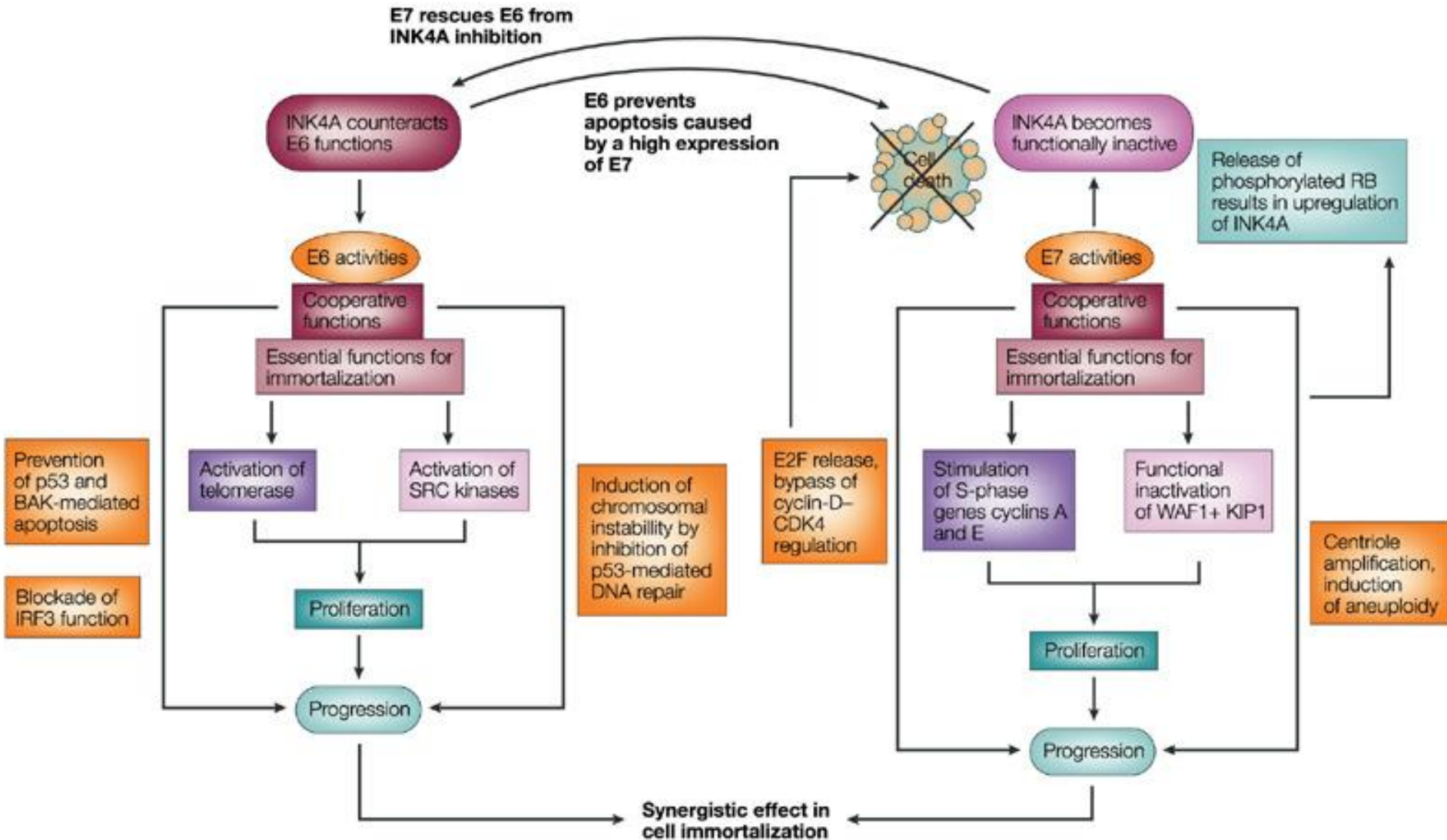
Natural course of HPV infection



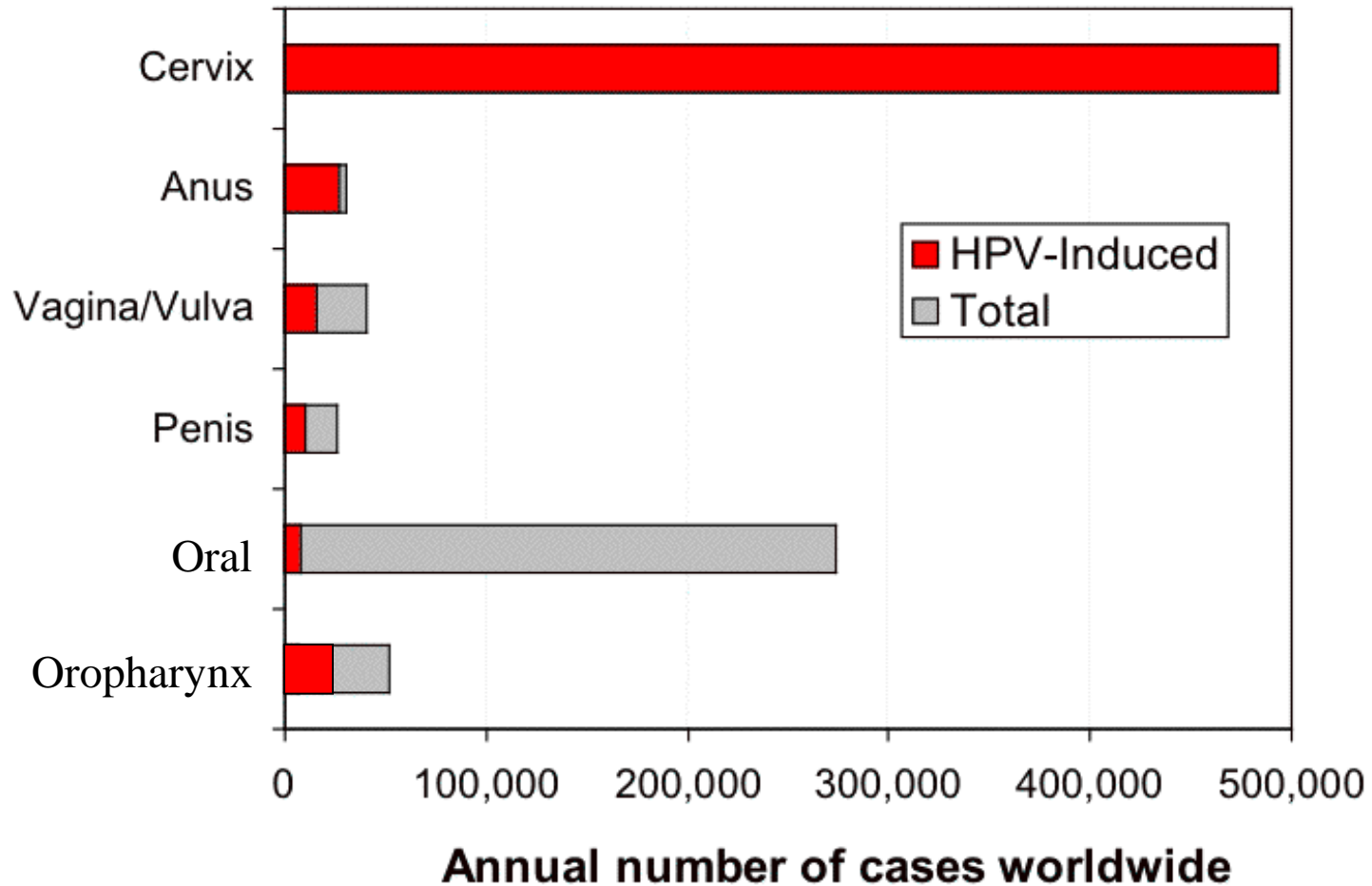
HPV related diseases



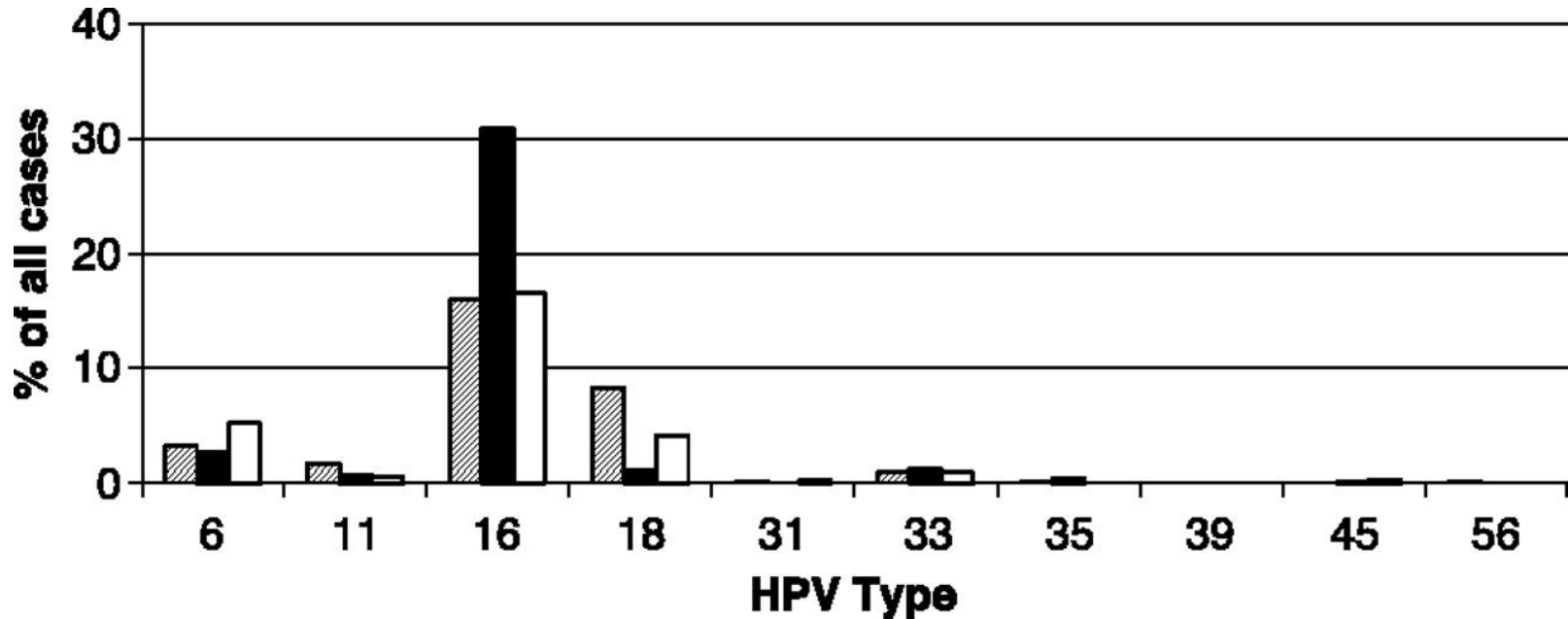
Mechanism of HPV induced oncogenesis



HPV associated cancer distribution

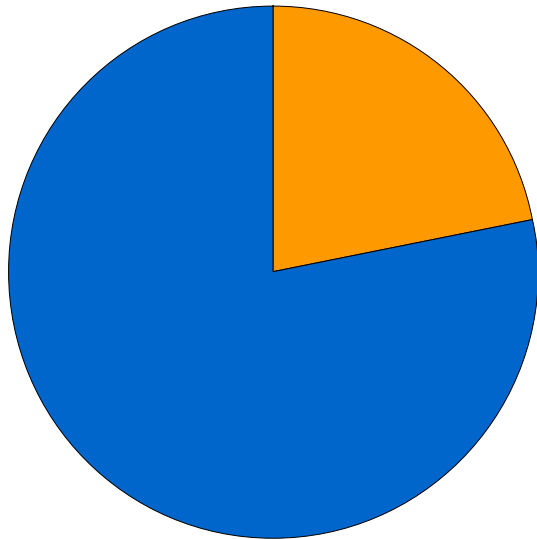


Distribution of HPV types in HNSCC



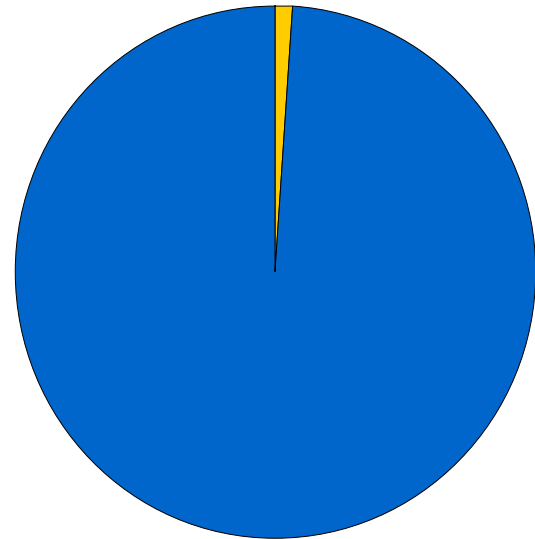
Increased prevalence in oropharynx

Is HPV a cause of HNSCC?



FA population

Cumulative incidence: 19%



SEER population

Expected incidence: 0.038%

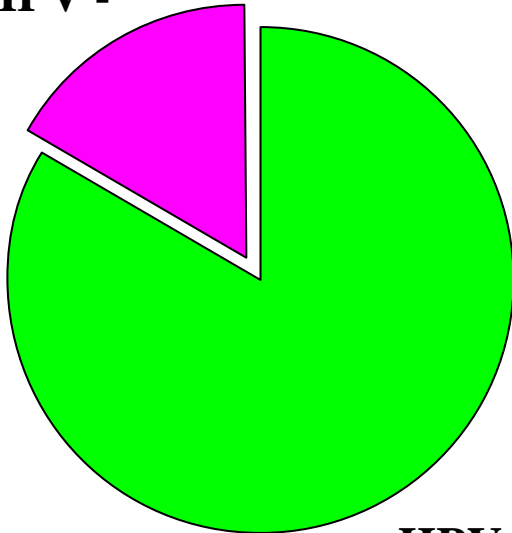
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HPV positivity

FA associated SCC vs. control SCC

FA-associated SCC

HPV -



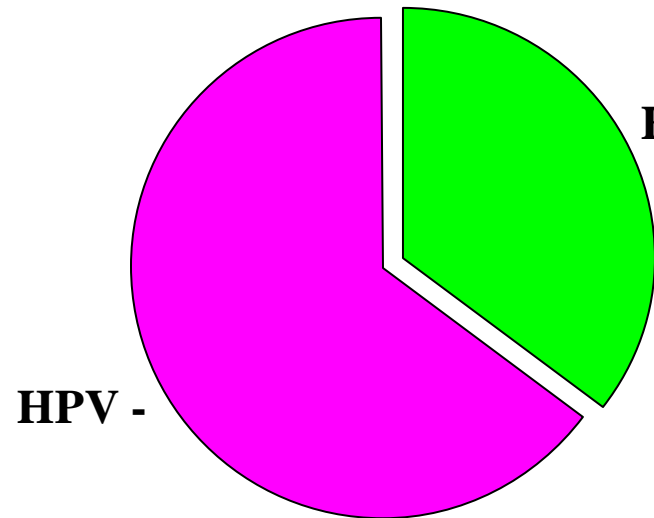
HPV +

83% HPV Positive

N=25

Normal control SCC

HPV +



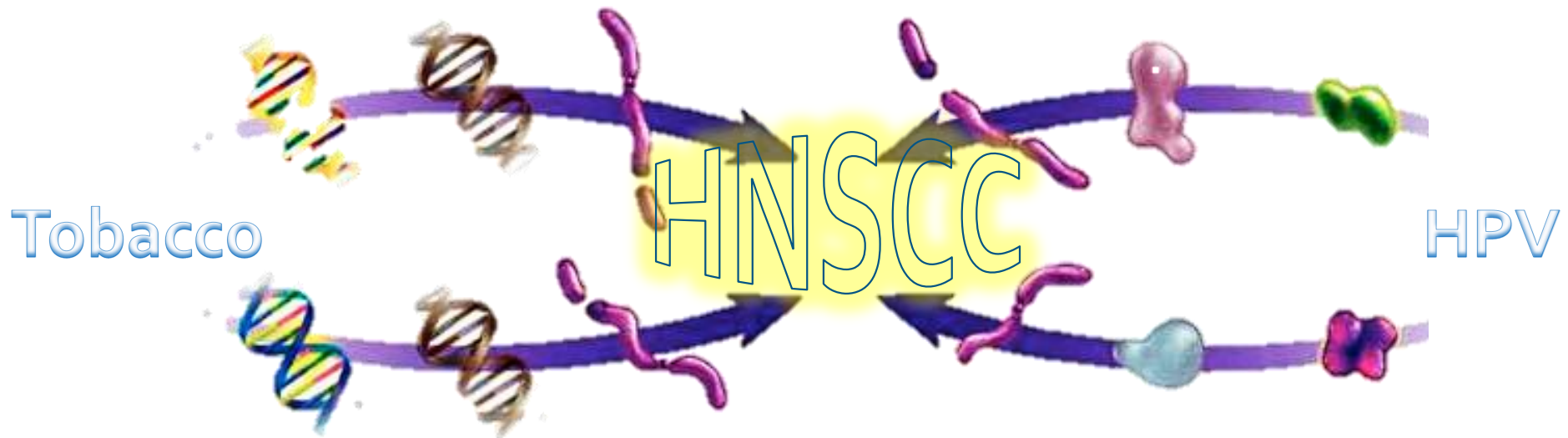
HPV -

36% HPV Positive

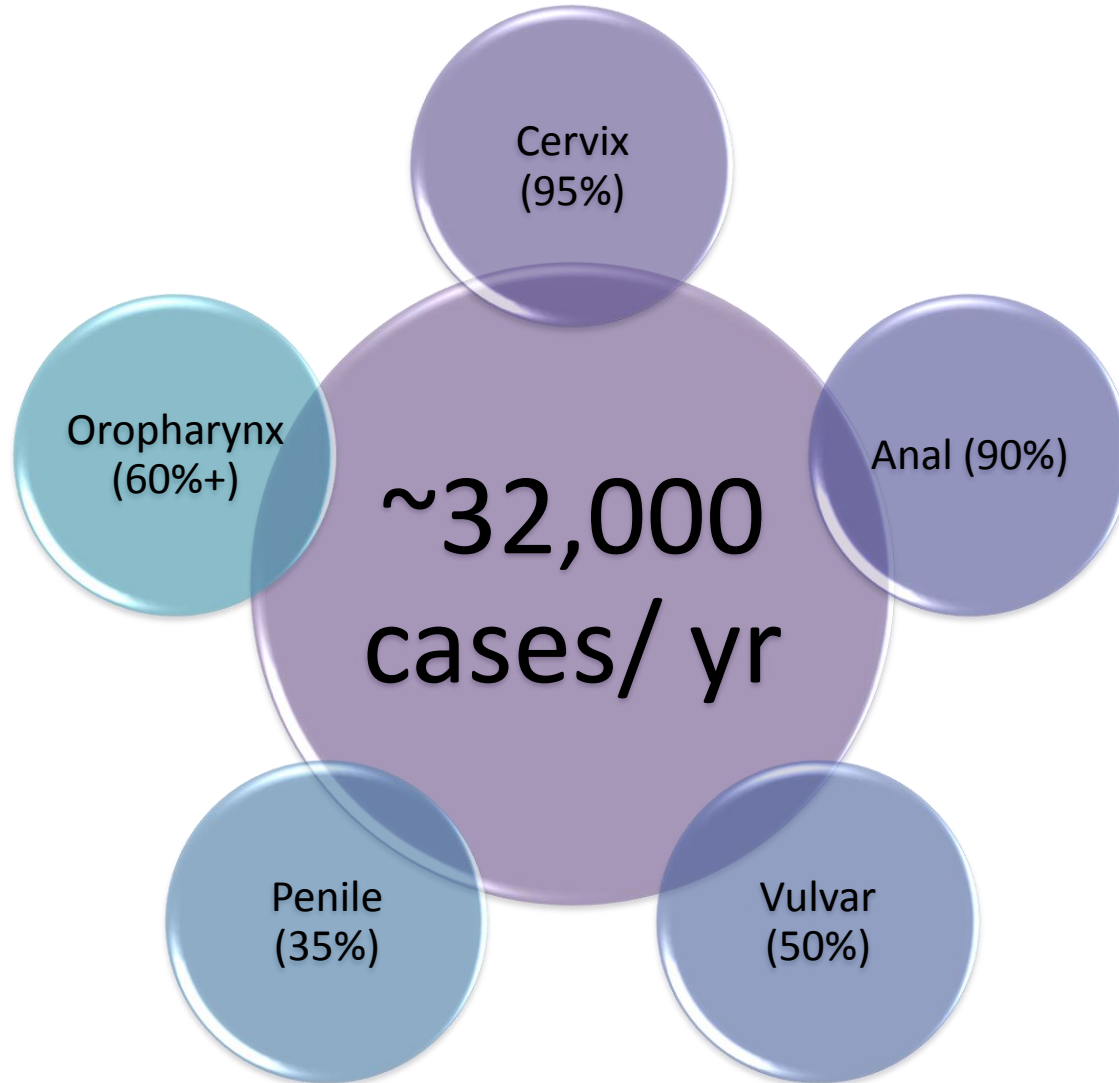
N=50

$P < 0.001$

Implications of HPV on HNSCC

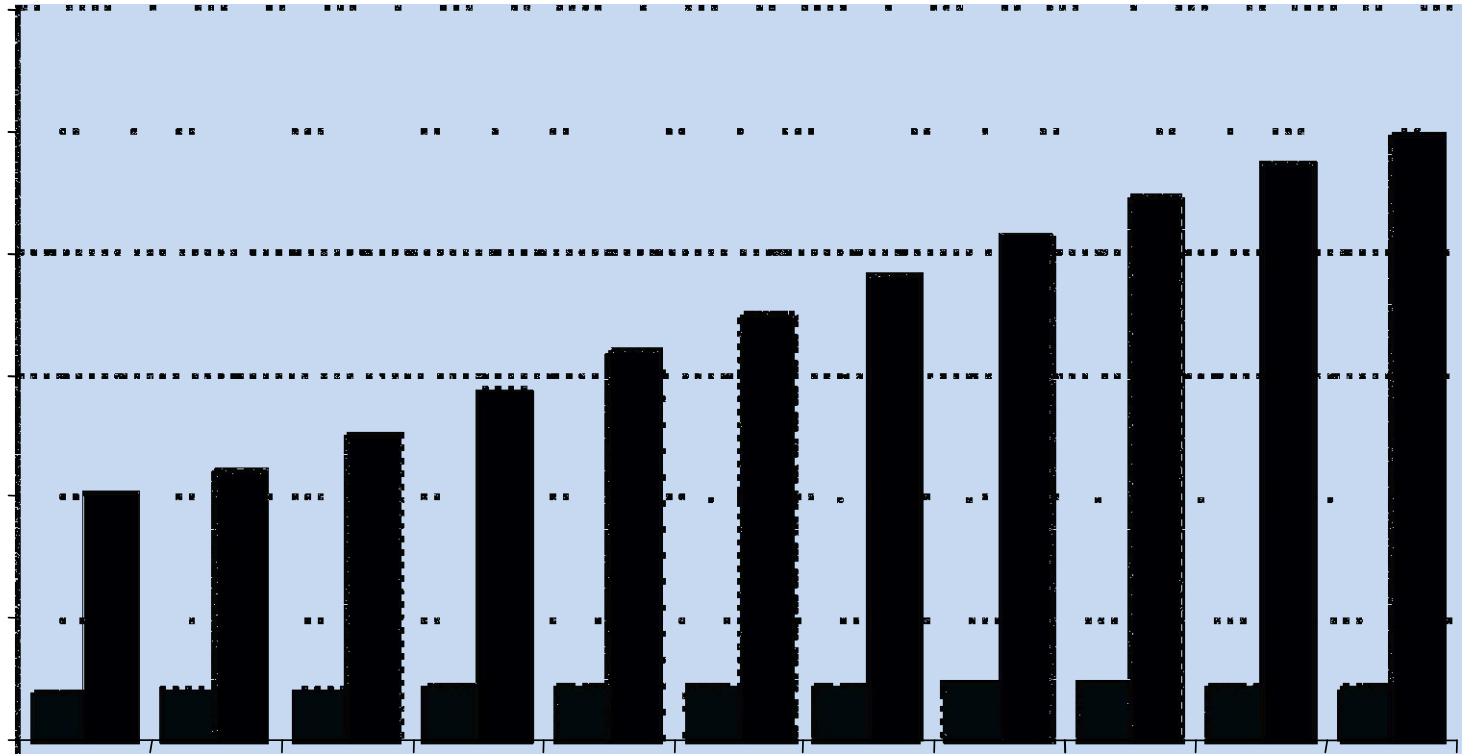


HPV related cancers



Projected cases of cervical cancer

of cases/yr cases



Projected cases in Developed Regions. 2002-2050
Projected cases in Developing Regions. 2002-2050