

**Trans-Divisional Research on  
Human Papillomavirus (HPV)**

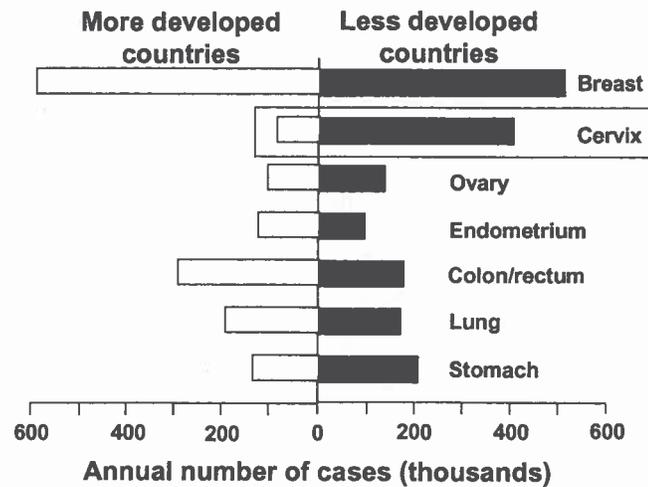
**National Cancer Advisory  
Board**

**December 5, 2002**

**HPV: The Central Cause of  
Cervical Cancer**

**Mark Schiffman**

## Cervical Cancer is One of the Most Common Cancers in Women



Adapted from Parkin et al, Eur J Cancer 37:S4, 2001

## Historical Background

- Several lines of evidence led zur Hausen to suggest (~1980) that HPV causes cervical cancer
  - Epidemiology: venereal etiology
  - Pathology: On Pap smear, HPV (“warty”) changes similar to cervical cancer precursors
  - Virology: HPV DNA found in a few cervical cancers and derived cell lines

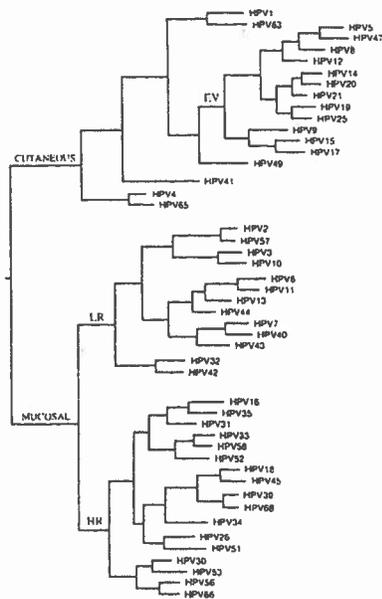
## Establishing Causality: Steps From 1980 to 2002

- Defining HPV infection (how to measure the many types)
- Satisfying causal criteria
- Developing a new schema of HPV and cervical cancer development
- Clarifying causal co-factors (If HPV is necessary but insufficient, what else is important?)

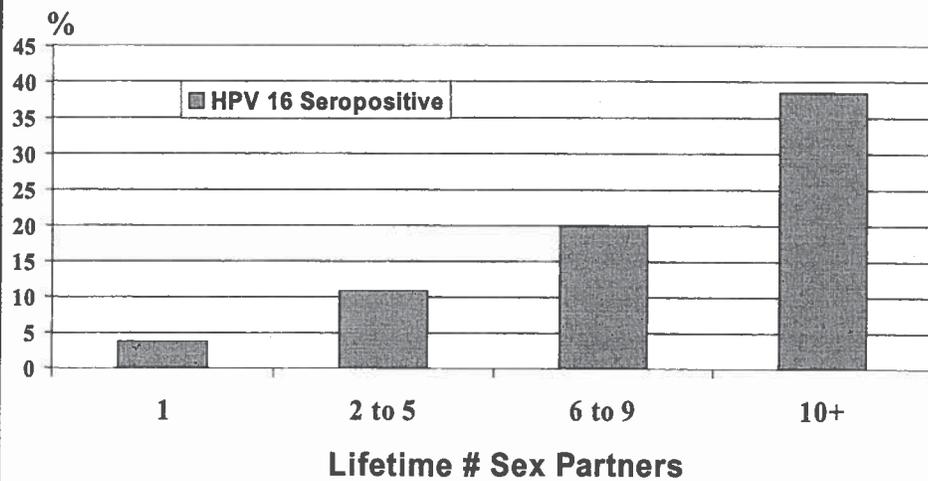
### 1. Defining HPV

- Over 100 types, > 40 genital
- ~15 types can cause cervical cancer; most common 16, 18, 31 and 45
- HPV 6 and 11 cause condyloma acuminatum (venereal warts)
- Many benign HPV types

# Phylogeny



## Sexual Transmission of HPV Established



## 2. Judging Causal Relations

### Major Epidemiologic Criteria

- Biologic plausibility
- Specificity of association
- Strength of association
- Consistency of associations on replication
- Time sequence of variables

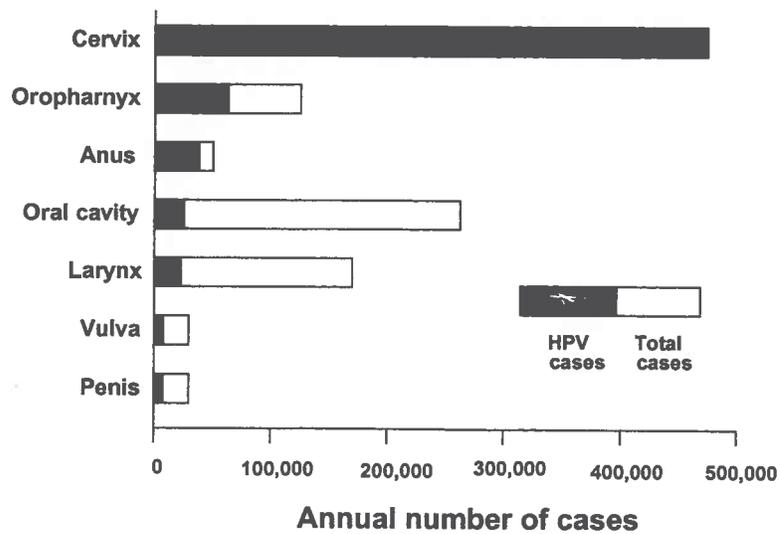
### Biologic Plausibility

- The regular presence of transcriptionally-active HPV DNA in tumor biopsy specimens
- The requirement of HPV expression for maintaining the malignant phenotype of cervical carcinoma cell lines
- The identification of transforming oncoproteins E6 and E7
- The interaction of these viral oncoproteins with growth-regulating host-cell proteins

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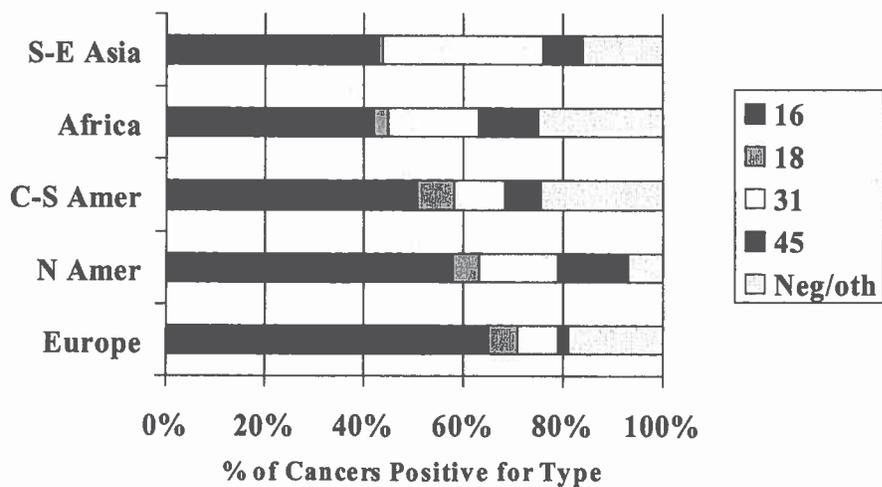
## Incidence and Distribution of Cancers Attributable to HPV



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### HPV 16, 18, 31, and 45 Cause Most Cervical CA Worldwide (Bosch et al., JNCI 1993)



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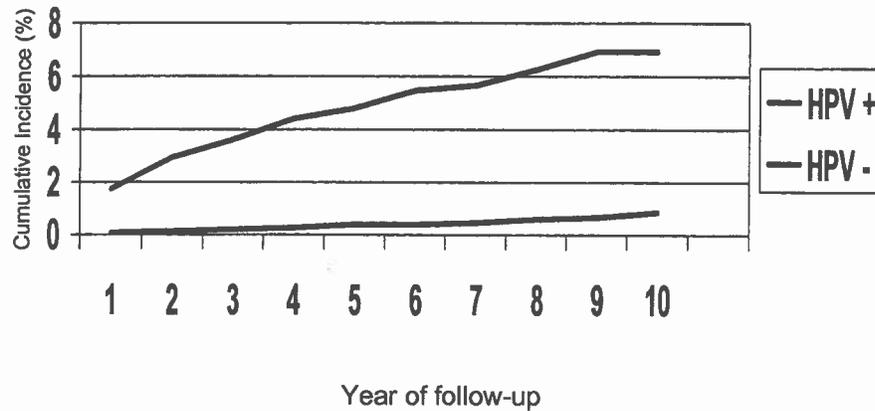
## Major Prospective Studies

- Portland Kaiser Permanente (20,000 women, 10 years, low-risk U.S. cohort)
- Guanacaste, Costa Rica (10,000 women, 7 years, high-risk and uncensored cohort)
- ASCUS-LSIL Triage Study (5,000 women, mildly abnormal Pap smears, 2 years, randomized clinical trial)

Large cohorts needed to look prospectively at sub-groups of interest (HPV types)

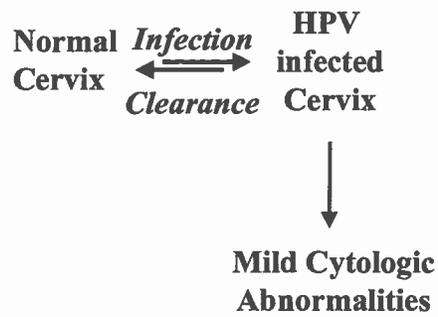
## HPV Infection at Baseline Predicts Subsequent Precancer and Cancer

Sherman et al. (JNCI, 2003)

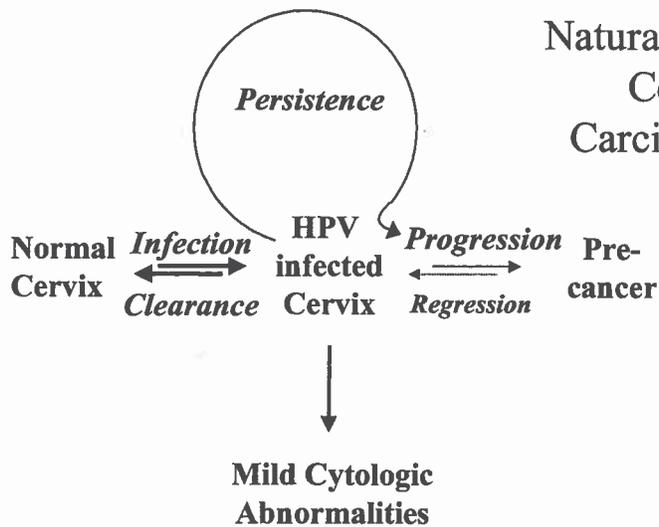


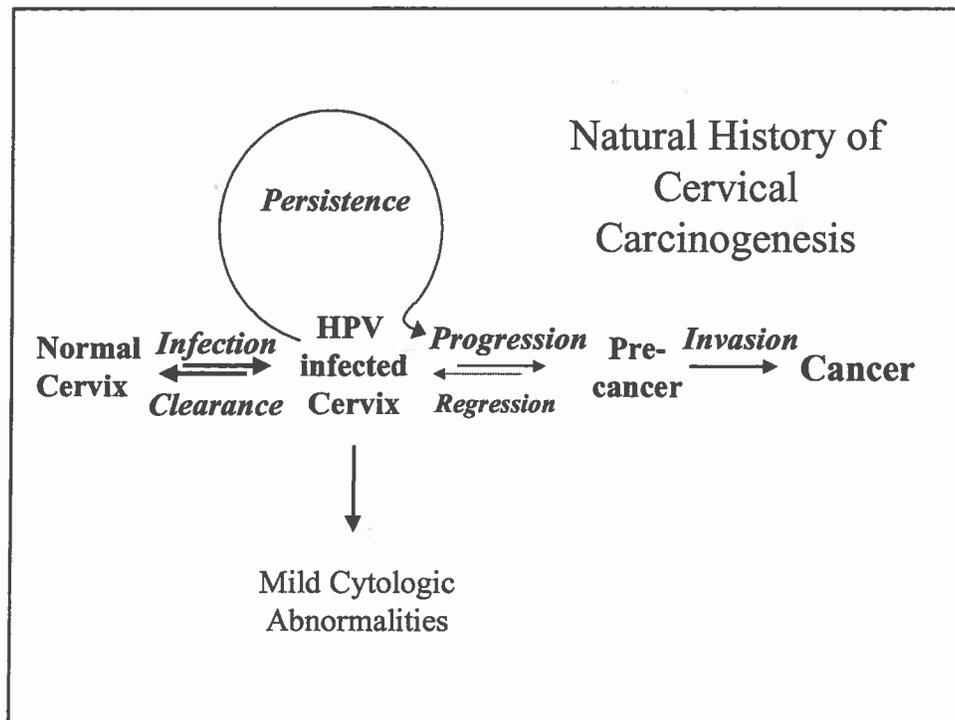
### 3. A Simple Natural History Schema of Cervical Carcinogenesis

## Natural History of Cervical Carcinogenesis



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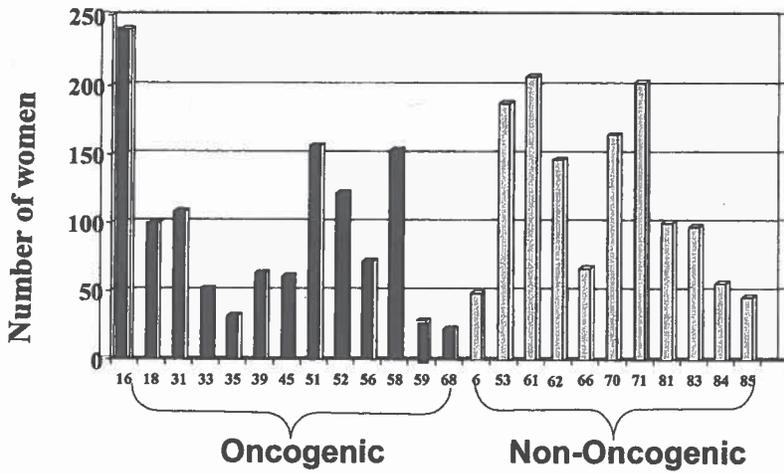




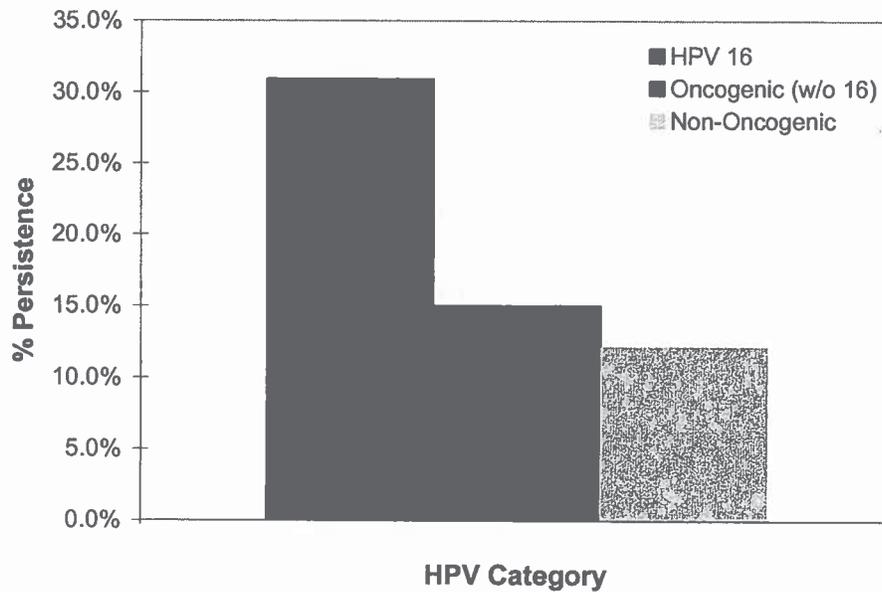
## Natural History of Specific HPV Types

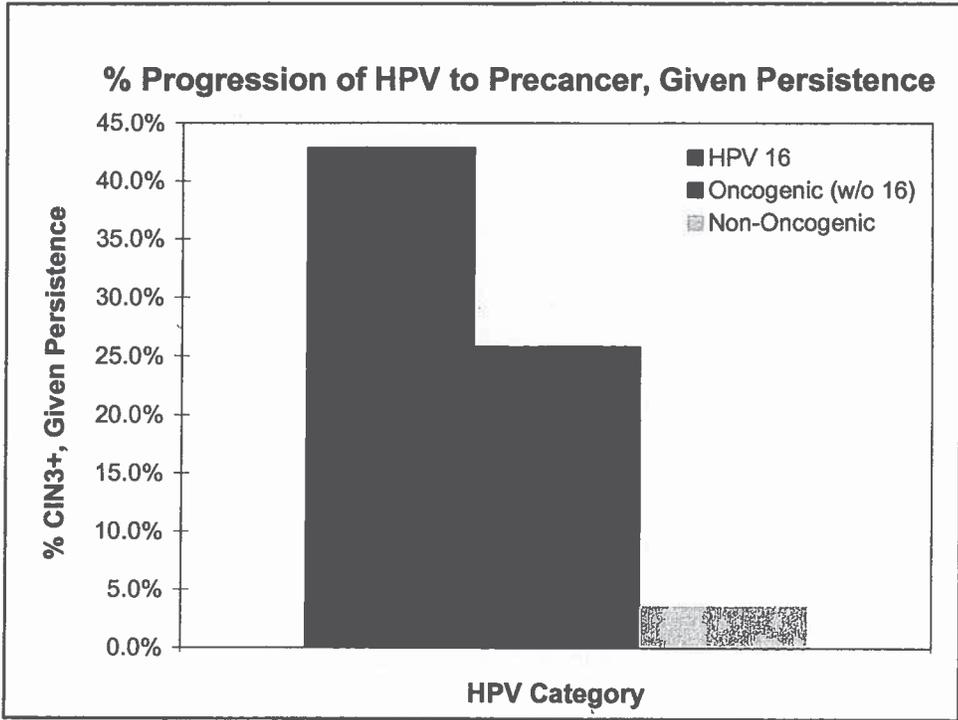
(HPV 16 is Uniquely Carcinogenic)

## Sub-Cohorts of Women with Specific HPV Types in Guanacaste Population

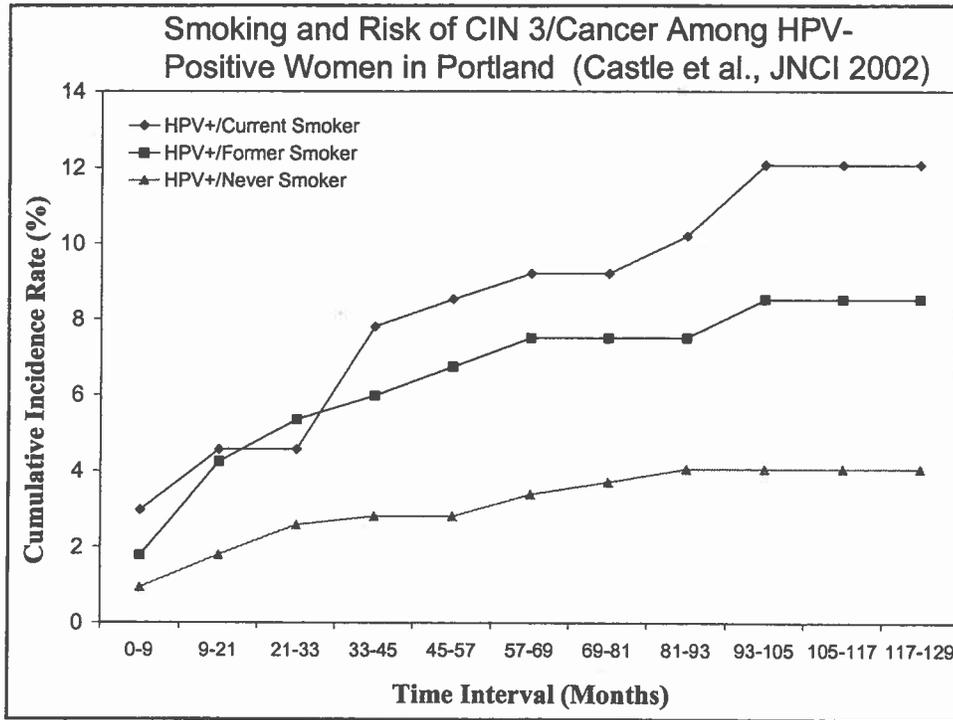


## % Persistence of HPV, for 5-7 Years, by Risk Group





## 4. Etiologic Co-Factors



**Next Steps Will be Even More Interdisciplinary**

