WHO COLLABORATING CENTRE
FOR RESEARCH IN HUMAN
REPRODUCTION

HUG
Hôpitaux Universitaires de Genève

Human Papilloma Virus (HPV) Screening

Saloney Nazeer

Department of Gynaecology & Obstetrics

State-of-the-Art in Cervical Cancer Screening *(Int J Can; 2000)*

- IEC + Organized screening programmes
- Pap-smear: the proven method
- Screen every woman at age 45
- When resources permit screen 10yrly at age 35, 45, 55
- If resources available, screen 5yrly age 35-59
- Once coverage achieved (80%)- expand to age 25 (if resources available)

HUG
Hôpitaux Universitaires de Genève

Reduction in cumulative incidence of invasive cervical cancer over the age range 35-64 yrs, with different frequencies of screening
(WHO, 1992)

Frequency of screening	Percentage reduction in cumulative incidence	No. of tests
1year	93	30
2 years	93	15
3 years	91	10
5 years	84	6
10years	64	3

Pap Smears

- Sensitivity: 11 to 99%
- Specificity: 14 to 97%
- False negative: 5 to 55%
  - **-Errors of Commission: laboratory errors-1/3**
  - **-Errors of Ommission: sampling errors-2/3**
- Costs

Fahey et al: 1995

HUG
Hôpitaux Universitaires de Genève

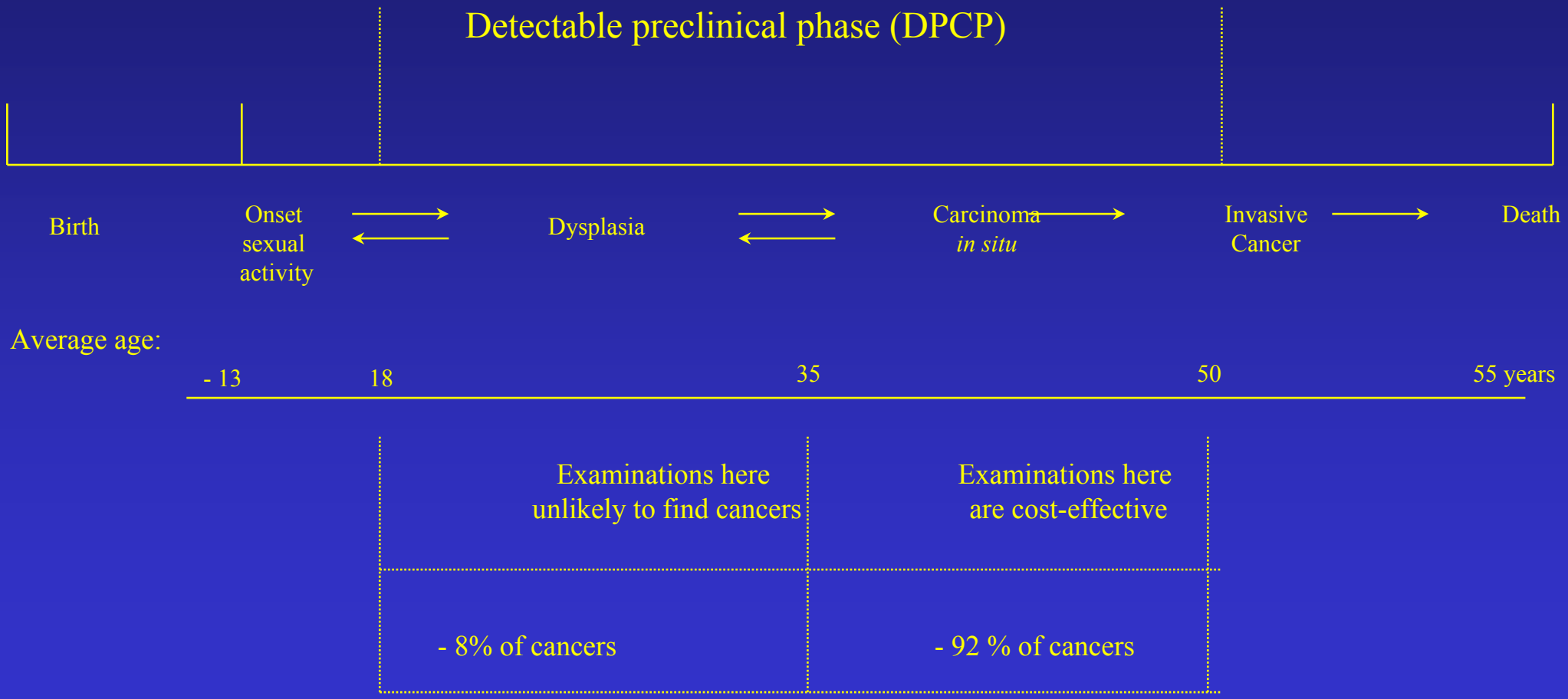
Potential Role of HPV in Screening

- Primary screening
- Triage of ASCUS / LSIL: improve management
- Post Treatment Surveillance (CIN / Insitu): to monitor complete excision

Limitations on Epidemiology data

- Logistic difficulties / Ethical issues
- Variable end points (cytology vs histology)
- Possible effect of biopsies on the future course of a cervical lesion
- Different definition & Dx of precancerous lesions
- Variety of populations studied:
  (age, disease state, concommitent STDs)
- Variety of HPV assays used
- Variable research methodologies

HUG
Hôpitaux Universitaires de Genève



HUG
Hôpitaux Universitaires de Genève

Natural History of HPV

- Largely sexually transmitted
- Risk factors: No. of sexual partners in the last few years; age at first intercourse
- Peak incidence: 20-24 yrs
- Incidence gradually declines upto 40-45 yrs
- May begin to increase slowly thereafter

(ref: Schifman et al 1993; Bosch et al,1995; Burk et al, 1996; Dillner et al, 1996; Meijir et al, 1999)

Natural History of HPV

- 80% infections transient: median range 12 mnths- no risk of CIN
- 10-20% infections persistent: high risk of CIN - only 30% of these progress if untreated
- Minor Cyto abnormality with HPV- : low risk of progression within 3-4 years
- RR of progression 40-180
- Persistence is the important factor for disease progression

(ref:Hildesheim et al, 1994; Wheeler, 1996; Koustky, 1992)

HUG
Hôpitaux Universitaires de Genève

Factors influencing persistence

- **Age:** > 30-35 yrs
- **? Viral load:** high
- **? Viral type:** 16
- **? Viral integration**
- **? Viral RNA transcripts**

Prevalence

In general population

- Prevalence: 4-44% (Data not comparable)

  age 20-30 yrs - 10-30%

  age> 30 yrs - 3-10%

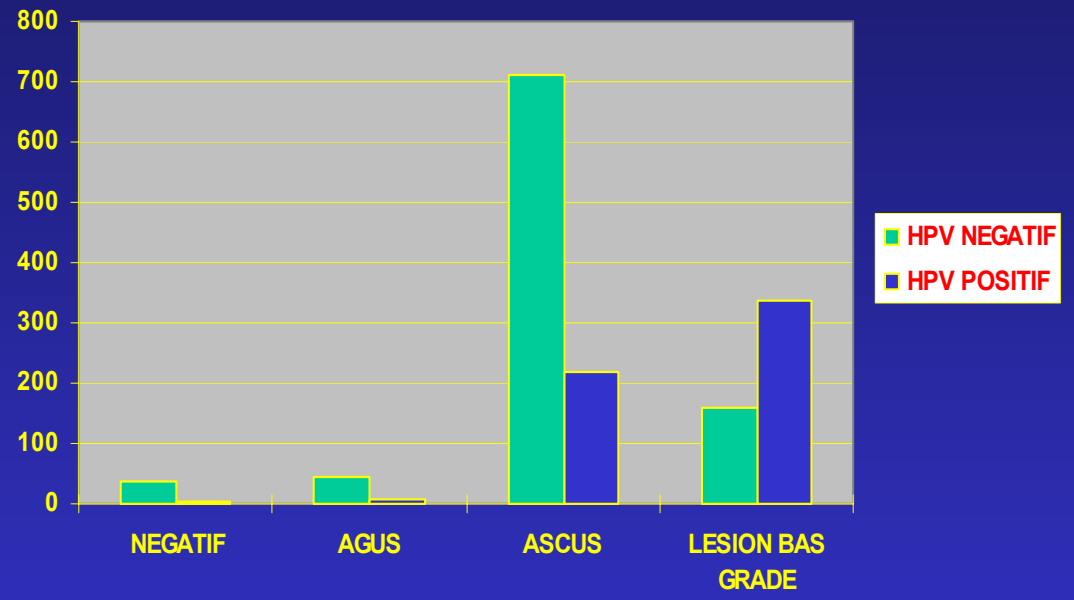
Prevalence

In cervical lesions

- Squamous carcinoma: 95% association
- HSIL/CIN II, III: 75 -95%
- LSIL/CINI: 60%
- ASCUS: 30%
- Adenocarcinoma: 60% association

(ref: Cuzick et al, 1992; Schiffman et al, 1993; IARC, 1995; Olsen et al, 1995)

Recherche de HPV haute risque par HC II, Geneve -‘99-00



DIAGNOSTIC	MANQUE	PAS FAIT	IAT. INSUFFISAN	IPV NEGATI	HPV POSITIF	TOTAL	% HPV NEGATIF	% HPV POSITIF
NEGATIF	0	1	0	36	5	42	88%	12%
AGUS	0	4	3	45	9	61	83%	17%
ASCUS	7	71	58	710	217	1063	77%	23%
LESION BAS GRA	3	51	20	160	338	572	32%	68%
total des cas	10	127	81	951	569	1738	63%	37%

Testing Methodologies

- Southern blotting
- Dot blot
- Filter in situ hybridisation (FISH)
- In situ hybridisation
- Hybrid capture HCI / HC II
- Polymerase chain reaction (PCR)
- Others: LCR, NASBA, in situ PCR

Prerequisites

SCREENING TEST:

- is valid for identifying pre-clinical lesions
- acceptable (easy to apply, no pain, no side-effects)
- screening interval
- affordable

Comparisons of HPV with Cytology

Author	HPV Test	Sensitivity for HSIL		Specificity for HSIL	
		Cytology	HPV	Cytology	HPV
Reid 1991	SB	52	55	92.3	95.8
Schneider 1996	HC	29	50	96	96
Ratnam 1999	HC	37.9	86.2	95.6	91.9
Cuzick 1999	HC II	79	95.2	98.7	95.1
Schiffman 1999	HC II	75.2	89.6	96.5	89.1

Issues to be resolved

- Age - appropriate for testing
- Testing methodology / Test interpretation
- Viral persistence - surrogate markers for
- Test sensitivity & specificity
- Acceptability - psychological impact
- Quality control measures
- Health economics - costs for high volume application

Ongoing & Planned Studies of HPV Testing

Investigator	Location	Population	Size	Investigats	Status
Nazeer	Suisse	Screening	2000	HPV HC II, Colpo, Liq Base cyt	Ongoing
Schiffman	USA	Ascus/LSIL smears	1500	HPV HCII Cervicogy, Liq base cyt	Ongoing
Cuzick	UK	Screening Age 30-60	12 000	HPV HC II	Ongoing
Dillner	Sweden	Screening Age 32-68	10 000	HPV HC II	Ongoing
Meijers/ Walboomers	Netherlands	Screening	44 000	HPV HCII	Pilot
Hakama	Finland		100 000	HPV New Techs	Planning

HUG
Hôpitaux Universitaires de Genève

Conclusions

- HPV is more sensitive than cytology for high grade CIN - but has low specificity than cytology esp. in young women

- HPV testing cannot currently be recommended for widespread implementation

Conclusions

- May be appropriate in certain limited situations - management of borderline smears esp in women >30 yrs

- May be used to disinvest in screening programmes - reduce No. of smears/ colposcopy / increased screening intervals

Conclusions

- Negative predictive value is uncertain - safety associated with reduced surveillance of HPV -ve women

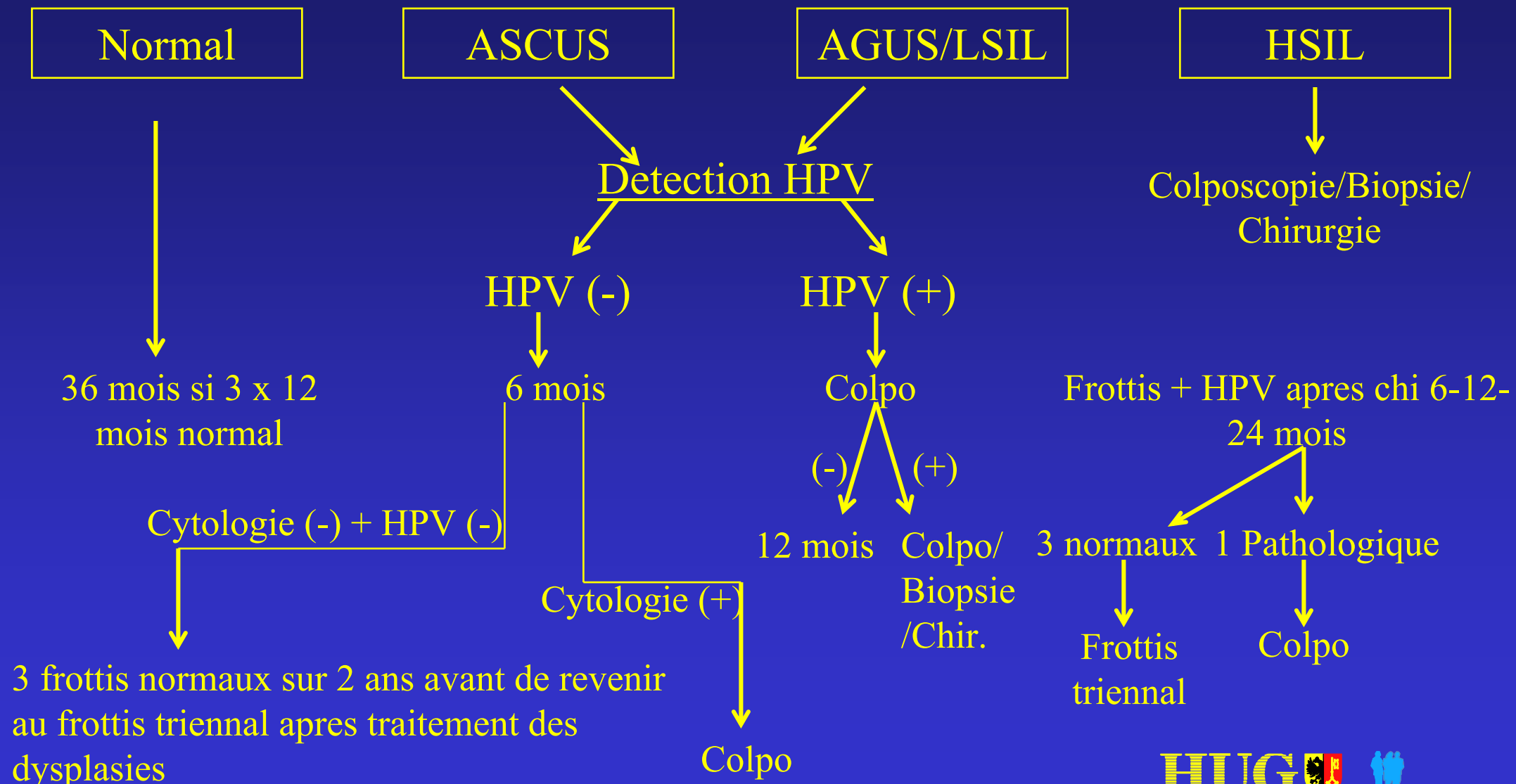
- Lack of evidence regarding independence of the two tests

Conclusions

- Longitudinal studies with an appropriate follow-up (6 yrs) are required to:

- determine appropriate screening intervals
- examine cumulative incidence of Cx Ca 1,3,5,10,15 yrs after various screening histories

Depistage du cancer du col



HUG
Hôpitaux Universitaires de Genève