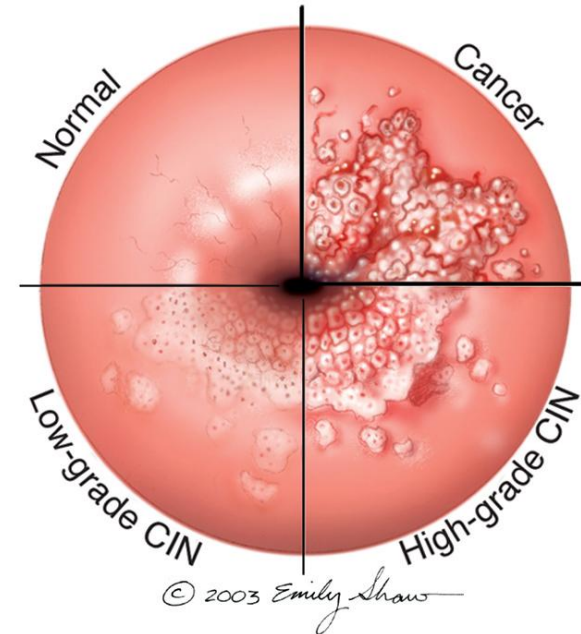
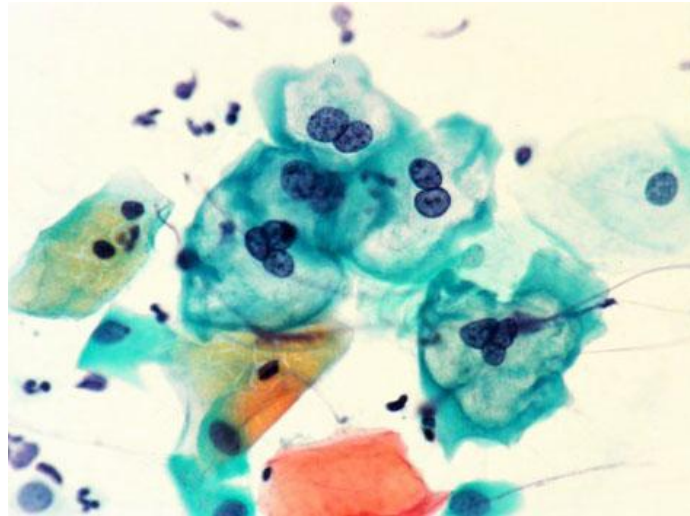
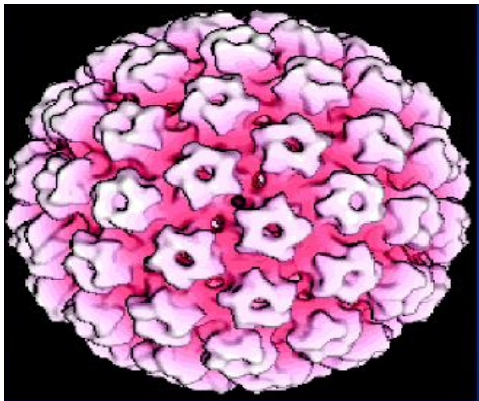




# Infections and Epidemiology of HPV



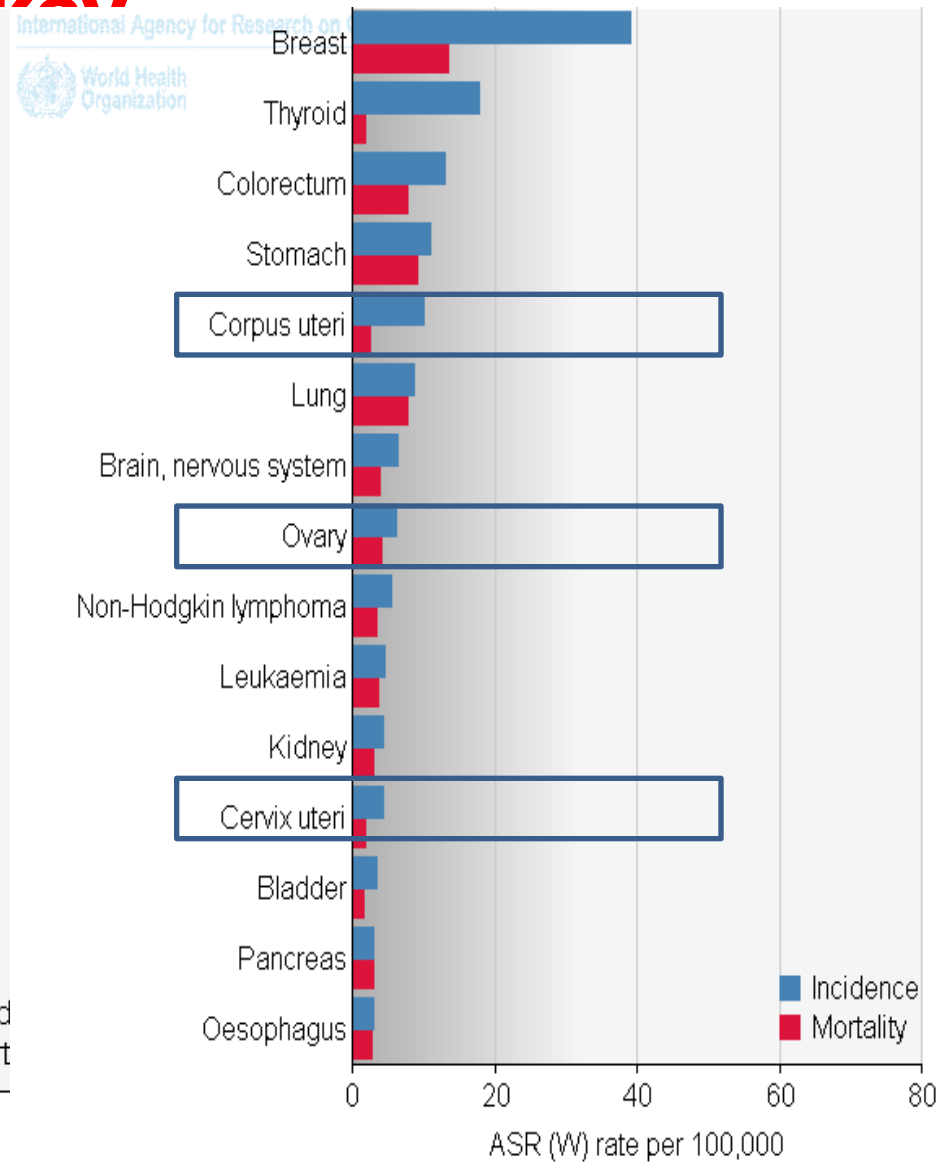
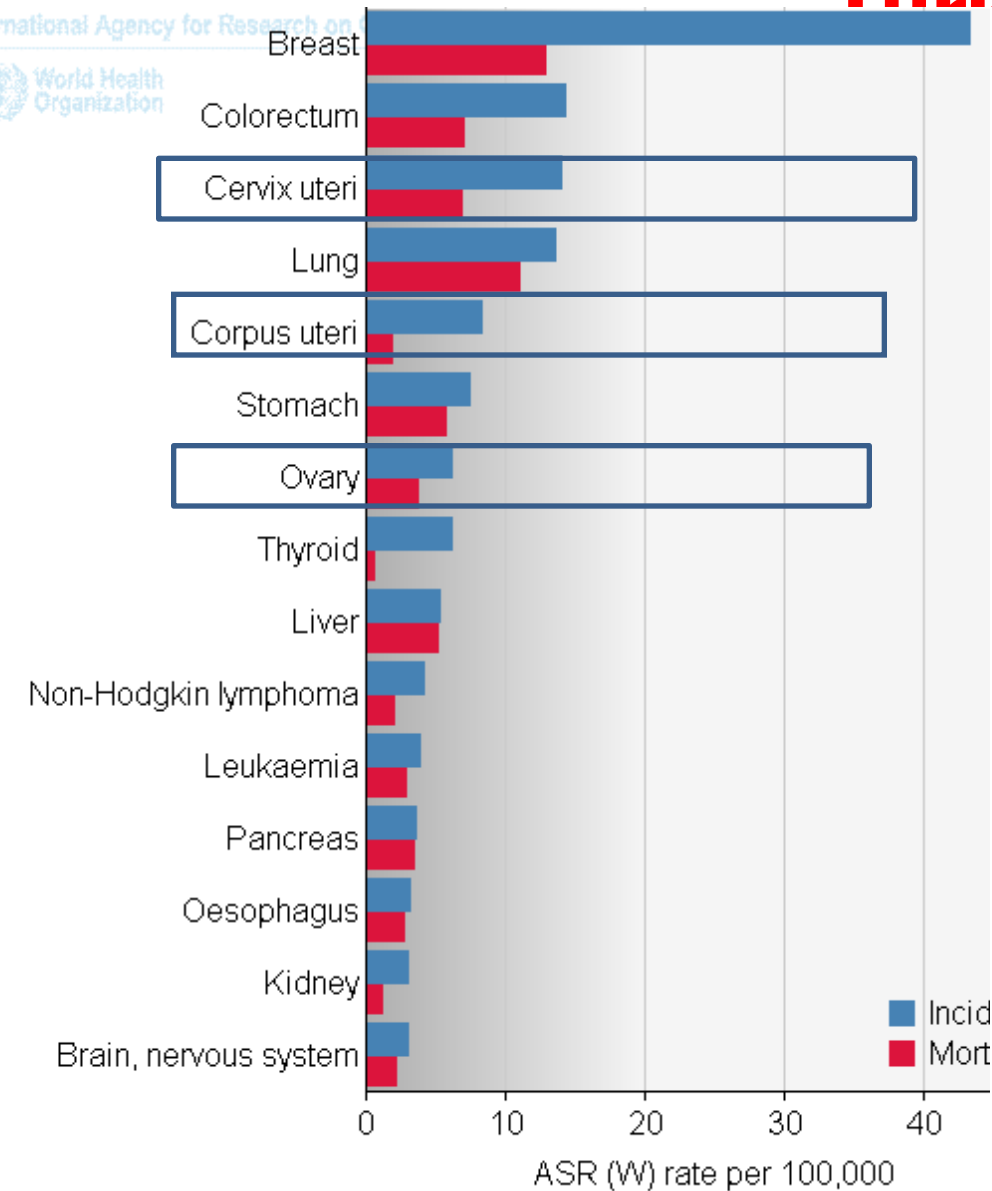
**Ali Ayhan, MD**

**Baskent University School of Medicine  
Department of Obstetrics and Gynecology  
Division of Gynecologic Oncology**

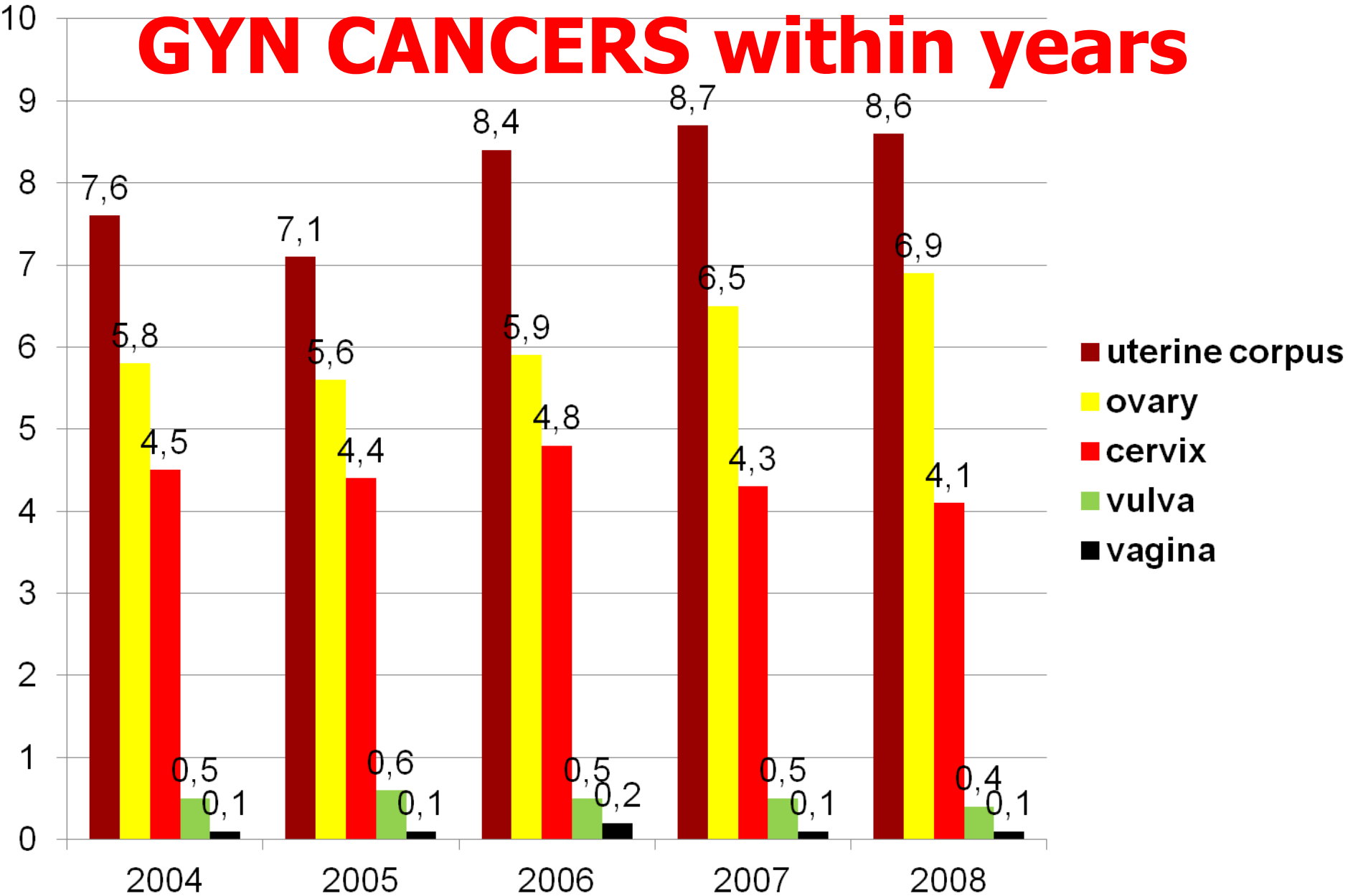
# Globocan 2012 World

# Globocan 2012

Turkey

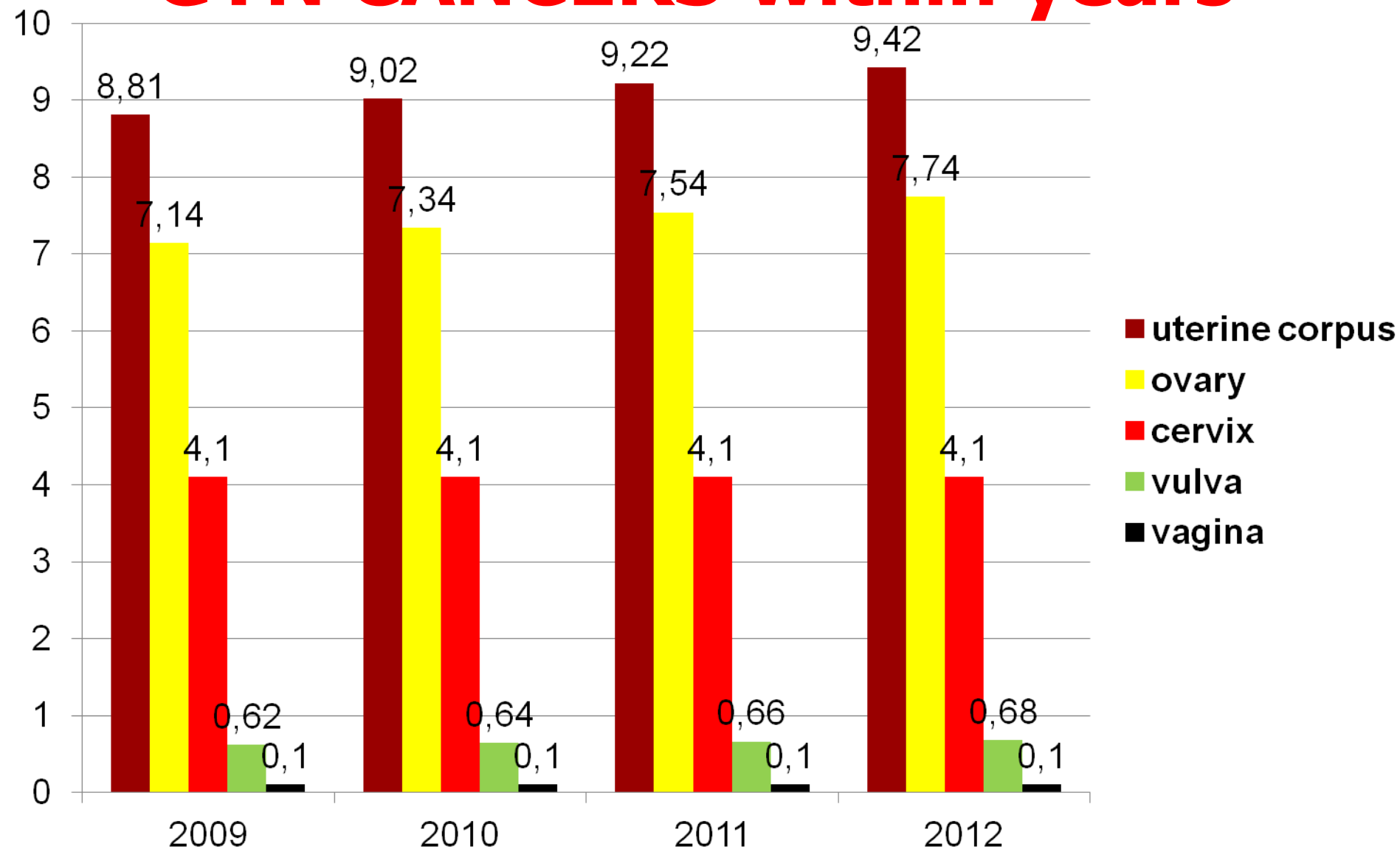


# GYN CANCERS within years



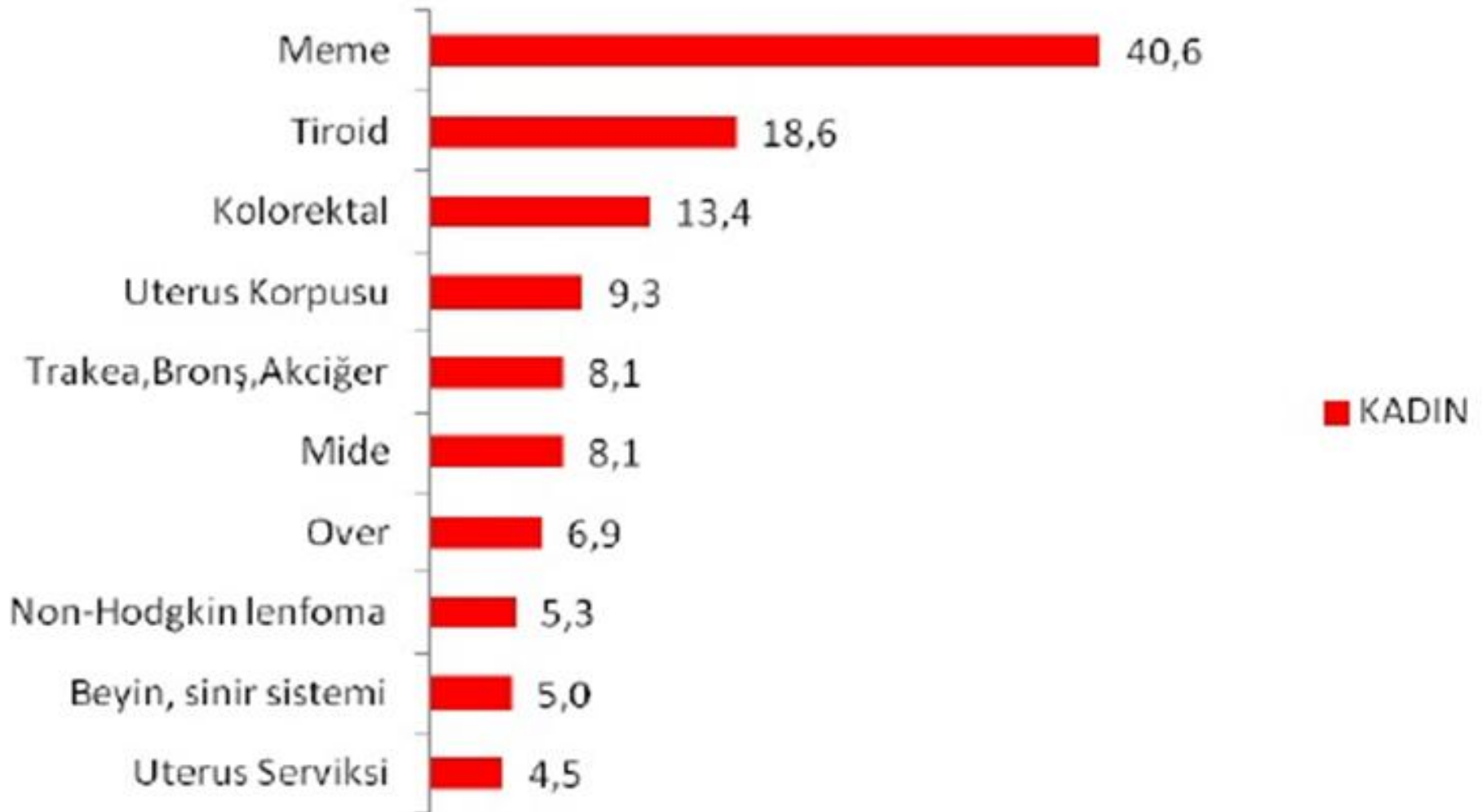
Data of Ministry of Health

# GYN CANCERS within years

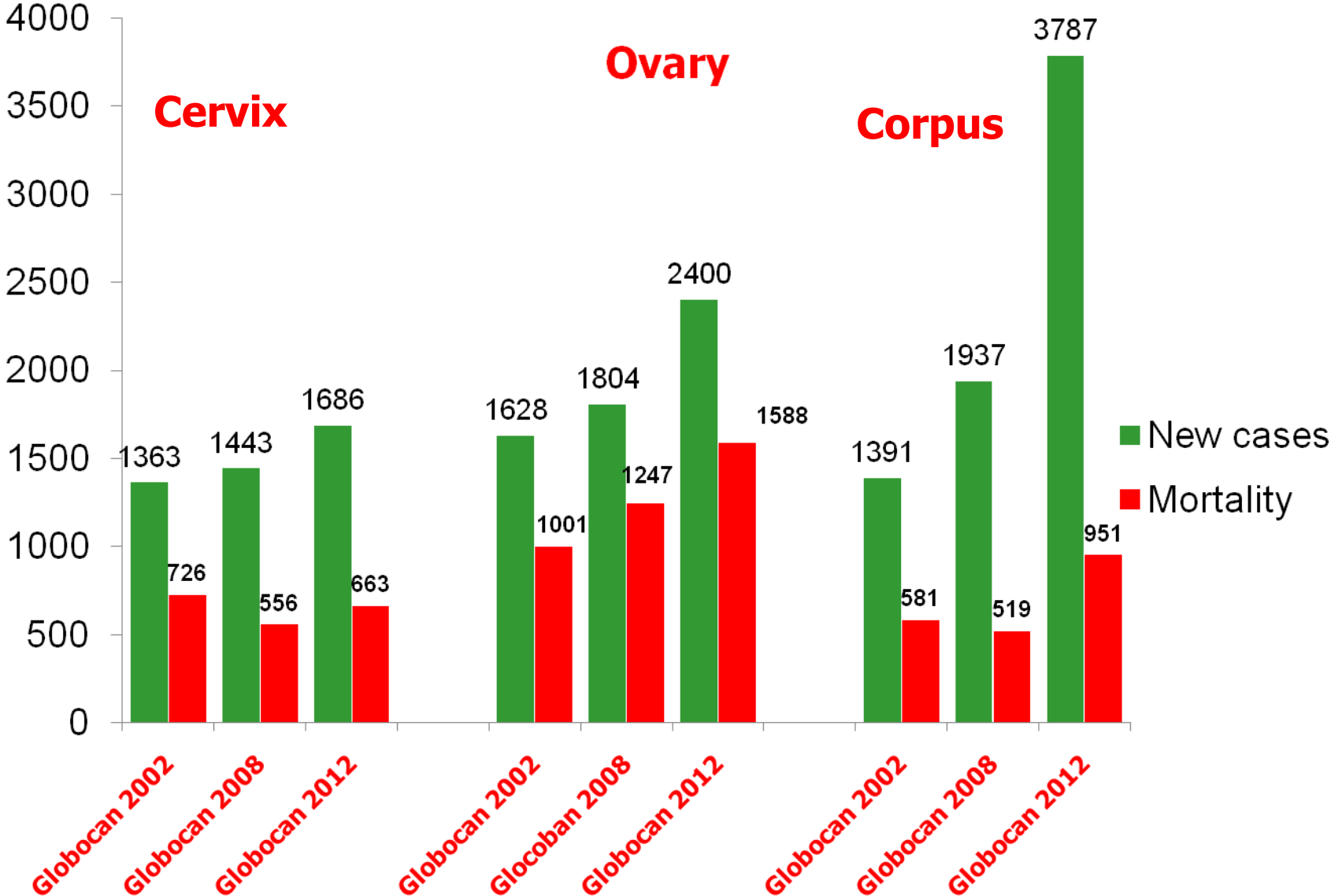


Data of Ministry of Health

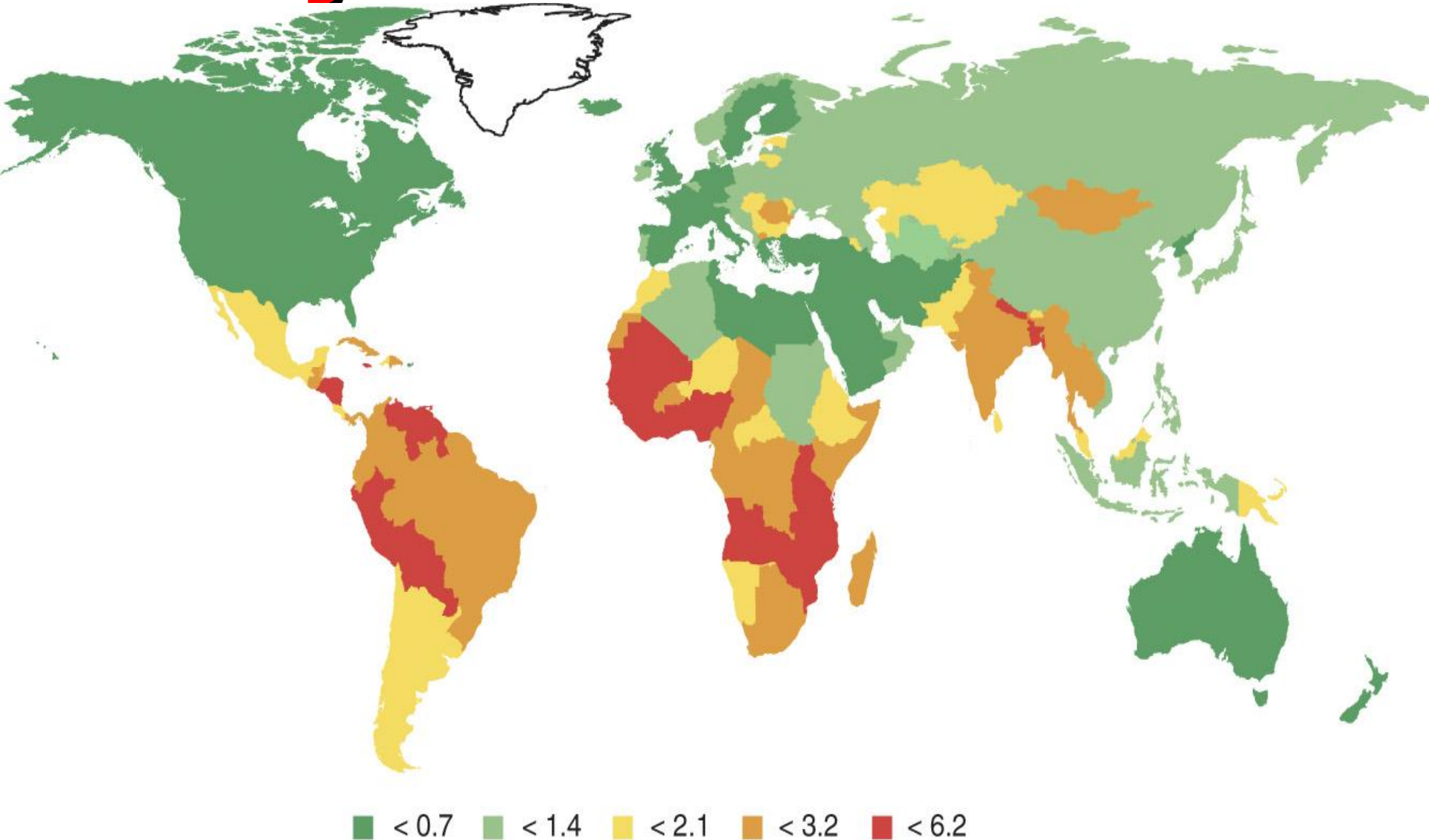
# The First 10 Women Cancers with in years (MoH)



# New Cases vs Mortality in Turkey



# Cumulative Incidence Risk Through age 74 based on GLOBOCAN



# Cervical Cancer

**Lifetime risk**



**0,68 %  
(1/147)**

**Median age at  
diagnosis**



**48 yrs**

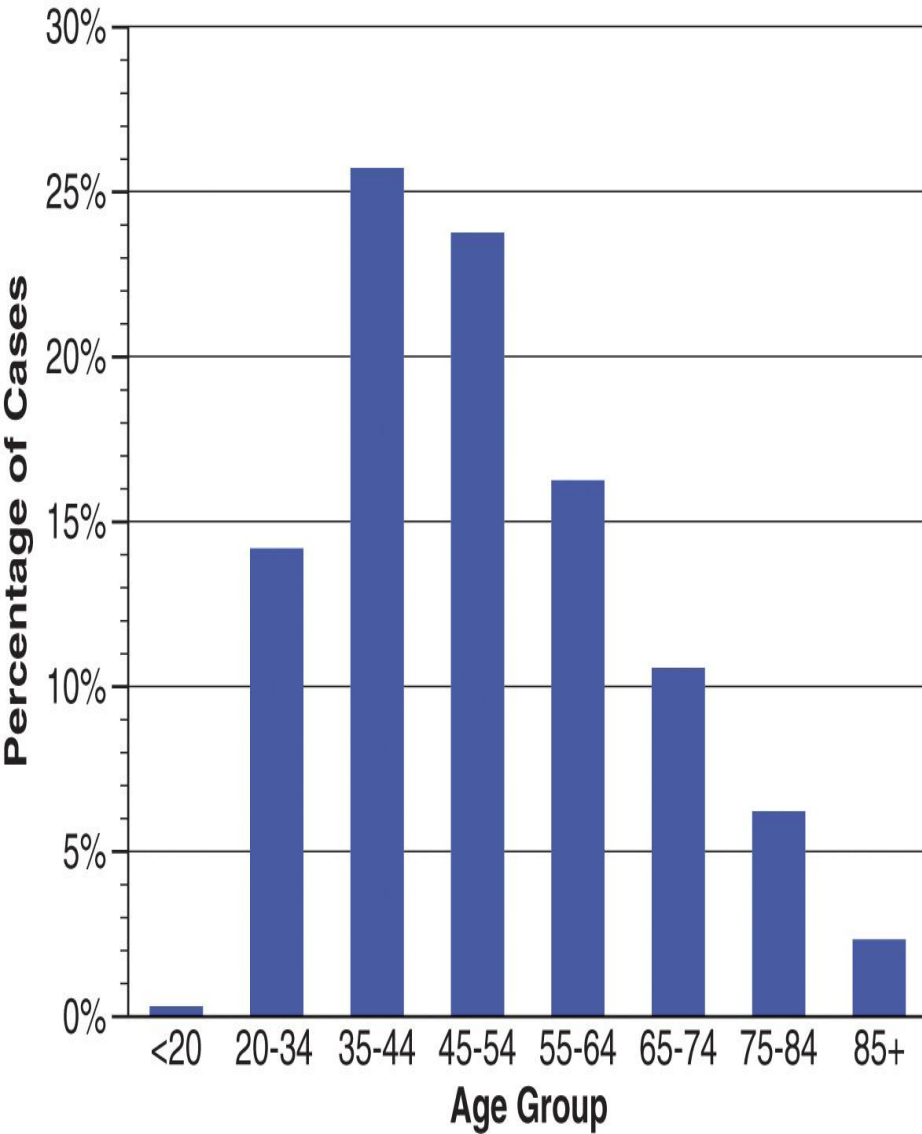
**Death rate  
(Per year)**



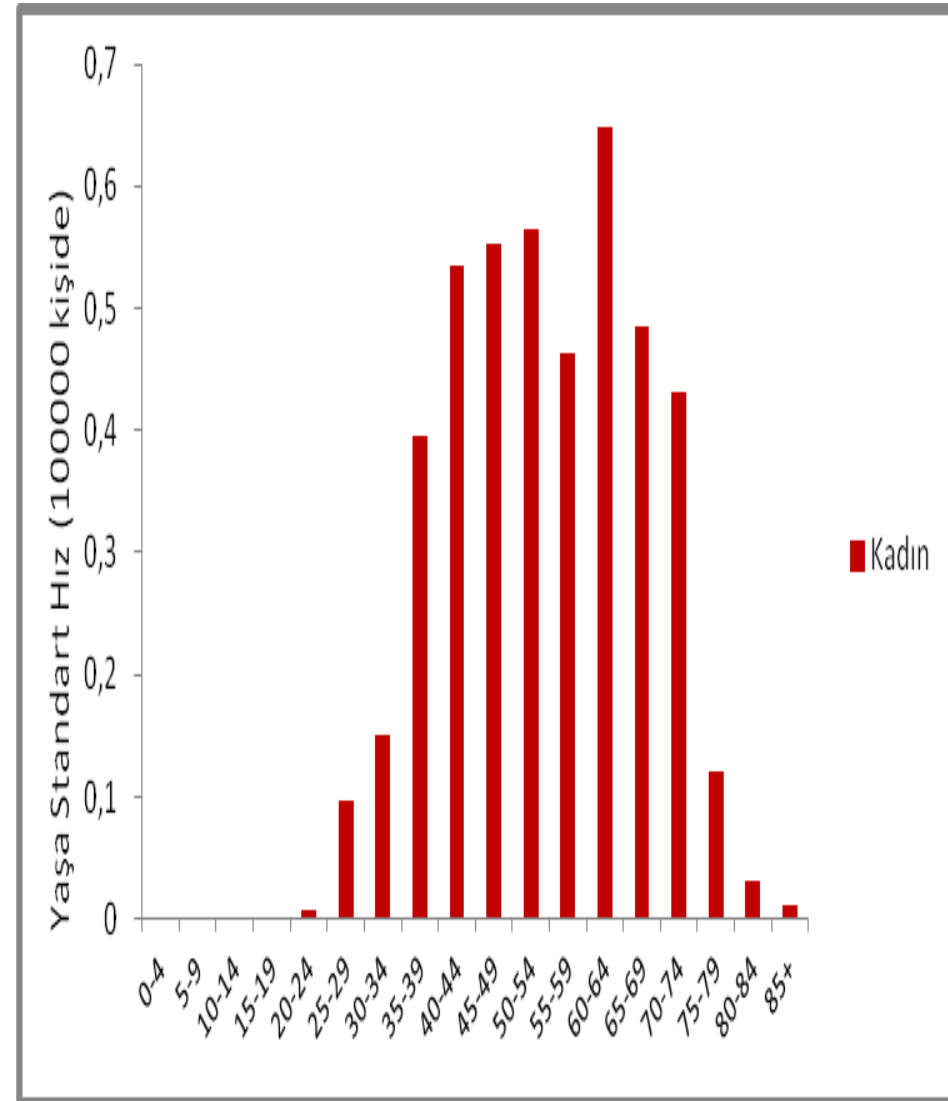
**2,4 per  
100,000**



# Age distribution of Invasive CC



**US 2004-2008**

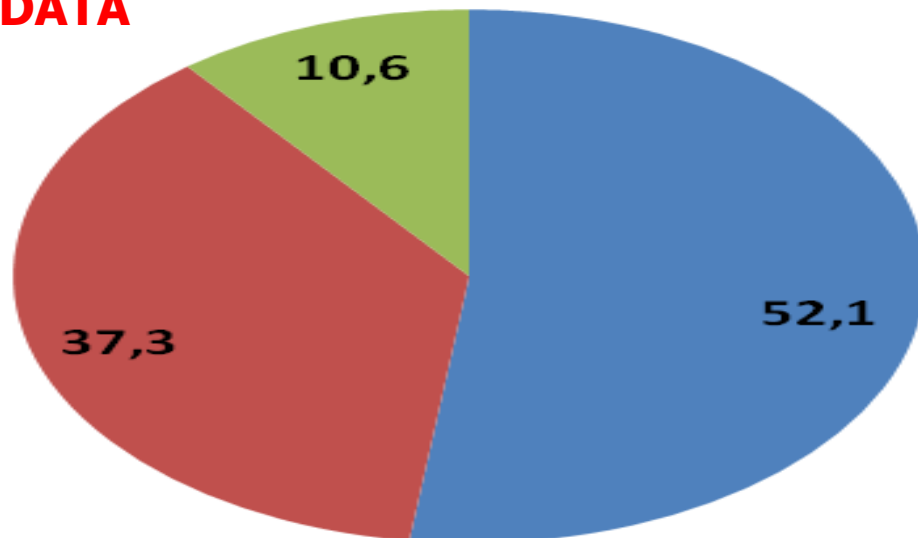


**TURKEY 2009**

# Stage vs Survival

	At initial diagnosis	5 year Survival
Localized Stage	49 %	91,2 %
Regional LN or beyond primary	35 %	57,8 %
Distant Met.	11 %	17,0%
Unknown (Unstaged)	5 %	58,1 %

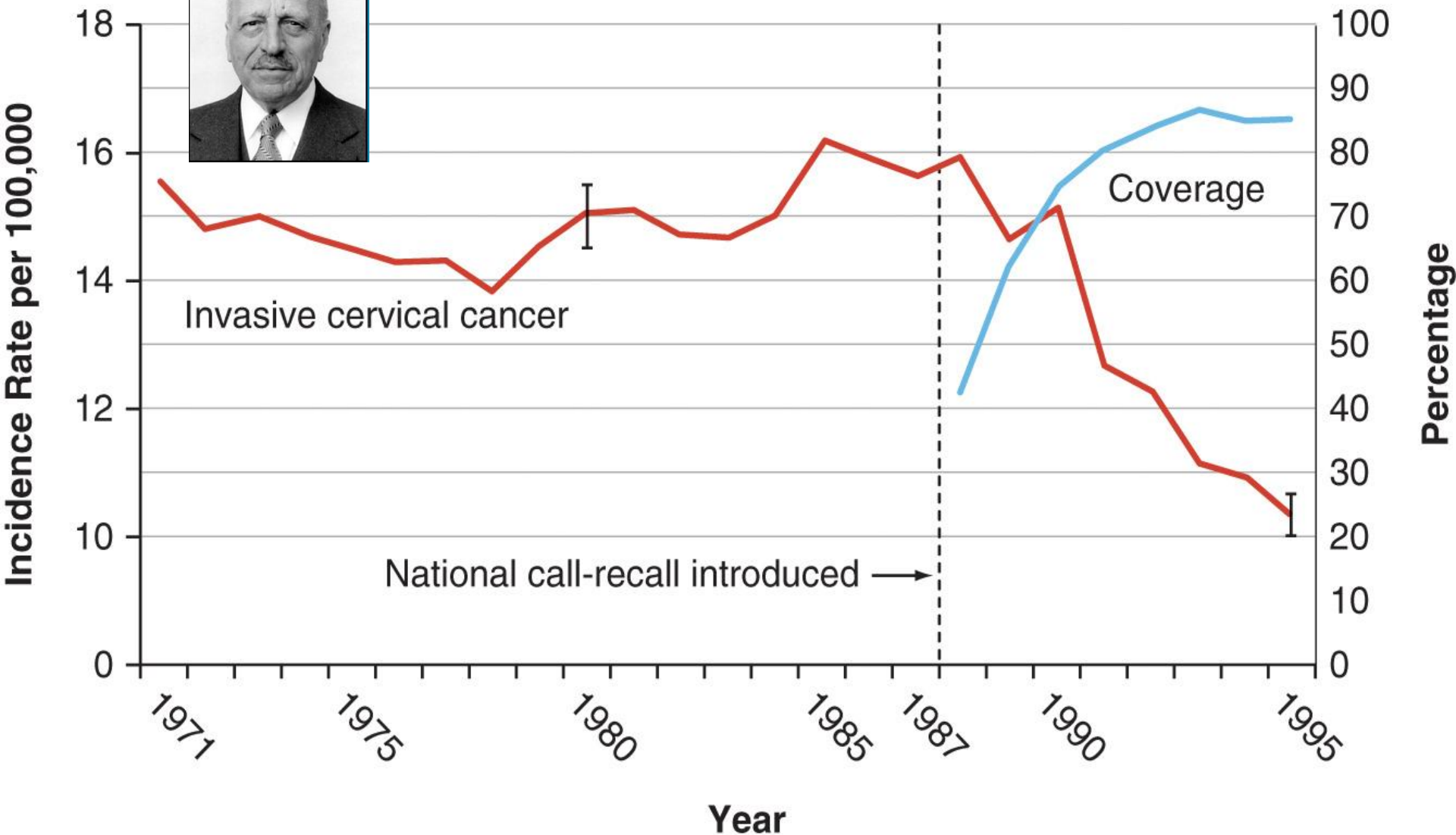
## TURKEY DATA



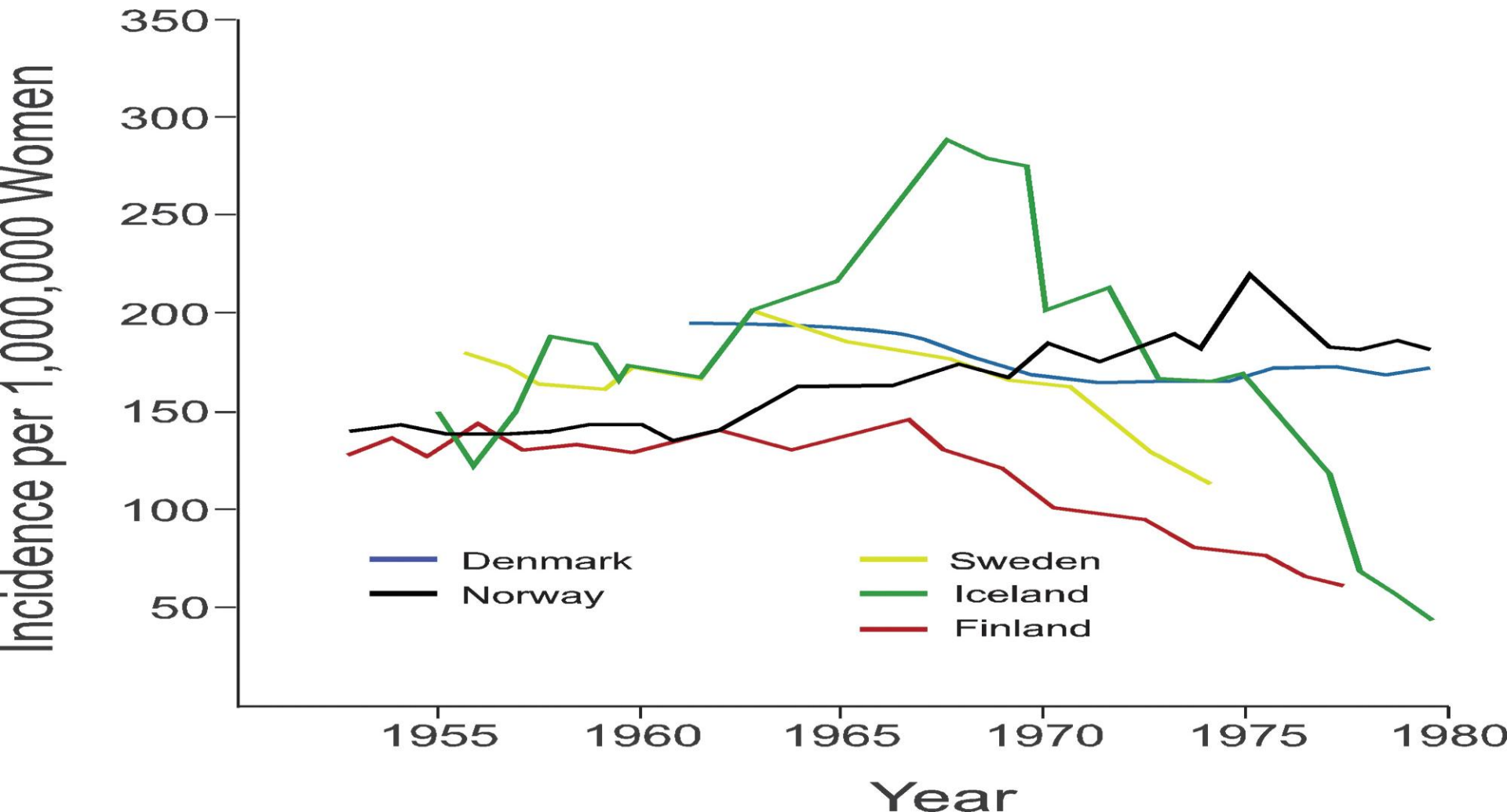
Survival 42,5mts

- Lokalize
- Bölgesel
- Uzak yayılım

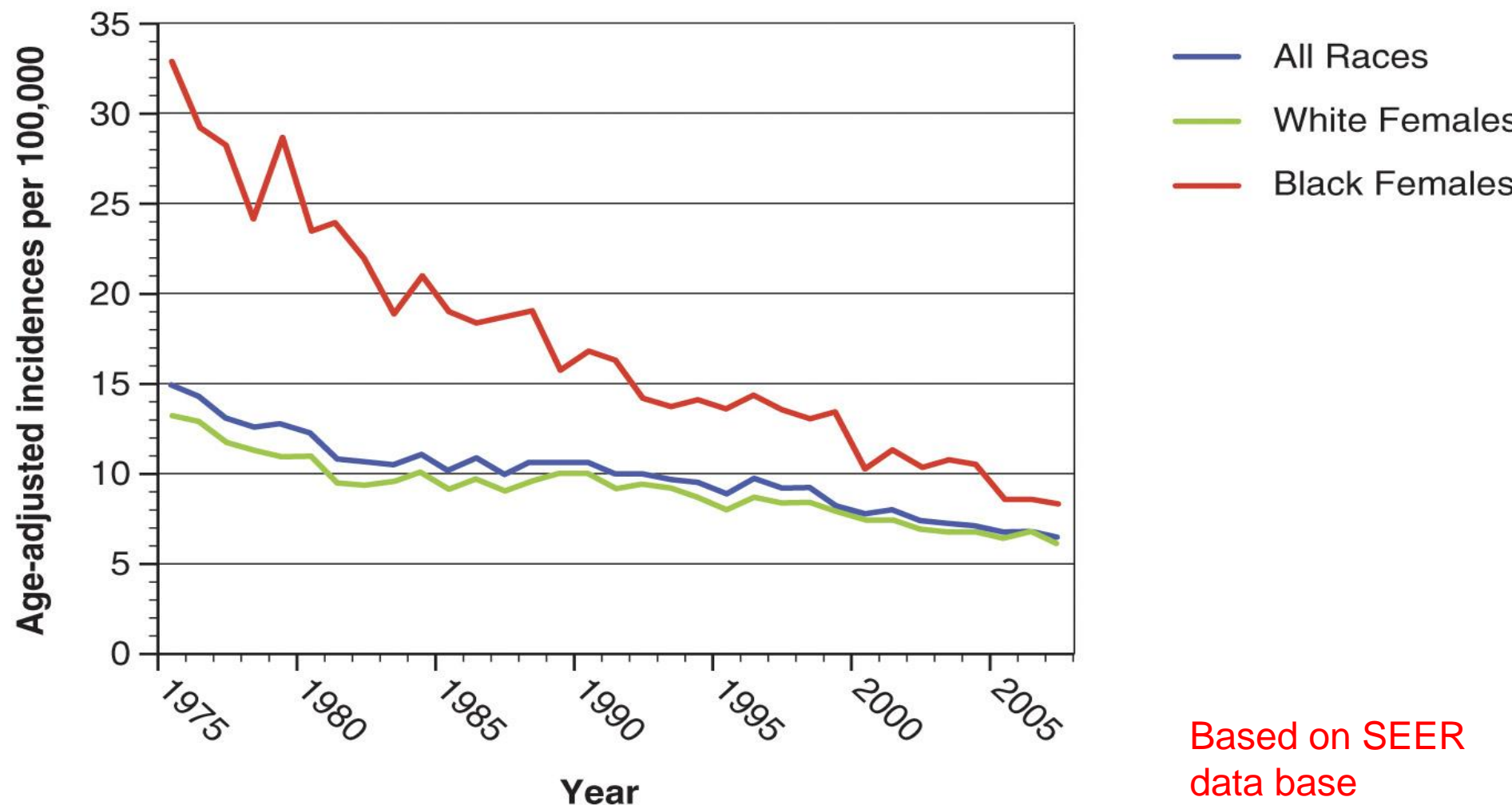
# ICC and coverage of Screening



# Incidence of Invasive CC In Scandinavia



# Age Adjusted incidence rates In USA



# Causative and cofactors for cervical cancer

**HPV**  
**1970** IARC  
WG

**High**  
**Intermediate**  
**Low**

**Co-factors**

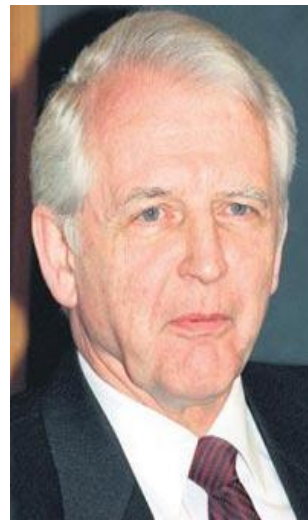
**Cigarette**  
**Multiple partner**  
**Early age intercourse**

**(Immature Metaplasia)**

**Possible  
co-factors**

**Chlamydia**  
**Herpes II**  
**HIV**  
**OC**  
**Low S.eco  
status**

# Nobel Prize in Medicine - 2008



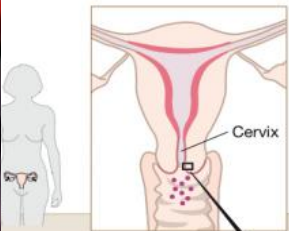
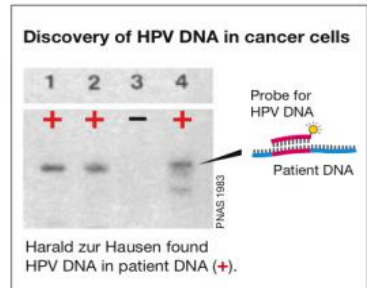
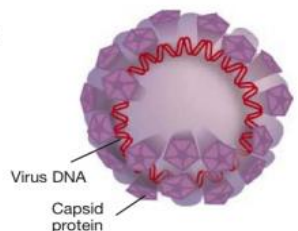
## Prof. Dr. Harald zur Hausen German Cancer Research Centre Heidelberg, Germany



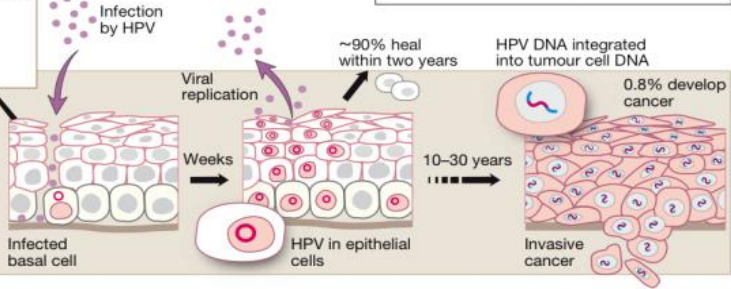
### HPV – human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.

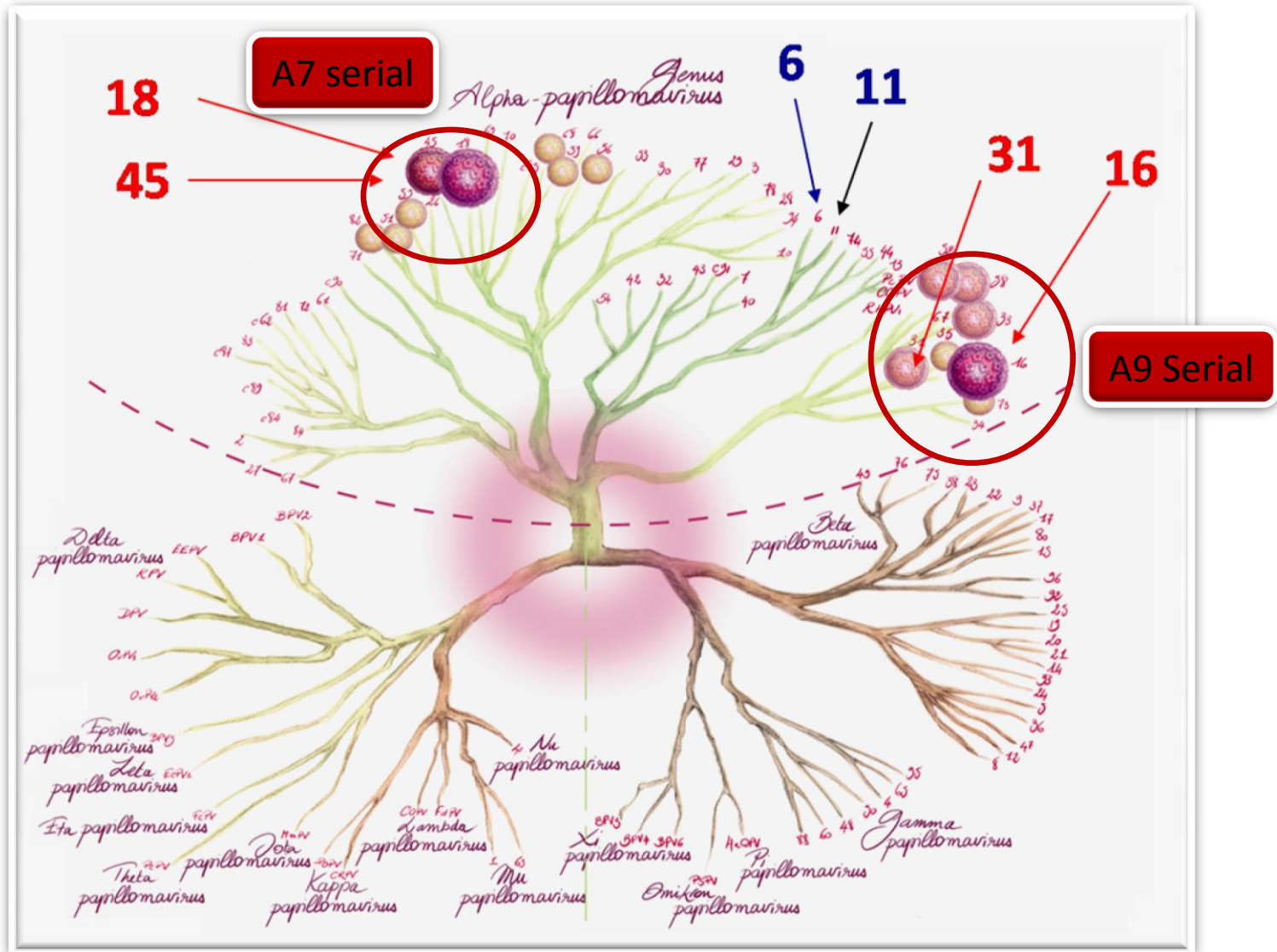


**Infection by HPV**  
HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.





# HPV Philogenetic Tree





# >130 HPV types

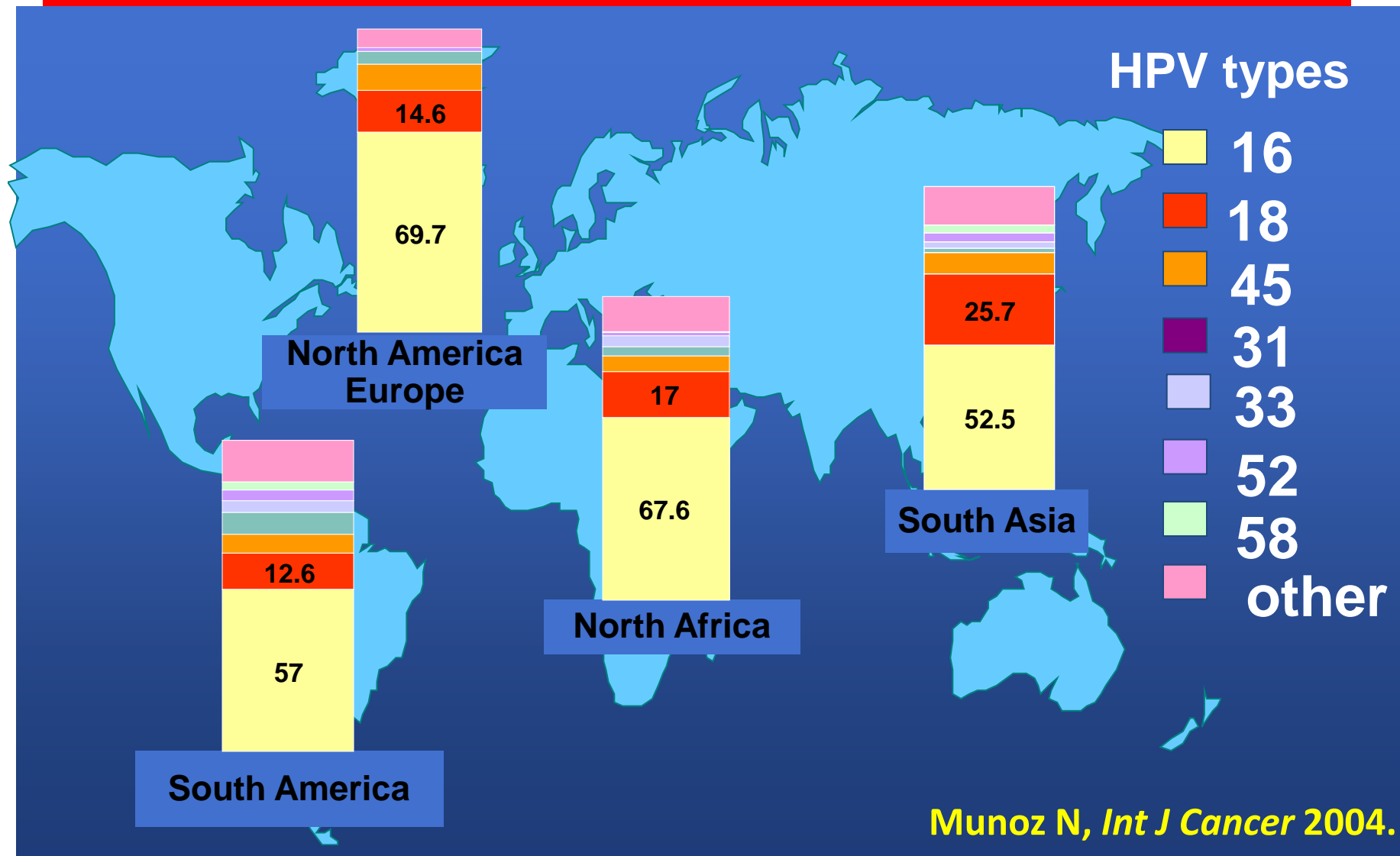
- **Mucosal (~40 types)**
  - **high risk (16, 18, 31, 33...)**
    - low grade cervical abnormalities
    - high grade abn / cancer precursors
    - anogenital cancers
  - **low risk (6, 11...)**
    - low grade cervical abnormalities
    - genital warts
    - respiratory papillomas
- **Cutaneous (~60 types)**
  - common warts (hand, feet)

# Estimated HPV DNA prevalence in the world

Meta-analysis of 67 studies involving 139.777 cytologically normal women

	%
Global	10.2 (10.0-10.5)
Africa	23.4 (22.0-24.8)
America	12.8 (12.1-13.5)
Europe	8.2 (7.9-8.6)
Asia	7.6 (7.2-8.1)

# HPV Type Prevalance at The Different Part of The World



# Transmission

- Sexual intercourse
  - Vaginal, oral, or anal
  - Not only penetration but also skin to skin contact
- HPV can be found in women who have never had sexual intercourse,  
(the rate of HPV infection in virgins is 14.8%)

Pao CC, Tsai PL, Chang YL, Hsieh TT, Jin JY. Possible non-sexual transmission of genital human papillomavirus infections in young women. *Eur J Clin Microbiol Infect Dis.* 1993;12:221–222.

# HPV-Age

**Life-time risk: %50-80**

**N. Cytology : %10 HPV**

**One or multipl type infection**

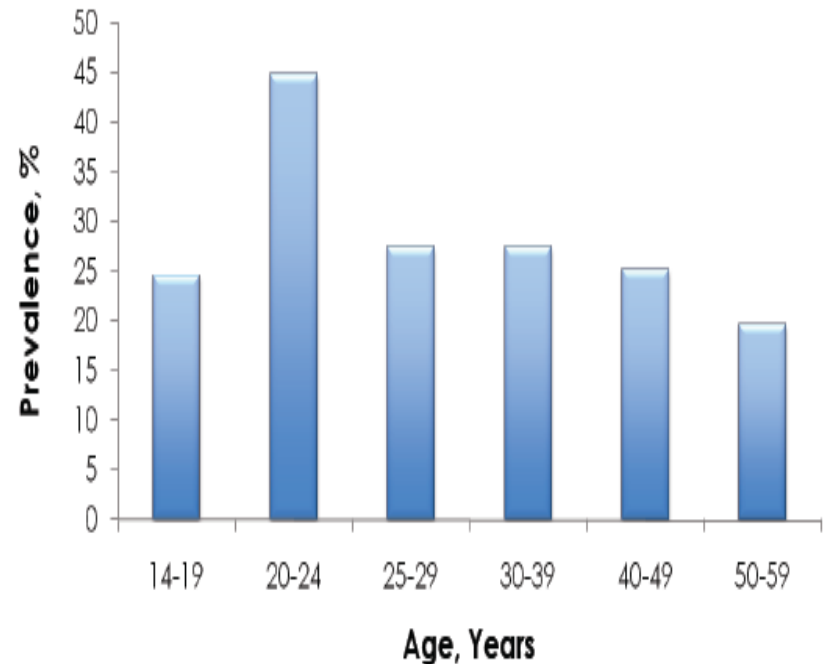
**Top 18-30y ,**

**30-40y decreases**

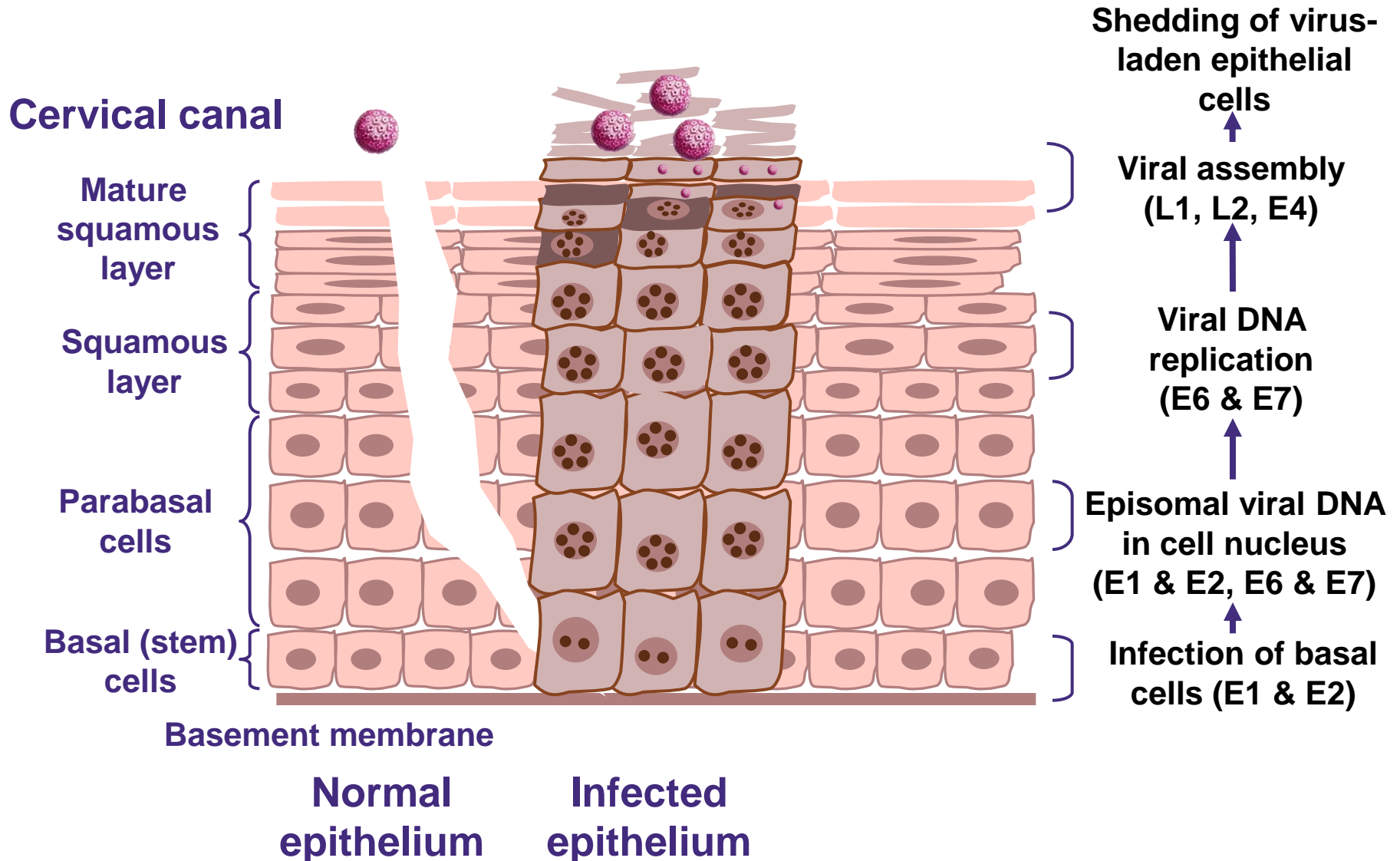
**Postmenoposal incereases**

HPV Prevalence Varies With Age in the  
General Population, NHANES<sup>a</sup>

Overall HPV Prevalence: 26.8%



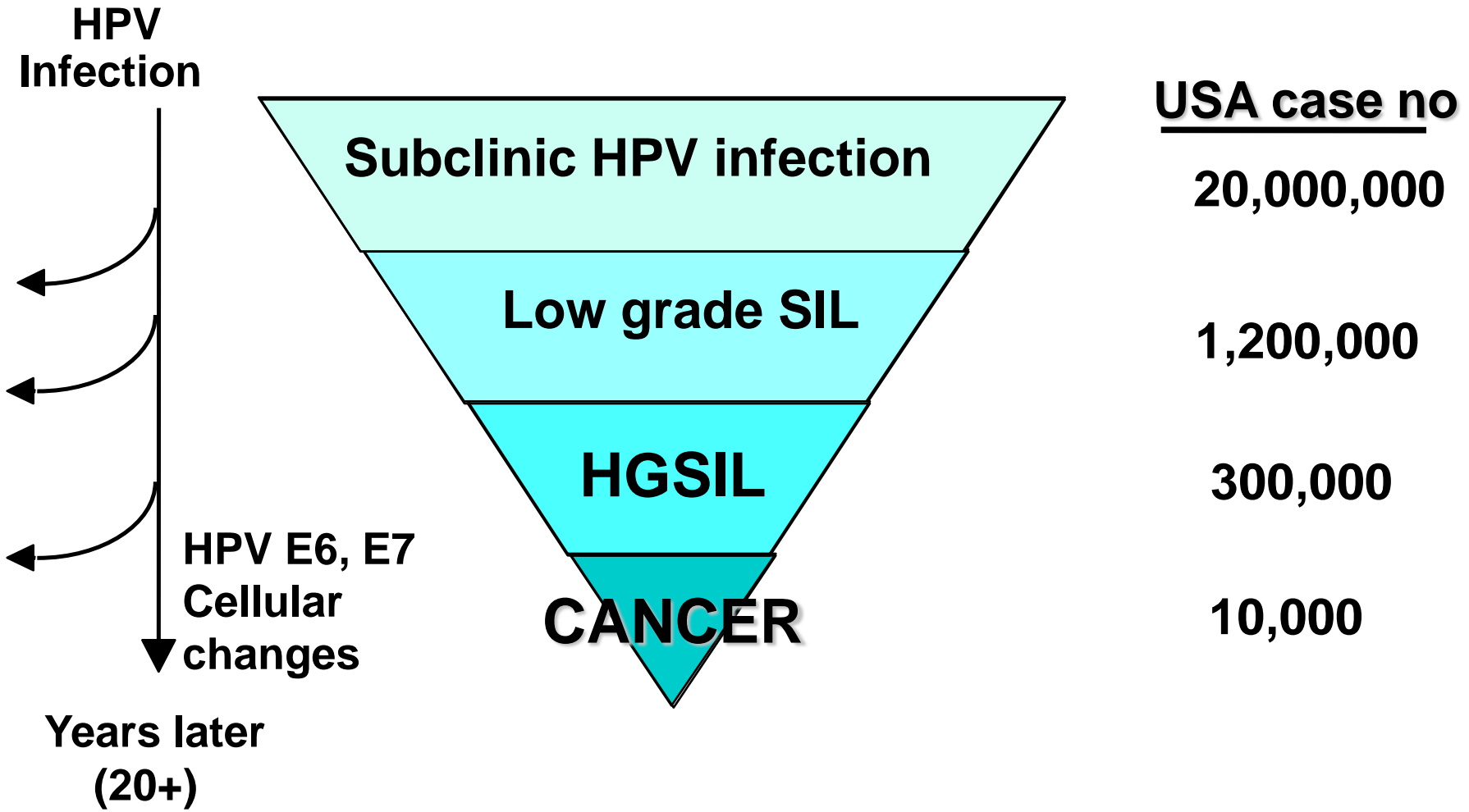
# HPV Lifecycle in the Cervix



# **Major Steps In Development of Cervical Cancer**

- **Infection of transformation zone with carcinogenic HPV**
- **Viral Persistence**
- **Clonal progression of infected epithelium to cervical cancer**
- **Invasion**

# HPV Infection Natural Course

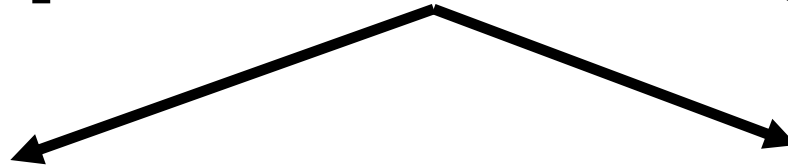




# HPV-DNA Genome



## Up Stream Region



**Region of  
Early Genes**



**Codes**

**E6, E7, E1, E2, E4,  
E5**

**Region of  
Late Genes**



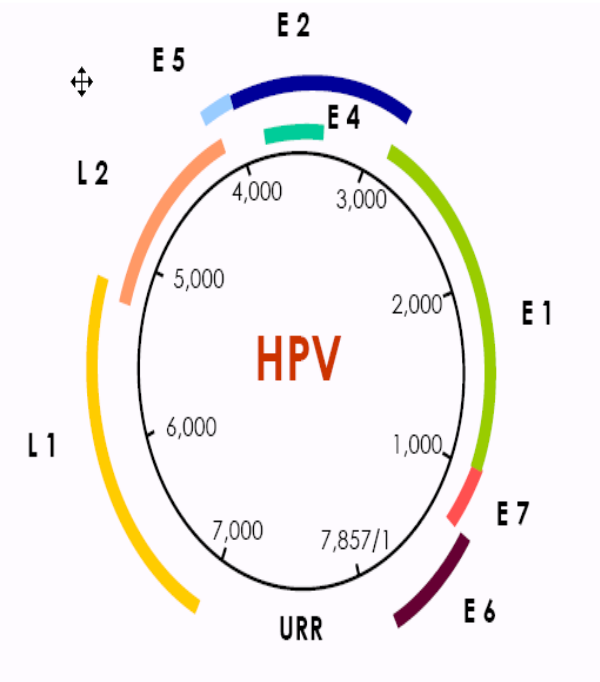
**Codes**

**L1, L2**

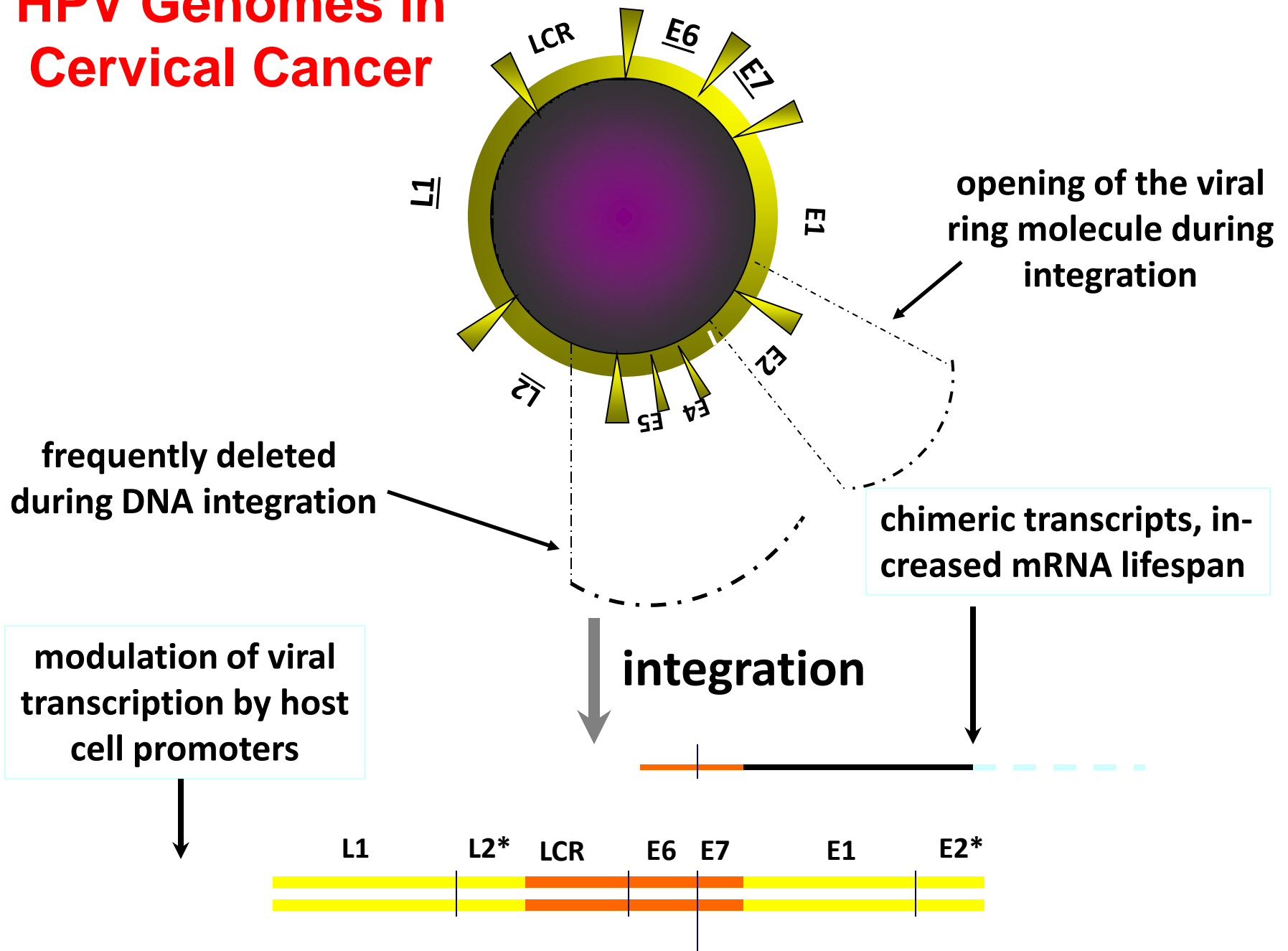
# Role of Early Proteins

E1	replication
E2	replication and transcription
E4	viral release
E5	immun evasion
E6	bind p53
E7	bind pRb

## SCHEMATIC PRESENTATION OF THE HPV GENOME



# HPV Genomes in Cervical Cancer



# CERVICAL CARCINOGENESIS

**E6**



**Degradation of p53**

**Activates Telomerase**

**E7**



**Degradation of Rb**

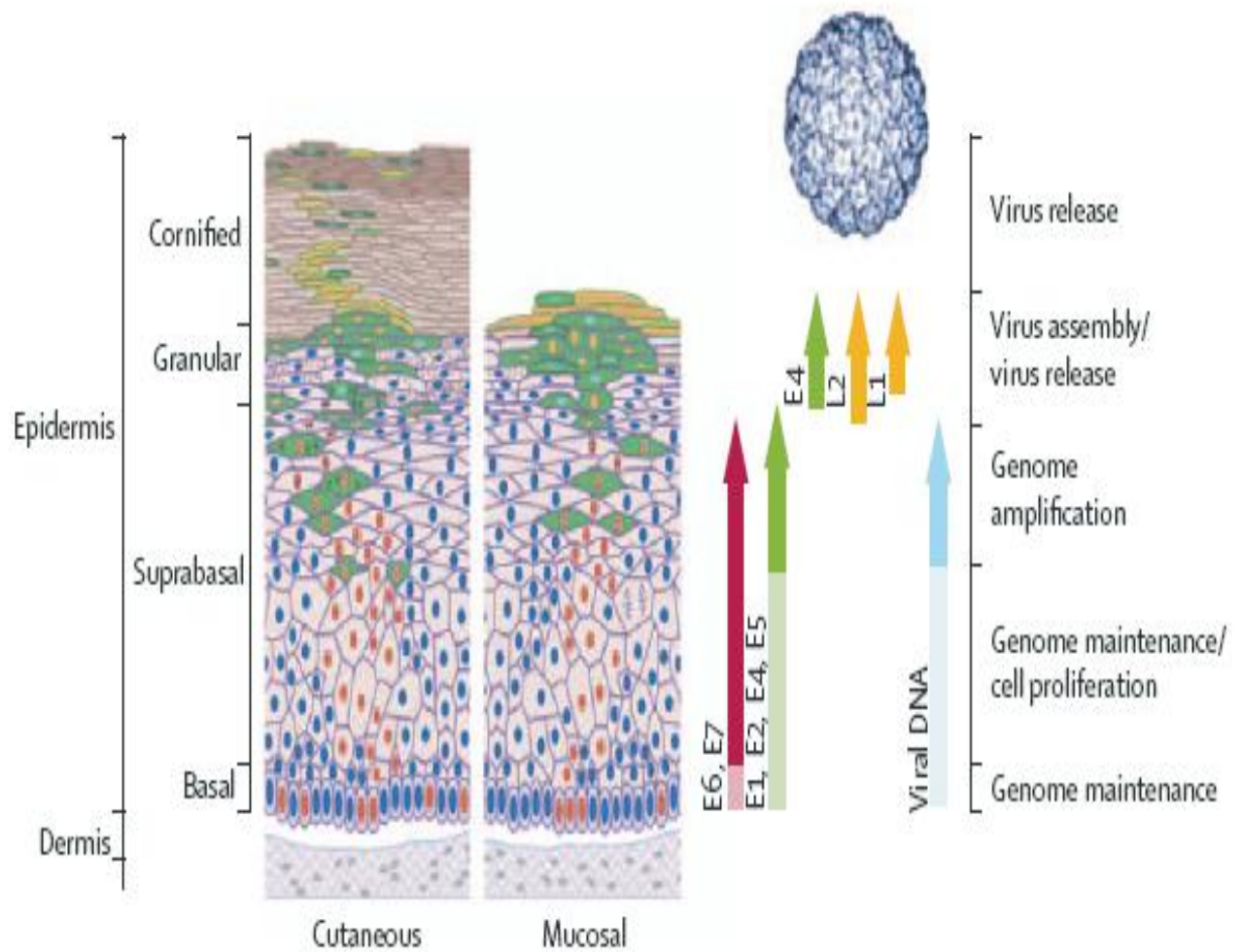
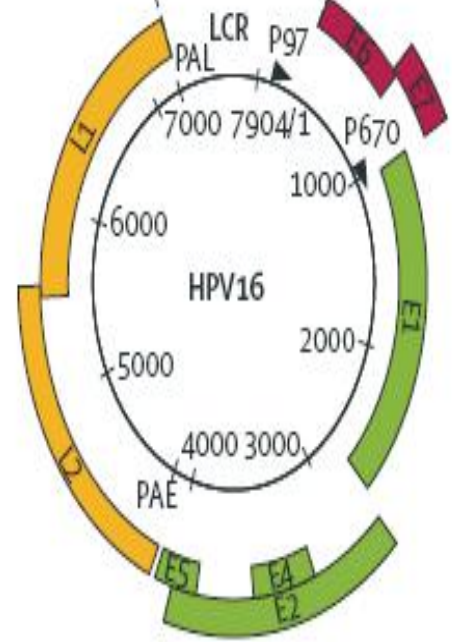
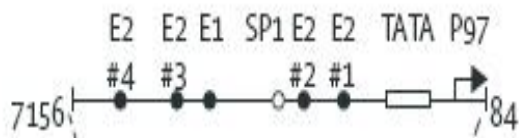
**Stimulates Cyclin A, E**



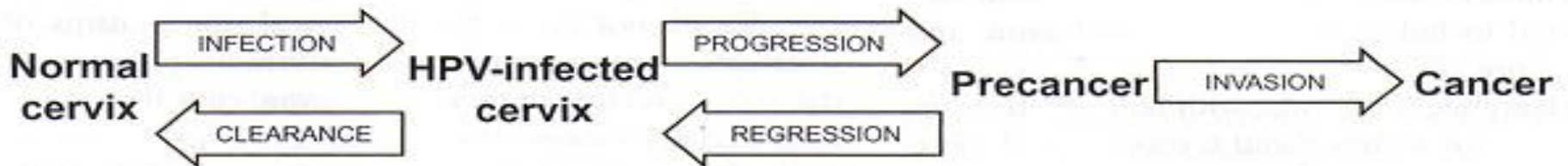
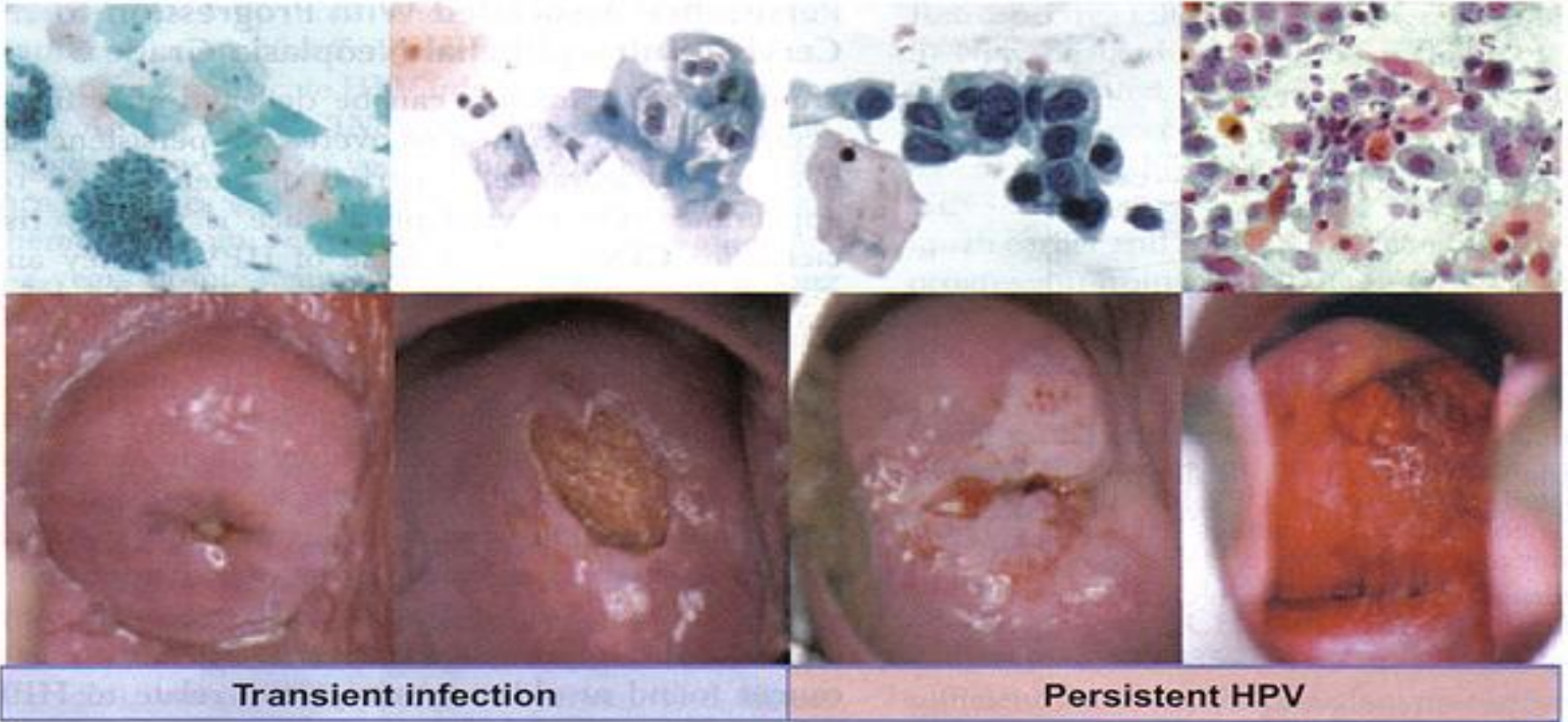
**CERVICAL CARCINOGENESIS**

**TSG**

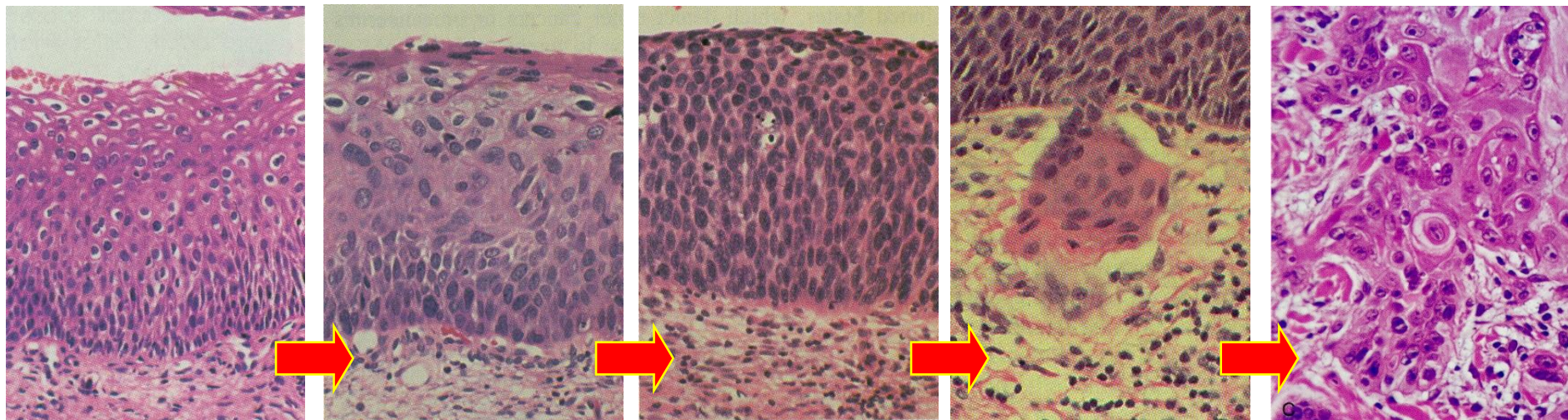
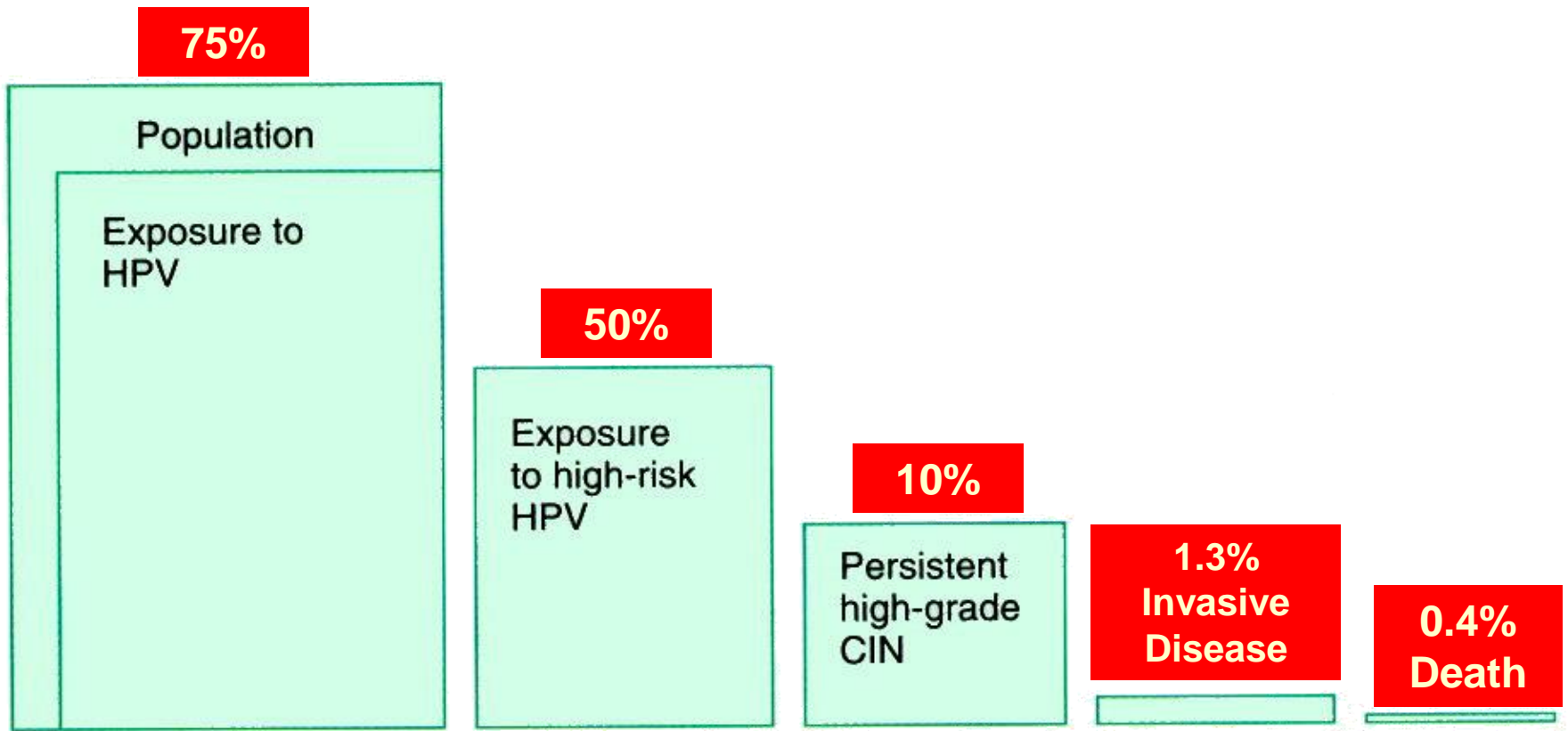
**Role of  
Carcinogenesis**



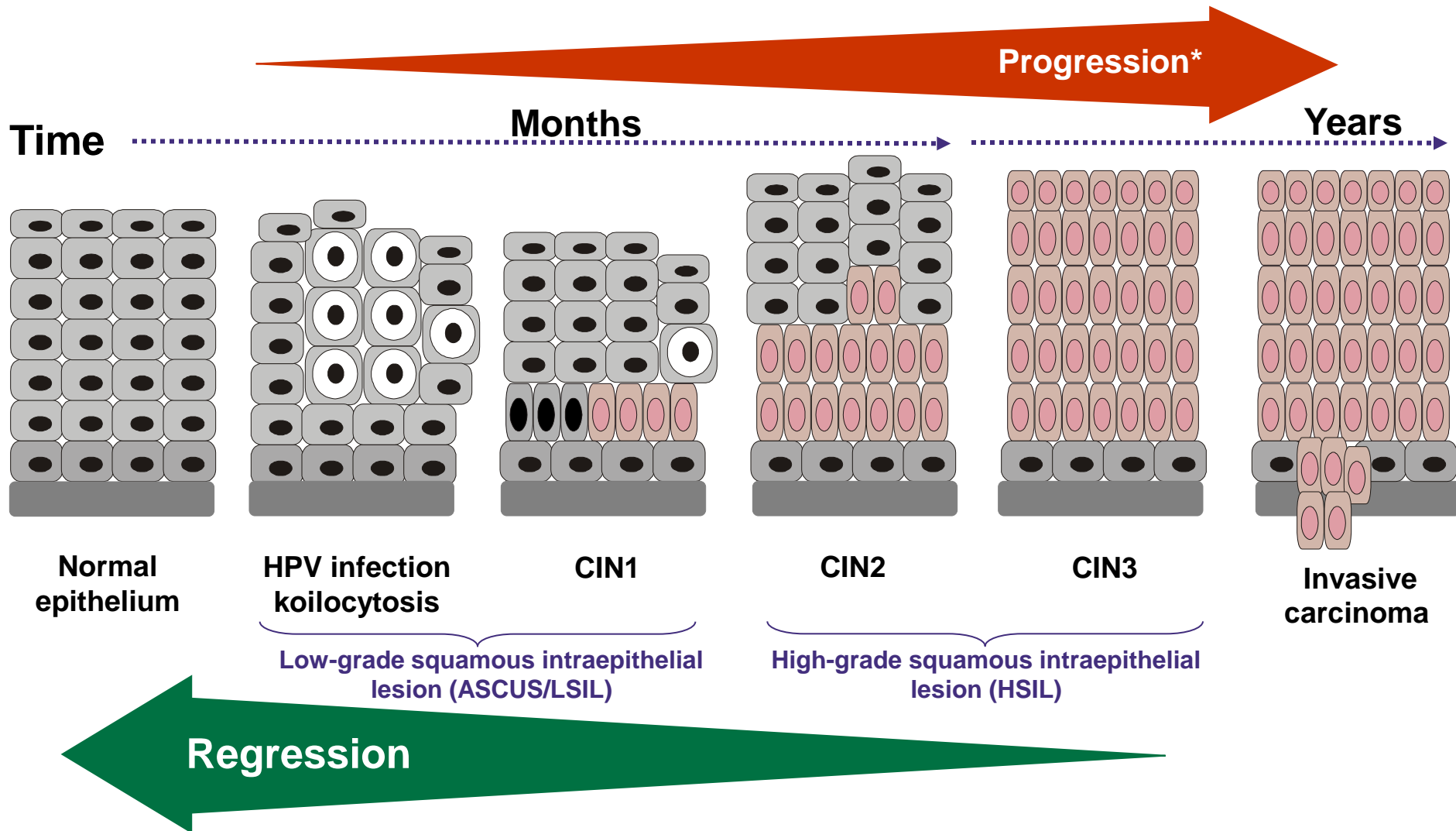
# Cervical cancer progression model







# Progression of Cervical Disease

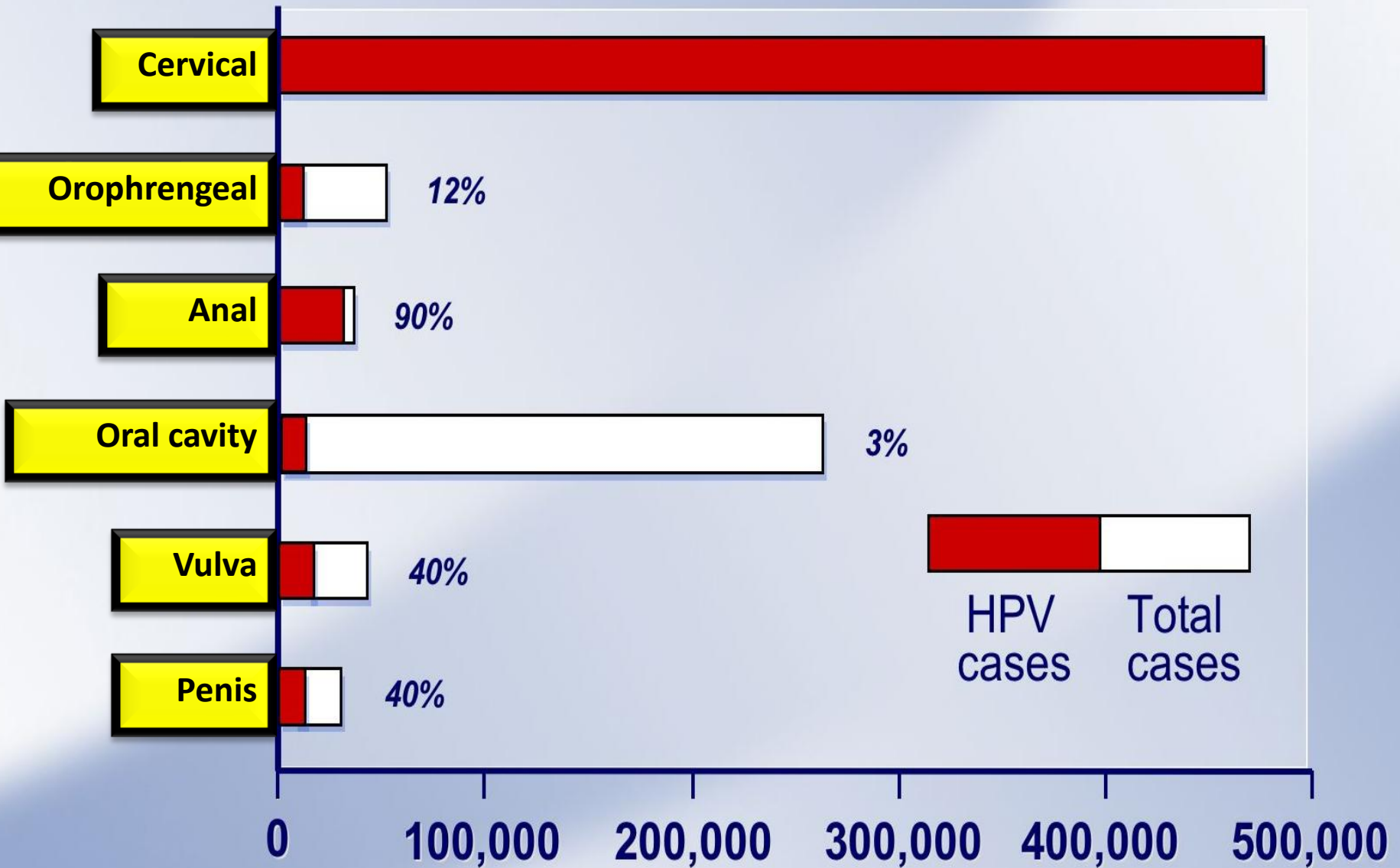


\* With increasing probability of viral DNA integration.  
 CIN = cervical intraepithelial neoplasia; ASCUS = atypical squamous cells of undetermined significance.

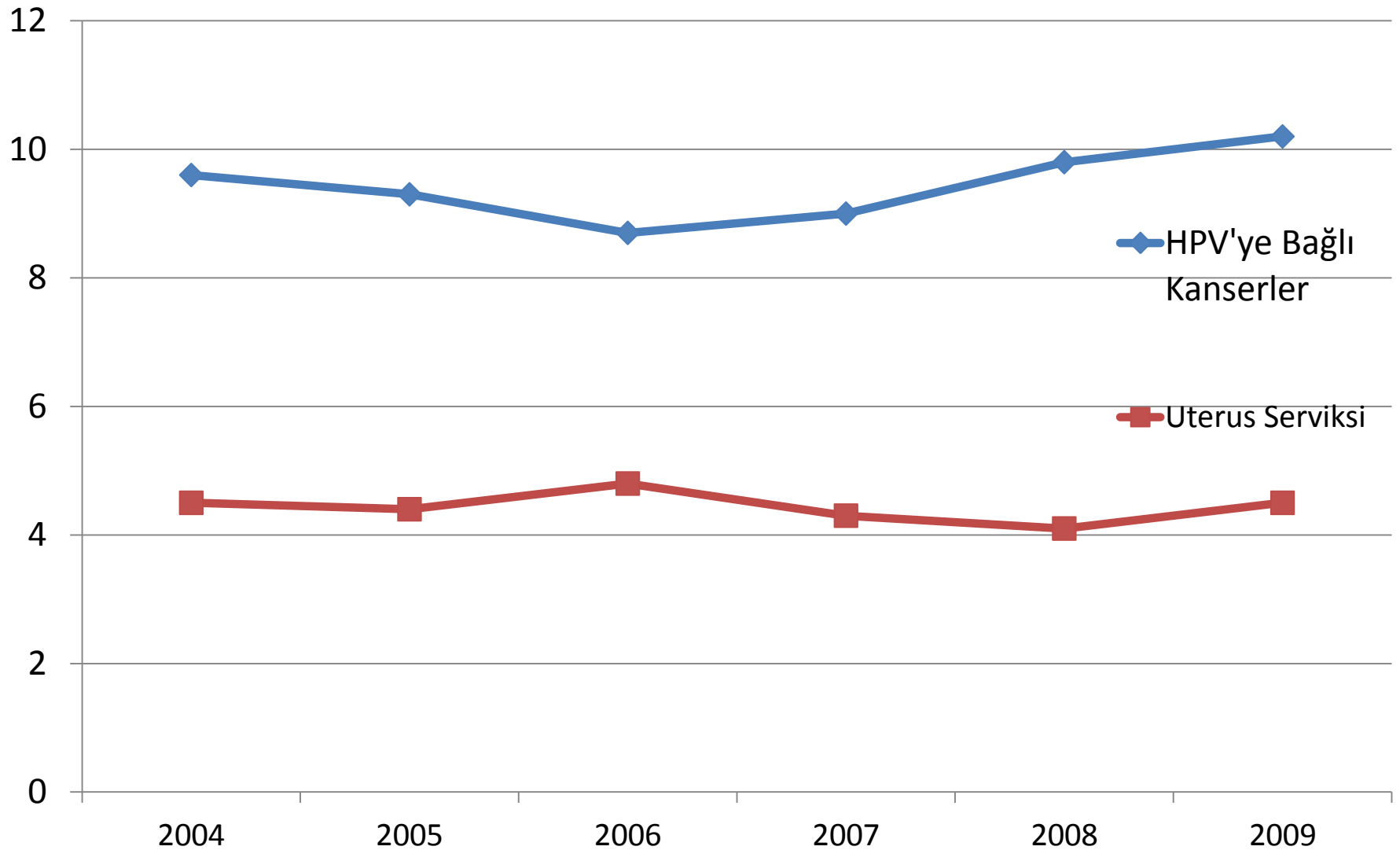
Burd EM. *Clin Microbiol Rev* 2003; 16:1–17;  
 Solomon D, et al. *JAMA* 2002; 287:2114–2119.



# HPV Related Diseases

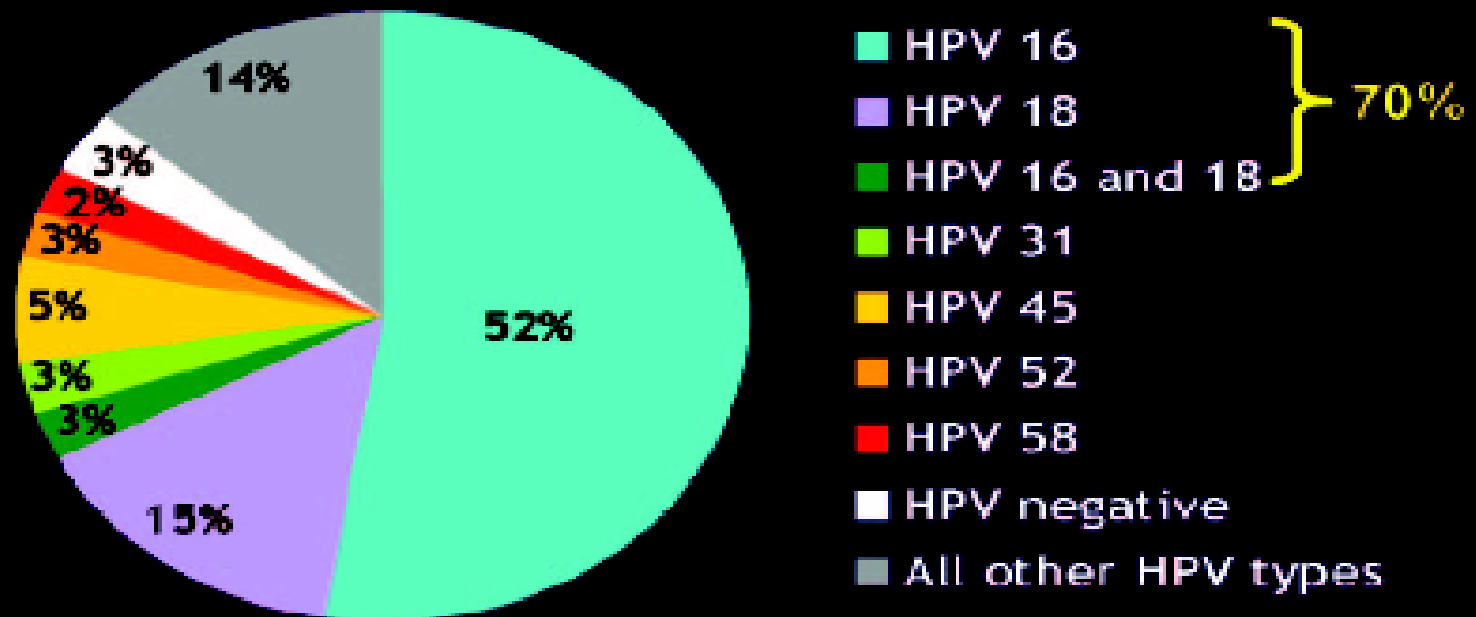


# HPV related Cancers in Turkey



# HPV & CERVIX CA

## HPV Types That Cause Squamous-Cell Cervical Cancer Worldwide

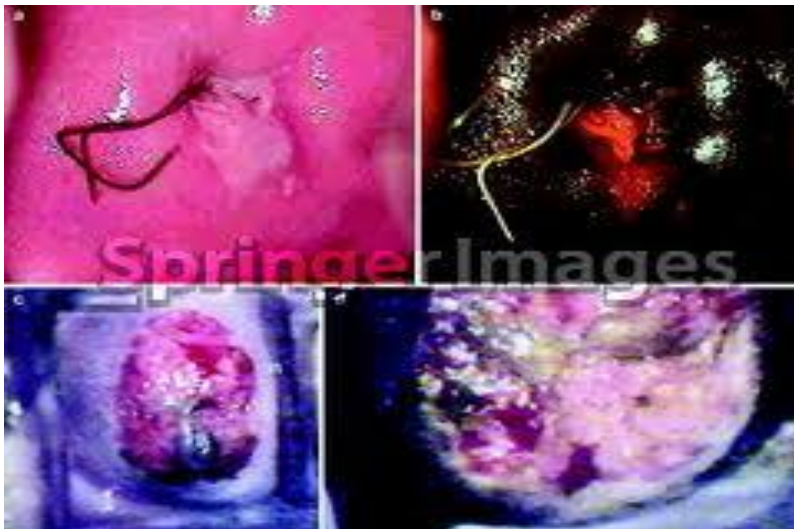


Munoz et al. *N Engl J Med*. 2003;348:518-527.

CIN acetowhite lesion



# Cervical



# Vulvar



Vulvar papillomas



Vulvar Cancer



# Vaginal



Vaginal warts

Vaginal cancer



# Anal

**Being infected with the human papillomavirus (HPV) can affect the risk of developing anal cancer.**



Anal papilloma

Anal cancer



# Laryngeal

- Papillomas are benign epithelial tumors that are caused by infection with the human papilloma virus (HPV).

Laryngeal (respiratory) papillomatosis is **NOT** considered a sexually transmitted disease.

- They are the most common benign neoplasms affecting the larynx and upper respiratory tract.

- Malignant degeneration to squamous cell carcinoma can occur, but is very rare.

- The overall prevalence ranges from 2 per 100,000 adults to 4.5 per 100,000 children

Laryngeal papilloma





# Oral Cavity



- Fifty percent to 90% of Oral Squamous Cell Cancers in the pharynx, tonsil, and tongue are HPV-positive

Oral cancer



Oral papilloma



# Oropharyngeal

Pharyngeal papilloma



•HPV is associated with 15% to 35% of head and neck cancers worldwide.<sup>11</sup>



Oral cancer

Oral cancer



## HPV and HNSCC

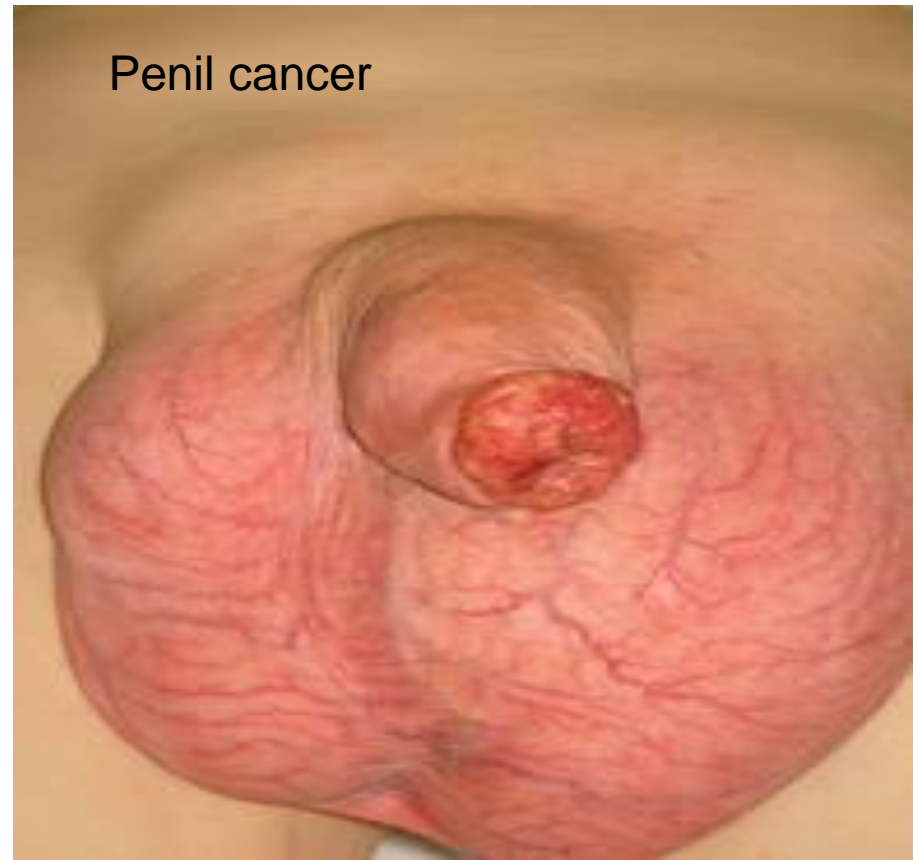
- High-risk HPV specific to tumor cell nuclei
- Clonal virus-tumor relationship
- Viral integration
- Genetic alterations indicative of E6/E7 function
- High viral copy number
- Viral oncogene expression
- Reversal of malignant phenotype

# Penile

- HPV infection is found in about half of all penile cancers.
- Genital wart infection (HPV) increases penile cancer risk. Around 5 out of 10 men with penile cancer have HPV infection.



Penile warts





# Other Warts



# Smoking

- **Breakdown products (nicotine..)**
- **BaP(benzo-a-pyrine) in mucus: HPV upregulation**
- **Persistent cellular proliferation**
- **Inhibition of apoptosis**
- **Stimulation of VEGF**
- **Decrease number of langerhans cells**
- **Squamous cell carcinoma!!**

# Other Infections

- **C.Trachomatis, N.Gonorrhoeae, HSV-2, T.Vaginalis**
- **Disruption of epithelial integrity**
- **Reparative metaplasia associated with acute cervicitis**
- **Chronic inflammation: Co-inf C.Trachomatis is associated with persistence of HR HPV**

# Sex Hormones

- **Pregnancy**

- **Condyloma acuminata increase rapidly in size**
- **Maternal estrogen status or immunosuppressive effect of pregnancy**

- **OCP use**

- **Reduced metabolism of mutagens with OCP induced folate deficiency**
- **Independent of sexual activity**
- **Long term Use !!!!**
- **There is no demonstrated data**

# Immunosuppression

**Iatrogenic**

**HIV**

**Systemic**

(Hodgkin's Disease,  
Leukemia, Collagen vasc. Dis. )

**Transplant  
patients**

**Increase in  
prevalence  
and  
persistence**

**Increased  
incidence and  
persistence**



# Nutritional Factors

Vitamin A,C,E and beta-carotene

**Deficiency** may increase CIN or cervical cancer

High **homocysteine** levels may correlate risk for ICC

High consumption may be protective by increasing the circulating **cis-lycopene**

# Circumcision

- **Penile HPV decreases from 19.6% to 5.5%.**
- **HR HPV decreases from 27.9% to 18%**
- **58% lower risk of cervical cancer with circumcised partners**

**What is HPV prevalence  
in Turkey?**

# **There are 3 Types of Studies for HPV in Turkey**

- Hospital based
- Population based
- Tissue based

# **Hospital Based Study**

**Number of patients: 6376**

**Overall HPV + : 30%**

**Turkish GOG Study 2012 by using PCR  
10centers**

# Studies comparing HPV prevalence in women with normal and abnormal cervical cytologies

Author and publication year	HPV detection method	Number of cases	HPV prevalence (%)		
			Overall	Women with normal cytology	Women with abnormal cytology
<b>İnal, 2007</b>	<b>HC-II</b>	<b>1353</b>	<b>2.14</b>	<b>1.5</b>	<b>100</b>
<b>Dursun, 2009</b>	<b>PCR</b>	<b>403</b>	<b>23</b>	<b>20</b>	<b>36</b>
<b>Ortaç, 2011</b>	<b>HC-II*</b>	<b>501</b>	<b>4.2</b>	<b>3.5</b>	<b>19</b>
<b>Yüce, 2012</b>	<b>PCR</b>	<b>890</b>	<b>25.7</b>	<b>21.4</b>	<b>48.8</b>
<b>Demir, 2012</b>	<b>AmpliTaq**</b>	<b>530</b>	<b>-</b>	<b>17.9</b>	<b>-</b>
<b>Tuncer, 2012</b>	<b>PCR</b>	<b>1797***</b>	<b>-</b>	<b>-</b>	<b>22.4</b>
<b>Akyar, 2013</b>	<b>PCR</b>	<b>1014</b>	<b>69.6</b>	<b>63</b>	<b>75.1</b>
<b>Turkish GOG, 2013</b>	<b>PCR+HC-II</b>	<b>6388</b>	<b>25</b>	<b>27</b>	<b>57</b>

\*Only hr-HPV is studied.

\*\*HPV is studied only in normal cytology.

\*\*\* Study is conducted among women with abnormal cytology

# **Population Based Study**

**Number of patients:3500**

**HPV Prevelance: % 2.9**

**Population Screening Centers(KETEM Study )**

**17 centers**

# Population Based Wart Study

Number of patients: 4,013,084

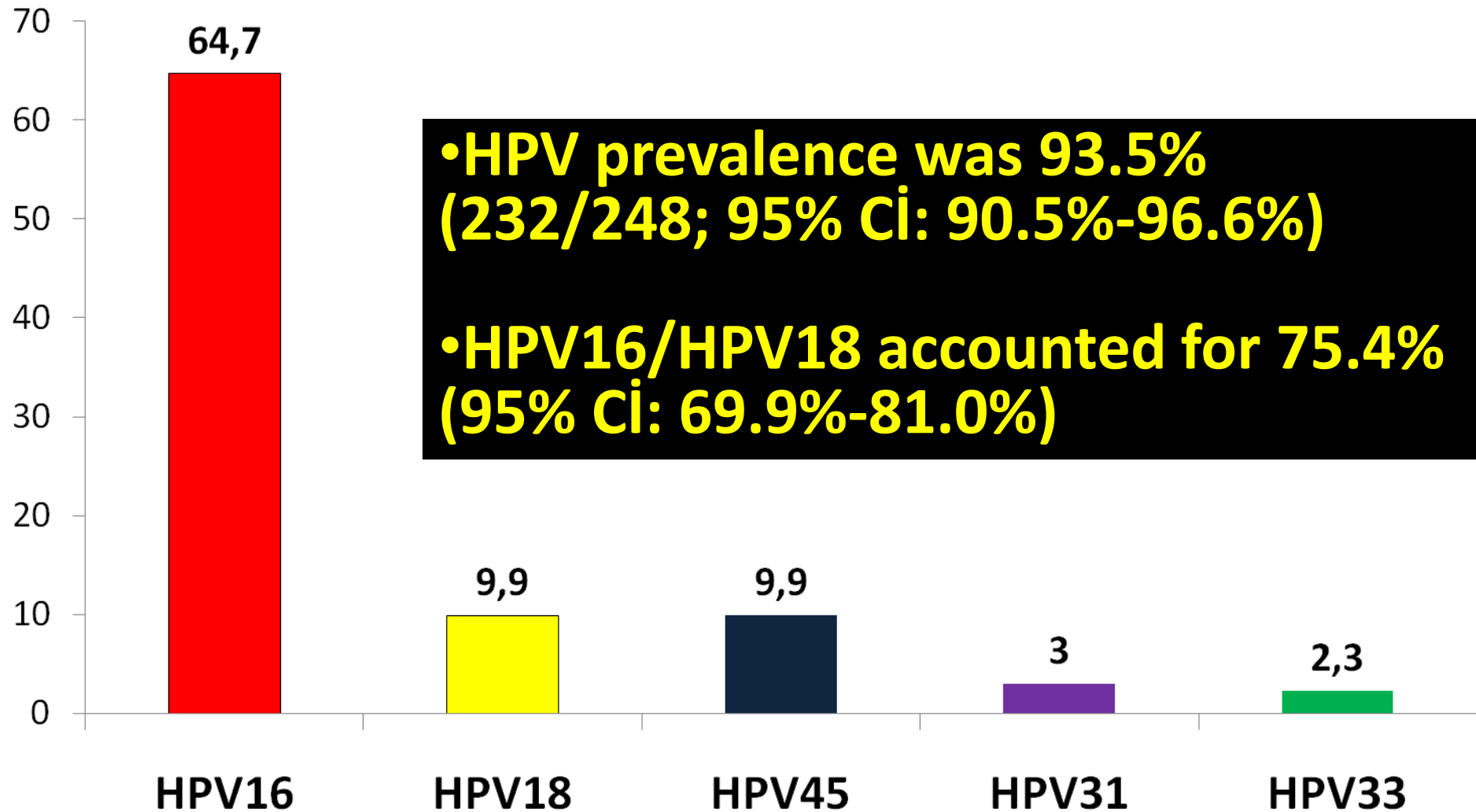
HPV : 154 / 100.000

Population Screening Centers(KETEM Study )

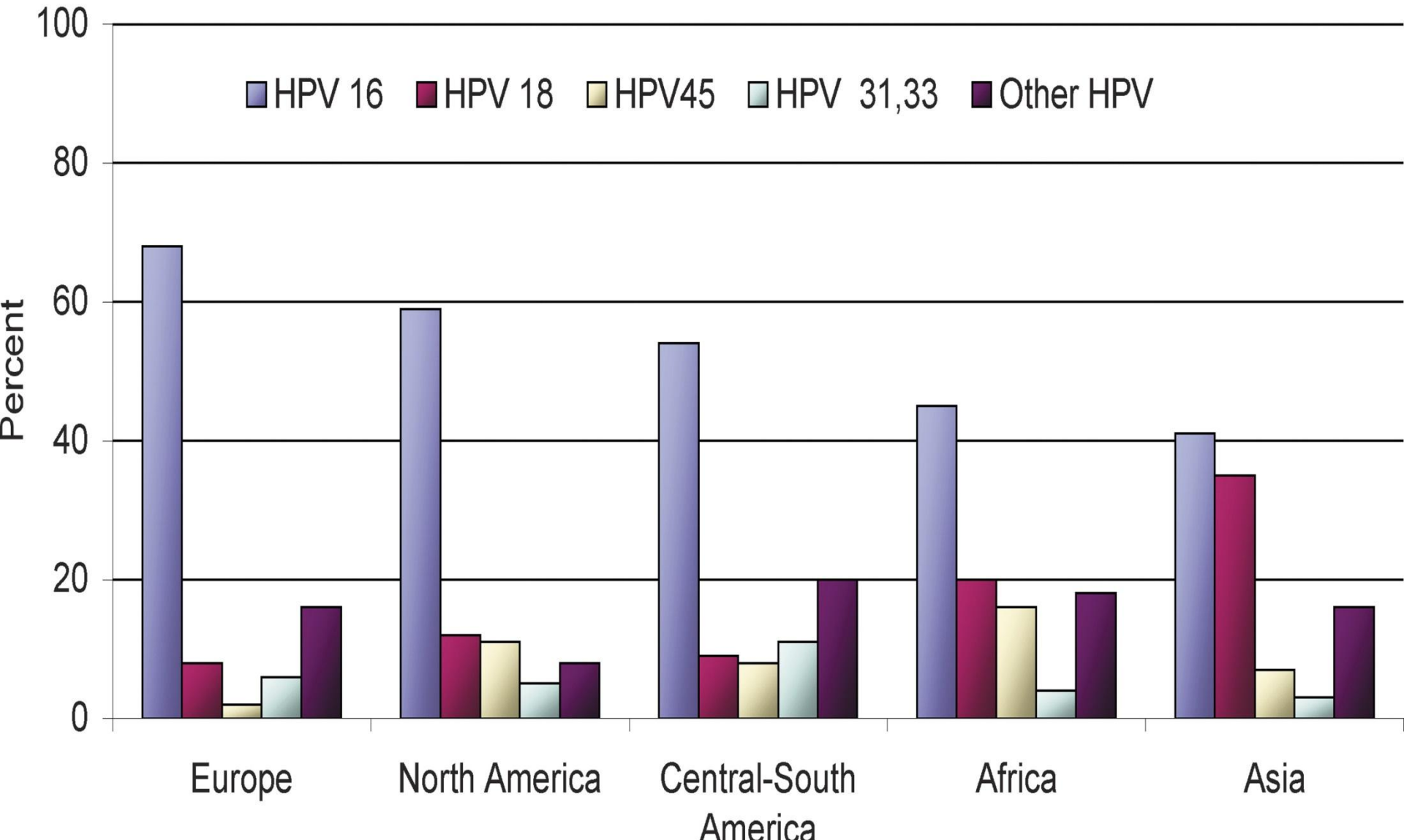
özgül et al



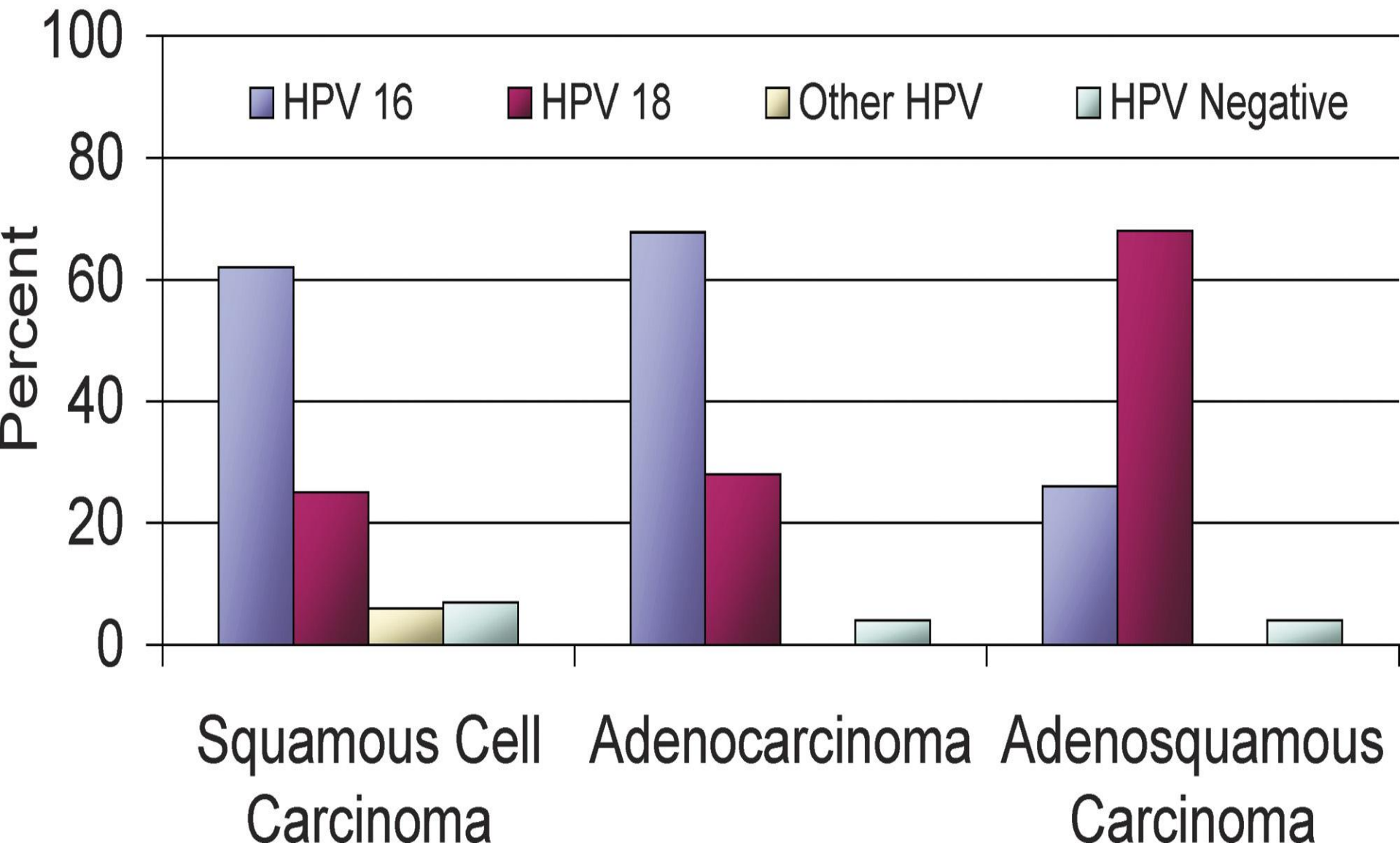
# HPV TYPES IN ICC, TURKEY



# Distribution of HPV types Worldwide



# Distribution of HPV types in ICC by Histologic Types



**What is the relation of  
HPV and abnormal  
cytology in Turkey ?  
(hospital based)**

# Abnormal Cervical Cytology in Turkey

A Turkish Gynecologic Oncology Group (TGOG) Study

## 140334 patients, 33 center



FIRAT ÜNİVERSİTESİ  
Üniversitemize Hoşgeldiniz...



AVRASYA HOSPITAL



Marmara  
Üniversitesi





# Abnormal Cytologic Findings:

**(The TBS, 2001)**

- **AS cells:**
  - ✓ **ASC – US**
  - ✓ **ASC – H**
- **LSIL**
- **HSIL**
- **AG cells**
  - ✓ **AGC – NOS**
  - ✓ **AGC – favor neoplasia**
- **AIS**
- **Invasive Cancer**

**Abnormal Cytology(2481/140334)**

**%1.76**

**%**

**1.66**

- **ASC (n=2341)**

---

  - **ASC-US rate (n=1510) %1.07**
  - **ASC-H rate (n=100) %0.07**
  - **LSIL rate (n=429) %0.3**
  - **HSIL rate (n=243) %0.17**

• **AGC (n=111) 0.07**

• **Cytologic Ca (SCC+Adeno, n=88) 0.062**





# University Hospitals (n= 82048)

	<u>%</u>
<b>ASC : n=1499</b>	<b>1.88</b>
<b>ASC-US : (n=994) %1.2</b>	
<b>ASC-H : (n=84) %0.1</b>	
<b>LSIL : (n=279) %0.34</b>	
<b>HSIL : (n=142) %0.18</b>	
<b>AGC : n=101</b>	<b>0.15</b>
<b>Cytologic Ca(SCC+Adeno,77)</b>	<b>0.09</b>



# G.Teaching Hospitals (n= 58286)

%  
**1.35**

**ASC :791**

**-ASC-US : (n=516) 0.88%**

**-ASC-H : (n=16) 0.02%**

**-LSIL : (n=150) 0.26%**

**-HSIL : (n=101) 0.17%**

**AGC : 10**

**0.01**

**Cytologic Ca (SCC+Adeno,11): 0.01**

# Studies comparing distribution of cervical cytology and HPV

## Abnormal Cervical Cytology

Author	Number of cases	Normal (%)	ASCUS (%)	ASCH (%)	LSIL (%)	HSIL (%)	AGC (%)	SCC (%)
Dursun 2009	403	20	22		51	60		
Ortaç 2011	501	3.5	21		16			
Akyar 2013	1014	17.7	16.9		11.9	1.2		
Turkish GOG 2013	6388	27	20	5	14	10	0.8	3

# Primary Prevention

- **Stop smoking**
- **Barrier Contraceptives**
- **Monogamy**
- **Diet (Folic ,VitB,Caroten etc)**
- **Vaccination**
- **Circumcision**

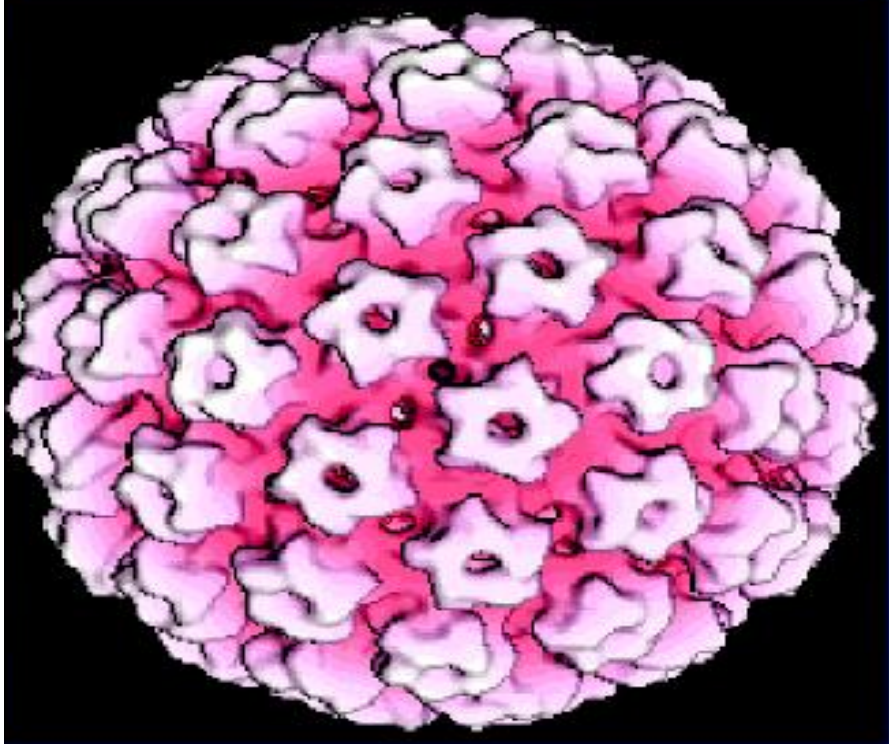
# Secondary Prevention

- **Screening**

# Conclusion

- **Incidence of ICC stable, increasing preinvasive**
- **HPV burden is higher in hospital based than population based**
- **HPV Prevalence seems higher in Turkey**
- **HPV types in Turkey and world are similar**
- **HPV 16 is higher in squamous type and 18 in adeno type**
- **Screening reduces ICC and mortality**

# Thank you for your attention



*Amelitya*