CERVICAL CANCER SCREENING

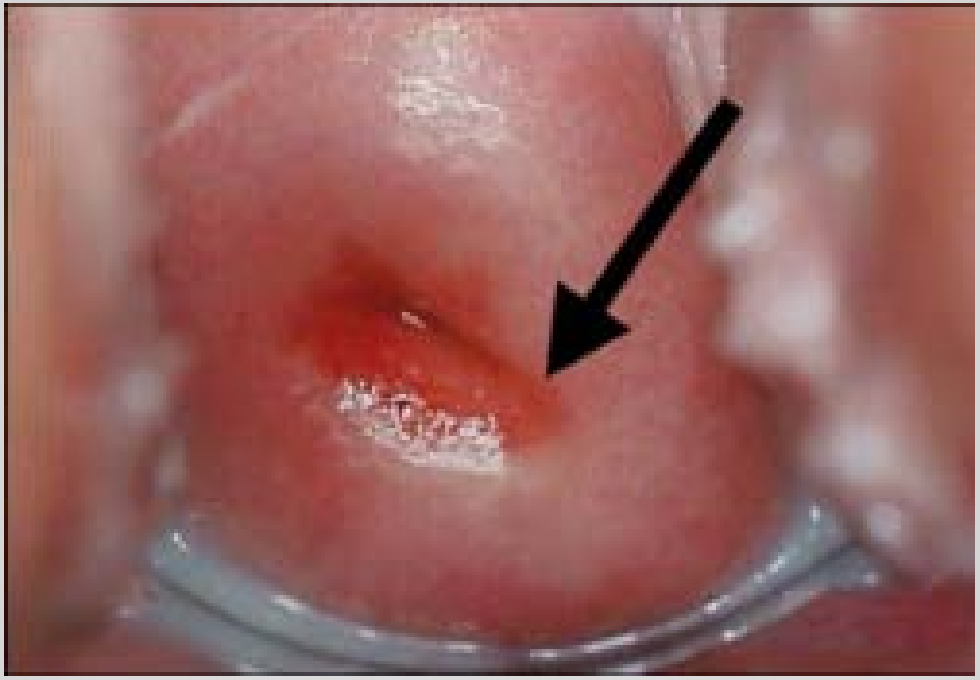
MARCH 15, 2012

- The USPSTF and the ACS (in conjunction with ASCCP and ASCP) released updated cervical cancer screening recommendations
- Not a coincidence
- Independently developed
- Remarkably similar conclusions/guidelines

BACKGROUND

CERVICAL CANCER

- Histologic types
  - Squamous cell
    - 70% of all cases (primary target of cytological screening)
    - Arises at squamocolumnar junction (transformation zone)
    - Primary target of cytology screening
  - Adenocarcinoma
    - ~18%
  - Mixed adenosquamous and other



A reminder: squamocolumnar junction

CERVICAL CANCER MORTALITY (PER 100,000)

	White	Non-white	Combined
1950 (unadjusted)	10.2	18.0	
2007 (adjusted)	2.2	4.3	2.4

This dramatic decline has been attributed to the implementation and dissemination of screening.

CERVICAL CANCER INCIDENCE & MORTALITY

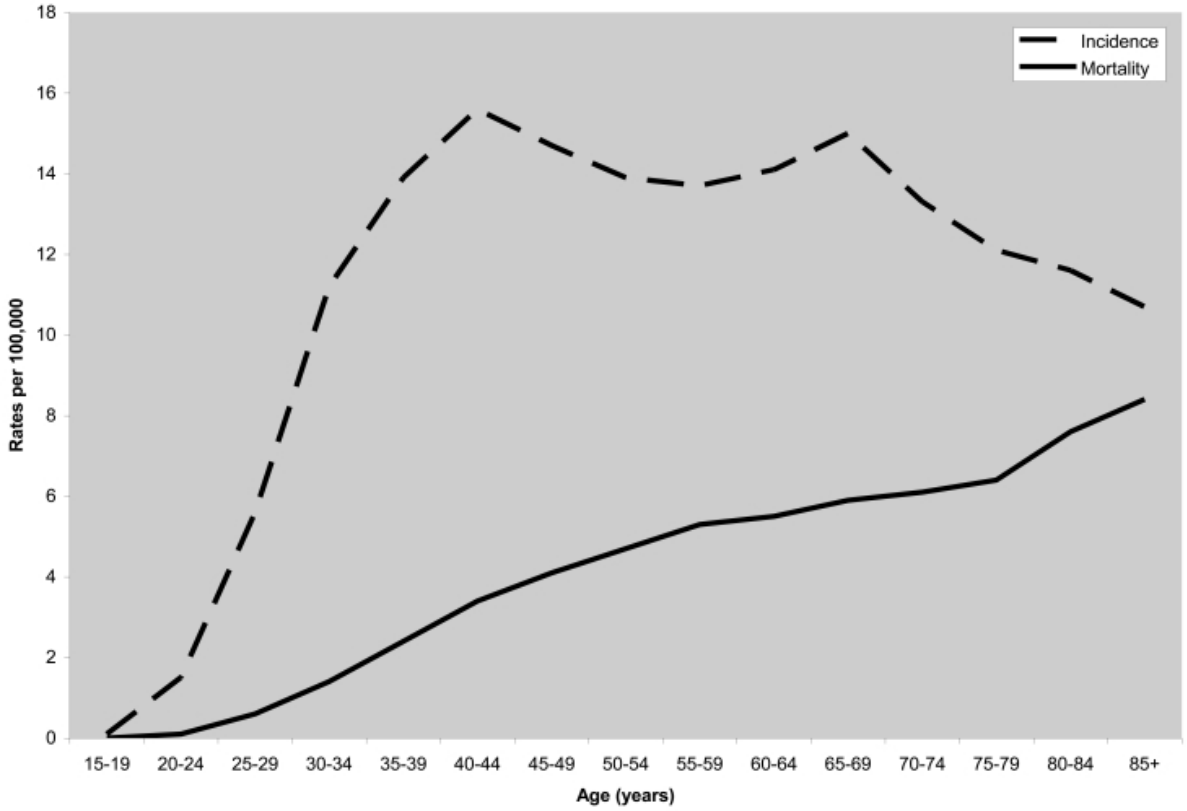


Figure 2 U.S. Age-Adjusted Incidence and Death Rates of Invasive Cervical Cancer By Age (SEER 2000–2008)[17]

BURDEN OF ILLNESS

- SEER data:
  - "It is estimated that 12,710 women will be diagnosed with and 4,290 women will die of **cancer of the cervix uteri** in 2011."
- For comparison, for every woman who will die of cervical cancer
  - 5 will die of colon cancer
  - 8 will die of breast cancer
  - 15 will die of lung cancer

INADEQUATE SCREENING

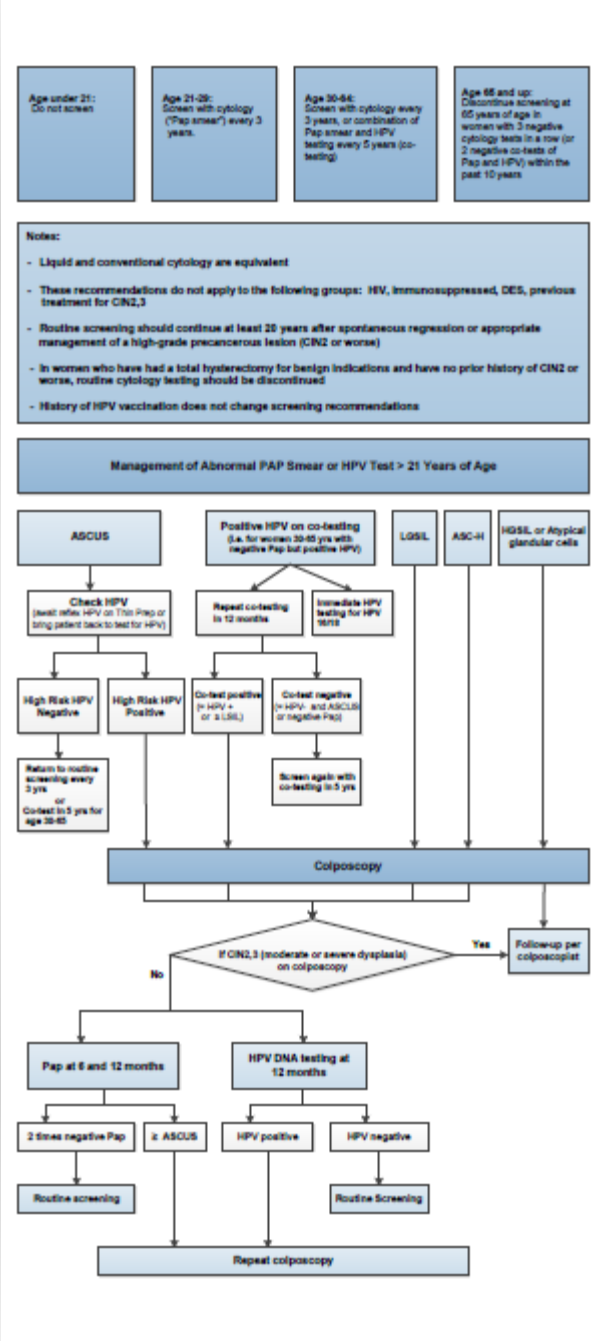
- About half of all cervical cancer deaths are in women who have not been screened or who have had incomplete follow-up to screening and treatment
- If we could assure adequate screening of the entire population, the residual preventable burden would be small
- *What goals should we have for a change in prevention strategy, whether immunization or a change in screening approach?*

POSSIBLE GOALS FOR NEW CERVICAL CANCER PREVENTION STRATEGIES (INCLUDING IMMUNIZATION)

- Further reduction in mortality
  - *Caveat: the* **elimination** *of cervical cancer and/or cervical cancer mortality is not a realistic goal of screening*
- Reduction in the burden and/or harms of screening and treatment of screen-detected disease

Draft University of Missouri Department of Family Medicine updated clinical algorithm for cervical cancer screening

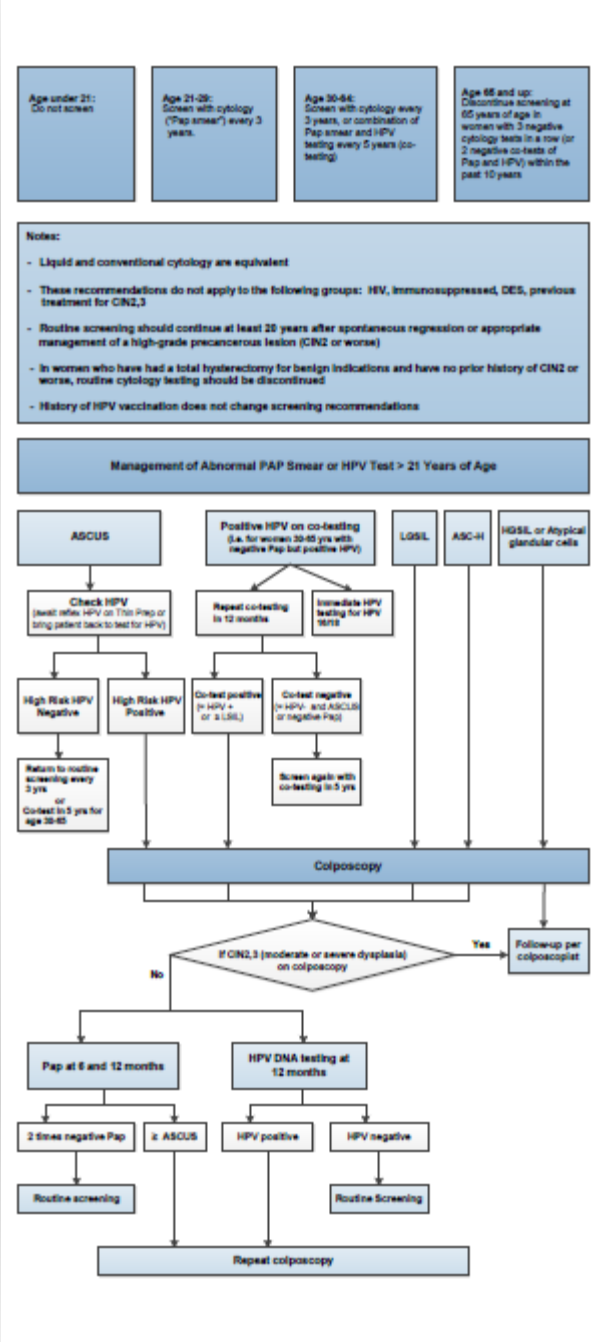
http://fcm-algo.umh.edu/Algorithms/CCS.htm



Screening

Evaluation of abnormal screen

Follow up post colposcopy



SCREENING

Age under 21:
Do not screen

Age 21-29:
Screen with cytology ("Pap smear") every 3 years.

Age 30-64:
Screen with cytology every 3 years, or combination of Pap smear and HPV testing every 5 years (co-testing)

Age 65 and up:
Discontinue screening at 65 years of age in women with 3 negative cytology tests in a row (or 2 negative co-tests of Pap and HPV) within the past 10 years

Notes:

- **Liquid and conventional cytology are equivalent**
- **These recommendations do not apply to the following groups: HIV, immunosuppressed, DES, previous treatment for CIN2,3**
- **Routine screening should continue at least 20 years after spontaneous regression or appropriate management of a high-grade precancerous lesion (CIN2 or worse)**
- **In women who have had a total hysterectomy for benign indications and have no prior history of CIN2 or worse, routine cytology testing should be discontinued**
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SCREENING

HPV INFECTION

- “It is well recognized that infection with oncogenic HPV types is a necessary, although not sufficient, cause of virtually all cervical cancer.[25]“
- Results from a large international collection of cervical tumor specimens revealed the presence of HPV DNA in 99.7 percent of cases.[3]

HPV INFECTION: NATURAL HISTORY

- From HPV infection to cervical cancer
  - HPV transmission,
  - Acute HPV infection,
  - Persistent HPV infection leading to precancerous changes, and
  - ICC.[45]

HPV TRANSMISSION

- Primarily as a result of skin-to-skin or mucosa-to-mucosa contact

HPV INFECTION AND PERSISTENCE

- A high proportion of sexually active women become infected with HPV, but only a small proportion of HPV infections become persistent
- 91 percent of prevalent HPV infections clear within 24 months (including infections with high risk subtypes)

PREVALENCE OF HPV INFECTION

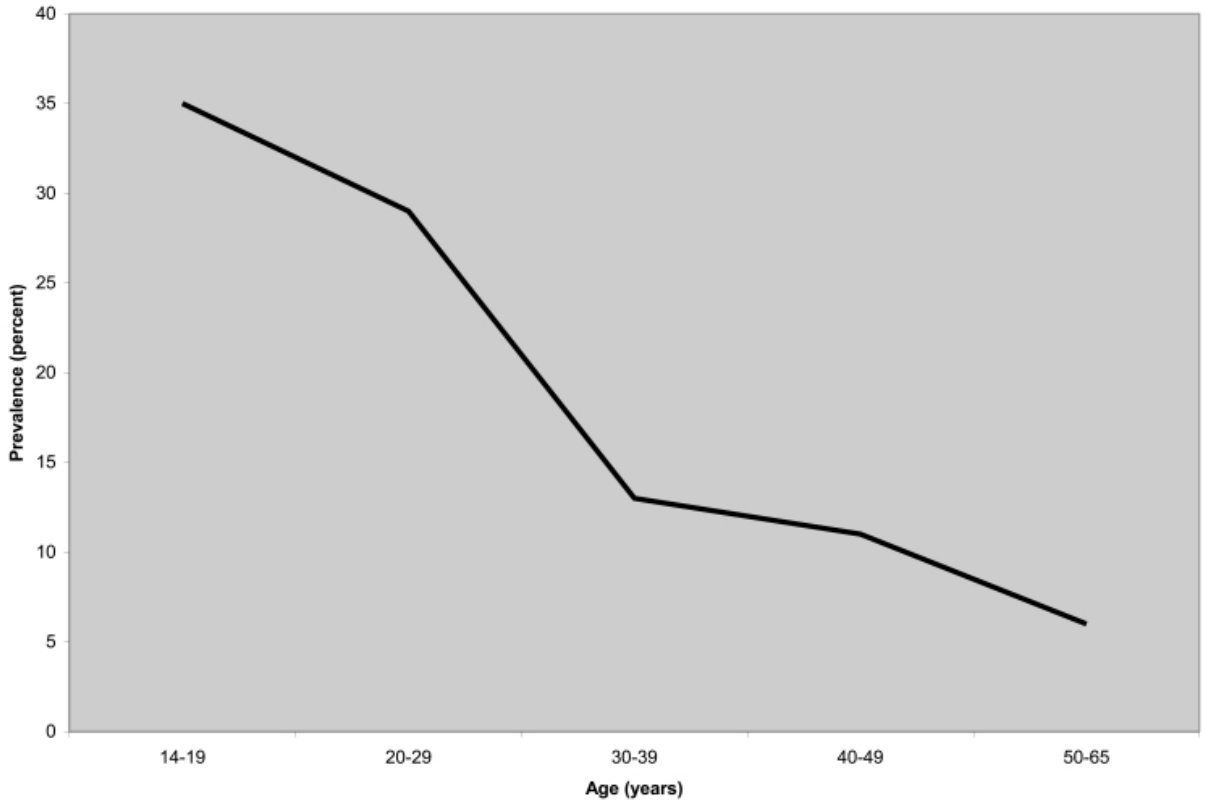


Figure 4 Prevalence of High-Risk Human Papillomavirus By Age[34]

WHY NOT SCREEN BEFORE AGE 21?

- Cervical cancer is rare in the younger age group

Table 2 U.S. Age-Specific Crude In 208

Age-Group	White NonHispanic	Black
00	0	0
01–04	0	0
05–09	0	0
10–14	0	0.1
15–19	0.1	0.2
20–24	1.5	1.9
25–29		
30–34		
35–39		
40–44		
45–49		
50–54		
55–59		
60–64		
65–69		
70–74		
75–79		
80–84		
85+	8.3	28.9	14.5	15.1	18.0

Per 100,000 women

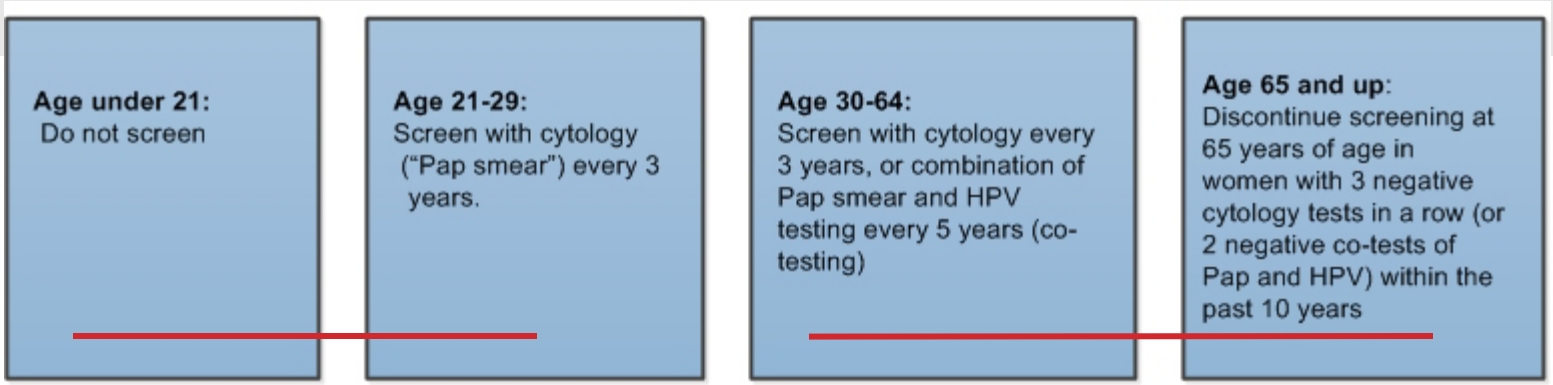
WHY NOT SCREEN BEFORE AGE 21?

- HPV infection is common and results in transient abnormalities of the cervix
- Detection and Rx of those abnormalities leads to harm

WHAT ABOUT SEXUAL HISTORY?

- Young women with multiple sexual partners are the most susceptible to the harms of screening
- The possibility of benefit is vanishingly close to zero
- *Just say no to screening for cervical cancer before age 21.*

SCREENING



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SCREENING INTERVAL FOR CYTOLOGY IN WOMEN AGE 21-65

- RCTs of screening programs at different intervals never exist
  - e.g. no one has done an RCT comparing colonoscopy for colon cancer screening every 5 years to every 10 years or 20 tears (decided to leave in the typo)
- Task Force has used modeling

WHAT OUTCOME, PARTICULARLY FOR HARMS?

- False positives
- Colposcopies
- CIN 2-3
- Cancer cases, cancer deaths

HARMS:COLPOSCOPIES

- Pain, bleeding
- Sentinel measure for downstream harms
  - Similar to using number of colonoscopies as sentinel measure of harm in modeling of colon cancer screening

HARMS: OVER-DIAGNOSIS

- CIN2 can/does regress – over-diagnosis and over-treatment are real risks
- CIN3 can also regress
- Standard of care currently to Rx all CIN2+

TREATMENT OF CIN2+

- Common treatments include LEEP or cervical conization
  - Short term harms of pain (67%), bleeding (87%), discharge (63%)
- Increased risk of adverse pregnancy outcomes
  - Perinatal mortality, preterm delivery, low birth weight
  - Evidence on specific procedures is incomplete and retrospective

MODEL: ENORMOUSLY COMPLICATED – EVEN IF YOU LIKE MATH

Table 8. Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Screening Beginning at Age 15 Years and Increased in 1-Year Increments to Age 25 Years, Among Women Followed for a Lifetime*

Strategy		Age 15	Age 16	Age 17	Age 18	Age 19	Age 20	Age 21	Age 22	Age 23	Age 24	Age 25
Cytology with repeat cytology for ASC-US												
q5	False Positives	220.74	223.01	220.20	217.50	214.84	211.69	213.97	211.17	208.49	205.85	201.86
q3	False Positives	367.97	362.65	352.67	358.93	353.61	343.65	349.92	344.62	333.82	328.80	323.33
q2	False Positives	542.21	529.73	533.19	520.72	524.19	511.74	515.26	501.94	494.23	480.77	472.93
q1	False Positives	1002.73	994.17	985.63	977.09	968.58	960.13	951.45	931.62	911.68	891.64	871.61
q5	Colposcopies	481.05	492.49	487.71	483.13	478.74	471.99	483.36	478.44	473.65	469.01	461.00
q3	Colposcopies	776.54	766.76	746.04	767.48	757.65	736.59	758.16	748.16	725.97	717.04	706.79
q2	Colposcopies	1,110.92	1,085.93	1,101.89	1,076.87	1,092.75	1,067.65	1,083.52	1,057.27	1,042.80	1,016.43	1,001.77
q1	Colposcopies	1,982.10	1,973.54	1,964.96	1,956.35	1,947.67	1,939.00	1,931.00	1,892.74	1,854.45	1,816.09	1,777.71
q5	CIN 2-3s	67.38	66.10	66.66	67.12	67.56	67.36	66.01	66.39	66.64	66.81	66.25
q3	CIN 2-3s	80.55	80.87	79.80	80.53	80.80	79.61	80.21	80.30	78.88	79.22	79.03
q2	CIN 2-3s	88.01	87.64	88.00	87.59	87.86	87.35	87.52	86.85	86.89	86.05	85.92
q1	CIN 2-3s	92.14	92.14	92.11	92.04	91.91	91.72	91.50	91.25	90.94	90.56	90.08
q5	Cancer Cases	12.70	12.67	12.65	12.66	12.73	12.70	12.69	12.69	12.74	12.85	12.89
q3	Cancer Cases	8.45	8.47	8.66	8.45	8.48	8.62	8.50	8.55	8.73	8.70	8.82
q2	Cancer Cases	5.73	5.73	5.73	5.73	5.75	5.77	5.80	5.84	5.93	6.01	6.14
q1	Cancer Cases	2.41	2.41	2.41	2.42	2.44	2.47	2.50	2.56	2.65	2.75	2.86
q5	Cancer Deaths	2.70	2.70	2.69	2.69	2.70	2.70	2.71	2.70	2.71	2.73	2.75
q3	Cancer Deaths	1.54	1.54	1.59	1.54	1.54	1.57	1.55	1.56	1.60	1.60	1.62
q2	Cancer Deaths	0.90	0.91	0.90	0.91	0.91	0.92	0.92	0.94	0.95	0.98	1.00
q1	Cancer Deaths	0.31	0.31	0.31	0.31	0.31	0.32	0.32	0.33	0.35	0.37	0.40

*Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared. Cases are per 1,000 women.

CYTOLOGY STARTING AGE 21, FOLLOWED FOR LIFE (PER 1000)

	Q1	Q2	Q3	q5
False positives	951	515	350	214
Colposcopy	1931	1084	758	483
CIN 2-3	91	88	80	66
Cancer cases	2.5	5.8	8.5	12.7
Cancer deaths	0.3	0.9	1.5	2.7

Quote from Task Force member: "All models are wrong, some are useful."

OBSERVATIONAL STUDY

- Lancet Oncology, vol 12, July 2011
- “Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population based study in routine clinical practice”
  - Katki et al followed *313,818 women* in Kaiser Permanente Northern California

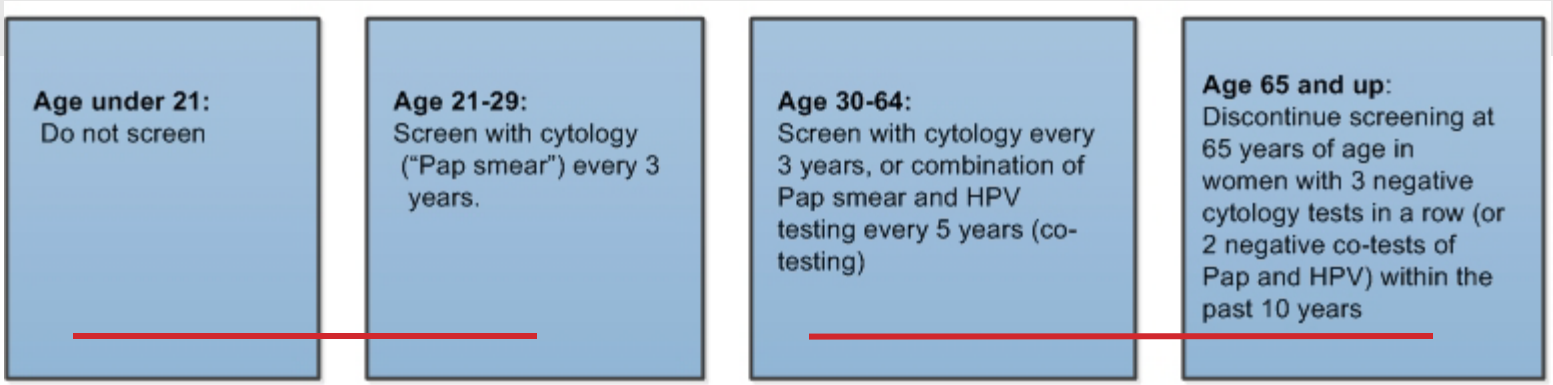
OBSERVATIONAL STUDY ON INCIDENCE

- 319,177 (96.2%) of women had normal Pap at baseline
  - CIN3+ at:
    - 3 years 0.17%,
    - 5 years 0.36%
  - Risk of invasive cancer at five years after normal cytology was 7.5 per 100,000 women (0.0075%)

SCREENING INTERVAL FOR CYTOLOGY IN WOMEN AGE 21-65

- Cytology every 3 years demonstrates a good balance of benefits and harms
- “Pap smears every three years are safe and effective at reducing cervical cancer, while minimizing the risks of false positive results and the harms associated with treating disease that will go away without treatment.”

SCREENING



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WHAT IS THE ROLE FOR HPV TESTING IN SCREENING?

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RECALL: PREVALENCE OF HPV INFECTION

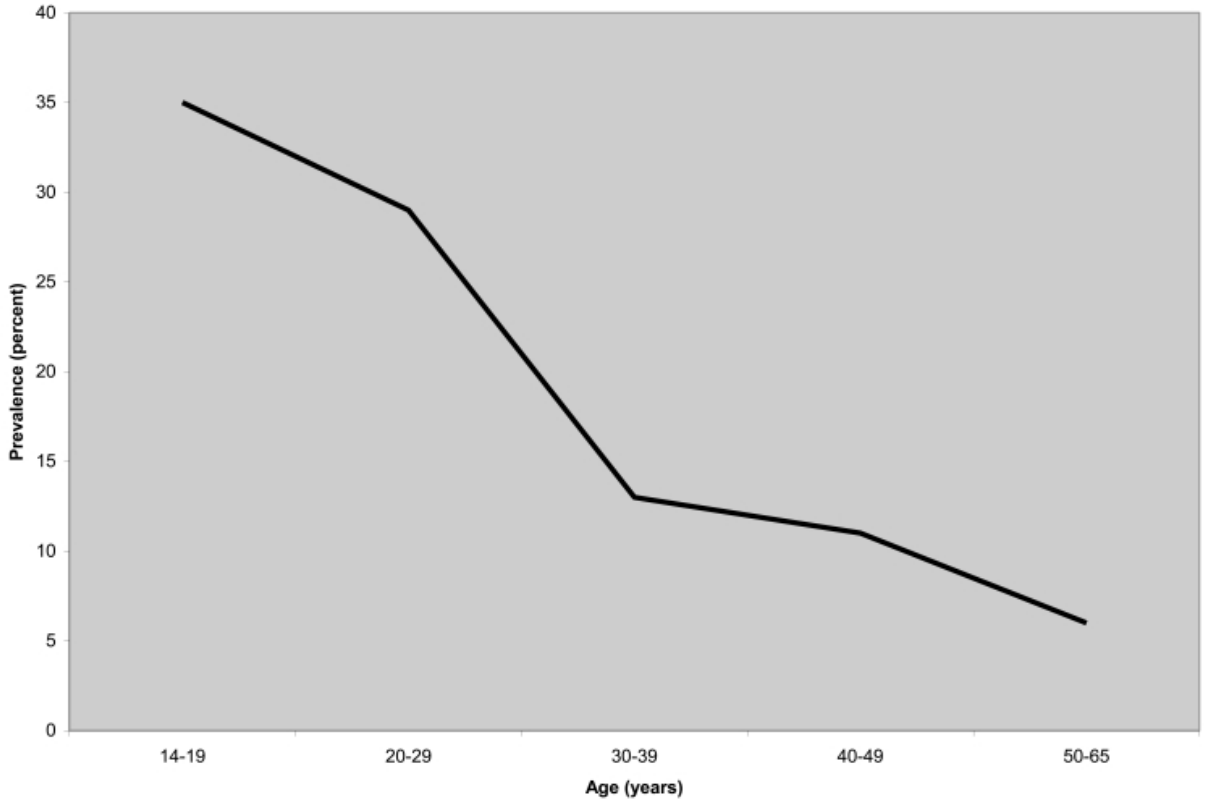

Figure 4 Prevalence of High-Risk Human Papillomavirus By Age[34]

HPV SCREENING BEFORE AGE 30

- Recommend against
  - Preva[illegible] false positi[illegible]
    - Fals[illegible] oes not mea[illegible] meone who[illegible]
    - False positive means identifying someone “in need of intervention” to prevent cervical cancer who does not need that intervention because her disease will regress spontaneously

Just say no to screening for cervical cancer with HPV before age 30.

HPV SCREENING FOR CERVICAL CANCER FOR AGE > 30 YEARS

- Multiple studies of varied design demonstrate that HPV testing is…
  - More sensitive than cytology for CIN2+
  - Less specific than cytology
- The Task Force had the challenge of being “moderately certain” about the balance of benefits and harms.

RCTS OF HPV SCREENING FOR CERVICAL CANCER

- EPC reviewed and presented the results of 6 European RCTs that included HPV in some way in the experimental group
- Inconsistent design, varying protocols, incomplete reporting and perhaps most importantly incomplete follow-up through two rounds of testing

DRAFT RECOMMENDATION

- Insufficient evidence to determine the balance of benefits and harms of HPV screening

POST DRAFT

- Two important publications
  - Completed follow-up of the second round of the RCT in the Netherlands
  - Kaiser observational data noted earlier in presentation

POBASCAM

- 44,938 women age 30-56 randomized to screening with conventional cytology vs. co-testing with HPV and conventional cytology
- Round two testing in five years – both groups received co-testing
- Complex protocol for referral for colposcopy – does not reflect current standard of care in the US
  - e.g. immediate referral only for HSIL

POBASCAM RESULTS

	Cytology round one	Co-testing round one
Cumulative CIN2	127	168
Cumulative CIN3	252	243
Round one cancer	6	12
Round two cancer	14	4
Cumulative cancer	20	16

Recall denominator in each group ~20,000

POBASCAM APPLICABLE TO US?

- We are more aggressive in use of colposcopy, so detection of CIN2+ likely to be higher
- Safe to conclude that co-testing every five years as good as (better?) than cytology every five years in an RCT
  - Reported harms (CIN2) modest

CYTOLOGY EVERY 3 YEARS VS CO-TESTING EVERY 5 YEARS

- Kaiser observational data
- Further exploration in the model to try to fill in gaps in evidence from POBASCAM and Kaiser

KAISER DATA

- Cumulative incidence of CIN3+ the same (0.17%) …
  - *three* years after normal cytology and
  - *five* years after double negative co-testing
- Other analyses confirm increased sensitivity and decreased specificity of HPV testing relative to cytology
- Did not report total colposcopies

MODEL DATA

	False positives	Colpos-copies	CIN2-3	Cancers	Cancer deaths
Cytology q3 years	350	758	80	8.5	1.55
Cytology q3 years until age 30 then co-testing q5 years	255	575	84	7.44	1.35

Note: model assumed women with normal colposcopy immediately returned to usual screening

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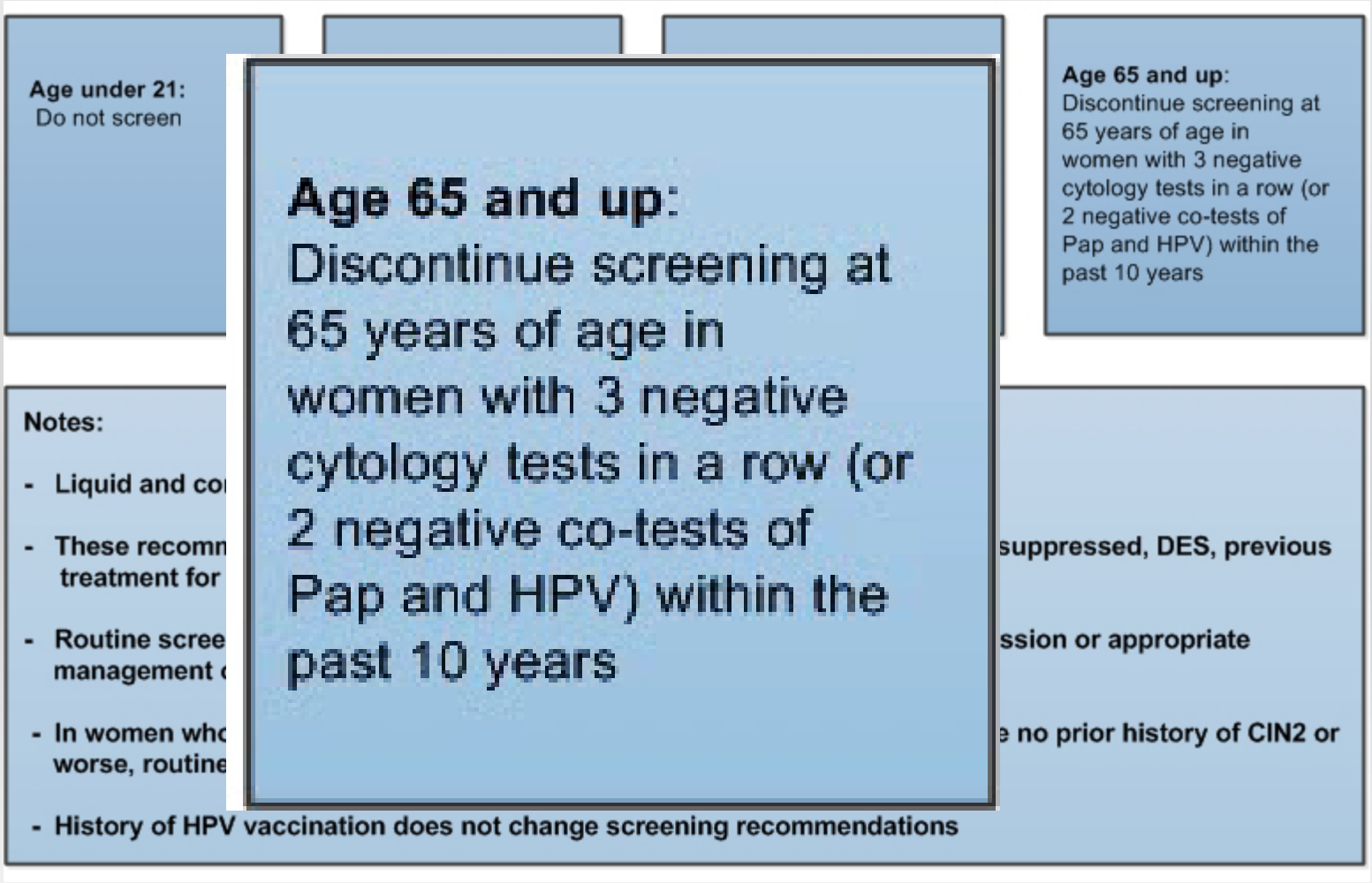

Age 65 and up:
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AGE 65 YEARS OR OLDER

- Potential for benefit in those adequately screened in the past whose screening tests are normal is very low, potential for harm at least small
  - Note women who have had CIN2+ should continue to be screened for 20 years
  - Consider screening women who do not have a history of adequate screening

TWO IMPORTANT CHANGES

- USPSTF did not address management of abnormal results – but ACS/ASCCP did make two specific recommedations
  - ASCUS/HPV negative – Rx as normal
  - Negative Cytology/+HPV
    - Repeat in one year and colpo if either is positive, or…
    - Test for HPV 16/18 and colpo if positive

QUESTIONS?