

Natural history of cervical neoplasia

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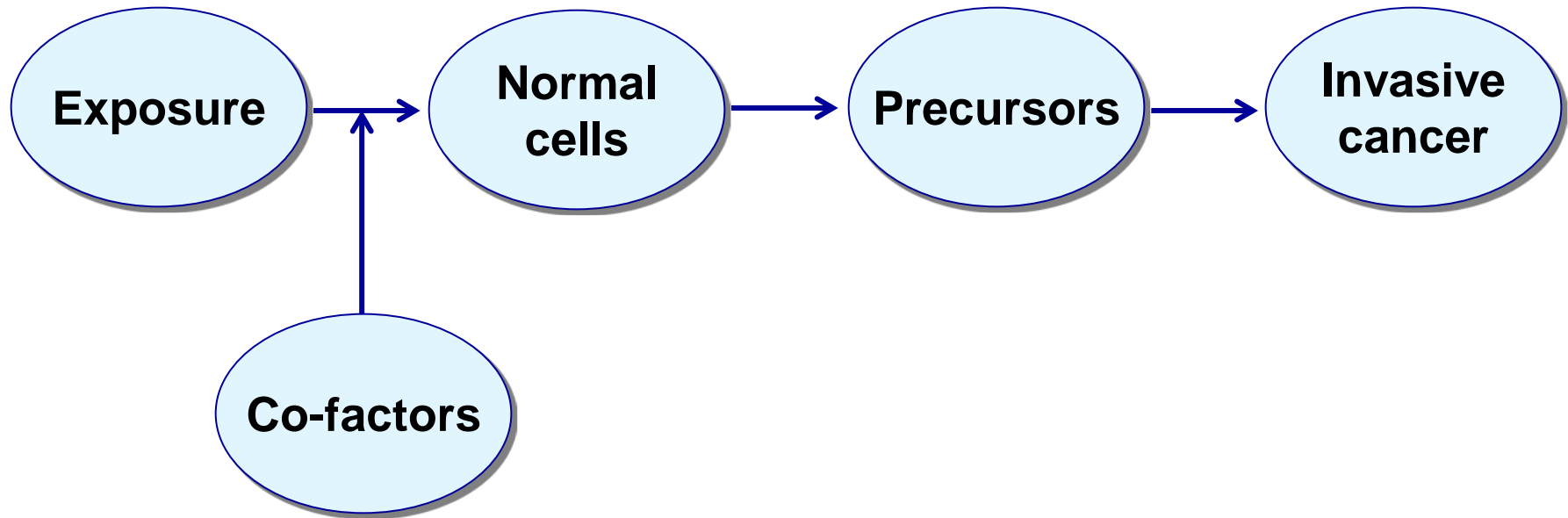
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Cervical Cancer

- A rare long-term outcome of a very common viral infection of the surface epithelium
- Well understood natural history
- Eminently preventable and treatable cancer
- Incidence/mortality heavily influenced by socio-economic development, screening and prevention efforts
- Both optimistic and pessimistic scenarios!
- Very little advocacy for its control in the third world!
- Major support given by the Bill & Melinda Gates Foundation to augment prevention efforts in the third world

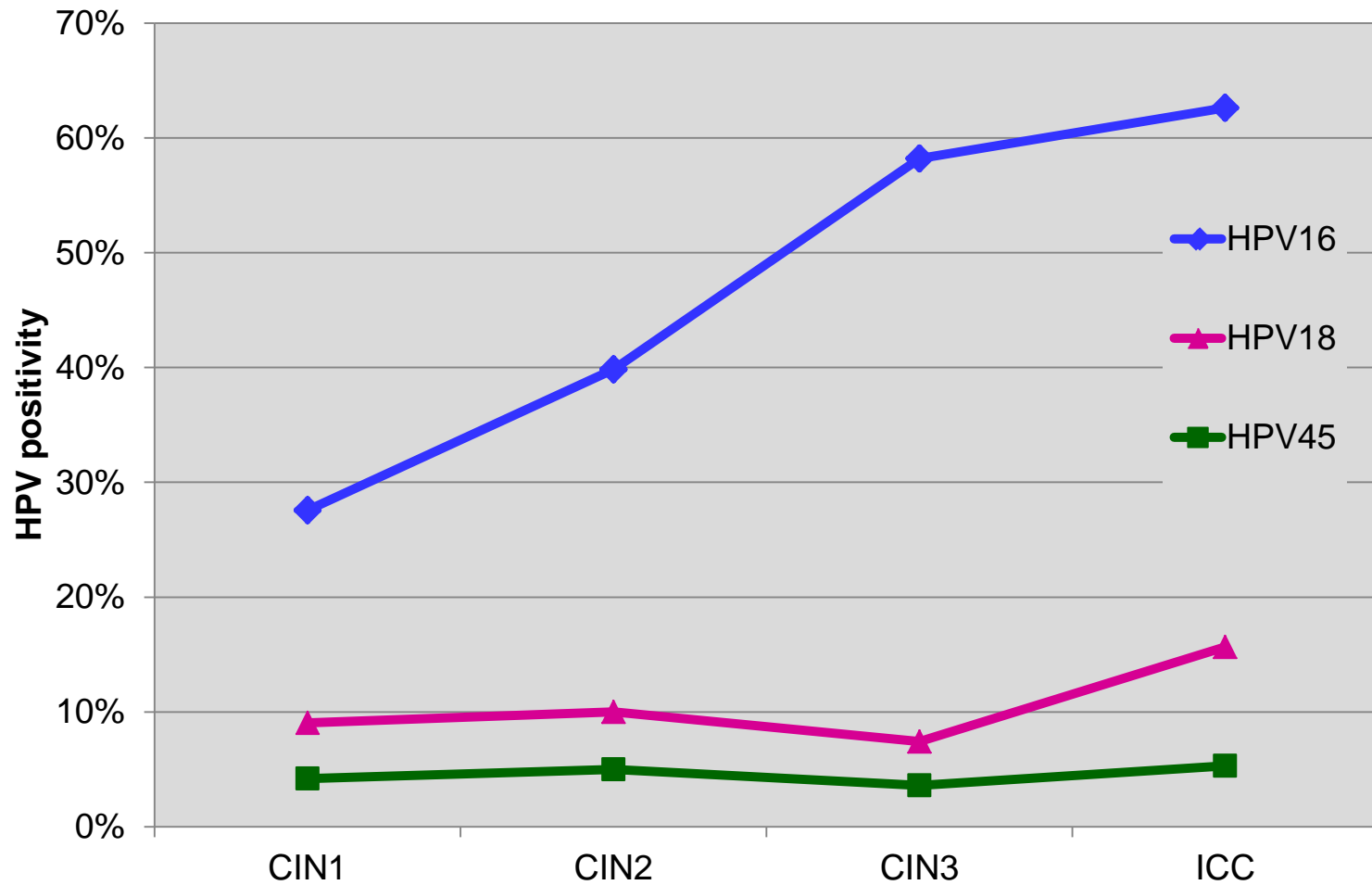
Natural history of cancer



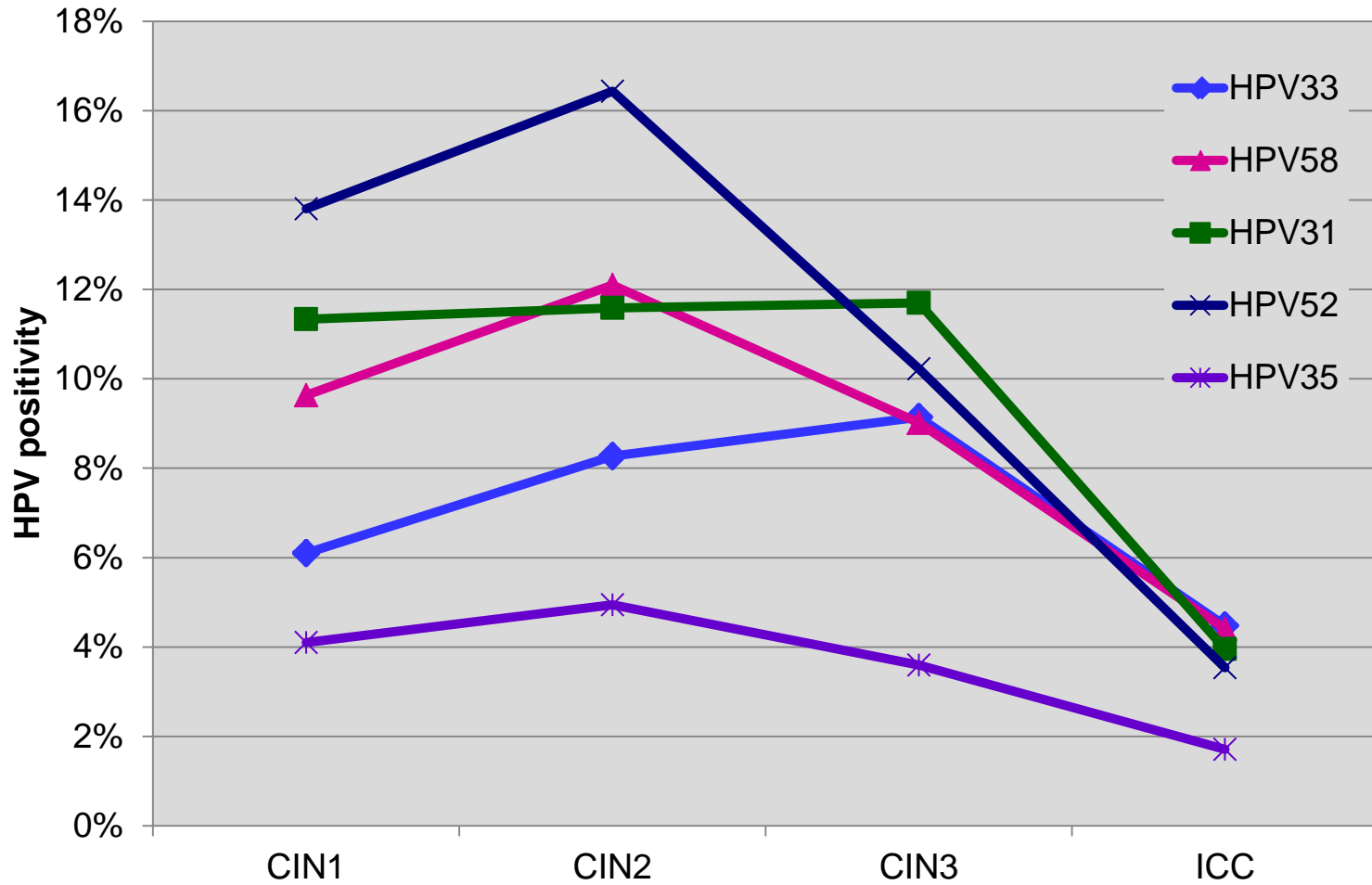
CERVICAL CANCER IS A RARE
LONG-TERM OUTCOME OF PERSISTENT
INFECTION WITH ONE OR MORE
OF HIGH-RISK HPV TYPES

(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82)

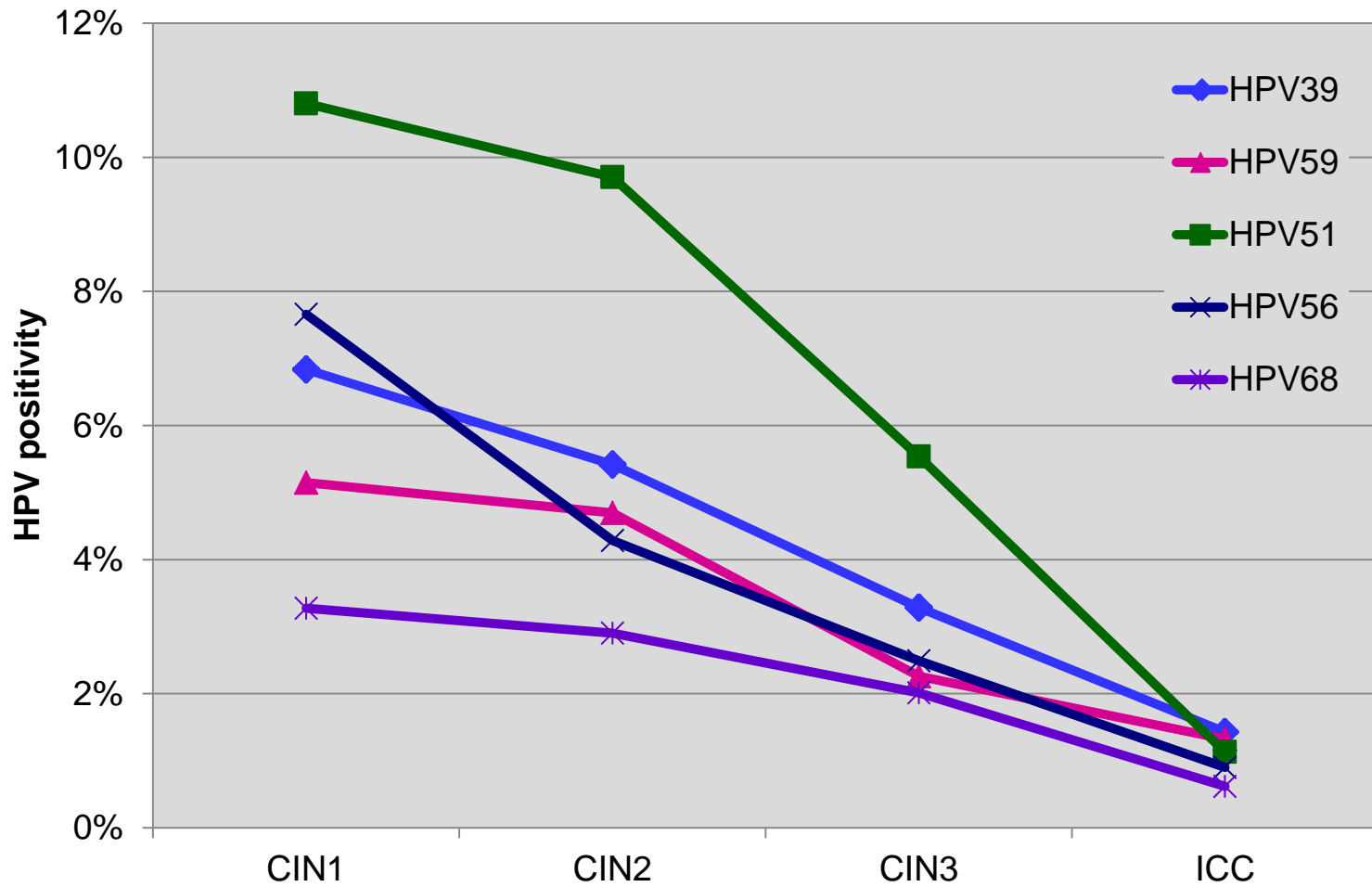
HPV 16, 18 and 45 DNA positivity, by cervical disease grade



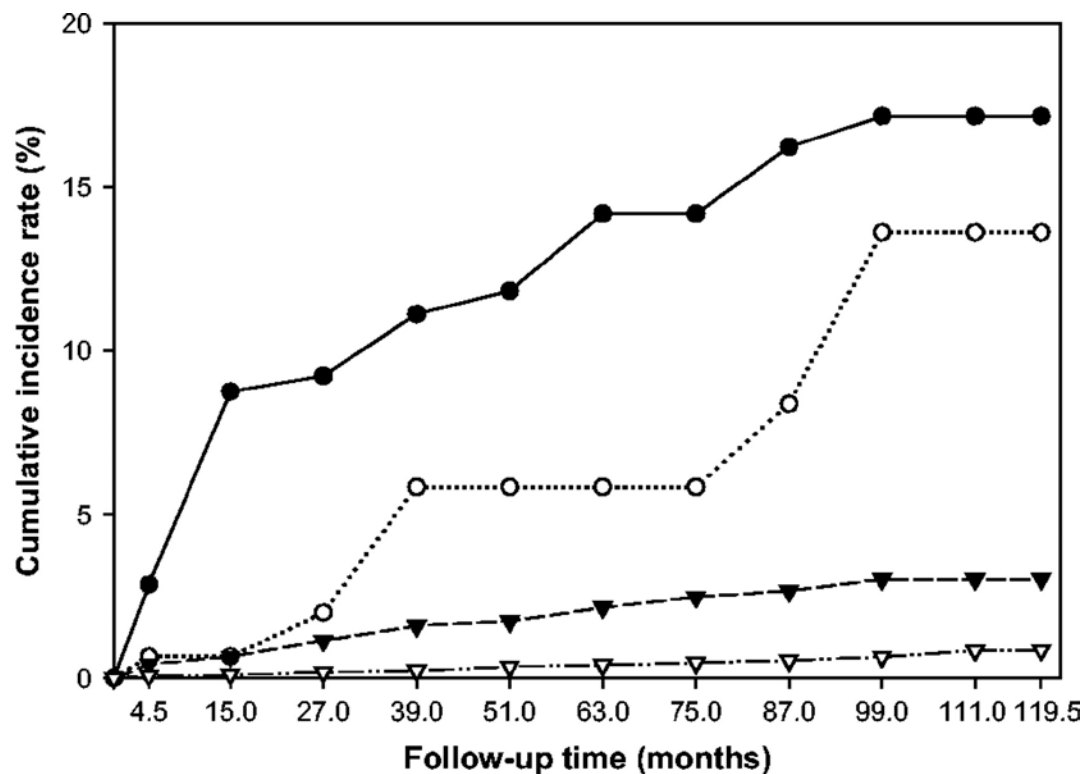
HPV 33, 58, 31, 52 and 35 DNA positivity, by cervical disease grade



HPV 39, 59, 51, 56 and 68 DNA positivity, by cervical disease grade



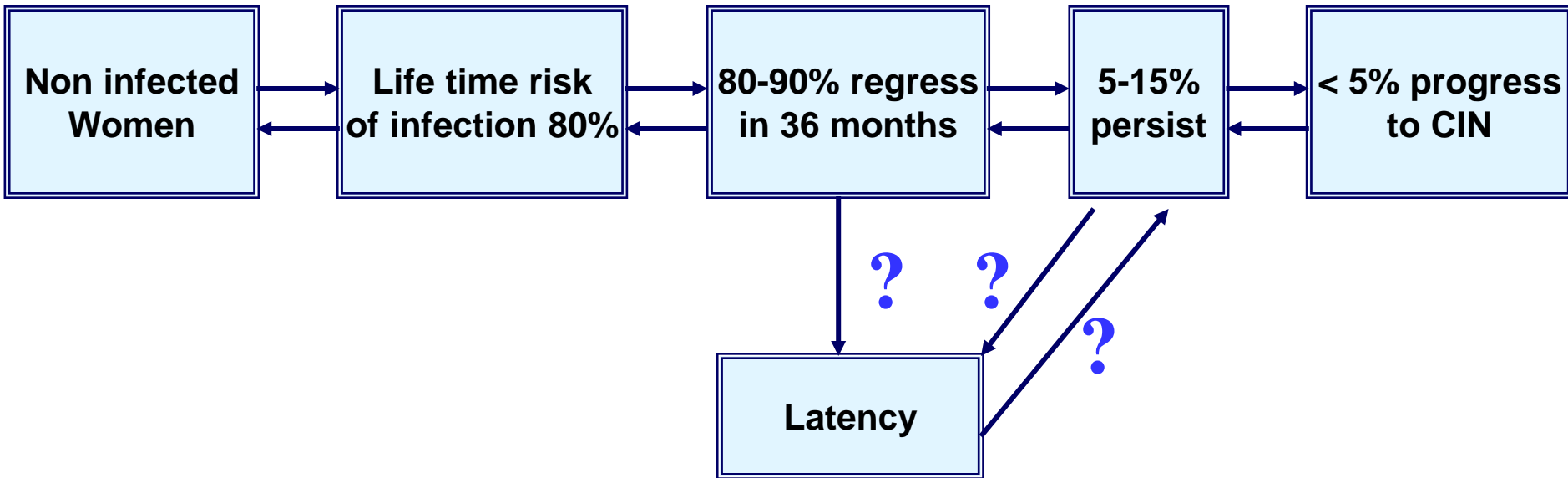
Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (\geq CIN3) over a 10-year period in 20 514 women according to oncogenic human papillomavirus (HPV) status at enrolment



No. of women seen during follow-up interval

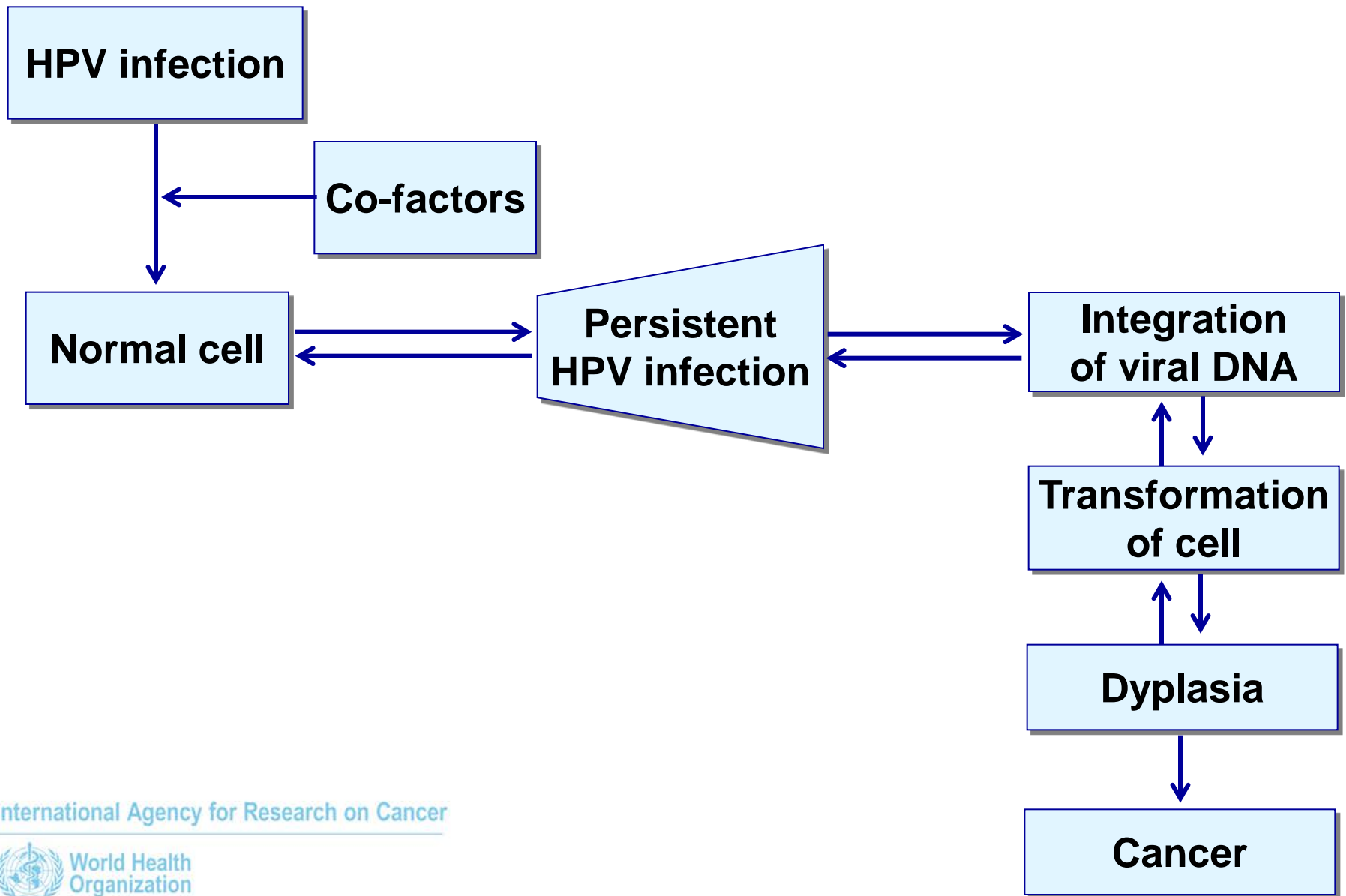
HPV16+	455	247	190	144	125	112	94	84	89	35	3
HPV18+	154	85	74	51	43	41	36	37	35	16	1
HC2+	2211	1208	1016	862	755	701	600	528	547	256	17
HC2-	17391	9759	8672	7813	7136	6479	5960	5551	5278	2621	156

Natural history of HPV infection



Median duration of new infection 8 months

Natural history of cervical cancer

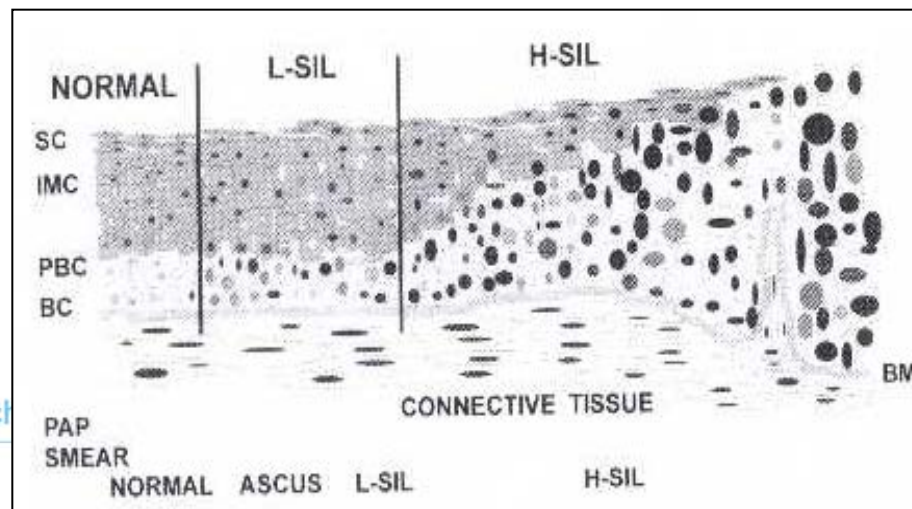
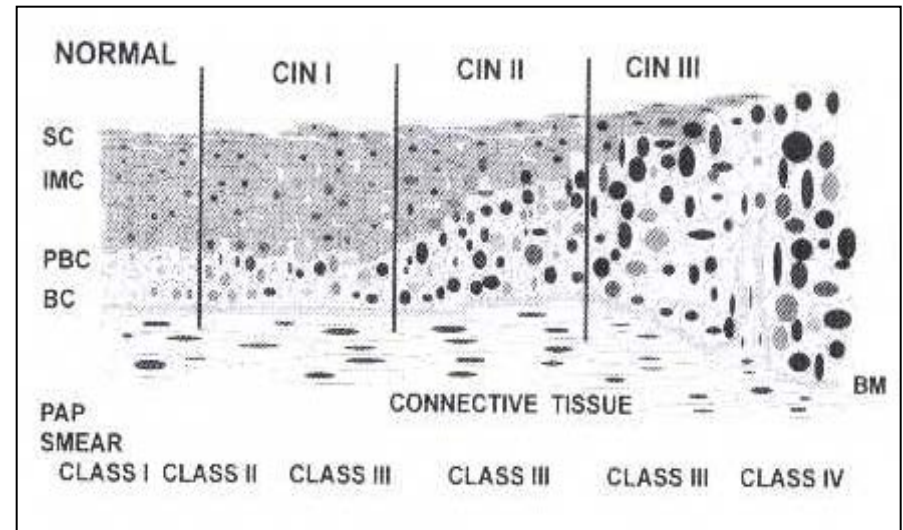
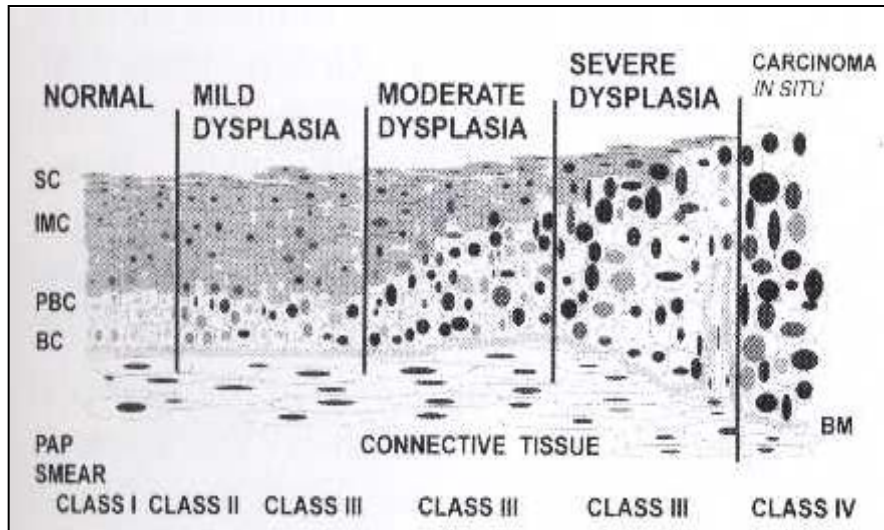


Natural history of cervical cancer precursor lesions

Pap smear classes	WHO system	CIN system	Bethesda system
Class I	Normal	Normal	Normal
Class II			
Class III	Mild dysplasia	CIN 1	LSIL
Class III	Moderate dysplasia	CIN 2	HSIL
Class III	Severe dysplasia	CIN 3	HSIL
Class IV	Ca in-situ	CIN 3	HSIL

Adenocarcinoma – *in-situ*

Natural history of cervical cancer precursor lesions



Natural history of cervical cancer precursor lesions

- **Cross-sectional studies**
- **Cohort (follow-up studies)**
- **Screening programmes**

Problems:

- **Small sample sizes**
- **Varying periods-often short- follow-up periods**
- **Varying degrees of lost to follow-up**
- **Inconsistent methods of assessing diagnosis**
- **Inconsistent assessment of diagnostic categories**
- **Variations in end points**
- **Effect of treatment/biopsy**

Natural history of dysplasia

Attribute	Mild	Moderate	CIS
No. studies	17	12	21
No. pts	4,505	2,247	767
Regress	57%	43%	32%
Persist	32%	35%	56%
Progress to CIN 3	11%	22%	-
Progress to invasive cancer	1%	5%	12%

Oster A.G. IJGP 1993;12:186-192

Toronto natural history study

- **Linkage of a single laboratory with Ontario Cancer Registry**
 - ***17,619 women during 1970 to 1980 included***
 - ***12, 058 (68.4%) mild dysplasia***
 - ***4834 ((27.4%) moderate dysplasia***
- **724 (4.2%) severe dysplasia**
- **Average length of follow-up 159,142, 86 months**
- **Conservative management of dysplasias during this time**

Holowaty et al., JNCI 1999;91:251-258

Toronto natural history study: % of progression

Dysplastic states	2 years	5 years	10 years
Mild to moderate or worse	11.1	20.4	28.8
Mild to severe or worse	2.1	5.5	9.9
Moderate to severe or worse	16.3	25.1	32.0
Severe to cancer	12.1	16.8	20.7

Holowaty et al., JNCI 1999;91:251-258

Factors influencing progression of CIN

- **HPV infection**
- **Aneuploidy**
- **Cytological abnormality**
- **Immune stains**
- **? Age**
- **? Large lesions**
- **? Dense acetowhite lesions**

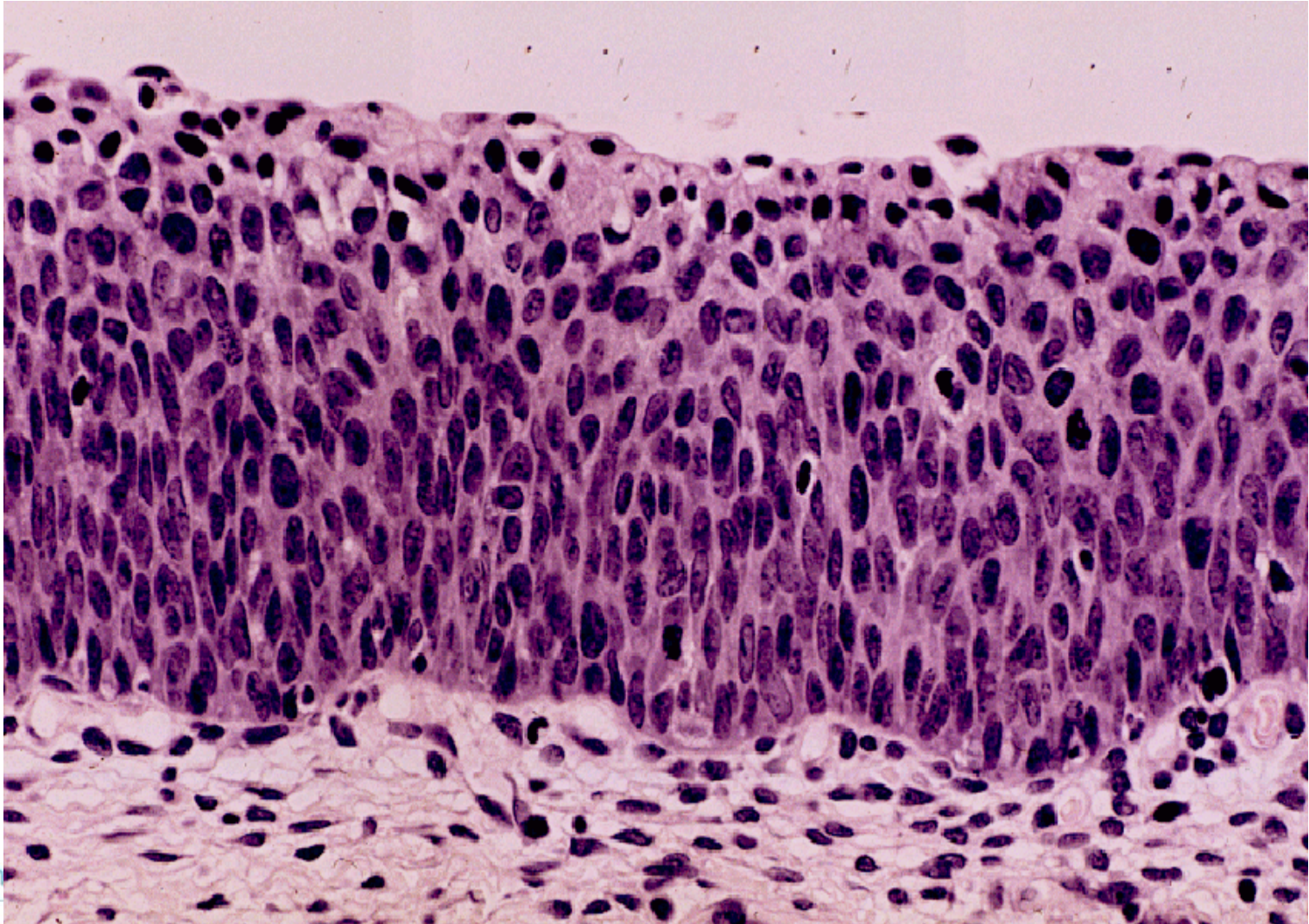
Natural history of dysplasia

Summary of studies:

- > 80% of CIN 1,2 regress by 10 yrs
- about 10% of CIN 1 progress to CIN 3
- about 20% of CIN 2 progress to CIN 3
- < 5% of CIN 1 progress to invasive cancer
- < 10% of CIN 2 progress to invasive cancer
- about 50% of CIN 3 progress to invasive cancer
- progression is a slow process

HIGH-GRADE CIN (CIN 2,3)

Considered to be “true” neoplasia or precursor



Cumulative cervical cancer incidence among women with histologically proven CIN who defaulted treatment, 2000-2009, Osmanabad District, India

	No. of women	Person years of follow up (PYO)	No. of cervical cancer cases (%)	Cervical cancer incidence rate (per 100,000 PYO)
CIN 1	1,542	15,091	6 (0.4)	39.8
CIN 2	37	347	1 (2.7)	288.4
CIN 3	39	357	5 (12.8)	1400.4

Cumulative cervical cancer incidence among women with histologically proven CIN who received treatment, 2000-2009, Osmanabad District, India

	No. of women	Person years of follow up (PYO)	No. of cervical cancer cases (%)	Cervical cancer incidence rate (per 100,000 PYO)
CIN 1	966	9,392	4 (0.4)	42.6
CIN 2	257	2,464	11 (4.2)	446.4
CIN 3	369	3,542	12 (3.3)	338.8

Natural History of Cervical Cancer Precursors

IMPLICATIONS FOR TREATMENT AND FOLLOW-UP

- **Most HPV infection (>90%) are transitory in nature – No Rx required (No Rx exists!)**
- **Most CIN 1 regress – If systematic follow-up can't be ensured TREAT!**
- **CIN 2/3 are true precursors of cervical cancer – SHOULD treat them**
- **The risk of invasive cancer is still high in treated women with CIN**