

**Circumcision, HPV vaccine, or both, to prevent ano-genital and oral cancers: justification for a trial of second generation HPV vaccines in males and females**

**RTD Oliver, L. Battery, R  
Ranganathan, J Ferley, D Forman**  
*Institute of Cancer, Barts and The London  
Medical School, QMUL, UK, MMTR Chenai  
and IARC Lyon*

# Introduction

- Vaccination of males against HPV is not economic when assessed from the view of cervix cancer.
- If it prevented other cancers and altered a surrogate end-point within 15 years of vaccination, the economic case would swing towards vaccinating both sexes.
- The aim of this presentation is to review the geographic epidemiology of ano-genital and oral cancers and the impact of circumcision as well as this surgery's role in preventing HIV infection in search for surrogate end-points to assess in future trials in males of second generation HPV vaccines

# HPV Studies in non-Cervical Tumours

(Oliver 2000)

	No of cases	Proportion positive
Anal carcinoma	388	75%
Head & Neck carcinoma	137	34%
Vulval carcinoma	152	34%
Penile carcinoma	235	26%
Bladder carcinoma	713	19%
Lung carcinoma	230	11%
Prostate carcinoma	541	17%
Normal prostate	62	13%

# P53 mutation and HPV detection in penile, head & neck and prostate oral cancer (Oliver 2000)

	No of cases	P53 mutation
<i>Penile cancer</i>		
HPV positive	9	22%
HPV negative	12	42%
<i>Head and neck cancer</i>		
HPV positive	126	28%
HPV negative	188	42%
<i>Prostate cancer</i>		
HPV positive	8	0
HPV negative	43	16%
<b>Total</b>		
<b>HPV positive</b>	<b>111</b>	<b>25%<sup>a</sup></b>
<b>HPV negative</b>	<b>243</b>	<b>41%<sup>b</sup></b>

***a v b  $\chi^2 = 8.373 p = < 0.025$***

# HNSCC 5 year survival and HPV/p53 status

(Licitra L et al J Clin Onc 2006;24:5630)

HNSCC subtype	No of cases	5 yr survival
HPV+p53 wild type	15	77%
HPV-p53 wild type	40	42%
HPV-p53 mutant	35	39%
HPV+p53 mutant	2	39%

# AIMS OF TALK

- Current evidence for health benefits of circumcision & the confounding variable of genital hygiene
- The interaction of HPV & HIV and why combined male & female HPV vaccination could reduce HIV infection
- Modern epidemiology of prostate cancer and how HPV could be involved in influencing PSA at an early age to provide a second surrogate marker for benefit of HPV vaccination of both sexes with the 2<sup>nd</sup> generation vaccines
- Possible design for a trial suitable for India +/- Brazil

# Circumcision and HR-HPV prevalence, acquisition and clearance

	Circumcised	Un-circumcised	
Castellsague et al NEJM 2002 (prevalence)	5.5% (n=292)	19.6% (n=847)	P <0.001
Gray et al J Inf Dis 2010 (acquisition)	27 HPV/100PY (n=226)	44 HPV/100PY (n=210)	0.61 (IRR)
Gray et al J Inf Dis 2010 (clearance)	216 per 100PY (n=205)	159 per 100PY (n=255)	1.36 (IRR)

# Comparison of Circumcision Status and Cervix or Prostate cancer occurrence

	<b>No of controls</b>	<b>No of cases</b>	<b>OR</b>
<b>Cervix cancer (Castellsague et al NEJM 2002)</b>	<b>936</b>	<b>977</b>	<b>0.72</b>
<b>Prostate cancer (Oliver in preparation)</b>	<b>1631</b>	<b>1550</b>	<b>0.86</b>

# Global Incidence and Mortality of Prostate Cancer (PC) & Cervix Cancer (CC) (GLOBOCAN 2008)

	Deaths <u>PC</u> per 10 <sup>5</sup>	Incidence <u>PC</u> per 10 <sup>5</sup>	Deaths <u>CC</u> per 10 <sup>5</sup>	Incidence <u>CC</u> per 10 <sup>5</sup>
Brazil c-	16.3	50.3	10.9	24.5
USA c+	9.7	83.8	1.7	5.7
Denmark c-	2.5	72.5	2.5	11
India c-	2.5	3.7	15.2	28.9
Bangladesh c+	1.2	1.9	17.9	27
Saudi Arabia c+	5.1	7.7	0.9	2.1
Israel c+	7.6	55	2.1	5.6
China c-	1.8	4.3	4.6	9.6
Japan c[-	5	22.7	2.6	9.8

# Impact of education and religion on cervix and penis cancer incidence in Madras

(Gajalakshmi et al Acta Oncol 1993;32:617-20)

<i>Education Level</i>	Cancer (rate/100,000)	
	Cervix	Penis
Illiterate	55	2.3
<12 years education	19	1.9
>12 years education	4.7	1.1
<i>Religion</i>		
Hindu	35	2.2
Christian	27	0.8
Muslim	14	nil

# Up-date Religion and Cancer in Chennai

(Madras Metropolitan Tumour Registry 2008)

	Hindu	Christian	Muslim
<b>Cervix Ca 1993/2003</b>	<b>35/28(-20%)</b>	<b>27/17(-37%)</b>	<b>14/9(-36%)</b>
Breast Ca 1993/2003	(21)/30	NA/30	NA/34
<b>Penis Ca 1993/2003</b>	<b>2.2/2.0(-10%)</b>	<b>0.8/0.5(-38%)</b>	<b>Nil/nil</b>
Prostate Ca 1993/2003	(2.9)/4.3	NA/2.3	NA/2.3

# Correlation between cervix and penis cancer geography in Brazil with sanitation facilities

(Proc 17<sup>th</sup> Int Cancer Congress 1998)

	Incidence per 100,000		Access to safe water	Access to sanitation
	Cervix	Penis		
<b>North</b>	47	5.3	40%	8%
<b>North East</b>	41	4.1	45%	15%
<b>Centro</b>	33	3.8	72%	29%
<b>South East</b>	40	1.4	90%	70%
<b>South</b>	30	1.2	85%	77%

# Circumcision and AIDS

	HIV+ circ vs non circ	Follow up med age	RR
Auvert et al 2005(n=3128)	22 vs 49	18 months 18-24 yrs	0.4
Bailey et al 2007(n=2784)	22 vs 47	24 months 20yrs	0.43
Gray et al 2007(n=4996)	22 vs 45	24 months 20-24 yrs	0.43
TOTAL 11208	66 vs 141	24 mths	

# Change in aerobic vs anaerobic colonisation of glans penis after circumcision

(Price, LB et al 2009)

	Statistical test	P value
All aerobic groups	$t = - 1.0294$	$p=0.3236$
All anaerobes	$t = 3.4765$	$p=0.0046$
Chlostridiales family	$t = 2.308$	$p=0.0210$
Prevotella family	$z = 2.469$	$p=0.0138$

# Oncogenic and nononcogenic human papillomavirus & HIV incidence

(Auvert et al J Acquir Immune Defic Syndr. 2010)

No of individuals studied	1683
High vs low risk HPV incidence	14% vs 17.3%
aIRR HIV infection of LR HPV infected	1.13
aIRR HIV infection of HR HPV infected	3.76

# Prevalence of HPV DNA in Semen samples

(Foresta et al Fertility & Sterility 2010)

Median age 37.2 +/- 5.5 yrs	Positive PCR	Positive FISH on sperm in PCR+
Genital warts	14/26 (54%)	43%
Partner HPV+	27/66 (41%)	63%
Infertile patients	11/108 (10%)	73%
Fertile patients	2/90 (2%)	0%

# Factors influencing serum PSA in gold miners attending STD clinic in South Africa

(Oliver JC et al 2001)

Anti chlamydial antibody response	No. of cases	PSA > 0.8 ng/ml
Titre < 1/64	201	17%
Titre > 1/64	61	27% (P < 0.001)
<b>Age at first sexual intercourse</b>		
≤ 16	34	35%
> 16	49	18% (P = 0.08)

# PSA pre, acute and post STI

(Sutcliffe et al 2005)

	Geometric mean PSA
30-39 non-infected African-American control	0.45
Pre-infection exudative urethritis	0.63
Acute phase exudative urethritis	0.75
3mths post exudative urethritis	0.71

# PSA in stored serum and later risk of prostate cancer

Prostate cancer verses matched control samples	OR for prostate cancer associated with raised PSA
Fang et al 2001 Age 40-49 (n=351)	3.75
Fang et al 2001 age 50-59 (n=445)	3.75
Lilja H et al 2007 age<50 (N=21,277, 462 PCa & 1222 Controls)	3.69

# The concept of post infective Proliferative Inflammatory Atrophy (PIA) as a cause of prostate cancer

- Franks LM 1954 First demonstrated PIA
- Feneley MR et al 1996 Increased Ki67 in PIA
- De Marzo AM et al 1999 PIA Assoc with PIN
- Isaacs WB Familial PCa genes linked to defective anti-viral, macrophage and Cox-2 genes.
- Platz EA et al 2005 regular aspirin RR PCa 0.71
- Khadra A et al 2006 increased IL-8 and prostatitis
- Riss J et al 2006 Ca as a wound that won't heal

Proposed 2x2 trial with surrogate endpoints of  
PSA, HIV and HPV culture at 18 & 21

	Elective circ +hygiene education	Education about genital hygiene M+F and treat phimosis in males
2 <sup>nd</sup> Generation HPV both sexes		
1 <sup>st</sup> Generation HPV for females and placebo for males		

# Conclusions

- The association of HR-HPV with wild type p53 and mutant p53 and history of smoking with HR-HPV negative tumours of the same organ supports concept of hit and run role in negative tumours.
- If true there might be a larger benefit from male HPV vaccination at puberty than previously recognised
- Raised PSA at 18-21 and frequency of HIV acquisition could be a surrogate early end points for evaluating HPV vaccine in males
- Accelerated acquisition of HIV in men infected with HR-HPV, suggests HPV vaccination of both sexes could reduce HIV

# Murine Model of HPV18 hit & run Oncogenesis

(Iwasaka et al. Act Obs Gynae Science. 1992; 71: 219)



HPV 18 transformed Syrian Hamster  
embryo cells outcome after cloning in  
nude mice

Number of HPV18 positive clones      9

Number of HPV18 negative clones      2

# Frequency of HPV in spontaneous and immuno-suppressed associated cancers



## Spontaneous tumours

## Tumours immuno suppressed

No. of cases

Proportion  
HPV +ve

No of cases

Proportion  
HPV +ve

High grade intra  
epithelial lesions

30

73%

30

90%

Low grade cervical  
87%

86

56%

62

Intra epithelial lesions

Squamous skin

76

3%

495

30%

# Interaction of HPV & smoking on Risk of Cervical Intraepithelial Neoplasia (CIN II/III)

*(Olsen et al. Epidemiology 1998;9:346-9)*

HPV-16 DNA Status	Smoking Status	Odds Ratio CIN II/III
-	-	1.0
-	+	NA
+	-	15
+	+	65.9

# Interaction of HPV & HSV on Risk of Cervical Intraepithelial Neoplasia (CIN II/III)

*(Olsen et al. APMIS 1998; 106:417-24)*

HPV-16 DNA Status	HSV Serology Status	Odds Ratio CIN II/III
-	-	1.0
-	+	8.5
+	-	29
+	+	247 (verses -/-) 11.1 (verses +/-)

# HIV and Ano-genital cancer in men and women

	Spontaneous (per 100,000)	HIV Infected (per 100,000)
Anal Ca(Women)	1.2	3.9
Anal Ca (Men/AAM)	0.9/15	18.2/23.9
Cervix Cancer	8.9	85.7
Prostate cancer	70	OR 0.7(c49)



# Prospective Serum Bank Sero-epidemiology of Human Papilloma Virus Infection and Ca Cervix, Prostate and Head & Neck.

	<b>CIN Cervix</b>	<b>Invasive Ca Cervix</b>	<b>Invasive Ca Prostate</b>	<b>Invasive Sq head &amp; neck</b>
<b>Size of Serum Bank</b>	15,000	700,000	20,243	900,000
<b>No Cases / no controls</b>	74/148	182/538	165/290	292/568
<b>HPV 16 O R</b>	5.8	2.7 (3.8/0)*	2.38	2.2
<b>HPV 18 O R</b>	N/A	2.1(1.9/3.1)*	2.59	N/A

\*(Squamous tumours / Adenocarcinomas)

# HPV serology and Prostate cancer risk

	Dilner (nested)	Hisada (nested)	Hayes (pbcc)	Rosenblatt/ Adami(pbcc)
HPV16	2.4	2.2	1.4	1.1/0.9
HPV18	2.9	ND	ND	1.4/0.5
HPV33	ND	ND	ND	2.69

# Prostate Intraepithelial Neoplasia (PIN) at autopsy in male accident victims.



(Sakr *et. al.* J Urol 1993;150:379-85)

Age at autopsy	Incidence of PIN at autopsy	Incidence of cancer
20-29	0%	0%
30-39	9%	0%
40-49	20%	27%
50-59	44%	34%