

# Cervical & Vaginal Cancer

1<sup>st</sup> November 2011

BSc Module 1:

Hormone dependent systems & cancers:  
gynaecology and endocrinology

IRDB

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# What we will discuss

- Cervical cancer
  - History of Cx cancer
  - Cancer statistics
  - HPV & Natural History
  - Cervical cancer screening & HPV issues
  - Diagnosis – Interventions
  - Management – Treatment
  - Innovations
  - Prevention – vaccination
- Vaginal cancer

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Page last updated at 09:52 GMT, Thursday, 22 October 2009 10:52 UK

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## Goody effect 'boosts screening'

Reality TV star Jade Goody's fight against cervical cancer led to a rise in women undergoing screening in England, experts believe.

The 27-year-old died earlier this year after being diagnosed in 2008.

The NHS Information Centre data showed the number of women aged 25 to 64 being screened rose by 12% last year.

Charities and the government said the increase - the first since 2002 - was a "lasting legacy" of the TV star's fight against cancer.

### Action

The NHS figures showed screening went up from 3.2m to 3.6m in 2008-9.

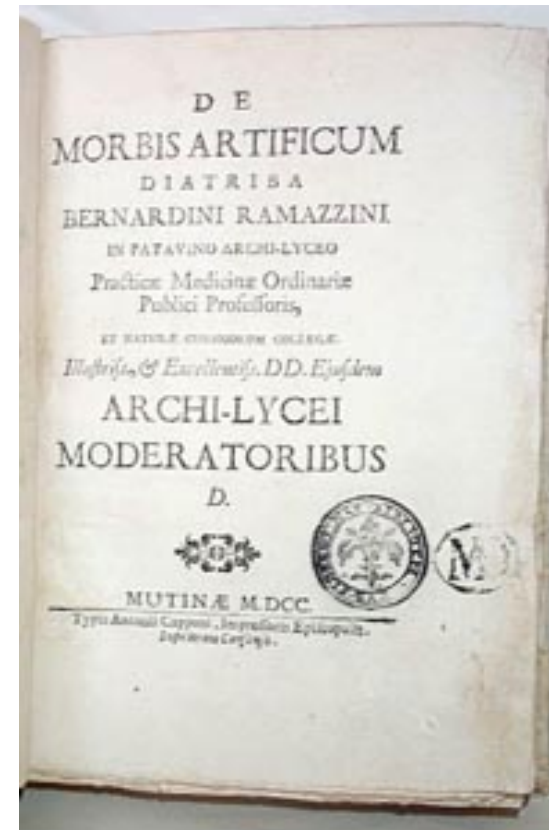


Jade Goody died earlier this year

# History of Cervical Cancer

# History of Cx cancer

- 1700 – Italian Dr Bernardino Ramazzini reported virtual absence of cervical cancer and high incidence of breast cancer in nuns – first indication that lifestyle may have an affect



# History of cancer

- The conventional cervical smear has been the most successful screening test
- 1941 first paper with Traut describing exfoliative cytology



# Harald Zur Hausen

- Nobel prize medicine 2008
- HPV and association with cervical cancer - 1976



# Landmarks in the prevention of Cx cancer

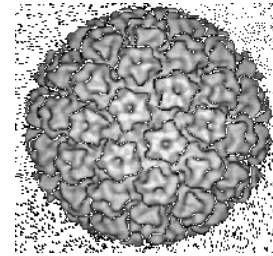
The past



Pap smear

Colposcopy

The present



HPV test

The future



HPV Vaccine

1950

1960

1970

1980

1990

2000

2007





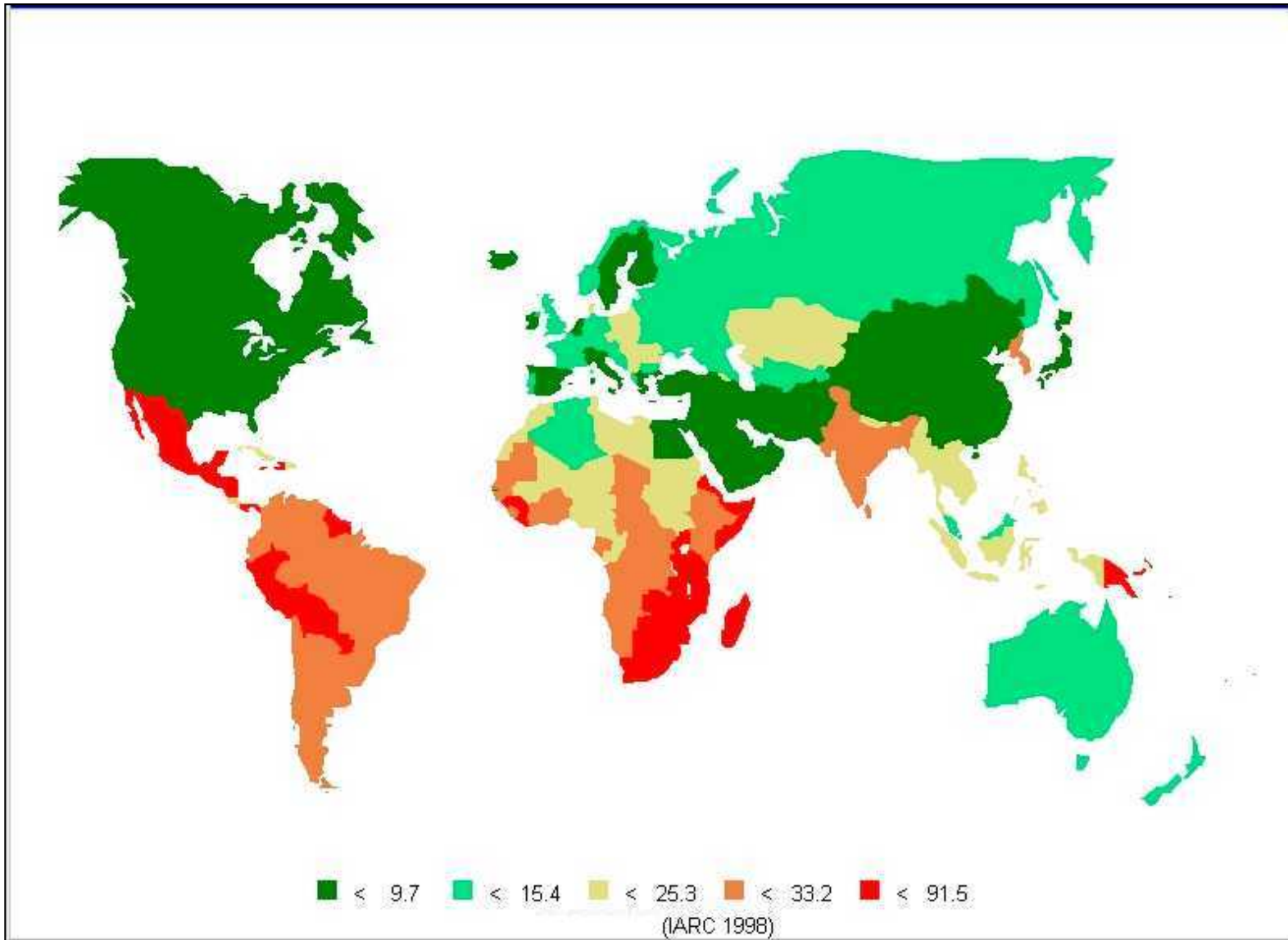
**EVOLUTION**

-PILBROW-

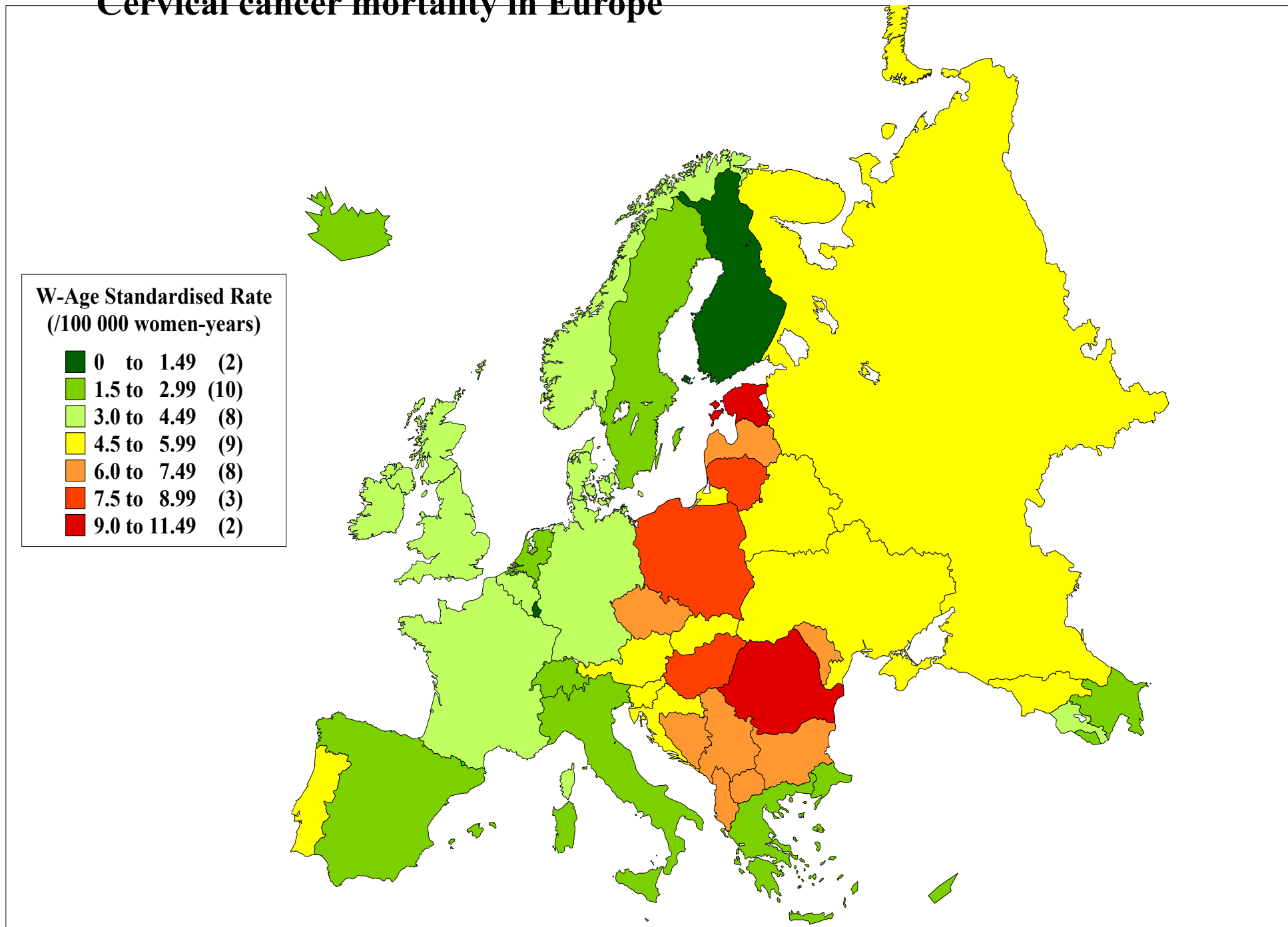
# Cancer Statistics

# Cervical cancer

- Worldwide: 2nd commonest female Ca
- 460,000 cases each year
- Developing countries
  - China 130,000
  - India 70,000
- 1 in 10 female cancers diagnosed worldwide are cervical
- Over 2.7 million years of life lost among women aged 25-64 worldwide
- 2.4 million of which occur in developing areas
- 0.3 million in developed countries

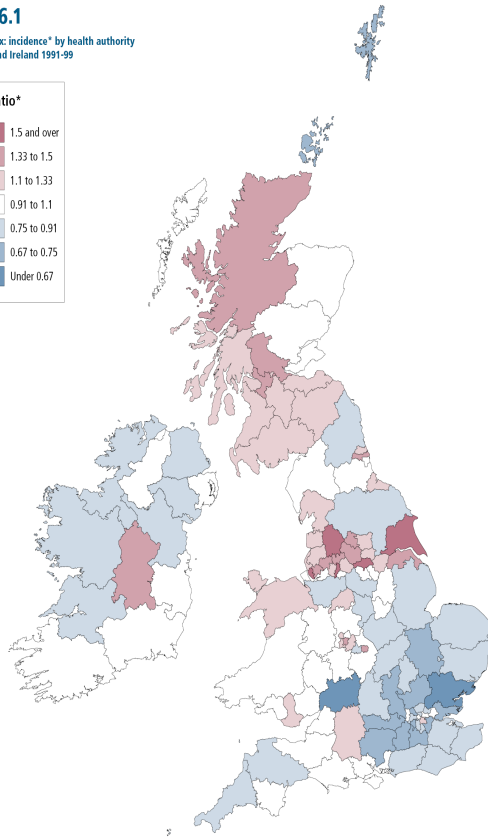
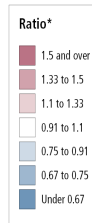


# Cervical cancer mortality in Europe

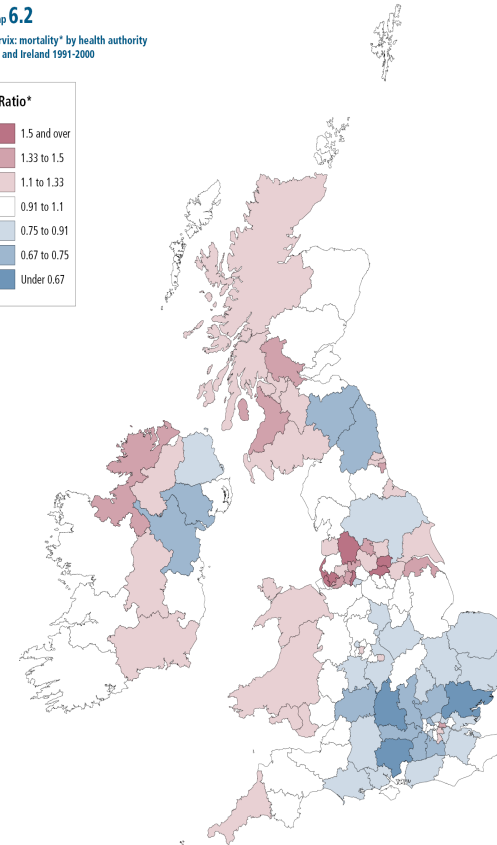
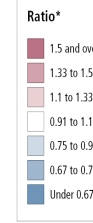


# Incidence/mortality cervical ca

Map 6.1  
Cervix: incidence\* by health authority  
UK and Ireland 1991-99



Map 6.2  
Cervix: mortality\* by health authority  
UK and Ireland 1991-2000



# Worldwide statistics

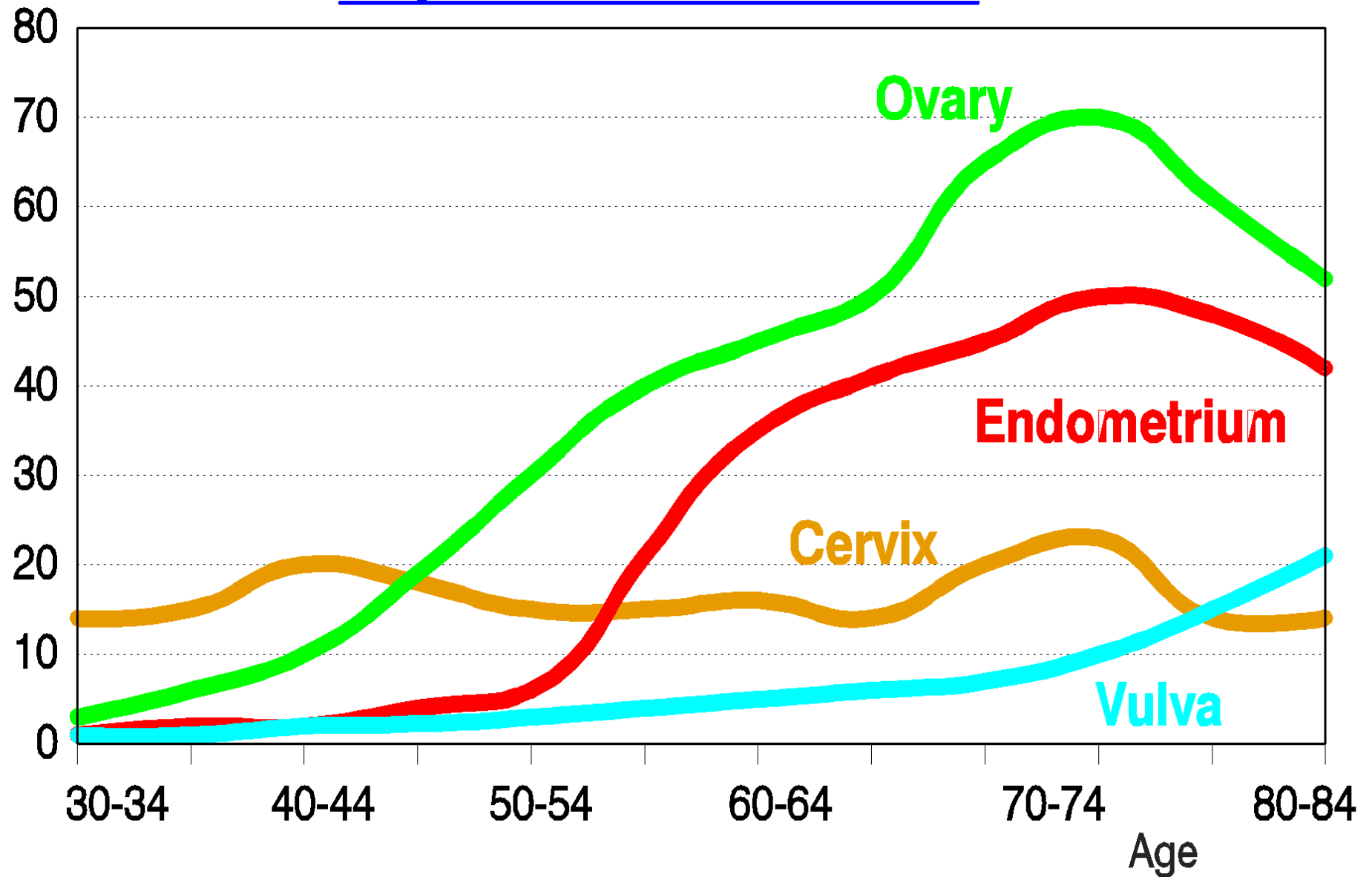
	Incidence	Mortality
Breast cancer	795,000	313,000
Cervical cancer	450,000	300,000
Ovarian cancer	165,000	101,000
Endometrial cancer	142,000	42,000

## Gynaecological Cancers: Incidence and Deaths England and Wales

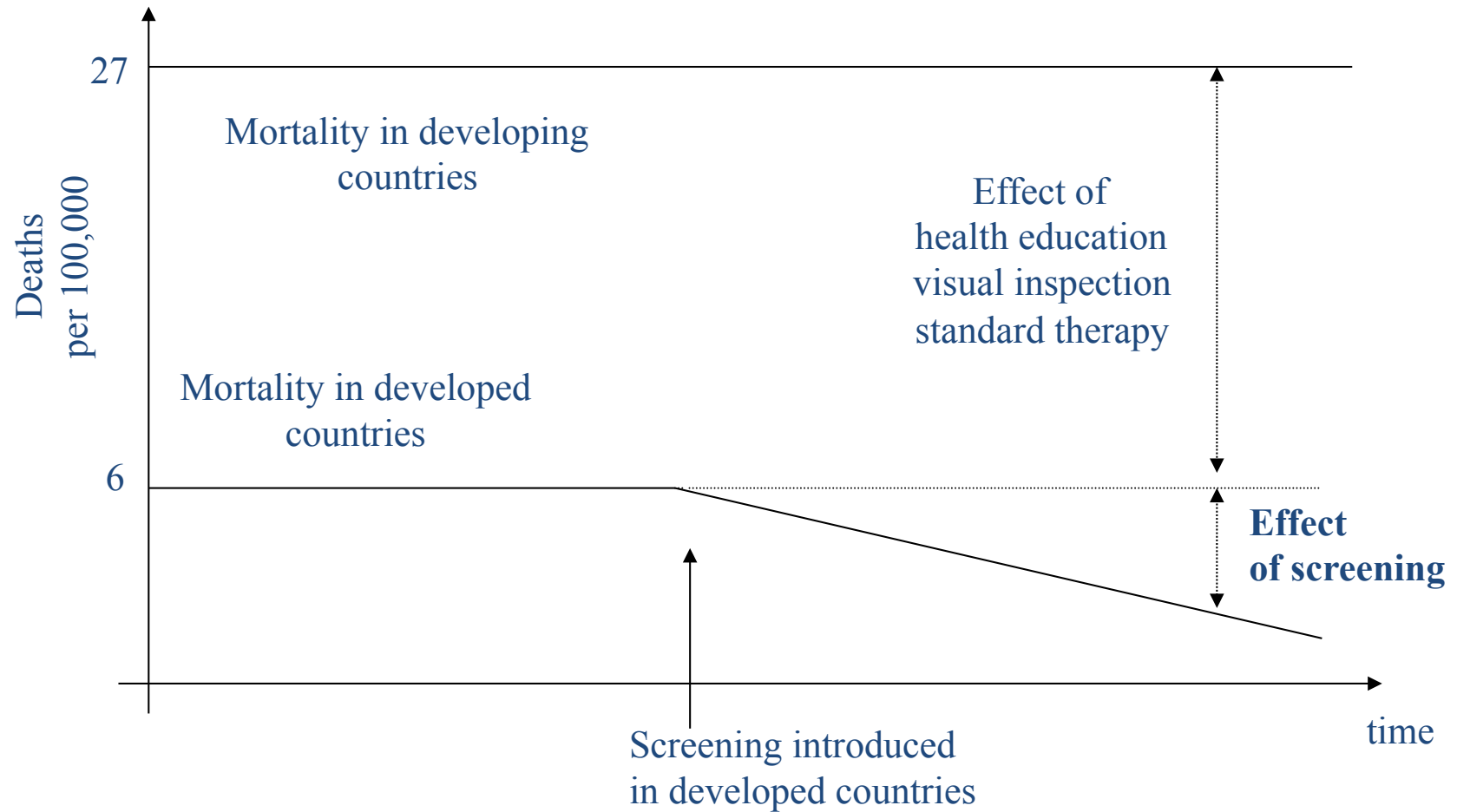
<b>Cancer Site</b>	<b>Number of Registrations 1992</b>	<b>Incidence Rate per 100,000 1997</b>	<b>Deaths 1997</b>	<b>Death Rate per 100, 000 women 1997</b>
<b>Ovary</b>	<b>5,388</b>	<b>20.3</b>	<b>3,985</b>	<b>15.0</b>
<b>Endometrium</b>	<b>3,912</b>	<b>13.9</b>	<b>774</b>	<b>2.9</b>
<b>Cervix</b>	<b>3,400</b>	<b>10.4</b>	<b>1,225</b>	<b>4.6</b>
<b>Vagina</b>	<b>209</b>	<b>0.8</b>	<b>89</b>	<b>0.3</b>
<b>Vulva</b>	<b>803</b>	<b>3.1</b>	<b>346</b>	<b>1.3</b>



# Rates of Gynaecological Cancers per 100,000 women England and Wales 1992



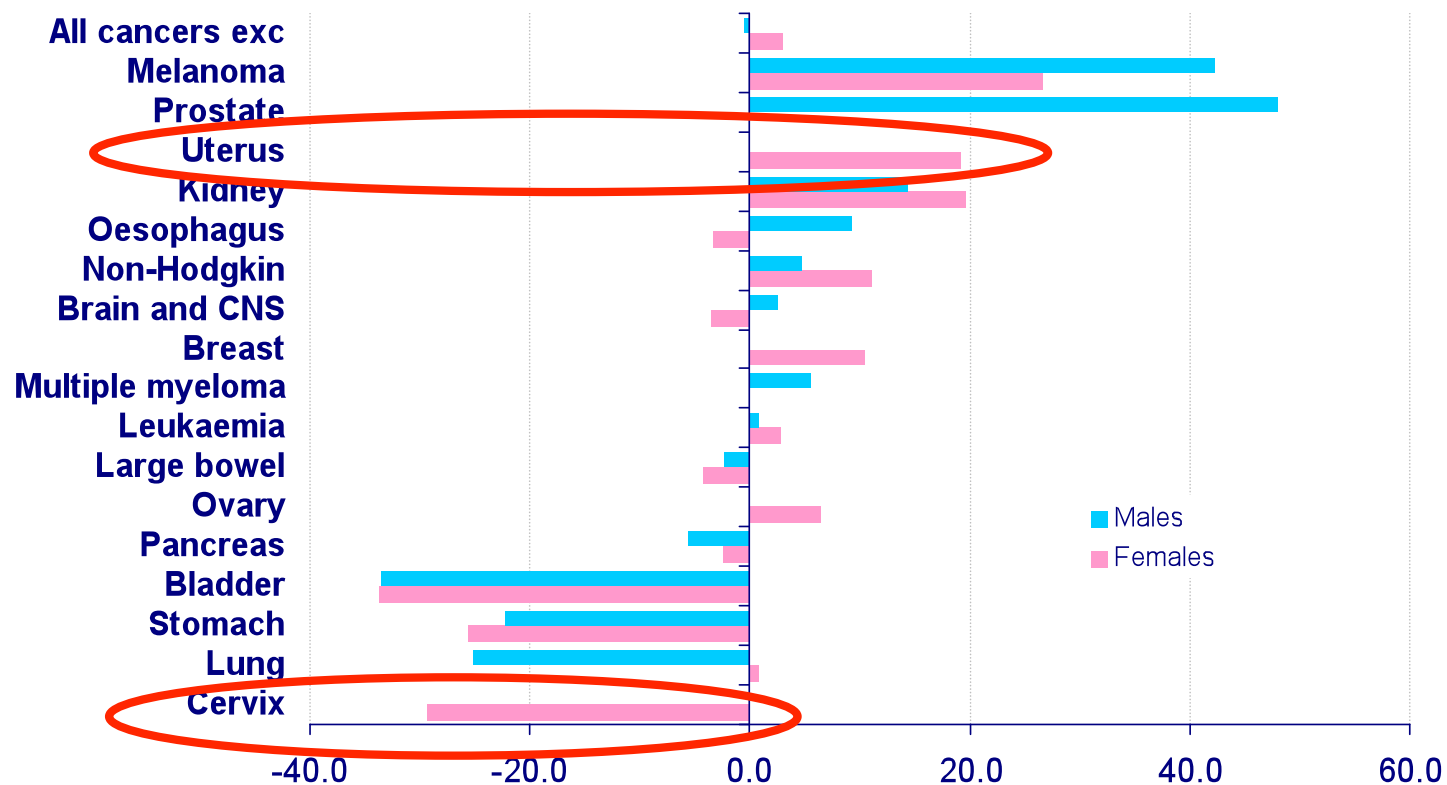
# Cervical cancer control



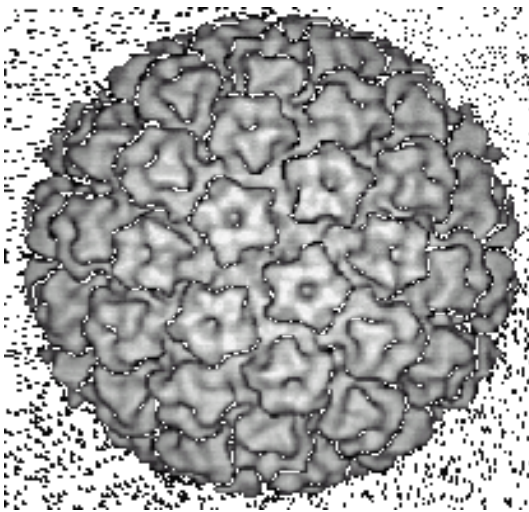
# Major cancers, UK, 1993-2002

% change incidence

Percentage change in the age standardised (European) incidence rates, major cancers, UK, 1993 - 2002



# HPV Virus



# Aetiological relation of HPV & Cx Cancer

- HPV DNA has been detected in 99.7% of cx cancers

Walboomers et al 1999

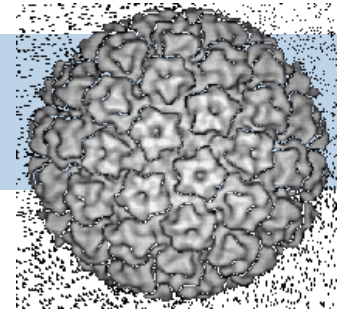
- Infection from high risk HPV subtypes is a necessary (although not sufficient) condition for the development of cx cancer

Bosch J et al 2002





# Human Papillomavirus (HPV)

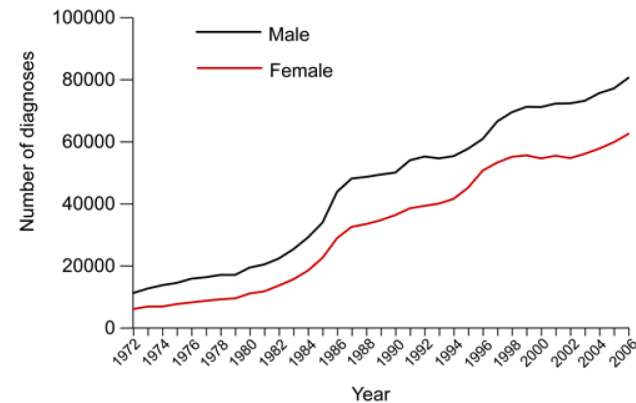


- Double strand DNA virus (>130 subtypes)
- Only infects epithelium (epitheliotrophic)
- Only 23 infect Cx - Only 13 are associated with CIN or Ca
- High-risk subtypes (16,18,31,45 etc): **Cancer**  
Low-risk subtypes (6,11 etc): **Anogenital warts**
- Mainly sexually transmitted
- Mainly asymptomatic and transient
- Chronicity & Persistence causes disease

# HPV TYPE RELATIVE FREQUENCY BY BY CONTINENT [RIS HPVTT]

EUROPE		CENTRAL-SOUTH AMERICA		AFRICA		ASIA		TOTAL	
HPV type	%	HPV type	%	HPV type	%	HPV type	%	HPV type	%
HPV 16	67.3	HPV 16	60.1	HPV 16	51.2	HPV 16	66.5	HPV 16	62.9
HPV 18	8.3	HPV 18	11.5	HPV 18	27.6	HPV 18	9.4	HPV 18	11.8
HPV 33	5.6	HPV 45	7.3	HPV 45	11.3	HPV 33	6.0	HPV 45	5.8
HPV 45	4.2	HPV 31	5.2	HPV 52	11.0	HPV 58	4.3	HPV 33	4.6
HPV 31	3.8	HPV 33	3.4	HPV 51	10.2	HPV 31	4.0	HPV 31	4.2
HPV 52	2.4	HPV 39	2.6	HPV 35	7.8	HPV 45	3.3	HPV 52	3.5
HPV 51	2.3	HPV 52	2.7	HPV 31	2.6	HPV 52	2.4	HPV 51	2.8
HPV 35	2.2	HPV 58	2.6	HPV 33	2.6	HPV 59	1.3	HPV 58	2.5
HPV 56	1.8	HPV 51	2.2	HPV 11	1.2	HPV 56	1.2	HPV 35	2.5
HPV 58	1.8	HPV 35	2.0	HPV 53	1.2	HPV 35	1.0	HPV 39	1.7

# HPV 6,11 associated disease



- Condyloma acuminata, laryngeal papillomas
- Cost £30-40 million / year



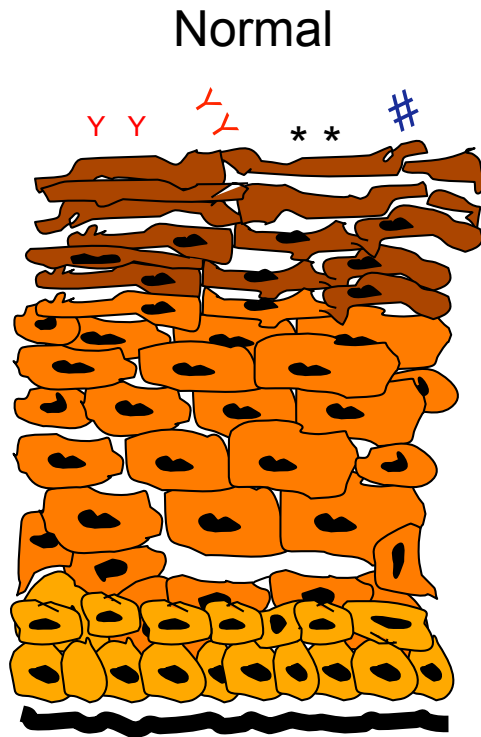


# Malignant disease burden attributable to HPV

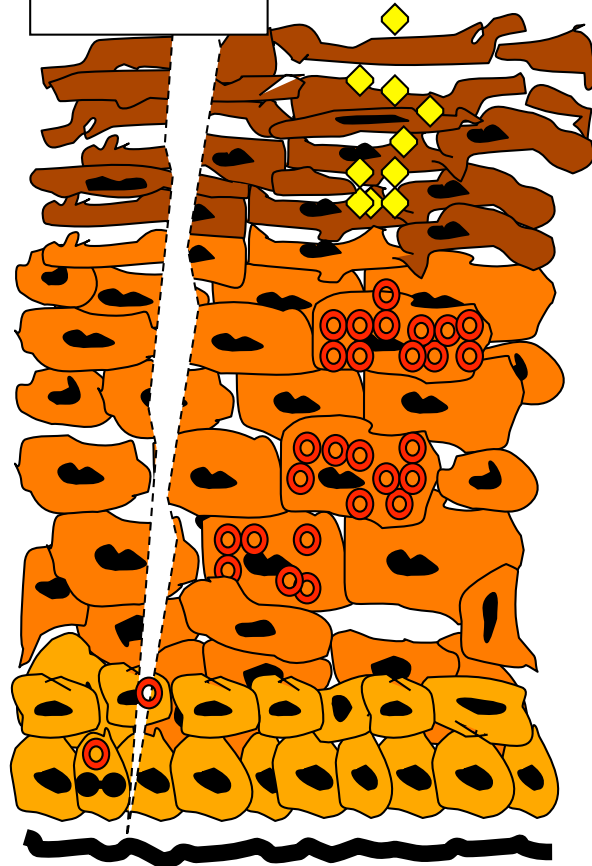
Site	Attributable to HPV%	Developed countries		Developing countries	
		Total cancers	Attributable to HPV	Total cancers	Attributable to HPV
Cervix	100	83400	83400	409400	409400
Penis	40	5200	2100	21100	8400
Vulva/vagina	40	18300	7300	21700	8700
Anus	90	14500	13100	15900	14300
Mouth	≥3	91200	2700	183100	5500
Oropharynx	≥12	24400	2900	27700	3300
Other	0	4779100	0	5148600	0
All sites		5016100	111500	5827500	449600

# Natural History of HPV

# HPV life cycle



1. Viral entry to basal cells



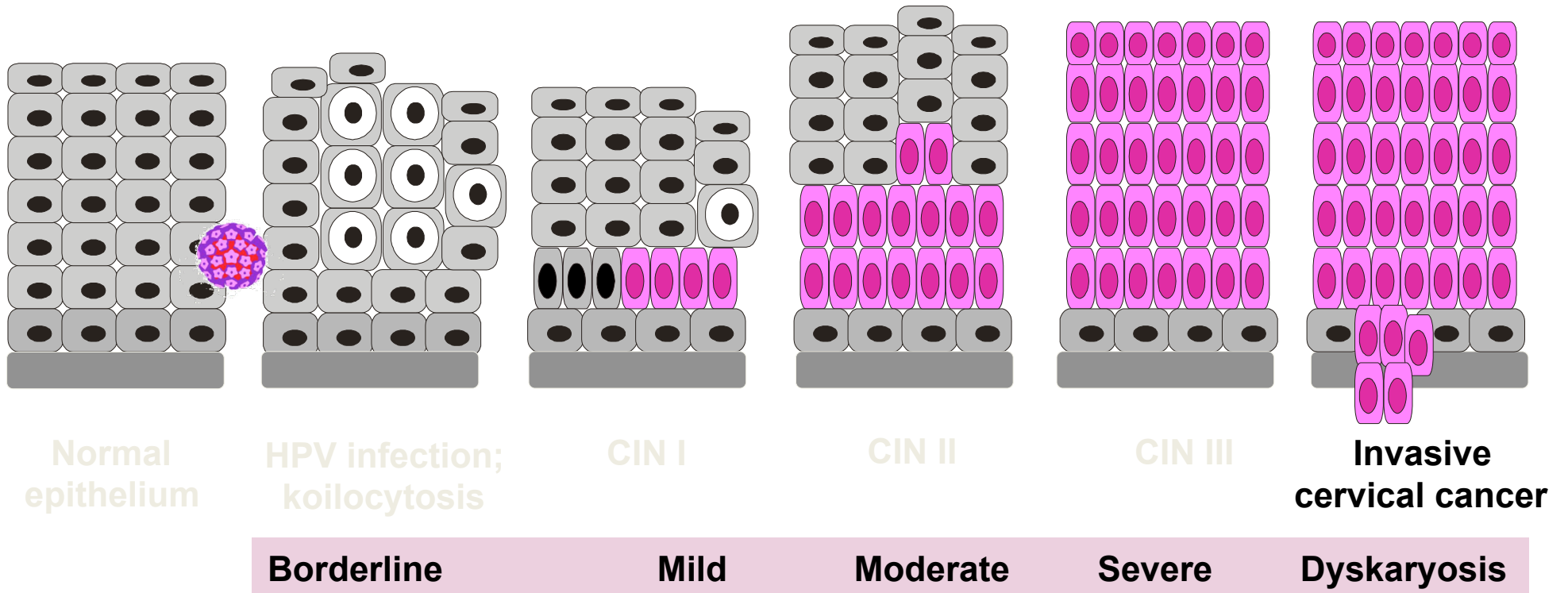
4. Assembly of late capsid proteins. Virions formed and released. L1 and L2 expressed.

3. Virus amplification. High copy numbers of HPV genome expressed. All early genes are highly expressed (E4, E6, E7, E1, E2)

2. Viral genes replicated and maintained as low copy episomes. Early genes (E6, E7) expressed at low levels. E1 and E2 most active

# Disease progression

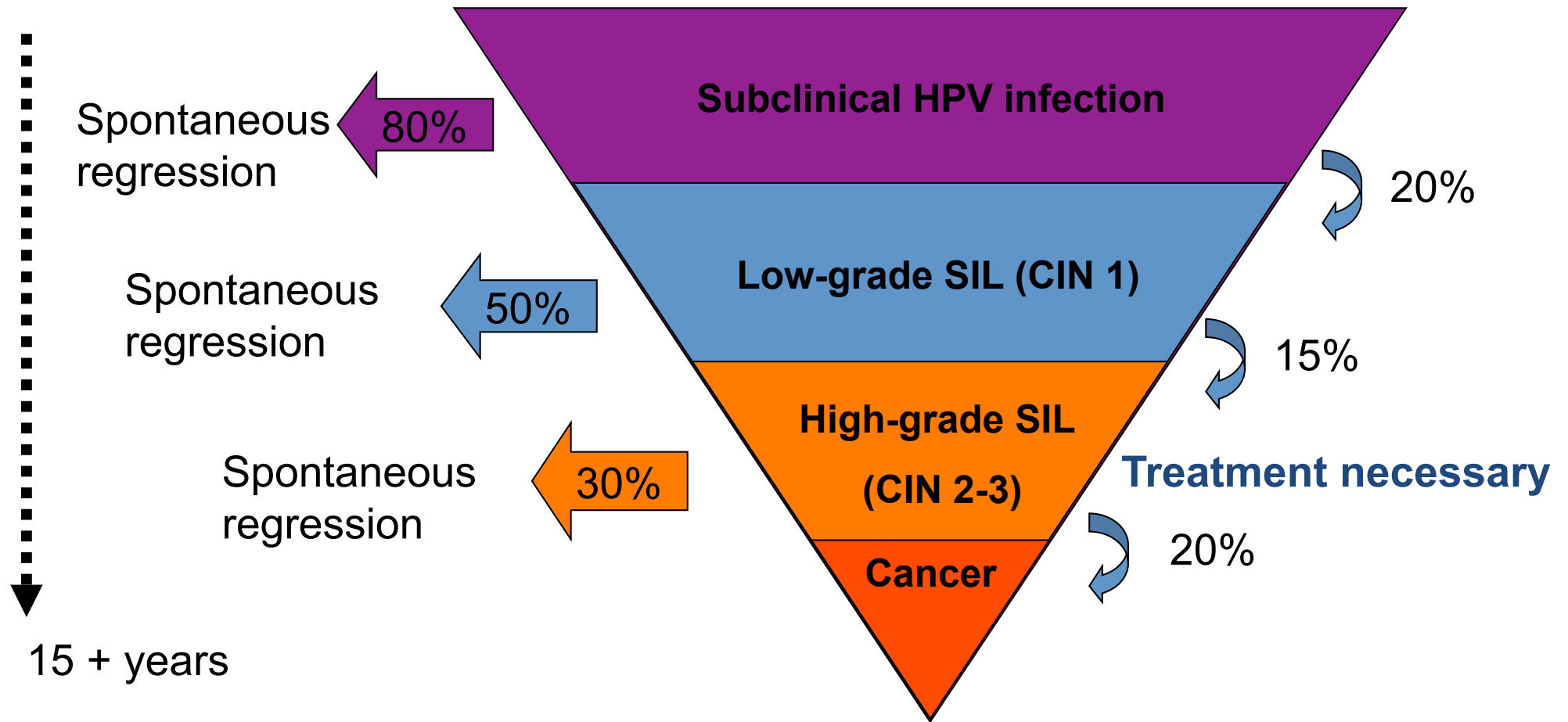
Time ..... Months ..... Years .....>



**CIN I 57%    CIN II 43%    CIN III 32%**  
**Approx. likelihood of regression**

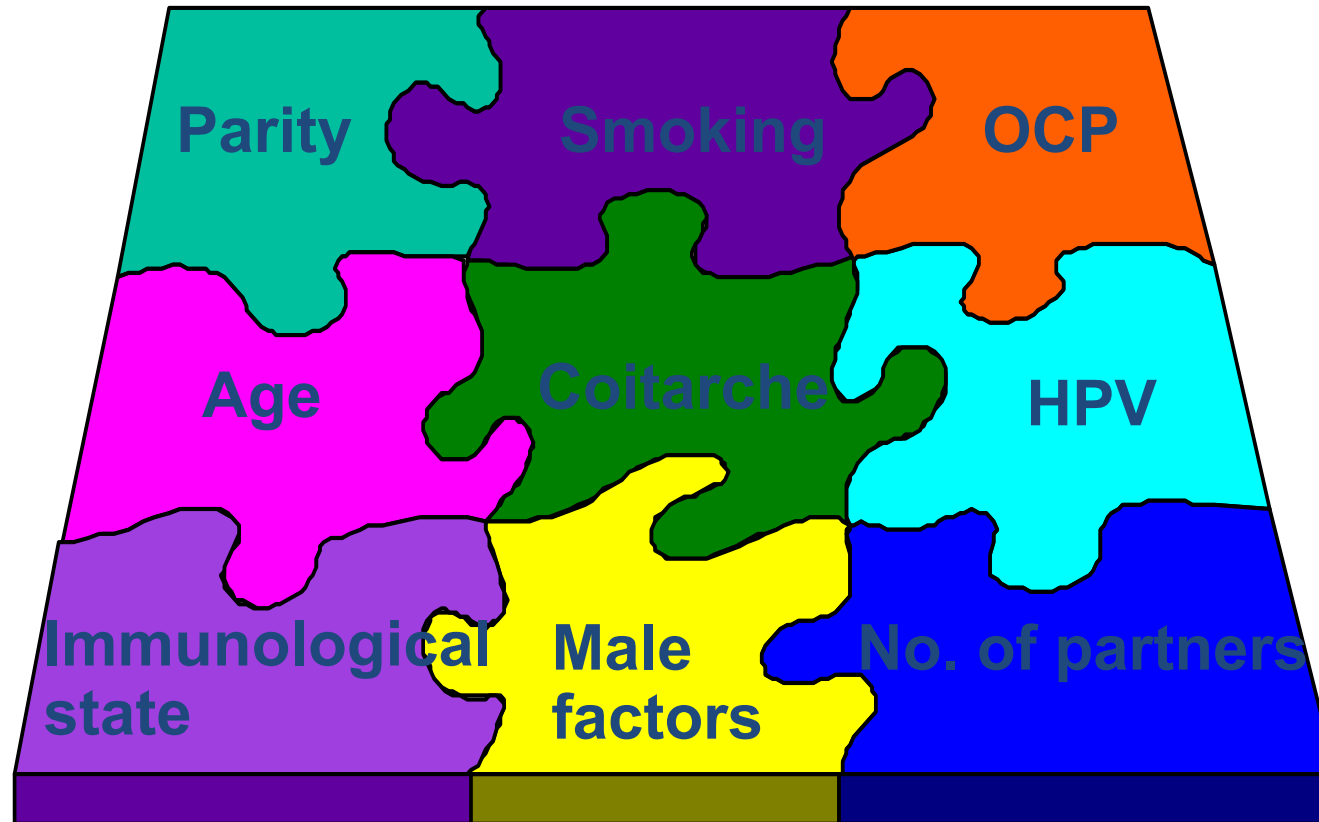
Burd EM. *Clin Microbiol Rev* 2003; 16: 1-17.  
 Ostor AG. *Int J Gynecol Pathol* 1993; 12(2): 186-192.  
 Solomon D *et al. JAMA* 2002; 287: 2114-9.

# Natural History of HPV infection



\*The number of cases (USA data) and percentages in each disease category are estimates.

# The full picture



- The majority will test negative for HPV within months of an initial infection
- Currently no way of predicting which infections will persist or lead to Cx Ca

# Cervical Cancer



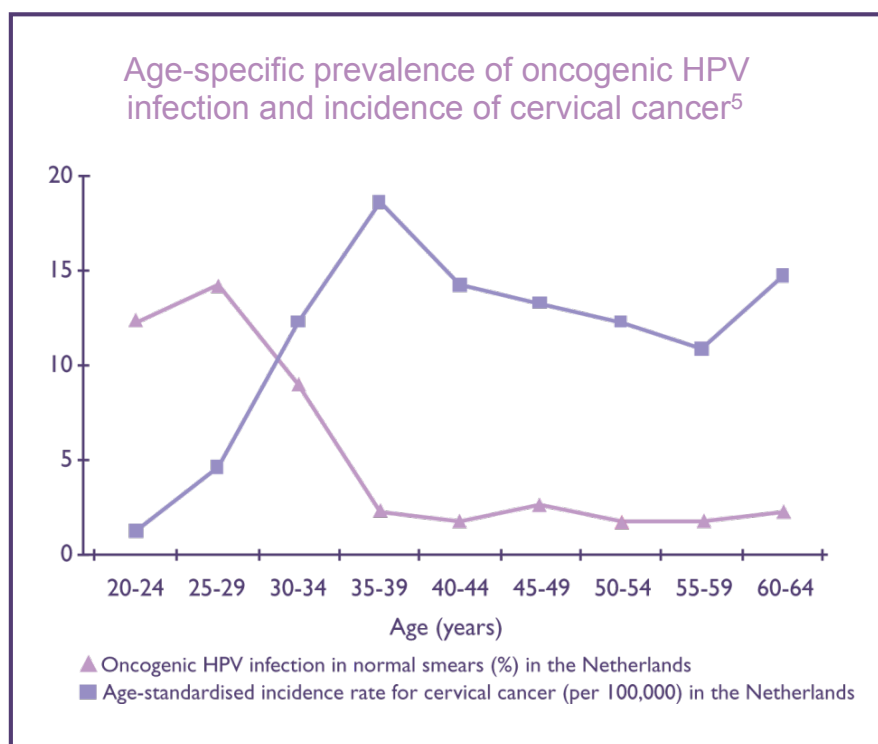
rare outcome ...

of a very common infection

# Acquisition of HPV

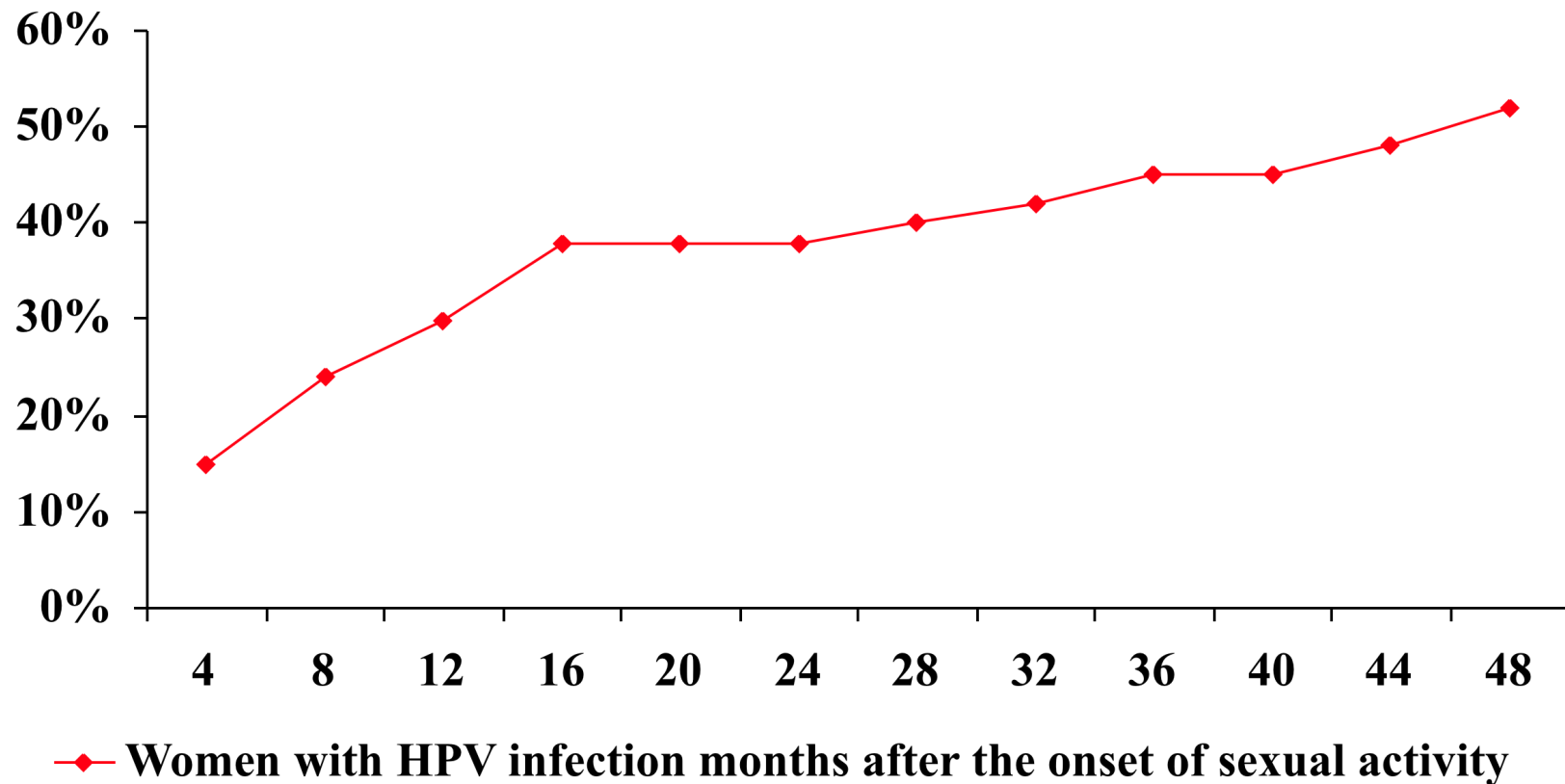


# HPV infection is very common



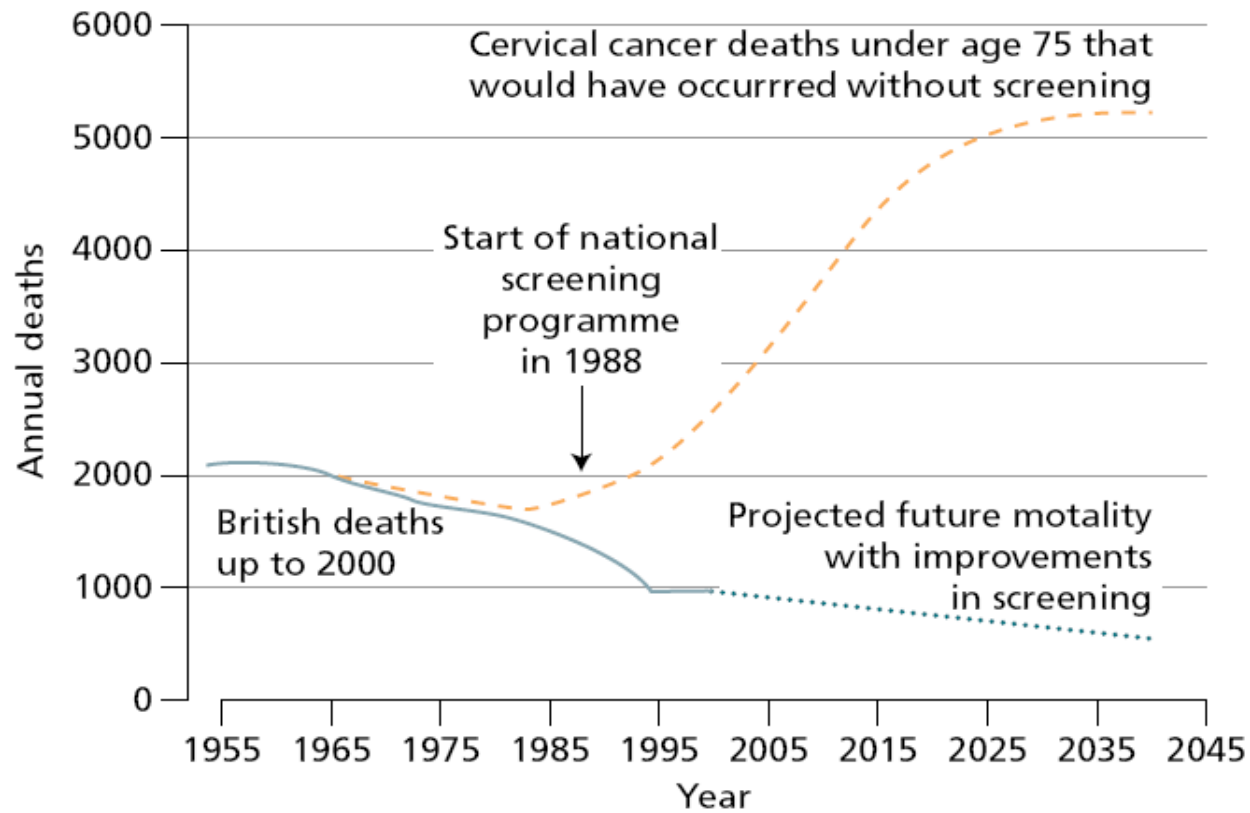
- HPV is easily transmitted through sexual contact. The risk begins with first sexual activity
- Up to 80% of sexually active women will be infected with HPV at some point in their lives
- Oncogenic HPV infection types have been found in up to 50-75% of HPV infections
- 80% infections will regress within 6-12 months
- 3-5% of over 30s persistently infected
- HPV is acquired by skin-to-skin contact in the genital area. Full sexual intercourse is not necessarily required
  - Although condoms reduce the risk, they do not fully protect against HPV infection
- Cervical cancer is a rare complication of a common HPV infection of the cervix

# Probability of HPV infection after initiation of sexual intercourse

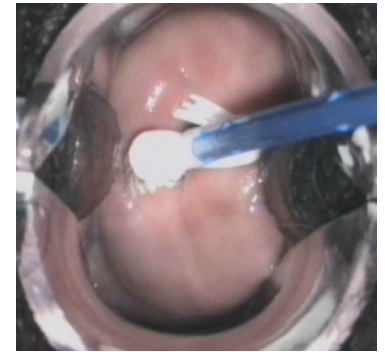


# Cervical cancer screening & HPV issues

# Effect of screening



# NICE recommendations 2003



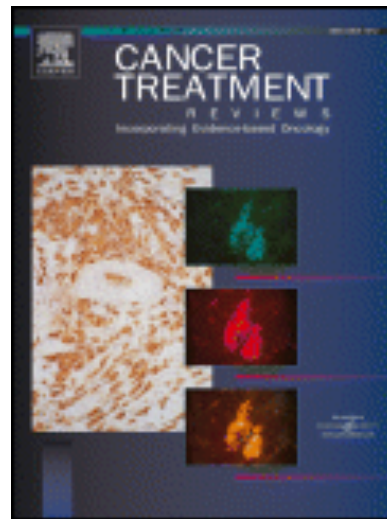
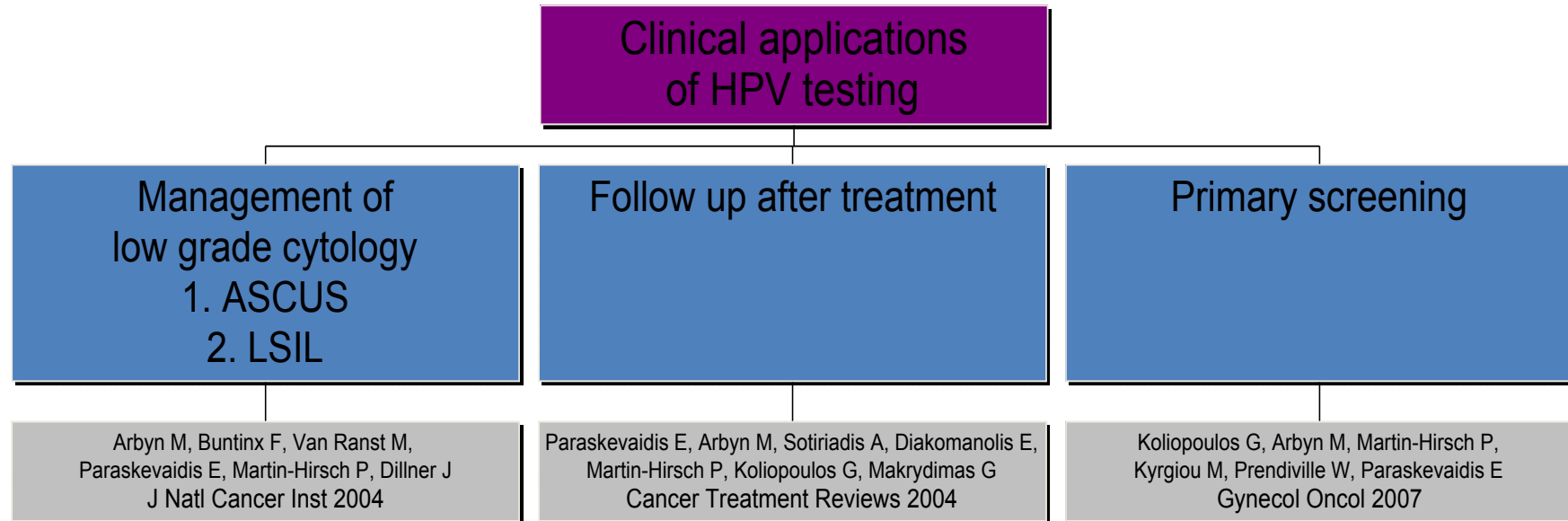
Age (years)	Screening interval recommended
Under 25s	No screening
25	First invitation
25-49	Three yearly
50-64	Five yearly
Over 65s	No screening

# Role of HPV testing

- Virtually all cervical cancers contain HPV DNA (99.7%)
- Women with HPV have an odds ratio of about 70 for developing high grade CIN
- Odds ratio even higher if infected with HPV 16

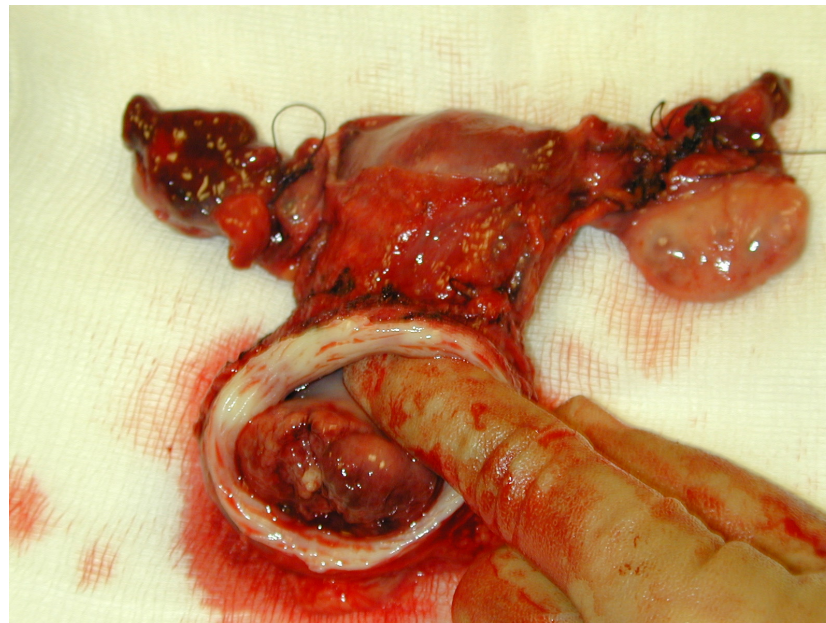


Organization Chart Title



NSCPC May 2010: no changes are planned at present

# Cervical cancer

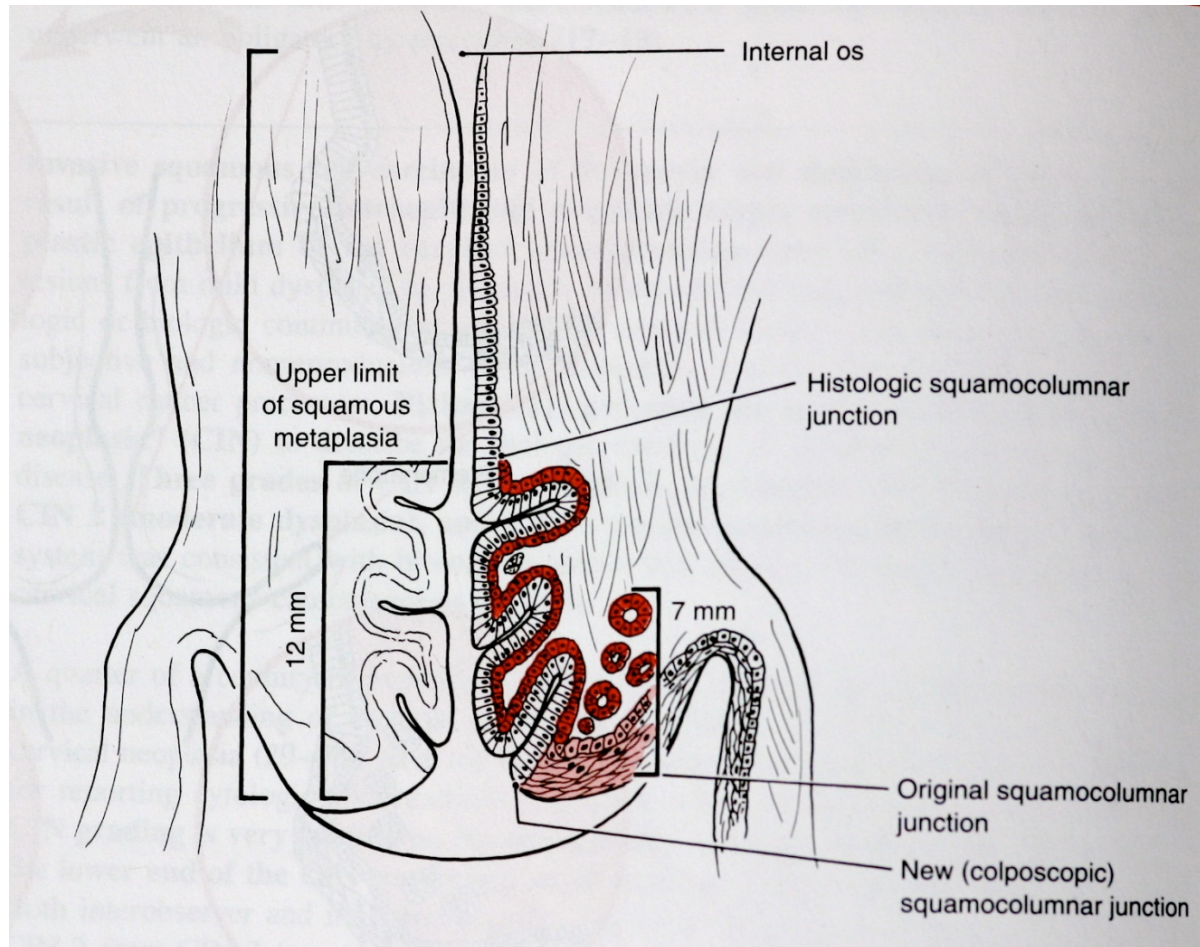




# Cervical Cancer

- Pathological subtypes
  - Squamous (70-80%)
  - AdenoCa (20-30%):  
poorer prognosis – delayed diagnosis – younger age – HPV18 – mixed (40%)
- Patterns of spread
  - By direct invasion: vaginal-parametrial first, bladder-rectum late
  - By lymphatics:  
Primary Nodes: Para-metrial, Obturator, External Iliac  
Secondary Nodes: Common iliac, Para-aortic  
**Lymph node involvement associated with decreased survival**
  - By blood-borne spread: although unusual

# Anatomy of the cervix



- Original squamous epithelium
- Original columnar epithelium
- Squamous metaplastic epithelium

# Cervical cancer presentation

- Early disease:
  - Asymptomatic
  - Cx sample or LLETZ
- Signs & symptoms:
  - Suspicious appearance
  - Irregular bleeding: PCB, IMB etc
- Advanced disease:
  - Offensive discharge
  - Backache, leg pain/oedema, haematuria, bowel changes, malaise, weight loss, anaemia

# Diagnosis & Staging

## Diagnosis

- Tissue for histological diagnosis
- Obvious Cx Ca : PB Only or small LLETZ
- Stage I Ca: Colposcopy - ideally CKC or LLETZ – Ablation CI

## Staging

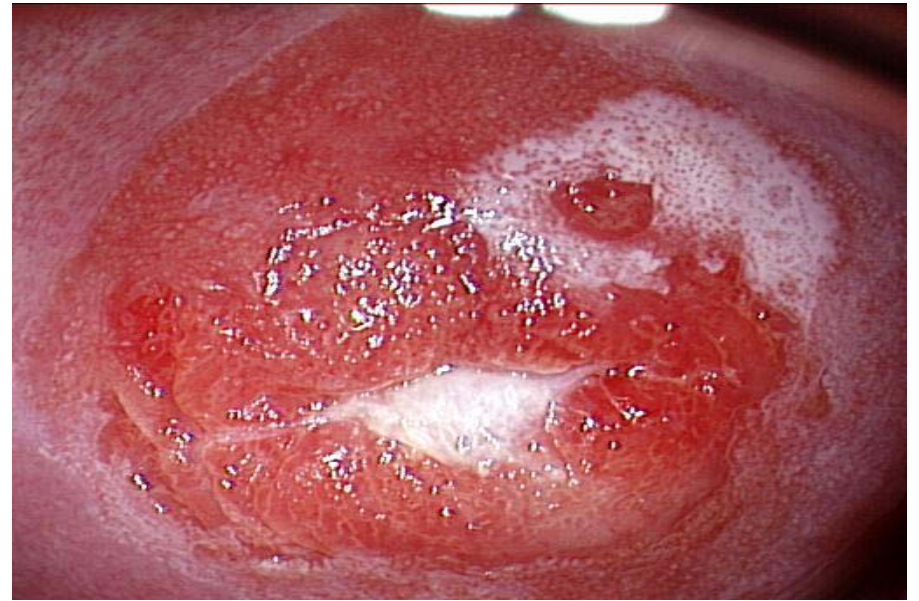
**Staging is clinical:** Assess disease extent & sites of spread

- EUA + rectovaginal examination: Size of tumour, vaginal & parametrial extension
- Cystoscopy - proctoscopy
- Radiology: CXR – IVU
- FBC, U+E's

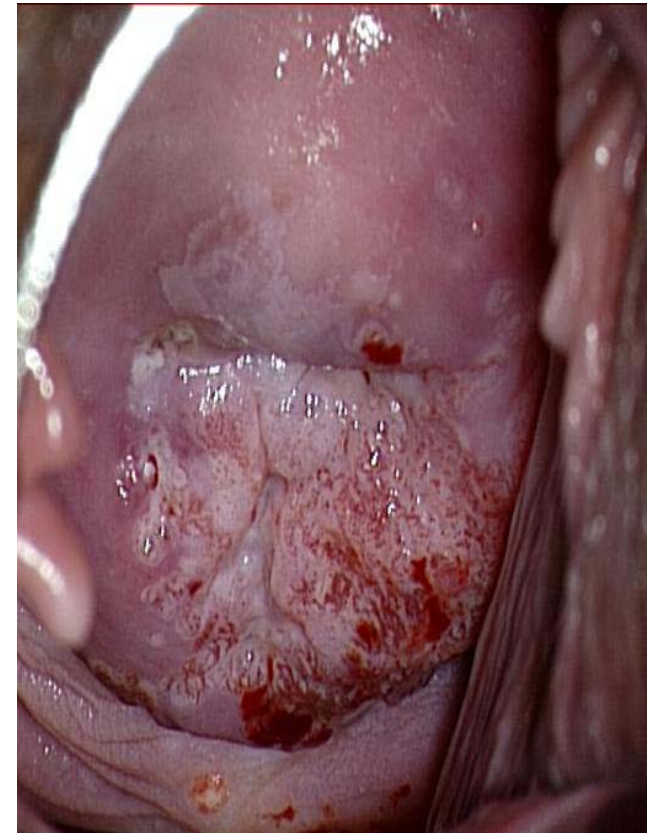
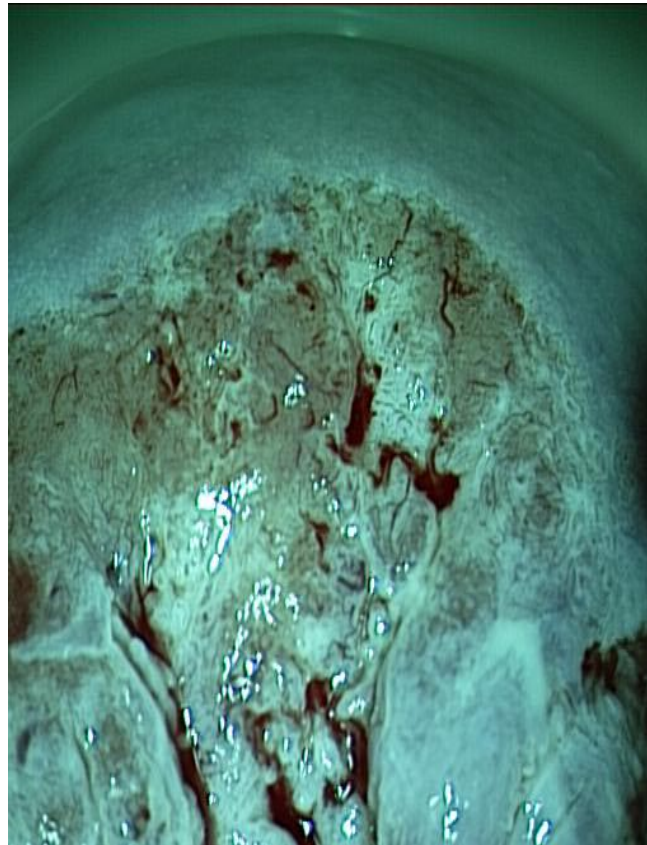
In practice

- CT & MRI
- ? PET-CT
- ? Laparoscopic LN dissection - ? Sentinel LN

CIN3 After Acetic Acid

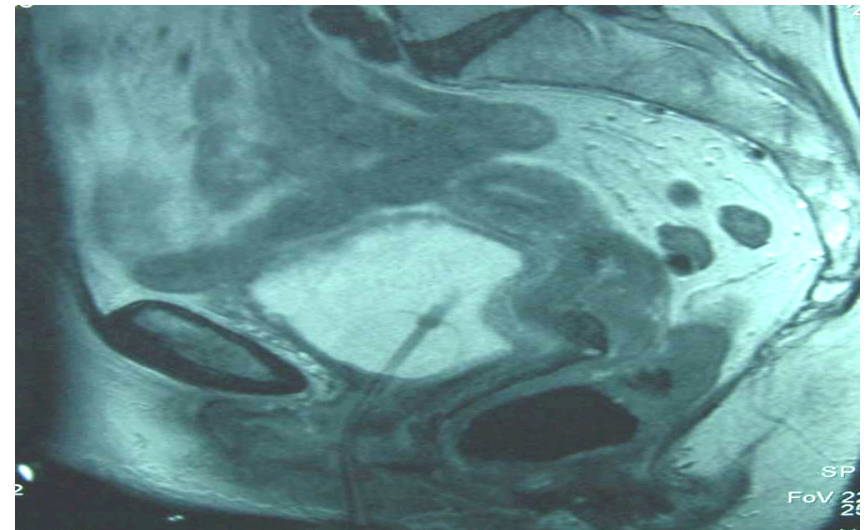
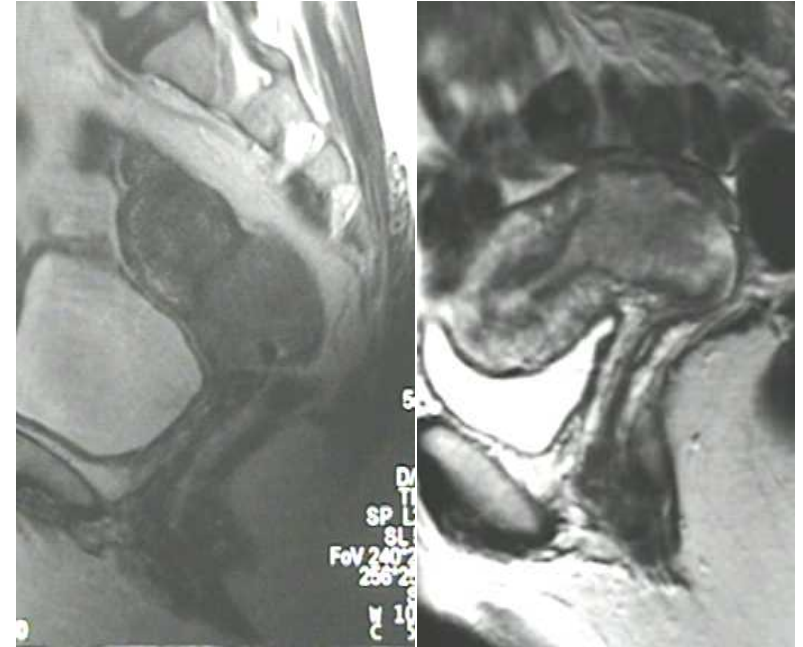


Micro-invasive Disease



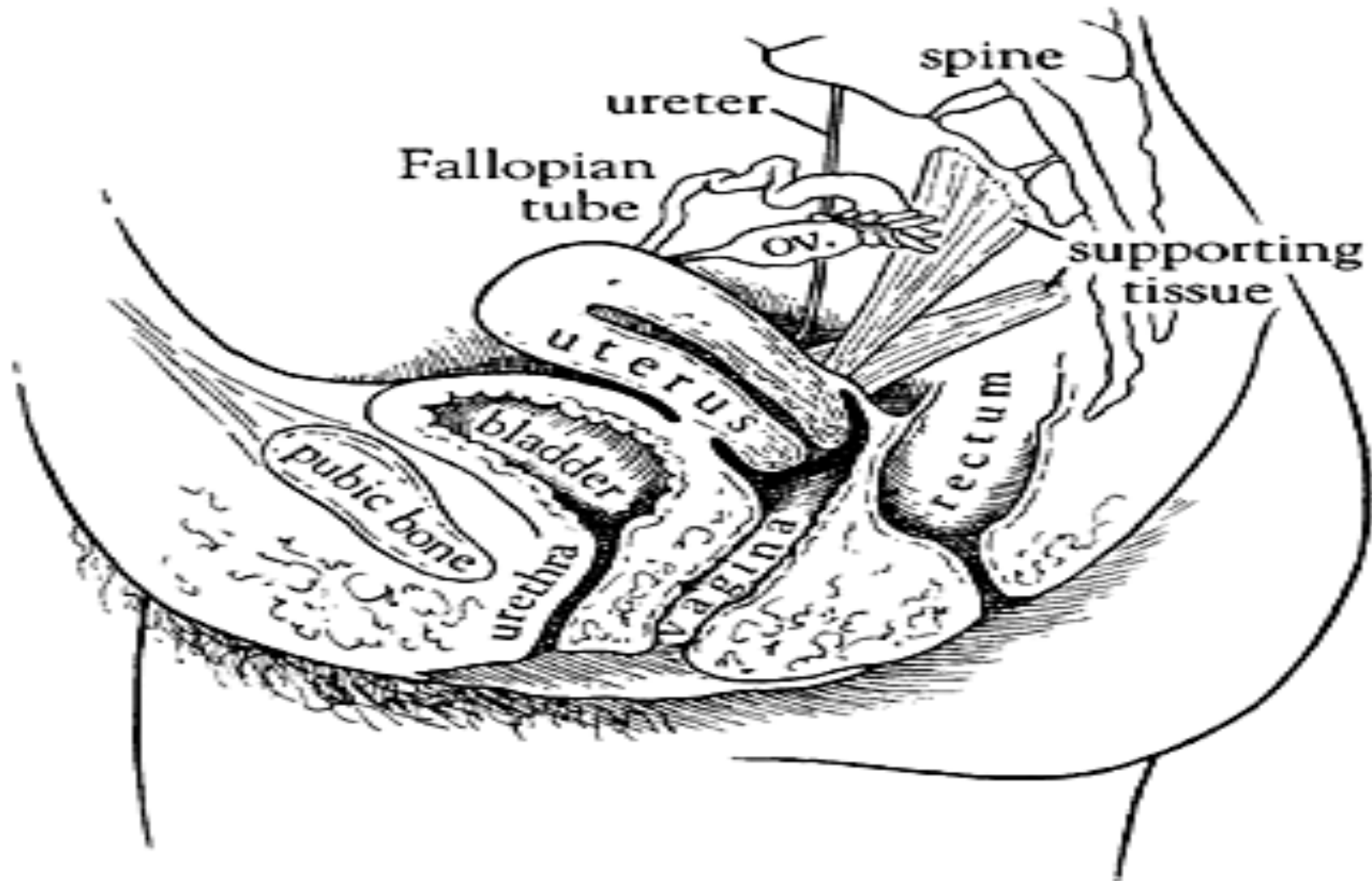
# MRI & Cervical cancer

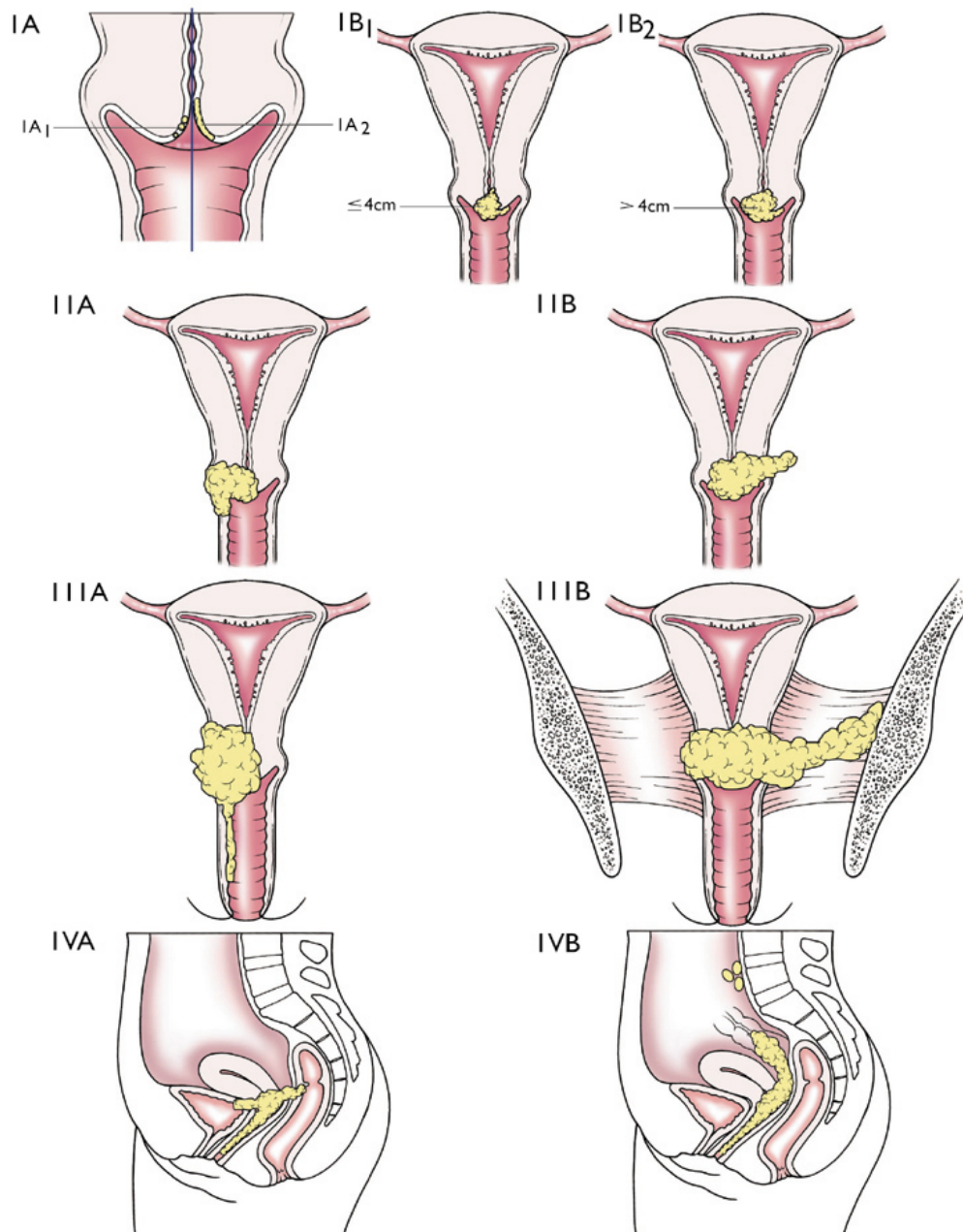
- Intermediate signal tumour
- Depth of invasion
- Tumour volume
- Assessment of LN
- Clinical staging inaccurate
- Accuracy: 90%



Stage 2a

## Clinical Staging of Cervical Cancers





## International Federation of Gynaecology and Obstetrics (FIGO) staging

### Stage I

**Stage I** The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)

Stage Ia Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion  $\leq 5$  mm and largest extension  $\leq 7$  mm

Stage Ia1 Measured stromal invasion of  $\leq 3.0$  mm in depth and extension of  $\leq 7.0$  mm

Stage Ia2 Measured stromal invasion of  $>3.0$  mm and not  $>5.0$  mm with an extension of not  $>7.0$  mm

Stage Ib Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage Ia<sup>a</sup>

Stage Ib1 Clinically visible lesion  $\leq 4.0$  cm in greatest dimension

Stage Ib2 Clinically visible lesion  $>4.0$  cm in greatest dimension

### Stage II

**Stage II** Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

Stage IIa Without parametrial invasion

Stage IIa1 Clinically visible lesion  $\leq 4$  cm in greatest dimension

Stage IIa2 Clinically visible lesion  $>4$  cm in greatest dimension

Stage IIb With obvious parametrial invasion

### Stage III

**Stage III** The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney<sup>b</sup>

Stage IIIa Tumour involves lower third of the vagina, with no extension to the pelvic wall

Stage IIIb Extension onto the pelvic wall and/or hydronephrosis or non-functioning kidney

### Stage IV

**Stage IV** The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.

A bullous oedema, as such, does not permit a case to be allotted to stage IV

Stage IVa Spread of the growth to adjacent organs

Stage IVb Spread to distant organs



## Incidence of nodal disease in cervical cancer according to stage

Stage	Positive pelvic lymph nodes (%)	Positive para-aortic lymph nodes (%)
Ia1 (<1 mm)	0	0
Ia1 (1–3 mm)	0.6	0
Ia1 (LVSI +ve)	4	0
Ia2 (3–5 mm)	4.8	<1
Ia2 (LVSI +ve)	11	<1
Ib	16	2.2
IIa	25	11
IIb	31	19
III	45	30
Iva	55	40