New Cancer Screening Guidelines

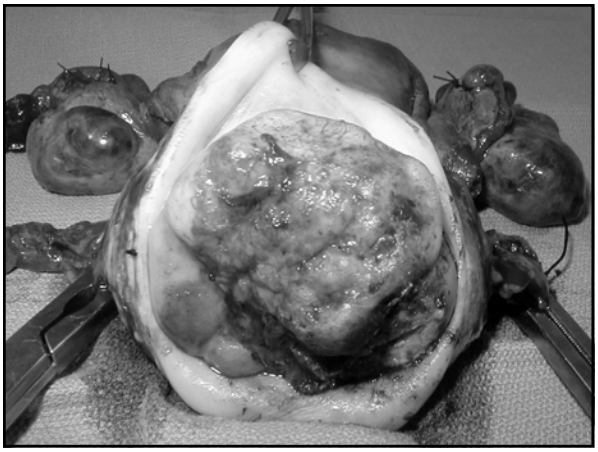
Fidel A. Valea, M.D.
Associate Professor
Division of Gynecologic Oncology
Duke University Medical Center

Disclosures

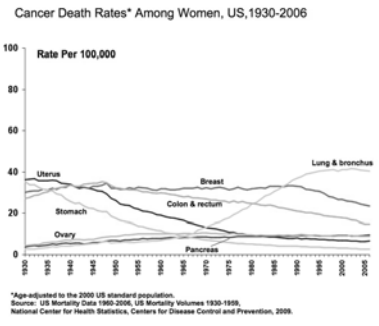
- Merck Speakers Bureau
- Genzyme Speakers Bureau
- Covidien Speakers Bureau

Learning Objectives

- To outline some of the data leading to the new guidelines for cervical cancer screening.
- To review the new screening guidelines for cervical cancer.
- To summarize the data surrounding the use of HPV testing and HPV genotyping

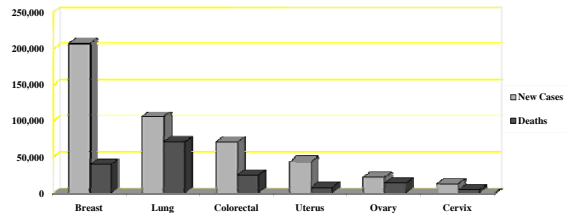


Age Adjusted Death Rates in the U.S.



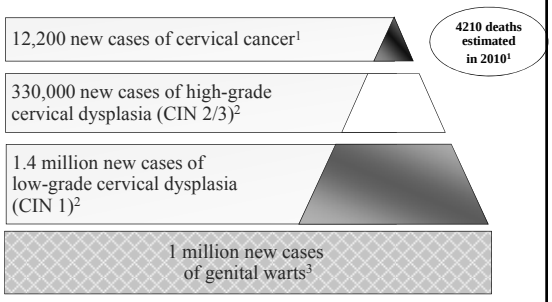
American Cancer Society

Estimates in Women



American Cancer Society. *Cancer Facts & Figures 2010.*

Estimated Annual Burden of HPV-Related Diagnoses in the US



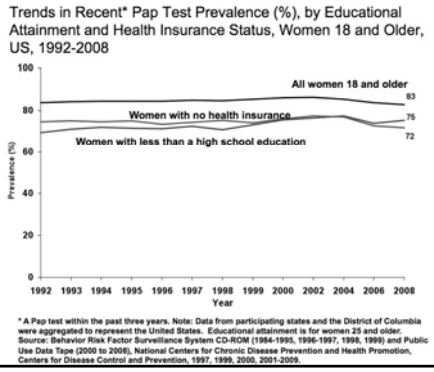
1. American Cancer Society. Cancer Facts & Figures 2010.
2. Schiffman M, Solomon D. Arch Pathol Lab Med. 2003;127(8):946-949.
3. Fleischer AB et al. Sex Transm Dis. 2001;28(11):643-647.

Current Problems With Screening

- Has been predominantly cytology-based
- Pap smear has poor sensitivity
- HPV testing is being over used
- What saves Pap testing is repetition
- Even with lifetime annual Pap tests, the estimated risk of getting cervical cancer is approximately 1/145*

**American Cancer Society. Cancer Facts & Figures 2010.*

Pap Test Prevalence



What are the Guidelines?

- ASCCP 2006… being updated
  - *Consensus guidelines for the management of women with abnormal cervical cancer screening tests*
- NCCN 2010… recently updated
  - *NCCN Clinical Practice Guidelines in Cervical Cancer Screening*
- ACOG 2009
  - *Practice Bulletin: Cervical Cytology Screening*

General Updates

- Don't start screening until age 21
- No need for HPV testing in adolescents
- ASCUS and LSIL should be managed similarly
- Relying mostly on liquid based technology
- CIN 3 should be treated, all the rest may be followed*
- Identified subgroups that can discontinue screening

**In select individuals…*

Background Info

- Cervix cancer is decreasing in the US with 12,200 new cases in 2010 but worldwide incidence is still about 500,000
- There are clearly ethnic and regional differences
  - Hispanics & Blacks > whites, south > north, etc.
- Incidence in 15 – 19 year old age group is still 14 per year (0.1 per 100,000)

Watson et al. Cancer 2008; 113(10 suppl):2855-64.

Age-adjusted incidence rates in US*

Age	Annual Average	Incidence (95%CI)	Incidence Rate
All	10,846	8.9 (8.8-9.0)	100
0-14	0	0	0
15–19	14	0.2 (0.1-0.2)	0.1
20-24	123	1.6 (1.5-1.7)	1.1
25-29	543	6.9 (6.7-7.2)	5.0
30-34	1045	12.3 (12.0-12.6)	9.6
35-39	1350	14.6 (14.3-14.9)	12.5
40-44	1534	16.3 (15.9-16.6)	14.1
45-49	1323	15.4 (15.0-15.7)	12.2
50-59	1958	14.5 (14.2-14.7)	18.0
60-69	1352	14.8 (14.5-15.1)	12.5
70-79	1008	12.9 (12.6-13.3)	9.3
≥80	595	11.2 (10.9-11.6)	5.5

**Watson et al. Cancer 2008; 113(10 suppl):2855-64.*

Why delay Screening until 21?

- Adolescents: Highest rate of HR HPV and Lowest rate of cervical cancer
- SEER data for adolescents is the same as 1973-77 *(before the recommendation to start by 18 years of age, ie screening earlier did not have impact)*
- No data shows screening women less than 21 impacts future rates of CIN 2,3.
- Screening in adolescents is difficult, at best, and may lead to more harm… must understand the natural history

Natural History in Adolescents

- More than 90% HPV, ASC-US, LSIL will clear spontaneously within 3 years*
- Epidemiologic evidence supports observation
- Note: 50% of pts that clear HPV will have a reinfection within 3 years! (*Moscicki et al 2009*)
- 70% of adolescents with ASC-US are HPV +
- 65% regression rate of CIN2 in adolescents!

**Moscicki AB et al Obstet Gynecol 1993;82:578-85,*
Ho GY et al NEJM 1998;338:423-8

Regression of CIN 2 in Adolescents*

Univ of Oklahoma Div Gyn Onc

- Retrospective review of Adolescents with dysplasia 2001-2005
- 177 had at least CIN 2
- 55 decided to be observed (only 23 available for review):
  - 65% regression rate at 18 months
  - 17% stable disease
  - 13% progression to CIN 3 but NO CANCERS

**Moore K et al. Am J Obstet Gynecol 2007; 197(2):141.e1-6*

Treatment Risks

- Meta Analysis 1960 – 2004 (27 studies)
- LEEP 3171 Laser 1488 CKC 28,378 cases
- Controls were matched in each study (all different!)
- Bottom line: All excisional procedures are associated with similar pregnancy related morbidity.
- All had trends towards neonatal morbidity but could not reach significance

Kyrgiou M et al. Lancet 2006;367:489–98

Excisional Procedure Meta Analysis Results*:

Outcome	CKC	LEEP	Laser
Preterm Birth	2.59 (1.80-3.72)	1.70 (1.24-2.35)	1.71 (0.93-3.14)*
Low Birth Weight	2.53 (1.19-5.36)	1.82 (1.09-3.06)	
PROM		2.69 (1.62-4.46)	
Cesarean Delivery	3.17 (1.07-9.40)		

**marginally non-significant*

**Kyrgiou M et al. Lancet 2006;367:489–98*

Registry Study – Finland 2009*

- 1996 – 2003 624 who delivered after a LEEP
- Preterm delivery risk after:
  - LEEP: 2.61 (2.02-3.20)
  - Repeat LEEPs 5.15 (2.45-7.84)
- Background preterm delivery rate: 4.61%
- 258 women had deliveries before and after LEEP
  - Preterm delivery rate: 6.5% vs 12.0%
    RR 1.94 (1.10-3.40)

**Jakobsson M et al. Obstet Gynecol 2009;114:504-10*

Pap Test: conventional vs liquid based technology*

- Data is very disparate
- NETHCON (NEtherlands THinPrep vs CONventional study) 89,784 women ages 30-60
- 18 month f/u
- main outcome: histologically confirmed CIN or greater
- Bottom line: detection rates and PPV were the same

**Siebers AG et al. JAMA, 2009;302(16):1757-64*

Screening Technique / Interval

- 90% Ob/Gyn use liquid based technology
- 10% use conventional pap smear
- Either one is acceptable starting at age 21
- Screening interval Q 2 YRS regardless of method
- Exceptions: (at least annual screening)
  - HIV patients
  - Immunocompromised patients (transplant pts.)
  - Hx DES or previous treatment for high grade dysplasia

ACOG Practice Bulletin number 109, December 2009

When to stop screening?

- Low risk women age 65 – 70 with 3 consecutive negative paps and no hx of abnl paps in last 10 yr
- After benign hysterectomy with no hx of CIN
- Continue annual screening for 20yrs after CIN
- *If screening is discontinued, assess risk factors during annual exam to determine if screening should be reinitiated*

ACOG Practice Bulletin number 109, December 2009

Why Screen With HPV Testing?

- 40%-50% of women with cervical cancer have had screening
- 10% had no screening
- Essentially 100% of cervical cancer is due to HPV
- Persistent high-risk HPV infection is necessary for development of cervical cancer
- Absence of high-risk HPV infection means risk of cervical cancer is extremely low

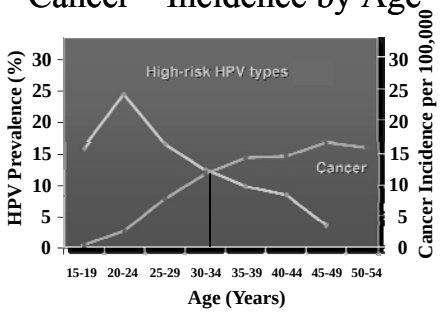
Wright TC Jr et al. N Engl J Med. 2003;348(6):489-490.

Role of HPV testing

- Absolutely no role for use in pts under 21 y.o.
- Limited role in under 30 age group:
  - Reflex testing after ASC-US
  - Follow up after treatment/observation CIN
- As an adjunct to cytology for primary screening of patients older than 30
- Reflex testing after ASC-US pap (>30 y.o.)
- Triage LSIL in postmenopausal patients

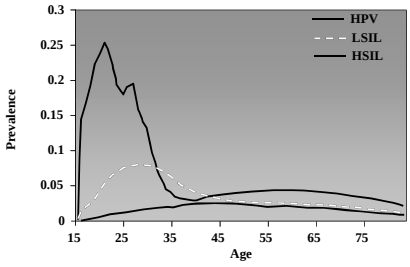
ACOG Practice Bulletin number 109, December 2009

HPV Prevalence and Cervical Cancer – Incidence by Age



Sellors JW et al. CMAJ. 2000;163(5):503-508.
Ries LA et al. Cancer. 2000;88(10):2398-2424.

Projected Age-Specific Prevalence of HPV
(Based on a Mathematical Model)



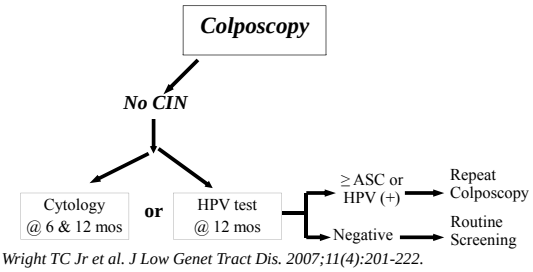
Myers ER et al. Am J Epidemiol. 2000;151(12):1158-1171.

Is There Any Other Role for HPV Testing?

- Postcolposcopy, because it is more sensitive than the conventional Pap smear
- Both ASCCP and NCCN guidelines support its use as a follow-up test
- Persistent high-risk HPV should have colposcopic evaluation on a yearly basis
- Only problem: no real internal control for adequacy of sample

Postcolposcopy

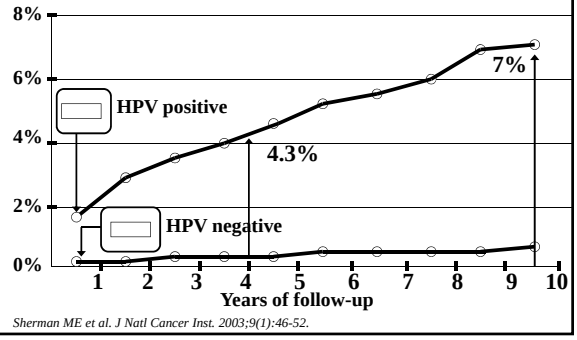
Management of women referred for an HPV (+) ASC-US or an LSIL Pap and not found to have CIN at initial colposcopy



Wright TC Jr et al. J Low Genet Tract Dis. 2007;11(4):201-222.

Kaiser Portland NCI Study 1990-1999

Risk of Developing CIN 3



Sherman ME et al. J Natl Cancer Inst. 2003;9(1):46-52.

Role of HPV Genotyping

- Test that detects only HPV 16 and 18
- Portland study:
  - CIN 3 was identified in 21% of HPV 16 pts and 18% of HPV 18 pts
  - Risk of CIN 3 in other high risk HPV… 1.5%
- Utility: to help triage pts with +HPV but –Pap, that's it!
  - 16/18 genotype posititve ➔ colposcopy
  - 16/18 genotype negative ➔ f/u in 1 yr

HPV Vaccination

- Two FDA approved types:
  - Bivalent against HPV 16/18
  - Quadrivalent against HPV 16/18/6/11
- Both are efficacious in preventing HPV 16/18 associated high grade dysplasia
- Bivalent HPV vaccine: 10 – 25 years of age
- Quadvalent HPV vaccine: 9 – 26 years of age
- Should NOT affect screening practices for now

Management Controversies

- Don't be limited simply by biologic age… a 23 y.o. nullip is still considered young
- Although CIN 3 should be treated in everyone, there is some room for observation in the "young" patient
- Be careful with glandular abnormalities, frequently encourage consultation with a specialist

Management Controversies *Pregnancy*

- In pregnancy, ECC should not be performed but brush cytology is safe
- The role of colposcopy in pregnancy is to evaluate a high grade lesion or cancer.
- The role of biopsy in pregnancy is to rule in/out invasive cancer… it should not be routine
- Most pap test abnormalities can be dealt with after pregnancy.

New Guideline Summary

- Start no sooner than age 21
- Screening interval now 2 years, may go 3 after age 30 if dual negative (cytology and HPV)
- Use of HPV DNA testing mostly limited to over 30 y.o. population
- HPV genotyping limited to cytology – and HPV + patient to help triage
- Very conservative management for under 21 and expanding to the young woman???

New Guideline Summary con't

- Colposcopy and cytology are used in the management of the patient with CIN 2,3 that is being observed not just cytology
- HPV DNA testing is helpful in the triage of patients with an AGC pap smear but cannot be used alone

Breast Cancer Screening

SBE self breast exam

- ACOG: reaffirmed in 2006
  - Q1-2 yrs bet 40 – 49, annual after 50, SBE is OK
- American Cancer Society
  - Annual mammogram starting at 40, SBE an option
  - MRI in addition to mammo for certain high risk pts (<2%)
- NCCN 2010:
  - Low risk: annual mammogram starting at 40, SBE "awareness"
  - High risk: start screening at 35* consider MRI for>20% lifetime risk

**may start earlier, depending on risk factor*

Breast Cancer Screening

*USPSTF 2009 Recommendations**

- biennial screening mammography for women aged 50 to 74 years
- *"The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms."*
- the current evidence is insufficient to assess the additional benefits and harms of
  - Screening over age 75
  - Clinical breast exam
  - Digital mammography or MRI instead of film mammography for screening
- Recommends against teaching SBE

**US Preventive Services Task Force. Ann Intern Med. 2009;151:716-726, W-236.*

Reaction to USPSTF

- Outcry over lack of screening in under 50 age grp
- Suspicion that it was driven by $$$
  - Risk reduction in breast cancer mortality is the same, 0.85 and 0.86 in 39-49 and 50-59 age groups
  - Due to low incidence in younger group, number needed to screen to prevent 1 cancer was 1904 vs 1339
- Senate passed 2 amendments to health care reform
  - Ignore the USPSTF recommendations
  - guarantee no-cost screening for women in their 40's
- Interestingly, strongly supported by 1^0 care groups

Evidence on Mammography

A total of 7 RCTs

- Mortality decreased 15 – 20%
  - Absolute benefit starting at 40: 4 per 10,000
  - Absolute benefit starting at 50: 5 per 1000
- Risks
  - 33% of cancers represent overdiagnosis or "insignificant" cancer
  - Additional tests in 50% of pts screened annually for 10 yrs
    - 25% of these will have a biopsy
  - 6% – 46% of women with invasive cancer have negative mammograms especially if young, dense breasts, mucinous or lobular cancers
  - 9.9 – 32 radiation induced cancers in 10,000 women over 10 yrs

Evidence on Clinical Breast Exam CBE

1 RCT with inference

- Data that CBE reduces mortality
  - Canadian study CBE ± mammo showed no difference
  - 2 other ongoing RCTs still collecting data
- Risks
  - Additional testing (false positives)
  - False reassurance (false negatives): 17-43% of women with cancer had a normal CBE
- Bottom line: data is too conflicting, not enough supporting its utility

Evidence on Self Breast Exam SBE

1 RCT, case control and cohort trials

- No difference in mortality after 10 yrs in Shanghai trial of SBE*
- Risks:
  - Biopsy rate in Shanghai trial 1.8 vs 1.0%
    - RR for benign biopsy: 1.57 (95% CI 1.48 – 1.68)
- Bottom Line: not enough evidence to support its use

**Thomas DB et al. J Natl Cancer Inst 2002; 94(19):1445-57*

Digital vs Conventional Mammogram*

- 33 centers (U.S. & Canada) 49,528 pts
  - both conventional and digital mammograms
- 42,760 (86.3%) had complete info
- Confirmation of cancer status:
  - Breast biopsy within 15 months of study
  - Mammogram done at least 10 months after entry
- ROC (receiver-operating-characteristic) analysis

** Pisano et al. NEJM, 2005; 353(17):1773-83*

Pisano et al Results

- For the entire group diagnostic accuracy of Digital and conventional mammography were similar
- Area under ROC curve: 0.03; 95% CI -0.02 to 0.08; p=0.18
- Digital mammography superior in certain groups:
  - Women < 50 y.o. (ROC, 0.15; 95% CI, 0.05 - 0.25; p=0.002)
  - Dense breasts (ROC, 0.11; 95% CI, 0.04 - 0.18; p=0.003)
  - Pre/Perimenopausal (ROC,0.15; 95% CI, 0.05 - 0.24; p=0.002
- *"The overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women."*

Evidence on MRI

*1 RCT

- Netherlands trial: 1952 women with genetic risk
- 45 "evaluable" patients with cancer
  - 32 seen on MRI (22 of these were missed by mammo)
  - Mammo detected 18 (8 of these were missed by MRI)
  - CBE detected one cancer that was missed by both
- Positive predictive value:
  - CBE 9.6%
  - Mammography 8.0%
  - MRI 7.1%
- Bottom line MRI v Mammo: 2x more tests and 3xs more biopsies

**Kriege M et al. NEJM 2004;351:427-37*

Final Comments USPSTF

- Individualize your recommendations based on risk and patient needs between 40 – 49
- In high risk patients: NCCN guidelines may be more helpful
- Clearly must communicate with your patient