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## Cervical Cancer Screening and Prevention: Historical Perspective

- 1988 Wall Street Journal article
- 1988 & 1991 Bethesda System provided more uniform terminology; highlighted problem of equivocal diagnoses
- 1992 NCI & ACOG Workshop
  - Interim Guidelines for ASCUS and LSIL
  - Impetus for clinical trial to compare management strategies: ALTS

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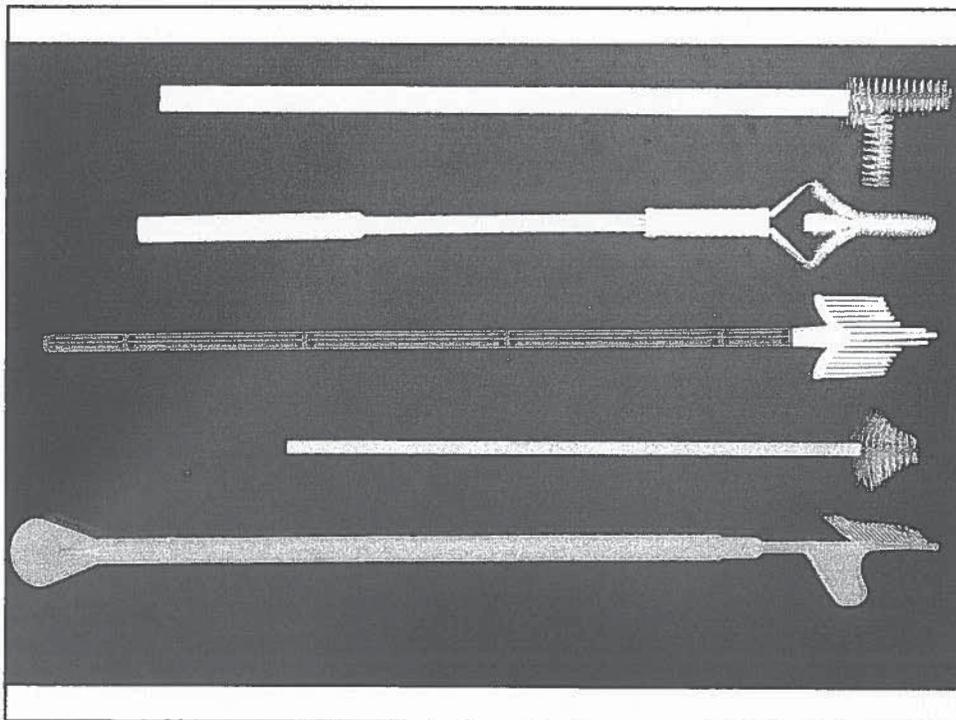
## Technological Developments

- New designs of collection instruments provided better sampling of transformation zone
- Liquid-based collection and preparation methods yielded more representative sampling
- HPV testing evolved through several generations of assays

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## Cervical Cancer Screening and Prevention: 2000-2002

- ASCUS LSIL Triage Study (ALTS) results
  - 2001 Bethesda System
  - ASCCP Management Guidelines
  - American Cancer Society screening guidelines
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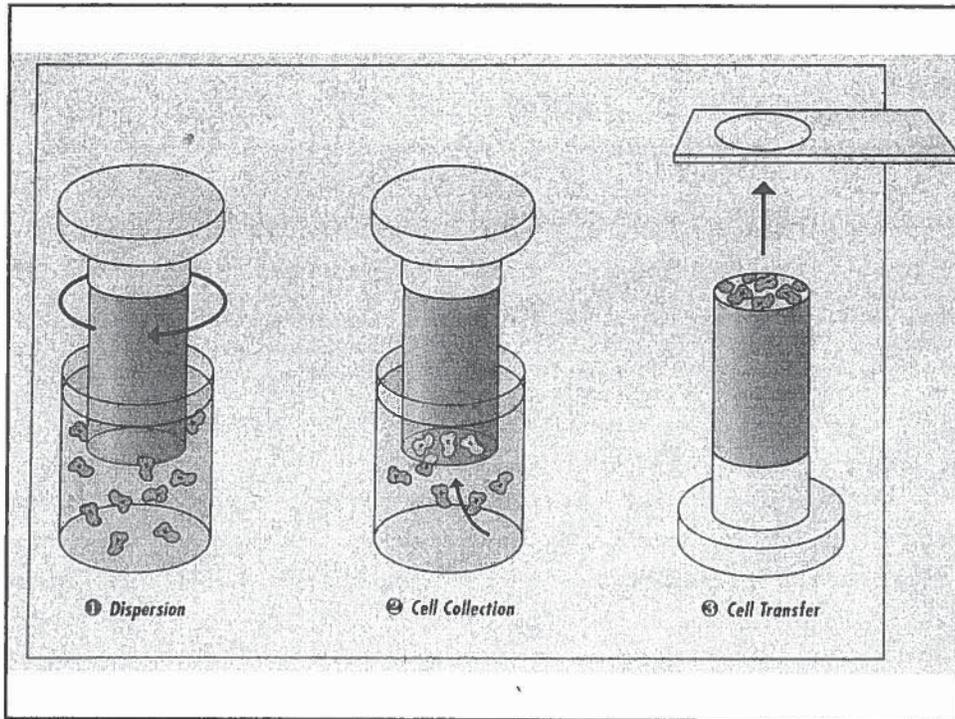




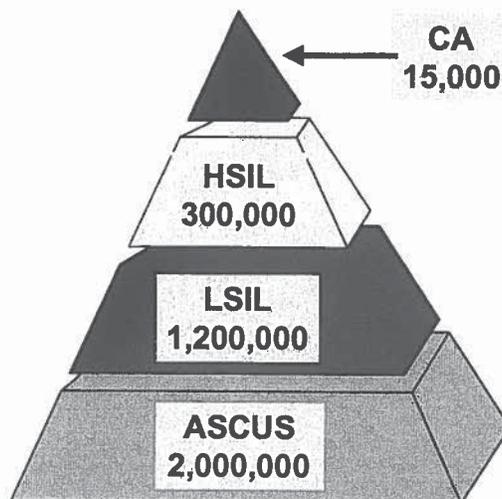
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## Liquid-Based Collection

- Harvests virtually all cells collected from cervix
- Thin layer cytologic specimen is easier to read than conventional smear
  - evenly distributed cellular sample
  - immediate fixation - no air drying artifacts
- Comparable or increased sensitivity in detection of abnormalities as compared to conventional smear
- Residual sample available for additional ancillary tests (HPV and others)
- Increased cost

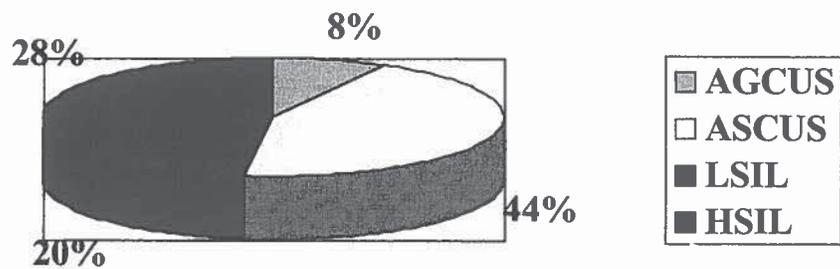


## Cervical Lesions: Pyramid of Diagnoses



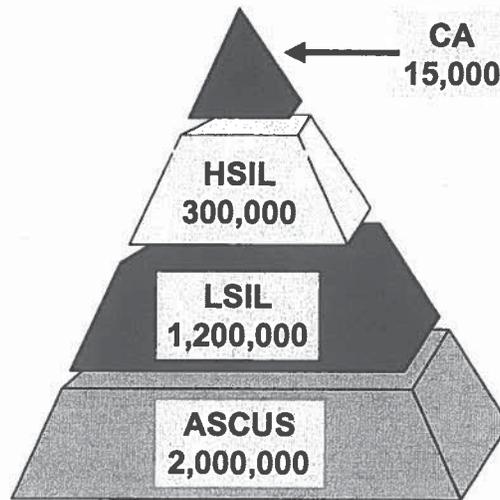


### Sources of Histologic CIN 2/3 in Women < 40

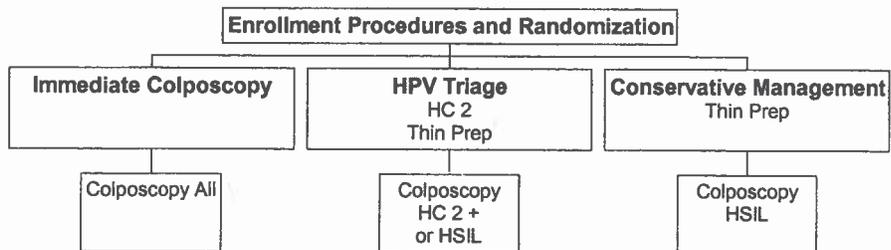


Kinney Obstet Gynecol 1998

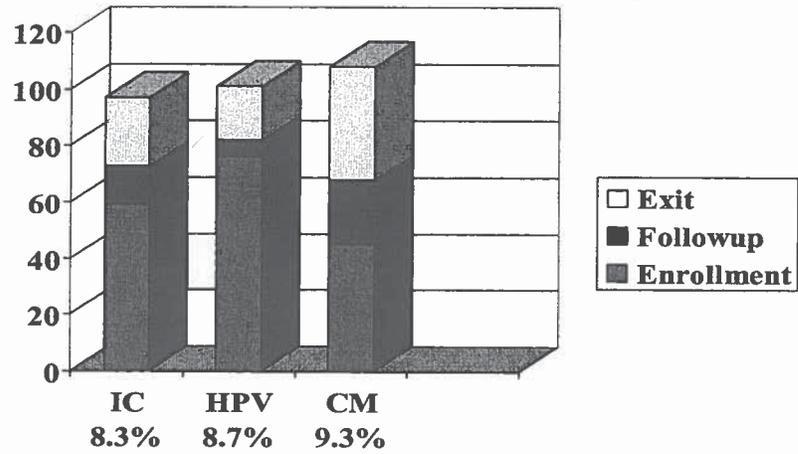
## Cervical Lesions: Pyramid of Diagnoses



## ALTS Enrollment Procedures



### ASCUS: Cumulative Detection CIN3+



### Conclusions

- CIN 3 equal in all arms; no evidence of regression
- Immediate colposcopy and biopsy, once considered the “gold-standard” for sensitivity, misses approximately 1/4 of prevalent CIN 3

## **ASCUS Management Conclusions**

- HPV DNA triage is at least as effective as immediate colposcopy in the timely detection of CIN 3; sensitivity 92% with 53% of women referred to colposcopy
- Repeat cytology surveillance is a safe option at a threshold of ASCUS, provided women are compliant with follow-up recommendations. However, the trade off of sensitivity with specificity is not as favorable as with HPV testing.

## **ASC-US Management: ASCCP Guidelines**

- Repeat cervical cytology, colposcopy, or HPV DNA testing are all acceptable methods for managing women with ASC-US
- If liquid-based collection or conventional smear with co-collection of a separate sample was done initially sampling, “reflex” HPV DNA testing is the preferred approach

## LSIL Management Conclusions

- Neither HPV testing nor repeat cytology provides useful triage to colposcopy in the ALTS population
- Both strategies had high sensitivity 95%-99% for CIN3, however more than 80% of women referred to colposcopy
- ASCCP Guidelines recommend colposcopy for all LSIL

## Histologic Outcomes: ALTS ThinPreps

Sherman AJCP 2001;116:386-394

Cytologic Category	HPV	CIN 3
ASC-US	63%	5%
ASC-H	86%	24%
HSIL	99%	38%

## ASC-H

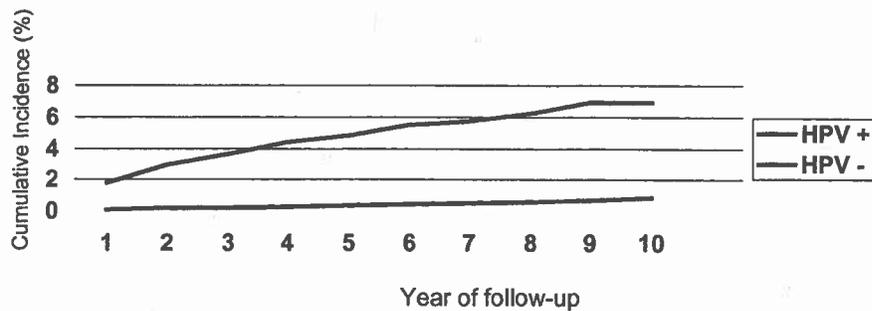
- The utility of ASC-H derives from its consistently high positive predictive value for an underlying lesion CIN 2/3
- ASC-H does not reflect a single biological entity; it is a mixture of CIN 2/3 and its mimics
- Incorporated into the 2001 Bethesda System terminology
- ASCCP guidelines recommend colposcopy for all ASC-H

## Cervical Cancer Screening and Prevention: 2000-2002

- ASCUS LSIL Triage Study (ALTS) results
  - Publications in JAMA; JNCI; gynecologic and pathology journals
- 2001 Bethesda System
  - JAMA 2002;287:2114-2119
- ASCCP Management Guidelines
  - JAMA 2002;287:2120-2129
- American Cancer Society Screening Guideline
  - CA Cancer J Clin 2002;52:342-362

## Negative Predictive Value of a Sensitive HPV DNA Screening Test

Women negative for oncogenic HPV types are at very low risk of developing CIN 3+ in the subsequent few years (Sherman, JNCI, in press)



## Cervical Cancer Screening and Prevention: Future Directions

- New screening paradigm with dual testing -- cytology and HPV -- in women aged 30 and older
  - Extend interval between screening events
  - Provide interim guidance on management of cytology Neg / HPV+ women
  - Identify research priorities to provide data for evidence-based recommendations
- New diagnostics: inexpensive; rapid; low tech
- Goal: improved performance of screening, not just added cost