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Summary of Recommendations

I. Women under 21 years

Females under the age of 21 should not be screened.

II. Women ages 21-29 years

Women ages 21-29 years should be screened with cytology (cervical cytology testing or Pap testing) alone every three years. Screening intervals should not be changed based on the number of previous normal results.

Women ages 21-29 years should:

- *Not* be screened every year or more frequently than recommended.
- *Not* be tested for HPV alone or in combination with cytology, unless for the triage of ASC-US results

Notes on Follow-up:
Women ages 21-29 years screened with cytology alone who have **ASC-US cytology results associated with negative HPV test results** should continue to be screened every 3 years with cytology.

III. Women ages 30-65 years

Women ages 30-65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable). Screening intervals should not be changed for either modality based on the number of previous negative screening results.

In most clinical settings, women ages 30-65 years should not be screened with HPV testing alone as an alternative to cotesting at 5-year intervals or cytology alone at 3-year intervals.

Women ages 30-65 years should *not* be screened every year or more frequently than recommended.

Notes on Follow-up:

Women ages 30-65 years testing **HPV positive, cytology negative** should have one of the following two follow-up options:

1. Repeat cotesting in 12 months
    - If the follow-up cotest is positive, women should be referred to colposcopy.
    - If the follow-up cotest is negative, women should be screened again with cotesting in 5 years.
2. Immediate, HPV genotype-specific testing for HPV16 or HPV16/18.
    - Women testing positive for either HPV16 or HPV18 should be referred directly to colposcopy.
    - Women testing HPV16 or HPV16/18 negative should be cotested in 12 months.
        - If the follow-up cotest is positive, women should be referred to colposcopy.
        - If the follow-up cotest is negative, women should be screened again with cotesting in 5 years.

A positive cotest is HPV positive OR LSIL or more severe cytology. A negative cotest is HPV negative AND ASC-US or negative cytology.

Women testing **HPV positive, cytology negative** should:

- *Not* be referred directly to colposcopy
- *Not* be tested for individual HPV genotypes other than HPV16 and HPV18 or for non-HPV biomarkers.

Women ages 30-65 years with **ASC-US cytology results associated with a negative HPV test should continue to be screened** with cotesting in 5 years or with cytology alone in 3 years.

IV. Women over 65 years of age

Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN2 or more severe diagnosis or cervical cancer within the last 20 years should not be screened for cervical cancer with any modality. Once screening is discontinued it should not resume even if a woman reports having a new sexual partner.

Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the last 10 years before ceasing screening, with the most recent test performed within the past 5 years.

V. Women with a history of CIN2 or a more severe diagnosis

Following spontaneous regression or appropriate management of CIN2 or a more severe diagnosis, routine screening should continue for at least 20 years (even if this extends screening past age 65).

VI. Women post-hysterectomy for benign reasons

Women at any age following a hysterectomy with removal of the cervix for benign reasons (i.e., no history of CIN2 or more severe diagnosis or cervical cancer) should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. Once screening is discontinued it should not resume even if a woman reports having a new sexual partner.

VII. Women with a history of HPV vaccination

Women at any age with a history of HPV vaccination should be screened according to the age-specific recommendations for the general population.

Comments

- ✓ These recommendations are for SCREENING only and do not relate to other uses of cytology and HPV testing such as follow-up of patients with untreated disease, post-colposcopic, or immediate post-treatment follow-up/surveillance. Testing at more frequent intervals may be appropriate under such circumstances. For management or abnormal screening results, women should follow ASCCP guidelines.

- ✓ "Cytology-negative" is Negative for Intraepithelial Lesion or Malignancy (NILM) in The Bethesda System terminology.

- ✓ HPV testing or HPV results refers to high-risk or carcinogenic HPV genotypes only. Other HPV types are unrelated to cervical cancer and should not be used in cervical cancer screening. Testing for low-risk HPV types has no clinical role in cervical cancer screening or evaluation of women with abnormal cytology.

- ✓ CIN2 or a more severe diagnosis represents a diagnosis of CIN2, CIN3, AIS, CIS, or any combination of these diagnoses and does not include invasive cervical cancer of any stage or histology.

- ✓ These guidelines were developed to address cervical cancer screening in the general population. These guidelines do not address special, high-risk populations who may need more intensive or alternative screening, including women 1) with a history of cervical cancer, 2) who were exposed in utero to diethylstilbestrol (DES), and 3) who are immune-compromised (e.g., infection with human immunodeficiency virus).

Conflict of Interest Policy

Disclosure

In planning this symposium, the Steering Committee (SC) critically examined some of the issues involved in defining conflict-of-interest (COI). Often, COI rules emphasize disclosure of an individual's association with commercial entities and remuneration or other financial interests in a company. However, the SC recognized other financial conflicts of interest may arise in conjunction with shifts in recommendations for standard practice. On an individual level, a clinician's practice and income may be affected by changes to the recommended frequency of patient visits, for example. At another level, an entire professional specialty might be adversely impacted, or advantaged, by such changes. The SC recognized that all such financial interests – whether an affiliation with a company, the success of one's clinical practice, the prominence of a professional specialty – represent potential conflicts.

Therefore, for this symposium, all participating individuals were required to disclose all real or potential conflicts of interest including but not limited to: association with relevant commercial interests, involvement with professional societies in an executive or policymaking role, and the nature of their primary employment. Commercial interests were defined as any proprietary entity producing health care goods or services consumed by or used on patients. These may include pharmaceutical companies, device manufacturers or distributors, service companies or other for-profit entities.

We recognized that under this broader definition of COI, virtually everyone has potential conflicts. In forming committees and working groups, the SC sought expertise and balance in the composition of group members so that a broad a range of interests were represented.

Levels of Review to Manage Conflicts of Interest

The development of recommendations involved five levels of review to ensure against bias:

1. Working Groups (WGs) reviewed current recommendations and developed draft recommendations for specific aspects of cervical screening based on review of the evidence. In forming the WGs, the SC sought varied expertise and balance in the composition of the members so that a diversity of perspectives and opinions were included. Clinicians, laboratorians, academics and individuals in public health were represented. WG co-chairs were free of financial ties to companies that market screening tests. All members of WGs agreed to base their efforts on the best available evidence.

2. An independent Evidence Evaluation Committee comprised of experts in literature reviews, evidence evaluation, and data analysis provided feedback and guidance to the WGs as they undertook these efforts.

3. The SC reviewed initial WG drafts to identify possible bias and/or gaps, provided feedback and confirmed that the documents reflect a balanced, evidence-based process. SC members were free of financial ties to companies that market screening tests.

4. At the Symposium, experts and society representatives from the multiple disciplines involved in cervical cancer screening reviewed the WG drafts in an open discussion forum.

5. The Chair of the Meeting, who was independent of the pre-meeting process, monitored the meeting discussion for bias and intervened as appropriate to maintain focus on an evidence-based guidelines process.

Figure 1: Literature Search String

uterine cervical neoplasms OR cervical intraepithelial neoplasia OR Cervix Uteri AND Humans AND Female AND English[lang] AND adult AND
Papillomaviridae OR papillomavirus Infections OR alphapapillomavirus OR tumor virus infections OR
mass screening OR
sensitivity and specificity OR incidence OR prevalence OR (predictive value of tests) OR technology assessment OR Cost-benefit Analysis OR Health Care Costs OR Health Policy OR Costs and Cost analysis OR Quality adjusted life years OR
Papillomavirus Vaccines OR HPV vaccines OR HPV vaccination OR Quadrivalent HPV vaccine OR
vaginal smears OR cytological techniques OR cervicovaginal cytology OR
Pregnancy OR Pregnancy Complications OR Premature Birth OR
Colposcopy OR Conization OR Electrosurgery OR Cryosurgery OR Ablation techniques

(uterine cervical neoplasms[All Fields] OR cervical intraepithelial neoplasia[All Fields] OR Cervix Uteri AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) AND ((Papillomaviridae OR papillomavirus Infections OR alphapapillomavirus OR tumor virus infections AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR (mass screening[All Fields] AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR ((sensitivity and specificity) OR incidence OR prevalence OR (predictive value of tests) AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR ((technology assessment) OR (Cost-benefit Analysis) OR (Health Care Costs) OR (Health Policy) OR (Costs and Cost analysis) OR (Quality adjusted life years) AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR (Papillomavirus Vaccines OR HPV vaccines OR HPV vaccination OR Quadrivalent HPV vaccine AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR (vaginal smears OR cytological techniques OR cervicovaginal cytology AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR (Pregnancy OR Pregnancy Complications OR Premature Birth AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))) OR (Colposcopy OR Conization OR Electrosurgery OR Cryosurgery OR Ablation techniques AND (Humans[Mesh] AND Female[MeSH Terms] AND English[lang] AND adult[MeSH] AND ("2011"[PDat] : "2011"[PDat]))))

Figure 2: Flow Chart of Literature Review and Selection

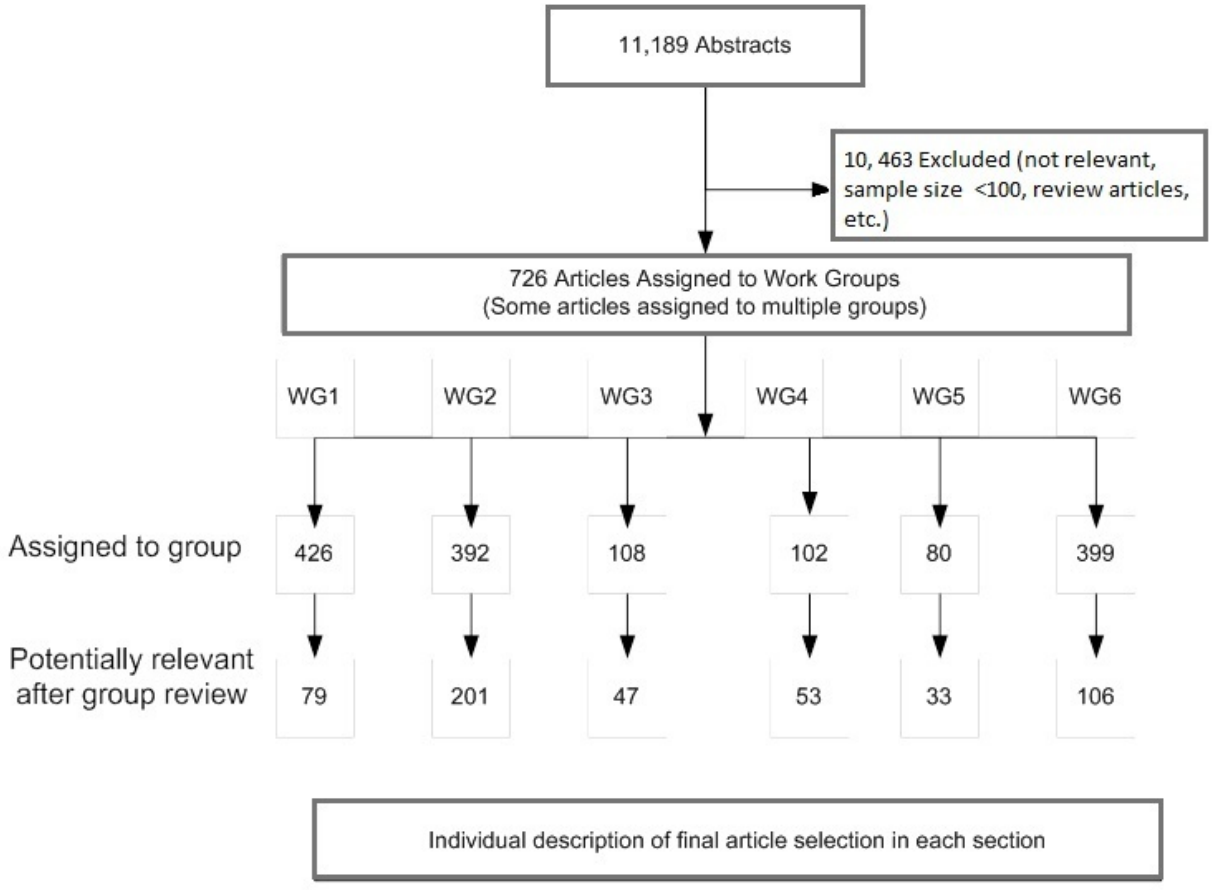

Table 1: Main Outcomes for Benefits and Harms

OUTCOME RANK	OUTCOMES					
	WG1	**WG2**	**WG3**	**WG4**	**WG5**	**WG6**
CRITICAL	CIN3+ (prevalently detected)	CIN3+ (prevalently detected)	CIN3+ (prevalently detected)	CIN3+ (prevalently detected)	CIN3+ (prevalently detected)	CIN3+ (prevalently detected)
	CIN3+ (subsequently detected)	CIN3+ (subsequently detected)	CIN3+ (subsequently detected)	CIN3+ (subsequently detected)	CIN3+ (subsequently detected)	CIN3+ (subsequently detected)
	False positive results/ Unnecessary colposcopies	False positive results/ Unnecessary colposcopies	False positive results/ Unnecessary colposcopies	False positive results/ Unnecessary colposcopies	False positive results/ Unnecessary colposcopies	False positive results/ Unnecessary colposcopies
	Cancer deaths (modeling)	Cancer deaths (modeling)				Cancer deaths (modeling)
	Cancer cases (modeling)	Cancer cases (modeling)		Cancer cases (modeling)		Cancer cases (modeling)
IMPORTANT	CIN2+ (prevalently detected)	CIN2+ (prevalently detected)	CIN2+ (prevalently detected)	CIN2+ (prevalently detected)	CIN2+ (prevalently detected)	CIN2+ (prevalently detected)
	QOL (anxiety/stress of positive test result)	QOL	QOL	QOL (Patient discomfort/pain from screening/diagnosis)	QOL	QOL (anxiety)
	Treatment Complications (Reproductive)	Treatment Complications (Cervical incompetence)		Treatment Complications		
	Impact on future screening	Increased protection of individuals with interrupted screening				False negatives
				Unnecessary treatments (CIN2)	High grade cytology	
USEFUL				Increased follow-up for positive results (QOL; false positives)		Morbidity

Cervical Cancer Screening and Prevention:
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American College Health Association
American College of Obstetricians & Gynecologists
American Social Health Association
American Society for Cytopathology
American Society for Cytotechnology
CDC - Division of Cancer Prevention & Control
CDC - Division of High-Consequence Pathogens and Pathology
CDC - Division of Laboratory Science & Systems (Epidemiology & Surveillance)
Centers for Medicare & Medicaid
College of American Pathologists
Food & Drug Administration (OIVD)
National Cancer Institute
National Comprehensive Cancer Network
Nurse Practitioners in Women's Health
Planned Parenthood Federation of America
Society of Canadian Colposcopists
Society of Gynecologic Oncologists
Society of Gynecologic Oncologists of Canada
Society of Obstetricians & Gynaecologists of Canada
United States Preventive Services Task Force
Veterans Health Administration

Observer Organizations
British Society of Clinical Cytology
Office of the Canadian Task Force on Preventive Health Care, Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada

Working Group 1: Optimal Screening Intervals for Cytology-based Screening

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Introduction

High quality screening with cytology has been shown to markedly reduce the incidence of and mortality from cervical cancer.[1,2] However, despite agreement that cytology-based screening is effective, approaches to the implementation of cytology-based screening vary from country to country. While a number of European countries, Australia and Canada have adopted screening intervals that range from every 2 years to every 5 years, the U.S. remains one of the only countries in the world where not only is annual screening considered acceptable, but many providers and patients prefer this approach.[3] To accommodate this preference, some U.S.-based guidelines recommend screening every 2-3 years, but allow for annual screening.[4,5] Evidence suggests that while the benefits of frequent screening are a very low risk of cancer incidence and mortality, this comes at the cost of increased testing and sometimes unnecessary procedures.[6] Minor abnormalities associated with cytology-based screening and follow up have been shown to be associated with potential patient harms including anxiety as well as potentially unnecessary excisional treatments including cold-knife conization and loop electrosurgical excisions (LEEP) that can be associated with an increased risk of adverse birth outcomes. Thus, screening frequency must take into account the benefits as well as the harms.[7]

Although some cervical cancer screening recommendations call for more frequent screening intervals in younger women (compared to women aged 30 years and older with a normal screening history), studies suggest that screening may be less effective at detecting cancer, especially in women younger than 25 years.[8] In addition, a majority of low grade lesions (defined as <CIN 2) and a proportion of CIN 2/3 lesions will spontaneously regress.[9] Thus, for women younger than 30 years, a different screening interval than is currently recommended may be warranted. Previous recommendations support less frequent screening in women 30 years or older, who have been previously screened and have multiple consecutive, negative cytology tests. This is based on evidence that suggests that these women have a reduced risk of cancer compared to younger women and/or women with either no or one prior negative cytology test.[5] Thus, for well-defined sub-groups of women, a less frequent screening interval may be optimal for balancing the benefits and harms of cytology-based screening.

To address these issues, the ACS-ASCCP-ASCP requested that a literature review be conducted to either support or revise the current ACS recommendations for cytology only-based cervical cancer screening.[5] It is important to note that the review and recommendations are applicable only to asymptomatic women at risk (defined as having a cervix) for cervical cancer who participate in cervical cancer screening in the U.S. The recommendations of this group are to be viewed as the minimum or base comparator of reasonable screening performance for the

alternative screening approaches being examined by the other working groups. Further, the reader is reminded that the evaluation was developed strictly on the basis of what the working group thought was, on balance, best for the patient, without regard to provider or other economic impacts. Finally, the group recognizes that the greatest impact on reducing cervical cancer incidence and mortality will come from encouraging women to participate in screening programs.

Key Questions

1. For women 21 to 29 years of age, should cervical cytology alone be recommended every 1, 2, 3, or 5 years?

    1.1 For women 21 to 29 years of age, with 2 or more consecutive negative cytology results, should the interval be increased further?

2. For women 30 years and older, should cervical cytology alone be recommended every 1, 2, 3, or 5 years?

    2.1 For women 30 years and older, with 2 or more consecutive negative cytology results, should the interval be increased further?

Recommendations

1. For women 21 to 29 years of age,* screening with cytology alone every 3 years is recommended. (*strong recommendation)*

    1.1. For women 21-29 years of age with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e. >3 years).
    1.2. For women 21 to 29 years of age,* there is sufficient evidence to recommend against annual screening. (*strong recommendation)*

2. Women ages 30-65 years* should be screened with cytology alone every 3 years. (*strong recommendation)*

    2.1. For women 30-65 years of age with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e. >3 years).
    2.2. For women 30-65 years,* there is sufficient evidence to recommend against annual screening. (*strong recommendation)*

* For women who are DES exposed, immunocompromised, HIV positive or women who have not been previously screened or who have not been screened per the recommendations above, a different screening interval and/or a different screening strategy (besides cytology only) may be warranted.

Regardless of whether a woman receives a cervical cancer screening test in a given year, it is critical that she have access to appropriate health care, including assessment of health risks, family planning and contraception, and prevention counseling, screening and treatment of sexually transmitted infections.

Evidence Review

As described separately, a literature review was conducted to identify articles for potential inclusion. PubMed was searched for relevant articles published between January, 1995 and July, 2011. Based on this strategy, a total of 426 publications were identified for initial review. Two reviewers were randomly assigned to review each article. Exclusion criteria were as follows: not relevant; no data on relevant outcomes; non-randomized studies with n<100; non-systematic reviews (excluding modeling studies); cross-sectional screening test studies including those lacking a reference standard. Based on these criteria 347 articles were excluded. A second round of reviews was conducted to identify articles that provided data on reductions and /or increases in disease detected over multiple rounds of screening and that also specifically addressed the age ranges of interest (21 to 29 years of age and 30 years or older). During this second round of article screening, we also excluded articles that focused only on adenocarcinoma or were modeling studies that provided cost-effectiveness data only. Based on these additional criteria, a further 60 articles were excluded, leaving 18 articles with data available to inform this set of recommendations.

Rationale and Evidence

Based on data from randomized controlled trials and meta-analyses that show no statistically significant difference in sensitivity or specificity for conventional cytology compared to liquid-based cytology, we did not distinguish studies for inclusion based on which of these tests were used.[10,11]

Screening Interval

Cytology-based screening conducted every 5 years does not appear to significantly increase the prevalence of CIN 3 detected or incidence of cancer detected over 2 or more rounds of screening.[12] Two observational screening studies report a 45 to 66% reduction in cancer incidence associated with a 5-year interval (defined as the difference in incidence associated with screening at a 5-year interval compared to incidence with no screening divided by the incidence with no screening).[13,14] The model predicted lifetime risk of cervical cancer in the U.S. in the absence of screening would range from 3.1 to 3.3%, representing approximately 30 incident[15] cancers per 1000 women.[16,17] This risk is predicted to decrease to approximately 1.3% or 13 incident cancers per 1000 women when screening is conducted every 5 years. This predicted reduction in absolute risk is similar to that obtained from screening studies by Herbert et al. of approximately 60%. In terms of colposcopies, screening every 5 years is

associated with an estimated 483 colposcopies per 1000 women screened; screening every 3 years is associated with a range of 275[17] to approximately 400 additional colposcopies per 1000 women screened (estimated based on data for a 10-year time horizon from Stout et al.[15]), representing approximately a 60% to 80% increase in total colposcopies.

Modeling studies predict a lifetime risk of cancer associated with screening every 3 years that ranges from 0.51% to 0.85% or 5 to 8 incident cancers per 1000 women.[15-19] Compared to no screening this range represents an approximately 55% to 80% reduction in risk. Screening every 2 years is associated with a lifetime risk of cancer that ranges from 0.41% to 0.60% or 4 to 6 incident cancers per 1000 women.[17,19] Screening annually is associated with a lifetime risk of cancer of approximately 0.30% or 3 per 1000 women.[17,19] In terms of relative reductions in risk, compared to no screening, screening every 2 years is associated with approximately a 70% reduction in lifetime risk of cancer (when adherence is assumed to be <100%) to almost a 90% reduction (assuming 70% sensitivity for cytology for a threshold of CIN 2+ and perfect adherence) and screening every year is associated with reductions in the lifetime risk of cancer that range from approximately the mid-80s to over 90%.

In terms of colposcopies (calculated over the lifetime of the cohort), screening every 3 years is associated with approximately 760 colposcopies per 1000 women. Compared to screening every 3 years, screening every 2 years is associated with an approximately 40% increase in the total number of colposcopies (to approximately 1080 colposcopies per 1000 women). Compared to screening every 2 or 3 years, screening every year is predicted to double the total number of colposcopies to close to 2000 per 1000 women.

Summary: In general, compared to no screening, screening every 5 years is associated with the fewest number of procedures (defined using colposcopies); it is also associated with an approximately 50 to 60% decrease in cancer incidence. Screening every 2 or 3 years is associated with a further reduction in risk of cancer (up to almost 90% for the 2 year interval) with an increase of 1.5 to 1.8 times the number of colposcopies predicted for a cohort of women undergoing screening every 5 years. Finally, an additional reduction in cancer risk of approximately 2.0% to 10.0% is predicted for annual screening compared to screening every 2 years, with a doubling of the total number of colposcopies.

Screening Interval for Women Younger than 30 Years

In a modeling study that examined outcomes for women aged 20 years screened for a 10-year time horizon, Stout et al.[15] predicted there would be 89 colposcopies per 1000 women screened every 5 years; this number was predicted to almost double to 157 for screening every 3 years and approximately quadruple to 333 for screening every year. The model also predicted an increase of approximately two CIN 2+ per 1000 women if screening was conducted every year or every 3 years compared to screening conducted every 5 years. These results are similar to those reported by Kulasingam et al.[17] Kulasingam et al also examined outcomes associated with screening every 2 years. Compared to screening every 3 years, screening every

2 years was associated with approximately 80 additional colposcopies for approximately 2 fewer cases of cancer per 1000 women (for over a slightly shorter time horizon -- 9 years -- than Stout et al).

Screening Interval for Women Ages 30-65 Years

A similar prevalence of CIN 2+ and CIN 3+ was reported comparing two rounds of screening conducted at a 5-year interval in women aged ≥30 years.[12] These results are similar to those reported by Siemens et al.[20] who reported rates of CIN 3+ and cancer that were essentially unchanged for 2 rounds of screening (conducted at an approximately 5-year interval) in women aged 30 to 60 years. They noted in their discussion that screening every 3 years was associated with a halving of the rates of CIN 3 (between rounds of screening) compared with screening every 5 years. Stout et al.[15] modeled the impact of screening every 1, 3, or 5 years on total colposcopies over the subsequent 10-year period for women who are followed from age 40 years. They predicted that screening every 3 years instead of every 5 years would almost double the number of colposcopies (from 70 to 127 per 1000 women screened). Screening every year was predicted to be associated with more than double the number of colposcopies (267 per 1000 women) compared to screening every 3 years.

Summary: The age-specific results are similar to the results for screening women at a set interval over their lifetimes reported above.

Prior Number of Negative Cytology Tests

With respect to the question of the impact of screening history and cytologic results on the length of screening interval, there is insufficient high quality evidence from randomized controlled trials in any age group. Miller et al.[21] calculated the odds ratio for invasive cervical cancer associated with different intervals since the last previous negative cytology test. The odds ratio associated with a 3-year versus a 2-year interval was 1.20 (95% confidence interval (0.65, 2.21)). Controlling for ever having had an abnormal cervical cytology or previous consecutive negative test did not substantially change the results. The study also reported a significantly increased odds ratio (3.16 or greater (unadjusted)) when the interval from the last negative cytology test was extended beyond three years. Gram et al[22] did not find a significantly reduced risk of cancer or CIN 3 associated with increasing numbers of prior negative cytology tests after controlling for time since last negative cytology test.

Women Younger than 30 Years

Using data from the Centers for Disease Control and Prevention's Breast and Cervical Cancer Early Detection Program, Sawaya et al.[6] estimated the prevalence of CIN 3 among women aged <30 years ranged from 0.46 (for women with one negative cytology) to 0.52 (among women

with 2 negative cytology tests) and 0.20 for women with 3 or more prior negative cytology tests; no cases of cancer were observed in this age group.

Women 30-65 Years

Viikki et al.[23] estimated the standardized incidence ratio (SIR) comparing the observed versus the expected incidence of cancer. Observed rates of cancer were calculated among women with a previous negative cytology test. Expected rates of cancer were calculated based on the incidence in the general population of women of the same age range. They reported a SIR of 0.5 to 0.6 for cancer (reflecting a 50% to 40% reduction) associated with a 5-year screening interval in older women (34 to 48 years and 49 years and older, respectively) who had a previous negative cytology test. They also noted that the SIR was low initially after screening, but then steadily increased over time until the next cytology test, approximately 5 years later. Sawaya et al.[6] reported that in women aged 30 to 64 years with three or more consecutive negative cytology tests, the prevalence of CIN 2 on a subsequent cytology test ranged from 0.06 (for women aged 30 to 44 years) to 0.01 (for women aged 60 to 64 years) and from 0.04 to 0.01 for CIN 3 (there were no invasive cervical cancer cases detected in either age group). The study included use of a decision model to determine the expected number of colposcopies and cancers detected if women were screened every year for 3 years, or once 3 years later, and showed that screening women 30 years and older three years after the last negative cytology instead of every year was associated with 3 additional cases of cancer per 100,000 women. To avert an additional cancer case (associated with screening 3 years later compared to screening once every year for 3 years), the authors estimated it would be necessary to perform more than 69,000 additional cytology tests and 3861 colposcopic exams in women aged 30 to 44. For women aged 45 to 59 years, they estimated an additional 209,000 cytology tests and 11,500 colposcopies needed to be performed to avert an additional case of cancer.

Rationale for Screening Interval

Based on the evidence, as discussed and summarized above, the rationale for the choice of screening interval for cytology-based screening in women aged <30 years and women aged 30-65 years is as follows:

1) For young women (age <30 years) there are very few studies (that met the inclusion criteria) to inform the decision regarding interval for cytology-based screening. Those that met our selection criteria are mainly modeling studies for which there is a lack of guidance regarding how best to consider them in terms of "evidence" alongside systematic reviews and appraise them in terms of quality. Considering the evidence, the group decided that while screening every 5 years is associated (by design) with the lowest burden of colposcopies, screening at this interval would also be associated with the smallest reduction in risk of cancer compared to no screening. While screening every year is associated with the largest reduction in cancer risk, the trade-off is an increased number of colposcopies (double that associated with screening every 3 years). Balancing harms with benefit, there is little evidence to support annual

screening as it results in excessive downstream risk of unnecessary procedures and treatments compared to a small additional benefit related to cancer prevention.

Regarding the choice of 2 or 3 year interval, there was only one study that met the inclusion criteria that reports the trade-offs between cancers detected and colposcopies for every 2 years versus every 3 years in this age group (<30 years). Since the results for both intervals were similar in terms of cancer burden (over a short time horizon), and given the findings of other studies (not included based on our criteria, but of relevance to interval)[24,25] that show no significant difference in reduction in cancer between an interval of approximately 2 compared to 3 years, the group determined that screening every 3 years would provide the best balance of the benefits and harms of screening in this group.

2) For women aged 30-65 years, especially those with a history of negative cytology test results, there is little evidence to support a less frequent screening interval. Studies of screening interval in women with a history of negative cytology results report an increased risk of cancer after 3 years even after controlling for prior number of negative cytology tests. Further, the modeling study that examined the interval after a history of prior cytology compared screening every year to screening every 3 years – a longer interval was not examined. Thus, given these considerations, the working group concluded that there was, at present, insufficient evidence to support a longer (i.e. less frequent) interval than every 3 years in women aged 30-65 years with a screening history of consecutive negative cytology tests.

Research Priorities and Recommendations

1) There are relatively few studies that specifically focus on the efficacy of screening in women aged <30 years or that present age-specific information that can be used to inform screening interval recommendations by age. Further, modeling studies that estimate risk over a lifetime and shorter time horizons coupled with different ages of screening and screening history will help elucidate the trade-offs between the burden and benefits of screening.

2) Although it is clear that women who are either never or under-screened need to be screened, the optimal approach needed-- whether by varying age and/or screening strategies besides cytology alone (to optimize sensitivity)-- requires further study.

3) Future research needs to include the potential effect of individual patient risk factors (e.g., HPV vaccination, immune suppression, HIV infection, family history) on screening intervals and the effect of prior negative tests and negative colposcopy on screening interval.

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Working Group 2: Screening Strategies for Women 30 Years and Older

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Introduction

Since 2003, multiple groups have recognized two acceptable cervical cancer screening options for women 30 years and older. These are: screening with cytology alone (liquid based or conventional) every 2 to 3 years or cotesting with cervical cytology plus high risk HPV DNA testing* on a 3 year interval if both are negative. Given the large amount of evidence that has emerged since that time, the working group was charged to evaluate the potential benefits and harms of screening strategies for women 30 years and older.

Key Questions

1. Are data sufficient to designate any screening strategy as the preferred approach for women 30 years and older?

2. Should a strong recommendation against cotesting using HPV DNA testing more frequently than every 3 years when screening be made?

3. Is the cutoff age of 30 years and older for cotesting with HPV DNA testing for routine screening supported?

4. What is the optimal and maximal interval for cotesting?

Recommendations

1a. Women aged 30-65 should be screened with cytology and HPV testing ("cotesting") every 5 years or cytology alone every 3 years. (*strong recommendation*)

1b. Cytology and HPV testing (cotesting) every 5 years is the preferred strategy over screening with cytology alone every 3 years. (*weak recommendation*)

2. We recommend that if both tests are negative, rescreening should take place every 5 years. *(strong recommendation)*

3. There are insufficient published data to address whether or not the currently recommended cutoff age of 30 for cotesting might reasonably be decreased.

4. We suggest that general population screening should not be performed at intervals shorter than 3 years in the presence of negative testing, regardless of the screening modality employed. *(strong recommendation)*

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. 392 articles were identified and 201 articles were included to inform this set of recommendations. Manuscripts and evidence reviews were selected based on their applicability to the charge and their country of origin. Due to differences in testing protocols, only evidence from the U.S., Western Europe, and Australia was included. In addition, data from the Guanacaste, Costa Rica trial were included because cytology testing evaluation was completed in the U.S. Data were extracted into the attached tables. This includes the U.S. Preventive Services Task Force (USPSTF) 2011 review.[1] Additionally, based on available evidence, the working group accepted liquid and conventional cytology as equal "cervical cytology" screening methods.

Qualifications of Evidence

Manuscripts and summary comments are reviewed below. In general, there was little to no evidence at fair or higher levels that would allow the group to make statements about the quality of life or treatment complications. Increased protection of individuals with interrupted screening is inferred from the rate of emergence of CIN 3+ at increasing intervals with cotesting.

Rationale and Evidence

Addition of HPV testing to cytology results in an increase in CIN 3+ prevalently detected and a decrease in CIN 3+ in subsequent rounds in the majority of studies reviewed. Addition of HPV testing to cytology was demonstrated to reduce the invasive cancer rate in the second screening round in a large, good quality randomized clinical trials (RCTs) conducted in a high resource setting with a well screened population. A negative HPV test has a high negative predictive value (NPV) for absence of CIN 3+ and cancer in the subsequent 5 years, permitting extension of screening intervals with less risk of developing invasive cancer than the use of cytology alone. This NPV provides reassurance that women screened at intervals substantially in excess of 3 years after negative/negative cotesting retain significant protection.

Addition of HPV testing to cytology enhances detection of adenocarcinoma of the cervix and its precursors. In comparison to squamous cancers, cytology has been relatively ineffective in decreasing the incidence of invasive adenocarcinoma of the cervix. Screening at intervals less than 3 years leads to unnecessary procedures, and to potentially harmful treatment of lesions destined to clear without intervention. These adverse effects are most pronounced with annual screening intervals.

Increased Sensitivity of Cotesting

Testing for high risk HPV is more sensitive and less specific for CIN 3+ than is cervical cytology.[2] In Arbyn's meta-analysis, the sensitivity of HPV tests for CIN 3+ was 37% higher than that of cervical cytology with cut point of LSIL or worse while the specificity of HPV tests was 7% lower.[2] When compared with negative cytology, negative HPV tests also have a lower subsequent risk of CIN 3+.[3,4] In Dillner's series, the cumulative risk of CIN 3+ six years after a negative HPV test was 0.27% [95% CI 0.12% to 0.45%] while the risk following a negative cytology was 0.97% [95% CI 0.53% to 1.34%],[3] and in Katki's series, the cumulative risk of CIN 3+ five years after a negative HPV test was 0.17% while the risk following a negative cytology was 0.36%, p=.02.[4] HPV tests are also more reproducible than cervical cytology.

There are four randomized trials[5-8] in which two rounds of screening are reported comparing cotesting with cervical cytology and HPV tests to cervical cytology alone; three of those trials provided adequate evaluation of Pap negative HPV positive women. Each of the trials has a complex protocol and each differs in the way that HPV positive women are evaluated. Kitchener's trial differed from the other three in that the lower age limit of eligible women was 20 years while for the other three trials, it was 32,[6] 29,[7] and 35 years.[8] Kitchener's trial also differed in that there was a low rate of evaluation of women who were HPV positive, cytology negative.[9] As the benefit of HPV testing is realized only when the women with positive HPV tests and negative cervical cytology are evaluated, it is therefore not surprising that Kitchener's trial did not show a benefit to cotesting. Castle et al have pointed out that if all of the HPV-positive, cytology-negative women had been evaluated and disease rates were comparable to the rates found in those who did undergo evaluation, the trial would have been positive.[9] Subsequent publication of three rounds of screening in the ARTISTIC trial demonstrated that the risk of CIN 3+ following a negative cytology at entry was 0.63% (95% CI 0.48% to 0.80%) in comparison to 0.28% (0.18% to 0.40%) following a negative HPV at entry, prompting a recommendation for HPV testing at increased intervals.[10] The other three trials[5-7] were powered to detect differences in the rate of CIN 3+in the second round of screening, but none of the four trials were powered to detect differences in the rate of cancer in the second round of screening, though the largest (Ronco) did detect a significant decrement in cancer rates associated with the addition of HPV testing. Trial protocols and results are described in detail in the Appendix.

Table 1: Comparison of percent of CIN 3 or cancer (CIN 3+) diagnosed in the first of two rounds of screening and rate of cancer diagnosed in the second round of screening for three randomized trials comparing screening with cytology alone to screening with cytology plus HPV testing

STUDY	% CIN 3+ found in Round 1, cytology alone	% CIN 3+ found in Round 1, cotesting	Cancer rate second round, cytology alone	Cancer rate second round, cotesting
Naucler[6]	64.7% (55/85)	81.8% (72/88)	Not stated	Not stated
Bulkmans[7]	42.6% (40/94)	73.9% (68/92)	.08% (7/8580)	.02% (2/8575)
Ronco[5]	68.3% (56/82)	92.9% (105/113)	.03% (9/34405)	.00% (0/34430)

In each of the three trials shown in Table 1, when compared to cytology alone, the cotesting arm (including HPV tests) detected a greater proportion of the CIN 3+ in the first round of screening. The difference in the rate of cancer in the second round of screening was not stated in Naucler's trial,[6] showed a trend towards improvement (not statistically significant) in Bulkmans' trial (0.08% vs. 0.02%),[7] and showed a statistically significant decrease in Ronco's trial (0.03% vs. 0%, p=.004.[4,5] The rates of colposcopy in the three studies are not clearly stated, so the increased number of colposcopies requires modeling to assess.

Based on the significant reduction in invasive cancer in the second round of screening in Ronco's trial,[5] we conclude that testing with HPV in addition to cervical cytology is beneficial. The downside of HPV testing reflected in the increase in the rate of colposcopy and diagnosis of CIN 2 is recognized but can be minimized by extending the interval of screening.

Rationale for and Safety of Interval Extension

The ability to detect CIN 3 with greater sensitivity implies that women with a negative cotest are at less risk of subsequently detected CIN 3, and may thereby undergo screening at increased intervals with the expectation of less risk of invasive cancer in the years following a negative primary HPV test or cotest than following a negative cytology alone. Dillner[3] pooled seven HPV primary screening studies involving 24,295 women, and compared the risk of CIN 3+ at 6 years following a negative HPV test (0.27%) or a negative cytology test (0.97%). The 95% confidence intervals did not overlap. They also noted that the risk of CIN 3+ at a 3-year screening interval after a negative cytology was 0.51%. Following a negative baseline cotest,

Katki et al.[4] reported that this same difference in protection from CIN 3+, as well as invasive cancer, was observed in clinical practice in the 3-year and 5-year follow-up of 330,000 women. Taken together, these reports indicate that women with a negative HPV test can rely on the negative predictive value to assure them they are at very low risk for CIN 3 and cancer for at least 5 years. This is welcome reassurance given that adherence with recommended intervals following a negative screening test is not uniform, and under-screening is a common antecedent of invasive cancer, especially in women without regular access to care.[11] Initially clinicians and women many feel more comfortable with a three-year interval, given the evidence that in clinical practice the risk of cancer after a single negative cotest at 3 years is similar to the risk of cancer at 1 year after a negative cytology result.[4] However, these are risks after a single test, and a screening program involves testing a woman multiple times over her lifetime. For a woman with sequential negative cotest results, the evidence strongly favors extending the interval to 5 years based on extremely low risk of cancer after sequential negative cotests.

Risks of Screening at Different Intervals

Most episodes of HPV carriage and many CIN 1 and CIN 2 cases are transient and do not proceed to CIN 3+.[12,13] If the screening interval is short compared to the time required for these conditions to resolve, the number of added colposcopies will be substantial, and there will be more detection and treatment of lesions that would otherwise resolve spontaneously. While there is not and can never be a randomized controlled trial to address the possible obstetrical harms associated with excisional management of cervical neosplasia that the observational literature suggests, the conduct of colposcopy, biopsy and cervical excision that does not contribute to cancer prevention constitutes a potential harm in and of itself. The surrogate marker of number of colposcopies has therefore been chosen as a metric to represent the harmful consequences of over-screening. Modeling from multiple sources indicates that there is a dramatic increase in colposcopy rates with minimal changes in invasive cancer incidence as screening intervals decrease below 3 years, regardless of the modality employed.[14] This recognition underlies the recommendation that screening by whatever method not occur more frequently than every 3 years. All three models, despite differing methods and assumptions, showed that colposcopies more than doubled with annual cytology starting at age 21 in comparison to annual cytology ages 21-29 and cotesting at 3 years intervals starting at age 30, with very similar outcomes in terms of life years saved.

Detection of Adenocarcinoma of the Cervix and Its Precursors

Case control studies in Australia and in Italy demonstrated only modest protection from adenocarcinoma associated with cytologic screening.[15,16] More recently the International Collaboration of Epidemiological Studies of Cervical Cancer group pooled screening data from 12 studies involving 1,374 women with adenocarcinoma and concluded that the predictive value of a negative Pap test was “significantly greater” for squamous carcinoma than for adenocarcinoma.[17]

High-risk HPV has been identified in 93% of 167 adenocarcinomas of the cervix (including 55 adenosquamous carcinomas) by Castellsague et al.[18] A case control study with these cases and 1881 controls was also reported. The overall odds ratio for cervical adenocarcinoma for HPV-positive women as compared to HPV-negative women was 81.3.[18] The potential utility of these observations in clinical practice is delineated in the report of Katki, wherein the women who were HPV positive, cytology negative at outset experienced 29% of the cancers diagnosed in the ensuing 5 years, including 63% of the adenocarcinomas.[4]

Research Priorities and Recommendations

Additional information to assess the tradeoffs involved in longer screening intervals would be welcome, particularly including colposcopy, biopsy, complications and quality of life parameters in the datasets. A randomized trial of 4- versus 5- versus 6- versus 7-year screening intervals is currently planned in Europe.

Appendix

Bulkmans[7] reported a prospective controlled trial in the Netherlands in which 17,155 women age 29-56 years were randomized in a ratio of 1:1 to screening with liquid-based cervical cytology vs. cotesting with cervical cytology and HPV (GP5+/6+ PCR) tests. Women with HSIL or cancer cytology were immediately referred for colposcopy. Women with normal cytologic results and negative HPV test were advised to return for screening in 5 years. Women with negative cytology and positive HPV tests and those with cytology of ASCUS, ASC-H, and LSIL were advised to return in 6 and 18 months. Women returning at 6 months were referred for colposcopy if repeat cytology was HSIL or cancer or if repeat cytology was ASCUS, ASC-H, or LSIL with positive HPV. Women returning at 18 months were referred for colposcopy if HPV test was positive or if cervical cytology was HSIL or cancer. At the 18 month recall visit, if the cervical cytology was ASCUS, ASC-H, or LSIL and the HPV test was negative, women were advised to return at their regular screening interval (i.e. at 5 years). The rate of positive HPV was 4.5%. With a median follow-up of 7.2 years, in the first round of screening, the cervical cytology group detected a lower number of CIN 3 or cancer (n=40) than did the cotesting group (n=68, p=.007). In the second round of screening, the cervical cytology group detected a higher number of CIN 3 or cancer (n=54) than did the cotesting group (n=24, p=.001). As a result, the total number of CIN 3 or cancer detected in two rounds of screening was similar in both groups (n=94 for cervical cytology and n=92 for cotesting, p=.89). The number of referrals for colposcopy for the two rounds of screening was 244 for the cytology alone group and 288 for the cotesting group. The number of invasive cancers found at the first screen in the cotesting group was 5 while for the cytology group it was 2. In the second screening, the cotesting group had 2 cancers while the cytology group had 7 (2 vs. 7, p not stated but not significant).

Kitchener[8] reported a prospective controlled trial in England in which 24,510 women age 20 to 64 years were randomly assigned in a 3:1 ratio to either cytology (liquid based Thin Prep) or to

cotesting with cytology and HPV (Hybrid Capture 2) testing. 18,386 women were in the cotesting group and 6,124 in the cytology only group. Women with negative screens were advised to return in 3 years. Women with negative cytology and positive HPV tests were offered colposcopy if the positive HPV test persisted for 12 months. Women were also referred for colposcopy if they had two consecutive mild dyskaryosis smears or three consecutive borderline results. At the time of analysis, 65.6% of women had attended their second screen. Results are based on the women that attended the two rounds of screening. The rate of positive HPV was 15.6%. Of the 1675 women with positive HPV and negative cytology in round 1 of the cotesting group, only 62.1% (1040/1675) attended repeat HPV testing before round 2 and only 42.2% (439 of 1040) of these were still HPV positive and only 66.3% of these (291/439) underwent colposcopy. The colposcopy rate for the cytology alone group (5.2%, 320/6124) was less than in the cotesting group (6.8%, 1247/18386). The rate of CIN 3 or cancer in round one was 1.27%, 233/18386 in the cotesting group and 1.31%, 80/6124 in the cytology alone group; p>.2). In round 2, the rate of CIN 3 or cancer was 0.25%, 29/11676 in the cotesting group and 0.47%, 18/3866; p=.042 in the cytology alone group. For the two screening rounds taken together, the rate of CIN 3 or cancer was 1.51% for the cotesting group and 1.77% for the cytology alone group, p=>.2. For women age 30 years and over, the rates of CIN 3 or cancer for the two rounds of screening were 0.14% for cotesting and 0.28% for cytology alone (p=.14). The authors note that some of the women that were persistently HPV positive did not attend colposcopy clinics for advised evaluation.

Naucler[6] reported a trial in which 12,527 women 32 to 38 years of age were randomly assigned (1:1) to have concurrent cytology and HPV or to cytology alone. 6257 women were in the cotest group while 6270 were in the cytology alone group. Women with cytology of ASCUS or worse (sometimes ASCUS was repeated prior to referral) were referred for colposcopy. In the cotest group, women with positive HPV with no record of referral for an abnormal cytology had a second HPV test in 12 months, and if that was positive, they were referred for colposcopy. At colposcopy, white lesions and those that did not stain with Lugol's solution were biopsied. If no lesion was seen, random biopsy was obtained at 12 and 6 o'clock and endocervical curettage was done. Follow-up was an average of 4.1 years. In the first round, CIN 3 or cancer was found in 55 women in the control group (cytology alone) and 72 in the cotest group (relative risk 1.31 (p not stated, but it is significant because the 95% CIs do not overlap). In the second round, CIN 3 or cancer was found in 30 women in the control group and 16 women in the cotest group (relative risk 0.53, again significant). For the two screenings, 85 cases of CIN 3 or cancer were detected in the control group and 88 in the cotest group. In the control group 5 women with invasive cancer were detected, while in the cotest group, there was just one case of invasive cancer. The authors do not say when the cancers were diagnosed, and they note that CIN 2 was diagnosed more often in the cotest group (n=53) than in the control group (n=34). These excess CIN 2s were diagnosed at the first screen (n=42 in the cotest group; n=21 in the control group).

Ronco[5] reported a complex trial that included two phases and two different colposcopy referral systems. In phase I, women age 25-60 were randomly assigned to cytology or to HPV testing

(HC 2) concurrent with cytology. Women with cytology of ASCUS or greater had immediate colposcopy, those age 35-60 years who were HPV positive, cytology negative had colposcopy, but those age 25-34 years and HPV positive, cytology negative had colposcopy only if they remained HPV positive for one year. In Phase II, women were randomly assigned to either cytology alone or HPV test alone (no cotest). A Phase II colposcopy referral was the same for the cytology group, but for the HPV only group only women with a positive HPV test were referred for colposcopy. In the second round, only cytology was done. Follow-up was a median of 1,277 days. The number of invasive cancers diagnosed in the HPV test arm (N=7) was less than that diagnosed in the cytology arm (N=18, p=.028). In the first round of screening there were 7 cancers in the HPV group and 9 in the cytology group (p=.62), while in the second round there were no cancers in the HPV group and 9 in the cytology group (p=.004). Combining phases I and II, for women age 35-60 years, in both rounds, there were 106 women with CIN 3/AIS in the HPV group and 64 in the control group (Ratio of Detection (hereafter "RD") of 1.65, 95% CI 1.1.21-2.26). Combining phases I and II, for women age 35-60 years, in round 1, the HPV group had 98 CIN 3/AIS while the control group had 47 (RD 2.08 with 95% CI 1.47-2.95), while in the second round, the HPV group had 8 CIN 3/AIS while the control group had 17 (RD 0.48 with 95% CI 0.21-1.11). For the combined phase I and II, in women age 35-60 years, the rate of CIN 2 in the HPV group was higher (116) than in the control group (69, RD 1.68). Most of the excess CIN 2 in the HPV group was diagnosed in the first round of screening.

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Working Group 3a: Management of Women with HPV-Positive, Cytology-Negative Results

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Introduction

Combined cytology and HPV DNA testing* is one option for primary screening in women over age 30.[1] Women with both negative cytology and negative HPV testing are at very low risk of developing cervical cancer and may be followed conservatively at routine screening intervals.[2-5] Women with cytology alone of LSIL or worse or with HPV positive ASCUS cytology are at higher risk, enough to warrant immediate referral to colposcopy.[1] Managing women who are HPV positive, cytology negative is challenging. The majority of HPV infections are transient, but a small proportion is associated with prevalent cervical cancer precursors that may be missed by cytology alone.[6] The main charge for this working group was to identify and evaluate management strategies for women testing HPV positive, cytology negative in primary screening. Additional tasks were formulated to determine which HPV types should be included in genotyping tests to triage HPV-positive, cytology-negative women and to identify evidence for other potential uses for HPV genotyping.

Key Questions

1. Based on the trade-offs between potential benefits and harms expected for specific strategies for the management of women cotesting cytology negative but HPV positive, determine which strategies can be strongly or weakly recommended.

2. Because the potential benefits and harms of HPV genotype-specific testing may vary depending on the specific combination of HPV types being detected, determine which specific HPV types can be strongly or weakly recommended for inclusion when HPV genotype-specific testing is used.

3. Determine whether there are other clinical scenarios in which the trade-offs between potential benefits and harms warrant either a strong or weak recommendation for the use of HPV genotype-specific testing.

* HPV refers only to high-risk HPV. Other HPV types are unrelated to cervical cancer and should not be used in cervical cancer screening. Testing for low-risk HPV types has no clinical role in cervical cancer screening or evaluation of women with abnormal cytology.

Recommendations

1a. Women cotesting HPV positive, cytology negative should be followed with either: (1) repeat cotesting in twelve months, or (2) immediate HPV genotype-specific testing for HPV16 alone or for HPV16 and HPV18. (*weak recommendation)*

1b. If cotesting is repeated at 12 months, women cotesting positive on either test[*] should be referred to colposcopy. *(weak recommendation)*

1c. Women testing negative on both tests[**] should return to routine screening. *(strong recommendation)*

1d. Women who screen HPV positive, cytology negative may be tested with HPV 16 or HPV16/18 genotype-specific testing. If immediate HPV genotype-specific testing is used, women testing positive for HPV 16 or HPV16/18 should be referred directly to colposcopy. Women testing negative for HPV16 or HPV16/18 should be cotested in 12 months with management results as described for women triaged initially with repeat cotesting (option 1b). (*weak recommendation)*

1e. Women who screen HPV positive, cytology negative should not be referred directly to colposcopy. *(strong recommendation)*

1f. Currently, there is insufficient evidence to support the use of non-HPV biomarkers. *(weak recommendation)*

2. (collapsed KQ 2 & 3) HPV DNA genotype-specific testing should be limited to type 16 or types 16 and 18 combined and should not be used for indications other than the initial triage of women who screen HPV positive, cytology negative. *(strong recommendation)*

2a. Genotyping assays should include HPV16. *(strong recommendation)*

2b. Genotyping assays may include HPV16 and HPV18 combined. *(strong recommendation)*

2c. Women who screen HPV positive, cytology negative should not be tested for individual HPV genotypes other than HPV16 and HPV18. *(strong recommendation)*.

3a. The use of HPV genotype-specific testing is currently not clinically indicated other than for the initial triage of women who screen HPV positive, cytology negative. *(strong recommendation)*

[*] HPV positive OR LSIL or more severe cytology

[**] HPV negative AND ASC-US or negative cytology

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. 108 articles were identified and 47 articles were included to inform the recommendations of Working Groups 3a and 3b.

Rationale and Evidence

Proportion of HPV-positive, cytology-negative women in a screening population

The prevalence of HPV-positive, cytology-negative screening results was reported in nine studies (data reported in 10 papers, Table 1).[4,7-15] The percentage of HPV-positive, cytology-negative women ranged from 3.4% to 18.3% in various populations. The highest proportions were found among younger women. In women above age 30, the proportion ranged from 3.4-8.2%. The proportion of HPV-positive, cytology-negative women among a screening population of women ≥30 years was similar to the proportion of abnormal cytology results in that population (3.7% compared to 3.8% in the Kaiser Permanente Northern California Study of 330,000 women). A strategy of immediate colposcopy referral for HPV-positive, cytology-negative women would double the number of colposcopies compared to abnormal cytology alone.

Risk of CIN3 among HPV-positive, cytology-negative women

The risks of CIN2 or CIN3 among HPV-positive, cytology-negative women were reported in 11 studies (data reported in 14 papers, Table 2).[4,7,9,10,12-21] The studies and risk estimates were very heterogeneous, and varied by population, disease ascertainment, and follow-up time. Follow-up time ranged from 1-16 years. Estimates for short time intervals that are relevant for management decisions were presented in only a few studies. The estimate for 12-month risk of CIN3 ranged from 0.8%[4] to 4.1%.[7] A cumulative 2-year risk of CIN3 of 8-10%, which has been considered a threshold for referral to colposcopy based on ALTS,[22] was not reached in any study. However, results were reported heterogeneously, either showing baseline risk or cumulative risk over several years, complicating the use of this threshold.

Assessment of management options for HPV-positive, cytology-negative women

<u>Immediate colposcopy</u>

Based on the prevalence of HPV-positive, cytology-negative screenings in the above cited studies, immediate colposcopy referral would double current colposcopy referral rates. The 12-month risk of CIN3 in the referred population (0.8-4.1%) is clearly below the currently used risk threshold for referral (8-10%) (Table 2), indicating that most of the additional colposcopy referrals would be unnecessary.

Repeat cotesting in 12 months (current recommendation)

There are no studies directly comparing different modalities of repeat cotesting, e.g. varying different time intervals, multiple rounds of screening, etc. There are data from cohort studies showing that the majority of transient infections have cleared after 12 months.[23,24] There is programmatic evidence for repeat cotesting visits at 6 months (with colposcopy referral based on abnormal cytology but not on HPV positive alone) and 18 months (colposcopy referral for either HPV positive or cytology positive) after the primary screen for HPV-positive, cytology-negative women from a Dutch population-based screening trial.[25] This approach can reduce the number of colposcopy referrals compared to a single repeat cotest at 12 months. However, there is concern about substantial loss to follow up in countries without organized screening, such as in the U.S., when relying on two rounds of repeat testing. Modeling results indicate that the rate of colposcopy referrals is only slightly increased (7-11%) when routinely co-testing at 3-year screening intervals (and triaging HPV positive, cytology negative women with repeat co-test at 12 months), compared to cytology screening alone at 3-year intervals; when moving to 5-year screening intervals for co-testing, the rate of colposcopy referrals is decreased (17%) compared to cytology screening at 3-year intervals[26] (Table 3).

HPV16/18 genotyping (current recommendation)

Several cohort studies have provided type-specific risk estimates. Khan[19] noted a 10% risk of CIN3 after 1 year in women who tested positive for HPV16; Kjaer[20] observed a 10% risk of CIN3 after 4 years in women aged 20-29 who tested positive for HPV16. Khan[19] noted a 10% risk of CIN3 after 2 years in women who tested positive for HPV18; Kjaer[20] observed a 10% risk of CIN3 after 5 years in women aged 20-29 who tested positive for HPV18. One industry-sponsored trial (ATHENA)[7] valuated the triage of HPV-positive, cytology-negative women with HPV16/18 genotyping. In this study, subjects with positive HPV16/18 testing had an 11.4% risk of CIN2+ and 9.8% risk of CIN3+; subjects with positive HPV16 testing had a 13.6% risk of CIN2+ and 11.7% risk of CIN3+.

Based on the ATHENA trial, positive HPV16 or HPV16/18 genotyping surpasses an 8-10% risk threshold of prevalent CIN3. These studies justify a recommendation for immediate referral to colposcopy if genotyping is done and results are positive for HPV 16 or HPV16/18.

Other molecular markers

There is insufficient evidence to recommend for or against the use of other molecular markers in HPV-positive, cytology-negative populations, but studies are ongoing. The potential use of $p16^{INK4A}$ to evaluate HPV-positive women was demonstrated in a screening trial in Italy, but no data were reported for the HPV-positive, cytology-negative population in this study.[27]

Viral load has been proposed as an indicator of risk,[28] suggesting a strategy where only women with high viral load are referred for colposcopy. However the quality of evidence is currently low.

Research Priorities and Recommendations

The current recommendations for management of HPV-positive, cytology-negative women include repeat cotesting after one year or HPV16/18 genotyping. There are no data on the performance of repeat cotesting at this interval in this population, but there is no evidence to recommend against this strategy. Retrospective studies could easily be conducted to assess the rates of CIN3+ in HPV-positive, cytology-negative women who have persistent positive HPV testing or repeat cytology results of ASC-US or worse after 1 year. Independent studies should be conducted to confirm the findings on risk related to HPV genotypes in the ATHENA trial, and recommendations should be adapted as more data become available. Studies evaluating molecular markers such as $p16^{INK4A}$ and viral load testing in HPV-positive, cytology-negative women are needed. As with HPV genotyping studies, as more data from HPV-positive, cytology-negative women become available for other biomarkers, recommendations may need revision. In some European countries, cotesting with cytology is not being implemented, but cytology or a molecular assay may be reserved to triage HPV-positive women. Thus, the data generated from these non-U.S. sites may have only limited and indirect relevance to evaluate the management of HPV-positive, cytology-negative women.

Research Recommendations

- Evaluate management strategies in HPV-positive, cytology-negative women.
    - Evaluate optimal intervals and number of repeated cotesting (e.g. two rounds at 12 and 18 months vs. a single co-test at 12 months).
    - Confirm risk estimates for HPV16/18 genotyping.
    - Evaluate other molecular markers ($p16^{INK4A}$, mRNA) in HPV-positive, cytology-negative women.

Summary Tables

Table 1: Proportion of HPV-positive, cytology-negative women in a screening population

Study	Age	Population	HPV positive, cytology negative (n)	Population %	HPV test
Castle 2009[8]	≥30	797,927	31,837	4.0%	HC2
Clavel 1999[9]	15-72	1,518	168	11.0%	HC2
Cuzick 2003[10]	30-60	11,085	590	5.3%	HC2
Datta 2008[11]	<30 ≥30	5,648 3,693	1,034 304	18.3% 8.2%	HC2
Katki 2011[4] *	≥30	331,818	12,208	3.7%	HC2
Kjaer 2006[12]	20-29 40-50	7,218** 1,305**	1,229 47	17.0% 3.6%	HC2
Peto 2004[13]	20-64	6462	312	4.8%	MY09/11
Rozendaal 1996[14]	34-54	1622**	86	5.3%	GP5+6+
Thrall 2010[21]	≥30	2686**	146	5.4%	HC2
Wright 2011[7]	≥30	32,260	2161	6.7%	Cobas

* Subset of the population from Castle 2009[29]

** Restricted to women with normal cytology results

Table 2: Risk of high grade CIN among HPV-positive, cytology-negative women

Study	HPV positive, cytology negative (n)	Absolute Risk	Follow-up time	HPV test
Briolat 2007[16]	29	15 CIN2+	not reported	HC2
Castle 2002[17] *	2020	16.8% ASC+ 6.4% LSIL+ 2.2% HSIL+	57 months	HC2 (lavage)
Clavel 1999[9]	168	5 HG-SIL	12 months	HC2
Cuzick 2003[10]	590	3 CIN2, 12 CIN3	12 months	HC2
Katki 2011[4]	12,208	Risk of CIN3: <1% (year 1) 3.1% (year 3) 5.9% (year 5)	5 years	HC2
Khan 2005[19] *	1,021** (age ≥30)	CIR of CIN3+: 0.8 (total) 20.7 (HPV 16+) 17.7 (HPV 18+) 1.5 (other onco+) 0.5 (non-oncogenic)	10 years	HC2 (lavage)
Kjaer 2006[12] ***	1,229 (age 20-29) / 47 (age 40-50)	Risk of CIN3+: 2.2%/4.3% (year 3) 5.5%/9.3% (year 5) 13.6%/21.2% (year 10)	10 years	HC2
Kjaer 2010[20] ***	1281 (age 20-29)	Type specific risks reported Risk of CIN3+: 26.7% (HPV 16+, 12 years)	13.4 years	HC2
Peto 2004[13]	232	2 CIN2; 20 CIN3+ (next screen) 16% CIN3+ (10 years) 28% CIN3+ (14 years)	14 years	MY09/11
Rozendaal 1996[14]	86	2 CIN2 6 CIN3	40 months	GP5+6+
Thrall 2010[21]	146	3 HGCIN	18 months	HC2
Schiffman 2011[15] *	948 (age <30) 459 (age 30+)	Cumul prob CIN2+ 15.2% (age <30) 8.9% (age 30+)	16 years	HC2; MY09/11

Chen 2011[18]	784	41 cancers (CIS/ICC) Incidence: 370.8/100,000 py HR: 23.8 (overall); 11.0 (age 30-44); 35.2 (age 45-54); 48.5 (age55+) *For HPV16:* Incidence: 675.5 per 100,000 py HR: 43.6 Cumul risk CIS/ICC 13.5% (16+) 10.3% (58+, non-16) 4.0% (other oncogenic positive)	16 years	ViraPap
Wright 2011[7]	2161	6.1% CIN2+ 4.1% CIN3+ *For HPV16/18:* 11.4% CIN2+ 9.8% CIN3+ *For HPV16:* 13.6% CIN2+ 11.7% CIN3+	12 weeks	Cobas

* Different analyses and follow-up times in the same Kaiser Portland cohort

** Sample size approximation based on numbers indicated at 4.5 months follow-up (not enrollment)

*** Different analyses and follow-up times in the same Danish cohort

Table 3: Model-predicted colposcopy referral rates [26] *

		Colposcopy referrals (per 1,000 women) using test performance data from three different studies		
Strategy	Interval	Vesco et al.[30]	Mayrand et al.[31]	Koliopoulos et al.[32]
Cotest	5-year	625.91	347.79	907.30
Cytology	5-year	483.36	274.01	693.97
Cotest	3-year	824.74	446.38	1209.54
Cytology	3-year	758.16	416.44	1090.56

*Time horizon is a lifetime. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 years; women with normal cytology and HPV positive results are assumed to undergo repeat cotesting at 12 months, with referral to colposcopy for cytology result of ASC-US or worse or if HPV test is positive.

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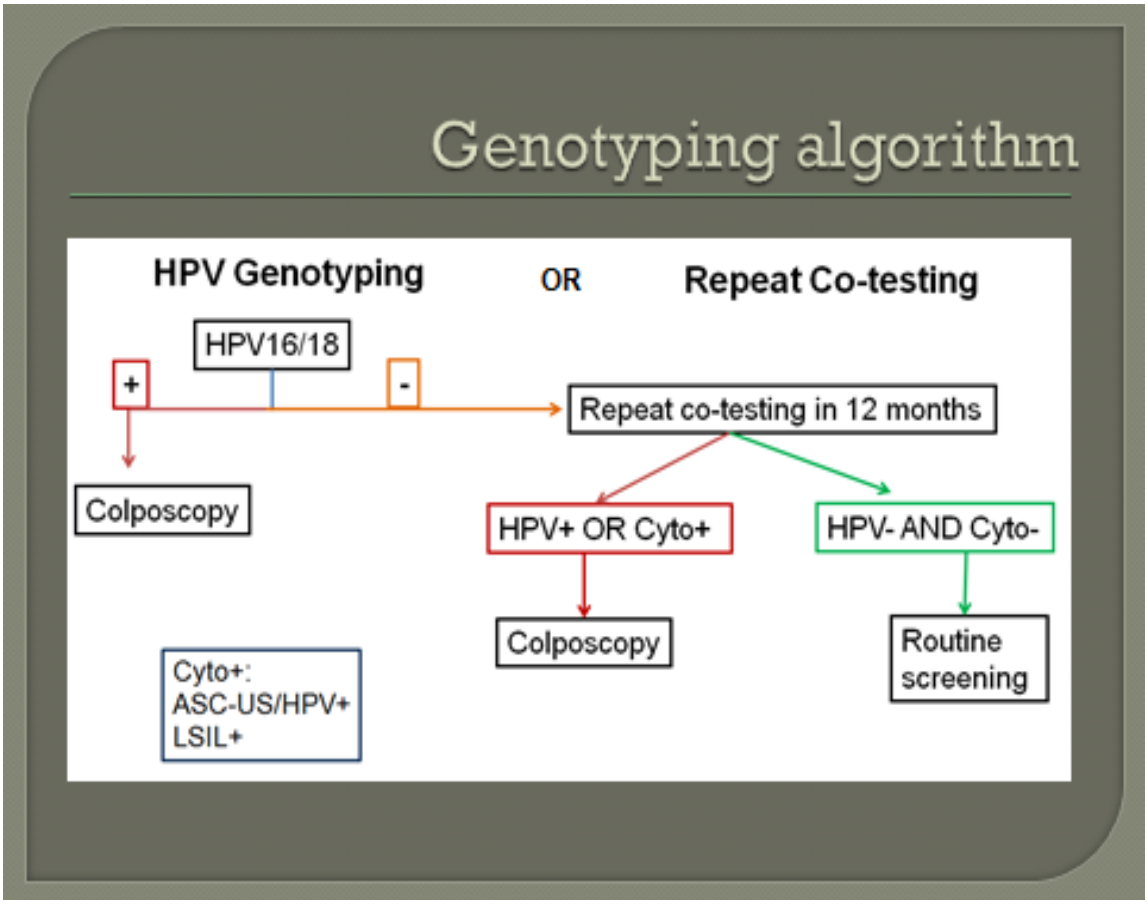

Working Group 3b: Management of Women with HPV Negative, Atypical Squamous Cells of Undetermined Significance (ASC-US) Results

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Introduction

Atypical squamous cells of undetermined significance (ASC-US) are often generated in response to events occurring in the vaginal environment that have nothing to do with high-risk human papillomavirus (HPV) or with neoplasia. The largest randomized trial on the management of ASC-US cytology, the ASC-US LSIL Triage Study (ALTS), demonstrated that women with HPV-positive ASC-US are approximately 18 times more likely to have CIN 2/3+ identified at initial colposcopy than women with HPV-negative ASC-US (20.0% vs 1.1%).[1] For this reason, testing for HPV* as the initial triage strategy for the management of women with ASC-US to determine risk for subsequent detection of CIN 2/3+ has become the "preferred" management strategy for women with ASC-US derived from liquid-based cytology.[2-4] Women positive for HPV are referred to colposcopy. Currently there is no age stratification except that HPV testing is done with ASC-US only in the ≥20 year old population.

The risk of CIN 2/3+ associated with an HPV-negative ASC-US cytology result is low. At the time the 2001 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for the management of women with HPV-negative ASC-US were initially discussed and ratified by a consensus conference, there were many proponents for consideration of designation of HPV-negative ASC-US as either "normal" or as HPV-negative ASC-US but with routine follow-up. However, the decision was made to not relegate HPV-negative ASC-US to either a normal cytology category nor to routine follow-up; instead 12 month repeat cytology was recommended.[2] The management of HPV-negative ASC-US was again widely discussed in the 2006 ASCCP Consensus Guidelines Conference, but was not changed.[3] The question remains as to whether the risk of CIN 2/3 for HPV-negative ASC-US is sufficient to require accelerated follow-up. Additionally, screening women ≥30 year with cervical cytology and an HPV DNA test provides further impetus to revisit this issue, as many women receive reports of HPV-negative ASC-US as a cotest result. Total ASC-US in the U.S. is estimated to be around 2 million per year or roughly 5% of total cytology tests, with about 50% testing negative for HPV.

* HPV refers only to high-risk HPV as other HPV types are unrelated to cervical cancer and therefore should not be used in cervical cancer screening. Testing for low-risk HPV types has no clinical role in cervical cancer screening or evaluation of women with abnormal cytology.

K**ey Questions**

1. What is the risk of CIN 3+ compared to the HPV- negative, cytology-negative population?
2. What is the risk of CIN 2+ compared to the HPV- negative, cytology-negative population?
3. Are there age-related differences in the above risks?
4. What should be the recommended follow-up of this population?
5. Are there age-related differences in follow-up?
6. Are there associated quality of life issues for women with HPV-negative ASC-US that might affect follow-up?

Recommendation

Women with ASC-US cytology and a HPV-negative test result should continue with routine screening as per age-specific guidelines. (*weak recommendation)*

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. 108 articles were identified and 47 articles were included to inform the recommendations of Working Groups 3a and 3b.

Rationale and Evidence

The current ASCCP and American College of Obstetricians and Gynecologists (ACOG) management guideline for women with ASC-US for which an HPV test is negative is to repeat the cytology in 12 months. The very low risk of CIN 3+ in the longest (0.85%; 5-year cumulative)[5] and the biggest (0.28%; enrollment – 47,208)[6] studies, along with the Katki data that showed little benefit from cytology above and beyond the utility of an HPV test, would argue for extending the interval of follow-up studies to a minimum of 3 years. Recommended follow-up methods are either cytology alone every 3 years or HPV and cytology cotesting every 5 years, consistent with routine screening as per age-specific guidelines. Based on the lack of direct prospective study evidence for either of these methodologies, this would be a recommendation based on strong but observational evidence. This recommendation applies only to ASC-US cases and not to ASC-H or AGC. No age stratification of this recommendation is warranted based on the studies reviewed.

There were 11 papers reviewed from which data on absolute and relative risk of CIN 2+ and/or CIN 3+ could be determined. For the purposes of this recommendation, absolute risks of CIN 2/3+ were considered most highly. Relative risks were compared between HPV-negative ASC-US and HPV negative, cytology negative (2 papers); and HPV-negative ASC-US and HPV-positive ASC-US (9 papers). The comparison between a HPV-negative ASC-US result and HPV-negative, cytology-negative result was considered most relevant for this recommendation. Both are given as these two comparisons show both the closest adjacent "low side" and "high side" comparators.

Risk of CIN 2+

The absolute risk ranged from a low of 0% to a high of 1.2%[7] based on enrollment data (0[8], 0.75[6], 1.2[7]); 3% to 4.3% based on 2-year cumulative data (3[9], 3[10], 4.3[11]); and in a 5-year cumulative study was 1.3%.[5] The relative risk of CIN 2+ for HPV-positive ASC-US compared to HPV-negative ASC-US ranged from a low of 4.1 to a high of 21 (4.1,[11] 8.3,[10] 14,[12] 18.6,[6] 20,[5] 21[7]).

Risk of CIN 3+

The absolute risk was 0.28%[6] based on enrollment data (one study); 1.4%[10] to 1.4% (HC2) or 1.9% (PCR)[9] based on 2-year cumulative data (two studies); and 0.54% in a 5-year cumulative study.[5] The relative risk of CIN 3+ for HPV-positive ASC-US compared to HPV-negative ASC-US ranged from 5.6 to 29.7 (5.6[11], 10.8[10], 16[5], 24[12], 29.7[6]).

As supporting comparison of the absolute risk of CIN 2+ and CIN 3+ in the cytology-negative population, Wright[13] noted absolute risks of 0.8% (CIN 2+) and 0.3 (CIN 3+) when the HPV test was negative, and relative risks of 7.3 (CIN 2+) and 14.4 (CIN 3+) comparing HPV-negative to HPV–positive, cytology-negative patients (enrollment data). The Katki study reported an absolute risk of CIN 3 or worse (5-year cumulative) in the HPV-negative, cytology-negative population of 0.16%.[5]

There was only one study which made recommendations for follow-up in the HPV-negative ASC-US population.[5] Conclusions from their study (which had very low rates of cumulative CIN 3+ (0.86%) in a 5-year follow up) suggest that a negative HPV test confers an "extremely" low risk of CIN 3+ at 5 years, that a negative cytology result confers no extra reassurance beyond the negative HPV result, and that an ASC-US also did not affect the risk of CIN 3+ in either the 3- or 5-year follow up period for patients negative for HPV. Katki, et al.suggest that screening intervals should be the same for HPV-negative patients regardless of an ASC-US or cytology-negative result, and that that interval should be 5 years.

Quality of Life Issues

One study[14] dealt with quality of life issues in patients triaged to various follow-up methods [HPV, cytology, or informed choice (where the patients were educated on the pros and cons of the triage methods)]. The study showed that at 2 weeks, quality of life issues scored worse for those triaged to HPV compared to cytology, but this changed at 12 months when HPV and informed choice scored better than cytology. The authors concluded that HPV testing most likely brought closure better than waiting long periods for a repeat cytology examination.

Research Priorities and Recommendations

Large prospective studies are required to assess the best follow-up interval for HPV-negative ASC-US cases.

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Working Group 4: Exiting Women from Screening

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Introduction

Although USPSTF, ACS, and ACOG have recommended that women with a history of negative cervical cytology screenings may or should exit screening at age 65-70, many clinicians continue to screen women though their 80s. The charge to this committee was to determine the potential benefits and harms of exiting screening and whether exiting screening can be strongly or weakly recommended.

Key Questions

1. (collapsed KQ 1 & 2) For women age 65 years and older with adequate negative prior screening, should cervical cancer screening be recommended?

2. For women with CIN2+ following treatment and either 2 negative cytology results (at 6 and 12 months) or 1 negative HPV result (at 6 or 12 months), for how long and at what interval should cervical cancer screening be recommended?

3. For women at any age, with or without adequate negative screening and no history of cervical pre-cancer or cancer, should vaginal screening be recommended following a complete hysterectomy (with removal of the cervix)?

4. For women who have exited screening (due to age or hysterectomy) should screening resume if a woman has a new sexual partner?

Recommendations

1. Women over 65 years of age with evidence of adequate negative prior screening[*] and no history of CIN2+ or cervical cancer within the last 20 years should not be screened for cervical cancer with any modality. *(weak recommendation)*

2. Following spontaneous regression or appropriate management of CIN2, CIN3, or AIS, routine screening (as defined in these guidelines) should continue for at least 20 years (even if this extends screening past age 65). *(weak recommendation)*

[*] Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the last 10 years before ceasing screening, with the most recent test being within the past 5 years.

3. Women at any age following a hysterectomy with removal of the cervix and no history of CIN2+ should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. *(strong recommendation)*

4. Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner. *(strong recommendation)*

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. 102 articles were identified and 53 articles were included to inform this set of recommendations.

Rationale and Evidence

Women older than 65 years of age

We sought to identify published articles where the following interventions were evaluated in women older than 65 years: a) cytology every 5 years vs. no screening, b) cytology every 3 years vs. no screening, c) HPV with cytology (i.e. cotesting) every 5 years vs. no screening, and d) cotesting every 3 years vs. no screening.

We identified only one study that modeled adequate negative screening to age 65 and then no further screening vs. screening with cytology alone every 3 years or every 5 years.[1] According to mathematical modeling, among women who have been screened every three years prior to age 65, continued screening even to age 90 prevents only 1.6 cancer cases and 0.5 cancer deaths per 1000 women. It extends life expectancy by only one year per 1000 women or less than one day per woman while resulting in 58 extra false positives, 127 extra colposcopies and 13 extra CIN2/3 requiring treatment. The authors describe that screening in this population yields small gains in life expectancy associated with a large number of colposcopies. There are additional studies that support this recommendation, but they do not meet the criteria to be considered in the GRADE/PICO review system.

Since the transformation zone of older women is smaller and less accessible than in younger women and since cervical cancer develops many years after an incident infection, screening this population would detect a very small number of new cases of CIN2+ and prevent very few cervical cancers and even fewer cancer deaths. The extended natural history of the disease also makes it less likely that newly detected CIN3 will have time to progress to invasive cancer in the woman's lifetime. There is also evidence that screening is associated with potential harms, including anxiety and discomfort during cytology sampling of some older women due to vaginal atrophy and cervical stenosis. The choice of exact age at which to cease screening is arbitrary. The choice of age 65 is based on the opinions of the expert panel members in an effort to balance the benefits and harms of screening older women. Some organizations have

chosen the age of 65 in their guidelines,[2] while others have chosen the age range 65 to 70.[3] Both are arbitrary. In the previous guideline review,[4] ACS set the age at 70 based on concerns about increased life expectancy and changes in sexual behavior (i.e. more women were having new sexual partners at older ages). We set the age at 65 in an attempt to coordinate with the USPSTF and hope that ACOG will modify their recommendations, giving practitioners a strong unified opinion that will minimize guideline confusion and increase compliance. Older women who choose to discontinue screening should continue to obtain appropriate preventive health care. Finally, there is no evidence to indicate whether women with a history of cervical cancer, those with in utero exposure to DES, and women who are immunocompromised (including HIV-positive women) should discontinue screening or a specific age at which to stop screening.

In well screened older women, HSIL rates are low[5] and cervical cancer is rare.[4] Most new cases of cervical cancer in U.S. women $\geq$65 years are in unscreened or infrequently screened women.[6,7] Reducing the burden of cervical cancer on older women is likely best achieved by focusing on screening those who have not been adequately screened. In a recent review on screening intervals and age limits, Sasieni and Castanon[8] note that a Markov model for disease progression produced by Fahs and colleagues determined that screening women older than age 65 years with previously adequate screening history would be inefficient.[9,10]

Women with a history of CIN2, CIN3, or adenocarinoma *in situ*

For key question 2 we sought to identify published articles where the following interventions were evaluated: a) routine screening vs. cytology annually for 5 years then routine screening, b) cytology annually for 5 years then routine screening vs. cytology annually for 10 years then routine screening, c) cytology annually for 10 years then routine screening vs. cytology annually for 15 years then routine screening, d) cytology annually for 15 years then routine screening vs. cytology annually for 20 years then routine screening, and e) cytology annually vs. cotesting every 3 years. We were unable to find any published articles meeting these criteria.

We were able to identify studies that did not meet GRADE criteria for recommendations but do offer data to guide our recommendation. As reviewed in the report by The Oregon Evidence-based Practice Center, women previously treated for CIN have a higher risk of later cervical cancer.[10] A cohort study in Finland found increased risk of cervical cancer in women treated for any CIN, compared to a standard population, although no increase in cervical cancer mortality was found in the same cohort.[11,12] Another cohort study in Sweden found increased cervical cancer risk after CIN3 treatment with greater risk for women aged 50 years and older, compared to younger women.[13] Thus they conclude that older women with a history of treatment for CIN represent one high-risk group who could continue screening. Kocken et. al. reported risk of recurrent CIN2+ and CIN3+ of 3.5% and 0.4% respectively in women who had negative screening at 6, 12 and 24 months; and a risk of 2.4% and 0.4% in women who were negative for cytological and HPV cotesting at 24 months.[14] A systematic review reported that the incidence of invasive cervical disease in treated women remains about 56 per 100,000 woman-years for at least 20 years after treatment, substantially greater than that in the general

U.S. population (5.6 per 100,000 woman-years),[15] suggesting the need for decades-long follow-up. These data suggest that risk for recurrent dysplasia and cancer remains high after treatment of CIN2+ and that screening should at least mirror that of the general population based on age and prior method of treatment (i.e. we should perform vaginal screening in patients who received hysterectomy for treatment of CIN2+). We endorse the ASCCP guidelines for continued regular screening of these women for 20 years after an initial period of more intense surveillance, even if that extends screening past age 65. We define *regular screening* as screening every five years using cotesting (preferred) or every three years using cytology alone (acceptable).

Women who have undergone hysterectomy and have no history of CIN2+

We sought to identify published articles where no screening vs. routine screening was evaluated. We were unable to find any published articles that meet GRADE criteria to address this key question.

As reviewed in prior ACS guidelines, use of cytology tests in women who have had their cervix removed for benign reasons screens the vaginal cuff. The incidence rates for all vaginal cancers combined were 0.18 per 100,000 female population for *in situ* cases and 0.69 for invasive cases.[16] The age-specific incidence is similar to or less than other cancers for which screening is not performed, such as breast cancer in men. Abnormal vaginal cytologic results are uncommon and rarely of clinical importance.

A retrospective cohort study of vaginal cuff cytology tests in 5,862 women who had undergone a hysterectomy for benign disease found abnormal results among 79 women (1.1 percent of all tests). The mean length of time from hysterectomy to abnormal cytology result was 19 years. The positive predictive value for detection of vaginal cancer was 0 (95 percent CI 0 to 33 percent).[17] A 10-year retrospective study among 697 women after hysterectomy for benign disease found that 663 vaginal cuff smears were needed to detect one case of vaginal dysplasia.[18] A retrospective study of 220 women selected at random from 2,066 women who had a previous hysterectomy for benign conditions and followed for an average of 89 months identified seven patients (three percent) who had intraepithelial cytologic abnormalities, but no vaginal cancers. Four of these patients underwent successful excision or laser treatment of the lesions, and dysplastic lesions in the remaining three patients regressed without any treatment. No benefit in patient outcomes was observed.[19] A cross-sectional study of 5,330 screening cytology tests in women who had had a hysterectomy found one case of dysplasia and no cancers.[20] In a study of 193 women with CIN at hysterectomy, the incidence of abnormal vaginal cuff cytology at least two years after hysterectomy was 0.7 per 1,000, and at 20 years 96.5 percent of the women continued to have normal cytology.[21]

Despite there being no direct evidence on the benefits and harms of vaginal screening after hysterectomy where our interventions or critical outcomes are addressed, based on observational studies and primarily on the very low incidence of vaginal cancer in the general population we recommend that these women not be screened.

Women who have exited screening (due to age or hysterectomy) and who have a new sexual partner

We sought published articles where the following interventions were evaluated: a) no screening vs. routine screening until adequate negative screening, then no screening and b) routine screening until adequate negative screening, then no screening vs. routine screening. There are no published reports that evaluated these interventions in our population.

Indirect evidence regarding the risk of not screening this population is found in the report by Chen et. al.[22] They performed a longitudinal study of women with negative cytology who were negative for HPV DNA at baseline and two years later. Newly detected infections were associated with very low absolute risks of persistence and CIN3+ regardless of the woman's age. Furthermore, in women aged 55 and older after two negative HPV tests two years apart the risk of subsequently developing CIN3 or cervical cancer was only 0.08% with only one woman developing CIN3 after 9.6 years.[22] In another large 7- year, population-based cohort study, newly detected infections were associated with very low absolute risks of persistence or progression. The rate of progression to CIN2+ (or CIN3+) after 3 years of follow-up was not higher for women aged 34 years and older than for younger women.[23] Based on this we can extrapolate that a new carcinogenic HPV infection in a woman with a cervix at age 65 years or older would clear spontaneously in most cases, and that only a small percentage of these patients would have persistent infection. Further we can extrapolate that since cervical cancer develops at a median 15-20 years after this incident infection, this would require routine screening for the purpose of detecting a very small number of new cases of CIN2+ at age 80 years or older. The risks associated with over treatment in the elderly population seem to outweigh the benefits. Thus, we do not recommend routine screening in this population.

Research Priorities and Recommendations

The most important research priority involves identifying strategies to increase screening coverage in unscreened or under-screened women, in whom a significant proportion of invasive cancers occur.

The incidence of new infections declines sharply with increasing age. They are usually benign regardless of a woman's age. It is long-term HPV persistence that causes cervical cancer, and carcinogenesis typically takes decades from infection to cancer. The great majority of cervical cancer cases arise from HPV infections that persist from acquisition at younger ages. Thus, it might be safe for consistently HPV-negative women to stop cervical cancer screening at younger ages than the 65 years recommended in these guidelines. Prospective studies among

older women are needed to establish the optimal age to cease screening among known HPV-negative women.

The recommendation for long-term follow up of women following treatment or spontaneous resolution of CIN2+ is based on evidence of an increased risk of recurrent disease in women who were followed with cytology. It is possible that in women with one or two negative post-treatment cotests, the prevalence of recurrent disease will be much lower and comparable to the general screening population. Long- term follow up studies are needed to establish the true risk of recurrent disease in women with negative post-treatment cotests.

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Working Group 5: Looking to the Future – Impact of HPV Vaccination

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Introduction

Prevention of cervical cancer in the U.S. has relied historically on screening tests that are capable of detecting treatable precancerous lesions. The mandate of this workshop is to define the "best" screening strategies based on the current literature. Prevention of cervical cancer has recently shifted to include protection from human papillomavirus (HPV) infection, the cause of cervical cancer, with a prophylactic HPV vaccine. How these two prevention efforts will "mesh" remains uncertain because of numerous factors which will influence cost-effectiveness and patient safety. Such factors include timing of vaccination versus exposure, durability of protection, vaccine coverage, and screening test performance. Currently, no randomized trials have examined performance characteristics of screening tests in a vaccinated cohort. Many published articles have discussed the impact the HPV vaccine may have on pre-invasive cervical cancer and implications for screening. These articles have centered on observational data, discussions, modeling, policy issues, but none include direct empirical data on which to base their results. Although there is no evidence to date to change the screening age or interval in the U.S., both screening age and interval are likely to change because of emerging evidence about vaccinated women. We review the evidence to date, projected models and gaps in knowledge and recommendations for research that will be needed to obtain substantial evidence to change current screening guidelines.

Key questions

1. For individual women vaccinated against HPV 16/18, should screening (cytology or HPV testing) begin at age 25 vs. 21?

2. For individual women vaccinated against HPV 16/18, should cytology vs. HPV testing be used for cervical screening? At what interval (e.g. 1, 2, 3, or 5 years)?

3. Should screening recommendations differ for cohorts of women vaccinated against HPV 16/18? At what population vaccine coverage with all three doses prior to age 16 (e.g. 30%, 50%, 70%, 80%)?

Recommendation

Screening practices should not change on the basis of HPV vaccination status.

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. Eighty articles were identified and 33 articles were included to inform this set of recommendations.

Evidence and Rationale

Vaccine performance

In the United States, the quadrivalent vaccine (HPV4; Gardasil, Merck and Co, Inc.) and the bivalent vaccine (HPV2; Cervarix, GlaxoSmithKline) have been licensed by the Food and Drug Administration (FDA) and recommended by the Advisory Committee on Immunization Practices for use in adolescent and young adult females to prevent cervical cancer.[1] HPV4 vaccine is also recommended for prevention of genital warts in females.[1] The vaccine is recommended routinely for girls ages 11-12 with catch-up for those girls or women ages 13-26 who haven't received the vaccine. HPV2 and HPV4 vaccines are both directed against two oncogenic types (HPV 16 and 18) estimated to be responsible for around 70% of cervical cancers, 65% of HSIL and 30% of LSIL. HPV4 is also directed against two non-oncogenic types (HPV 6 and 11), estimated to cause 90% of genital warts, 8 % of LSIL and <1% of HSIL.

Vaccine Efficacy

Recent HPV vaccination clinical trials (both Phase II and III) have shown considerable protection against HPV and more importantly, some of these seminal trials have also demonstrated reduction of cervical disease in the context of a clinical trial setting. A double-blinded, randomized controlled Phase III trial evaluating the efficacy of the bivalent (HPV16/18) ASO4 adjuvant vaccine showed a 61.9% reduction ($p < 0.0001$) of CIN2+ associated with any oncogenic HPV type.[2, 3] In 2007, an analysis which combined four randomized clinical trials (RCTs) (three with the quadrivalent vaccine and one with the monovalent, HPV-16, vaccine) revealed a 44% reduction in HPV 16/18 related CIN2/3 or AIS, with specifically a reduction of 50%, 39% and 54% reduction of CIN2 CIN3, and AIS , respectively (in the intention-to-treat population).[4] Another combined analysis of two Phase III efficacy trials of the quadrivalent HPV vaccine[5, 6] sought to determine the reduction of CIN and AIS not associated with HPV 6/11/16/18. A 29.2% reduction of HPV-31/33/45/52/58 -associated CIN1-3/ AIS was observed in this analysis. An overall reduction of 32.5% for CIN2-3/AIS associated with the 10 non-vaccine high risk HPV types was seen in this study, and the most notable effect was seen with HPV-31.[7] Another study that assessed the longer term efficacy of the bivalent vaccine ASO4 adjuvant vaccine demonstrated a 71.9% reduction of CIN2+ associated with any HPV type. This

reduction was observed up to 6.4 years.[8] Although there is a significant reduction of HPV-associated disease, abnormal cytology and CIN2/3 continue to appear at low rates even in the vaccinated cohorts.

Vaccine coverage in the U.S.

The large clinical trials showed that the vaccine has the greatest efficacy if given to HPV naïve women (i.e., prior to exposure to infection). Consequently, ACIP targeted an age group that is likely not yet sexually active, recommending routine vaccination of females 11 or 12 years of age with three doses of either HPV2 or HPV4 vaccine.[3, 7] Catch up vaccination with either vaccine is also recommended for females 13 through 26 years of age who have not been previously vaccinated or who have not completed the full series.[9] This was based on the observation that most of the sexually active women in the trial did not have evidence of previous exposure to the 4 vaccine types. The high efficacy of the vaccine in the trials was demonstrated in a population where all the women received all three doses on schedule. Since the ACIP recommendations in 2006, HPV vaccine coverage of adolescent females has been monitored via the National Immunization Survey, a random-digit-dialing telephone survey followed by a mailed survey to children's immunization providers. In the latest survey, 48.7% of females ages 13-17 had their first dose of the HPV vaccine and 32.0% reported all 3 doses.[10] While HPV vaccine coverage varies by state (HPV vaccine 1st dose coverage ranges from 73% in Rhode Island to 29% in Idaho), there is also substantial difference by racial/ethnic groups. Fewer White adolescent females initiated the HPV series than Hispanic and American Indian/Alaska Native females. Among females who initiated the series and had sufficient time to receive all 3 doses by the survey date, Black and Hispanic females were significantly less likely to complete the HPV series than White females. Although there are no disparities by poverty status for the 1st dose of HPV, adolescent females below the poverty status are less likely to complete the HPV vaccine series compared to those above the poverty status. Among adult females ages 19 to 26, reporting is from self-reported surveys like the National Health Interview Survey, which shows that in 2009, 17% of 19-26 year old females report having received at least one dose of the HPV vaccine, an increase of 6.6% from the previous year.[11] Again, substantial racial/ethnic disparities exist, with approximately 20% of white women from this age group reporting receipt of at least one dose and approximately 13.3 of black women and 12.6% of Hispanic women reporting the same. Previous analysis found that more than half of the women getting at least one dose completed all 3 doses, but variation did occur by demographic characteristics.[12]

The lack of good coverage remains a considerable barrier to making any changes in cervical cancer screening. However, the coverage threshold at which changes would be cost-effective for the population and yet safe for the individual remains unknown. This likely will be influenced by how herd immunity will impact the prevention of significant cytologic abnormalities. Even in countries with high coverage, changes to cervical screening practices are not immediately anticipated without empirical data. Both ACIP and ACS have emphasized that vaccinated women should continue cervical cancer screening per guidelines. The rationale for

these recommendations were many[9, 13] but includes the fact that there are many other oncogenic HPV genotypes not targeted by the HPV 16/18 vaccines.

Type-specific prevalence and impact of vaccine on abnormal cytology in young women

The potential impact of the HPV vaccine can be extrapolated from the results of the prophylactic HPV vaccine trials. Munoz et al[14] reported on 17,622 women aged 16-26 who participated in one of two multinational phase III trials of a quadrivalent HPV vaccine. Subjects were restricted to ≤ 4 lifetime sexual partners and had no history of abnormal Pap tests or genital warts. The prevalence of any of 14 HPV types tested at enrollment was 32.4%. Among the ITT population, vaccination reduced the incidence of any high-grade cervical lesions, irrespective of causal HPV type, by 19% (95%CI 7.7-28.9%; 520 CIN2+ lesions among placebo recipients vs. 421 among vaccine recipients). In addition, an 11.3% reduction in abnormal Pap tests and a 23% reduction in cervical treatments were also seen. The authors predicted that, per 100,000 women vaccinated, 1,320 Pap test abnormalities, 1,280 colposcopies, and 590 cervical treatments could be prevented annually. Enrollment restrictions in this study, however, limit generalization of these results to the population at large.

It is also useful to examine HPV type-specific prevalence by age and grade of cervical cytology outside of the vaccine trials, since these enrolled women selected on number of sexual partners and history of previous HPV disease. The ARTISTIC trial, from the United Kingdom NHS Cervical Screening Programme, is a population-based trial of 24,510 women aged 20-64.[15] The trial compared the sensitivity and cost-effectiveness of liquid based cytology ± HPV testing. HR HPV infections were more common in women under 30 years of age. In women aged 20-29, HPV 16, 18, 52, 51 and 31 were most common. In these young women, about 40% of HPV 16/18 infections occurred in women with other HR HPV infections. Multiple infections were less common in women 30+. Two limitations in interpretation of the trial were that a large number (31.5%) of hc2 positive samples could not be verified for the presence of the hc2-HR HPV types using line blot assay and also that low risk HPV 6 and 11 were not considered. Sargent et al calculated that, when multiple infections were taken into account along with negative hc2 samples, there would be a 45% reduction in the number of women with HSIL but only a 7% reduction in the number of low-grade lesions. The paper concluded that the majority of low-grade lesions will not be reduced by vaccination and that HSIL will be reduced by only 45-66% in young women vaccinated against HPV 16/18. Absolute relevance to the U.S. is not known, since the U.S. has no organized screening program.

In general, data regarding HPV genotype distribution in pre-invasive and invasive cervical cancers in the U.S. are sparse. Wheeler et al studied 1200 *in situ* and 800 invasive cancers from the 1980s to 1999. Among *in situ* cervical cancer cases, 56.3% were attributed to HPV 16, 12.6% to HPV 31, and then 8% to HPV 33. The most common genotypes in invasive cancers were HPV 16 followed by HPV 18 and HPV 45 reflecting 70 of cancers. Interestingly, HPV 16 and 18 were diagnosed at younger ages than non HPV16-18 cancers including HPV 45 cancers (mean age of diagnosis for HPV 16, 18 and 45 was 48.1 vs. 45.9 vs. 52.3 years, respectively).[16] More

importantly, they were able to show that the proportion of HPV 16 *in situ* and invasive cancers declined with more recent years of diagnosis. Implications from these suggest that, given the younger age of diagnosis of HPV 16/18 cancers, it may be reasonable to expect that the effect of vaccination will be greater in young women.

Potential real-life impact of the HPV vaccine

Australia's HPV vaccination programs started in 2007 and targeted 12-13 and 15-18 year olds in school programs with a catch up for the 13-15 year olds starting in 2008. The three-dose vaccine coverage estimates were 79% in first year high school students. Brotherton et al[17] reported on cytology and histology results by age using data from the country's National Cervical Screening Program and compared rates of abnormalities by age between a pre- (1/2003- 3/2007) and a post-vaccination period (4-2007 to 12-2009). In women < 18 years of age, the incidence of high grade histologic abnormalities (HGA) decreased from 0.85% pre-vaccination to 0.22% post-vaccination (p=0.003). No significant change was noted in the women aged 18-20, and no decrease was noted for low-grade cytologic abnormalities in either age group. In the < 18 year olds, the incidence rate ratio (per 3 month interval) for high grade abnormalities was 0.99 (0.96-1.02) before and 0.87 (0.78-0.97) after vaccination, demonstrating a linear trend for a decrease in HGA after introduction of the vaccine. This was not seen for the 18-20 year olds. Limitations include a young population currently not undergoing screening for cervical cancer in the U.S., a potential time bias introduced as the numbers of women <18 years undergoing screening significantly declined during the observation period, and the fact that the data are not linked with vaccine status. Although these are promising data, linkage between screening and vaccine registries needs to occur to permit estimation of the true impact of vaccination on lesion rates. Even Australia has not changed the previous recommendation to begin screening at age 18, given the Brotherton study.[17]

Models of the impact of HPV vaccine

Each year in the United States, the total costs of following up abnormal Pap test results exceed the total costs of treating invasive cervical cancer.[18] Thus, reductions in abnormal Pap tests and precancerous lesions are an important potential health and economic benefit of HPV vaccination. Mathematical modeling is useful in assessing the timing and magnitude of potential reductions in these outcomes.

Notable lifetime reductions in CIN2/3 prevalence would be observed in vaccinated cohorts of 12-year-old girls compared to non-vaccinated cohorts, according to a model calibrated to match epidemiologic data in Spain.[19] Specifically, the model predicted that fully vaccinated cohorts would achieve a 95% lifetime reduction in CIN2/3 associated with HPV 16 and 18 and a 75% reduction associated with all oncogenic HPV types.

In a model using Canadian-specific data regarding demographic, screening, and treatment parameters, HPV vaccination was predicted to reduce the lifetime risk of CIN2/3 by 47% overall.[20] Substantial reductions in CIN3 were also predicted in the United Kingdom as a result of HPV vaccination.[21] Specifically, the 80% vaccine coverage of girls aged 12 to 13 years was expected to lead to a 51% reduction in CIN3 and a 27% reduction in cytological abnormalities in women aged 20 to 29 years. However, for an HPV vaccine program initiated in 2008, it may be 2025 before reductions are observed. Reductions in cytological abnormalities and CIN3 were expected to be observed sooner in areas where screening starts at age 20 years than in areas where screening starts at age 25 years.

In the U.S., over the long term, vaccination of females is projected to reduce CIN2/3 attributable to HPV vaccine types by about 70% under base-case coverage assumptions.[22, 23] The magnitude and timing of the predicted decrease depend not only on coverage of 12-year-old girls but also on catch-up coverage of females over age 12 years. Examples of the potential impact of HPV vaccination on CIN2/3 over time under different coverage assumptions are shown in Figure 1.

Models of the cost-effectiveness of HPV vaccine

A consistent finding across modeling studies is that the addition of HPV vaccination of pre-adolescent girls to an existing cervical cancer-screening program can be a cost-effective use of public health resources.[24] Models also suggest that HPV vaccination could be even more cost-effective if, over time, cervical cancer screening programs were modified (i.e., delayed age of onset of screening and reduced frequency of screening) as a result of vaccination.[25-28]

Several published modeling studies illustrate the potential for HPV vaccination to facilitate less frequent screening while achieving overall gains in life expectancy and reductions in cost compared to the baseline screening strategy before onset of HPV vaccination. In the U.S., for example, a strategy of HPV vaccination combined with cervical cancer screening every 5 years

beginning at age 25 could result in greater quality-adjusted life expectancy and lower costs than a strategy of cervical cancer screening (without HPV vaccination) every 2 years beginning at age 21 years.[25] When applying the same modeling approach to Spain-specific data, results suggested that HPV vaccination combined with screening every 4 years with onset at age 25 years could reduce cervical cancer incidence by as much or more than a strategy of annual screening beginning at age 18 years (without HPV vaccination), at a lower cost.[29] Another model, using Australian data, suggested that HPV vaccination in combination with screening every 3 years beginning at age 25 years could result in lower costs and greater life expectancy than a screening-only strategy of every 2 years beginning at ages 18 to 21 years.[30]

Although numerous models suggest that current cervical cancer screening recommendations could be modified after onset of HPV vaccination programs, there is no clear consensus of what the "optimal" screening recommendations might be in the context of HPV vaccination. A general area of agreement, however, is that it will take more than a decade to see the full impact of vaccination on screening outcomes in young women.[21, 23] As a result, changes in screening recommendations in the context of HPV vaccination will likely not be warranted in the immediate future.[27, 31] Another important consideration is to ensure that benefits of vaccination are not offset by reductions in screening coverage due to complacency or an erroneous belief that vaccination eliminates the need for screening.[25, 28, 32, 33] One study, for example, suggested that with vaccine coverage of 12-year-old girls at 84%, a reduction of screening from about 80% coverage to about 60% coverage could lead to reductions in life years compared to no HPV vaccination with 80% screening coverage.[33]

Finally, an additional type of modeling work involves the prediction of the impact of vaccination on the performance of screening. The expected impact of vaccination in reducing the prevalence of cervical lesions will likely reduce the positive predictive value of screening tests. Deterministic[34] and stochastic[35] models have been proposed to analyze the potential changes in performance of Pap cytology screening subsequent to vaccination. Although not empirically based, these models provide valuable insights concerning the role of cytology or other core technologies used in screening and alert to the need for reassessment of future screening practices to guarantee acceptable quality and safety.

Potential Benefit and Harms

Potential benefits of HPV vaccination include decreased abnormal cervical cytology, decreased pre-malignant cervical disease and therefore fewer procedures related to these gynecological diagnoses. End-of-study results from the quadrivalent HPV vaccine trials have been reported, and these women were followed for an average of 3.6 years post vaccination.[14] This publication summarized findings in subjects who were naïve to HPV, approximating a population vaccinated prior to sexual debut. There was an overall reduction of 17.1% in abnormal cytology, a 19.8 % reduction in colposcopy, a 22 % reduction in cervical biopsies and a 42.3 % decrease in treatment for pre-malignant cervical lesions. An individual woman who is vaccinated prior to sexual activity should experience these benefits. However, the duration of protection after HPV vaccination is unknown at this time and subsequently the duration of these benefits is unknown. This same study also presented an ITT analysis, which included women who may have been previously exposed to HPV. This analysis showed an 11.3 % reduction in abnormal cytology and a 23 % reduction in treatment for pre-malignant cervical disease.

Although the vaccine studies showed that getting three vaccine doses is highly protective, the populations in these studies were closely observed with intensive cytology and included screening starting at ages 15 or 16 years of age; hence there are no data on the "individual" to show that either postponing screening or increasing intervals is safe in a woman vaccinated with HPV before or after onset of sexual activity. Vaccine trial data based on intention-to-treat (ITT) analysis show that reduction in abnormality rates is far less than those observed in the per protocol (PP) analyses and that abnormalities from all HPV types continue with a much lower reduction of abnormal cytology results than for vaccine-associated types. Vaccine study data give an estimate of protection for CIN3 associated with vaccine-targeted and nonvaccine HPV types if a girl is vaccinated prior to sexual activity. There are no data that would permit informing an individual woman what her immediate risk for CIN3 is if she was vaccinated post onset of sexual activity.

Potential harms of changing cervical cancer screening strategies in vaccinated populations have been explored in population-based models. There are little data on potential harms in changing screening in individual vaccinated women. In one study based in Belgium[33], the authors modeled a potential decrease in compliance with cervical cancer screening. If compliance decreased by 10 %, the population level benefits of vaccination were negated. Another publication examined the interaction of vaccination and screening in Iceland.[31] These authors favor keeping the current three-year screening interval in their country. The reason for this concern is the high prevalence of non-vaccine HPV types in women under thirty; a portion of these infections will develop into pre-malignant cervical disease, of which most will not progress.

The Centers for Disease Control and Prevention has recently created special studies in the U.S. for CIN 2+ in women aged 18-39 years of age. HPV vaccine history is obtained from adult

women with CIN2+ as part of a system established in 5 sites across the country to monitor population-based impact of HPV vaccine on type-specific CIN2+ in the U.S. by the Centers for Disease Control and Prevention. Data on vaccination status and timing of vaccination relative to diagnosis among a subset of women diagnosed with CIN2+ from 2008-2010 was recently presented at the International Papillomavirus Conference.[36] The data indicate that receiving the HPV vaccine is not uncommon in this population of women aged 19-26 years, and that over 50% of vaccinated women with CIN2+ initiated vaccine after their abnormal Pap or histology diagnosis. Among those vaccinated after diagnosis, approximately 50% had HPV16 or 18 type-associated lesions. Changing screening strategy in women vaccinated after exposure to targeted HPV types may be a potential harm as the vaccine is not therapeutic.

One Dutch study explored the optimization of cervical cancer screening in a vaccinated population.[37] These authors note that the positive predictive value of any cervical cancer screening will decrease in a vaccinated population.

The results of the large clinical trials indicate an individual woman will have a decreased risk of CIN2/3 even if she develops abnormal cervical cytology, especially if vaccinated prior to exposure to HPV. Currently in the U.S. we have accepted some harm (referral to colposcopy but no CIN2/3) because the benefit (referral to colposcopy with identification of CIN2/3) outweighs the harm. It is expected that with vaccination, the harms (colposcopies performed without identifying CIN2+) will remain constant but the benefit will decrease (fewer cases with CIN2/3) resulting in an increased harm-to-benefit ratio. Although there are no RCT data to support this, it is plausible that if screening recommendations remain the same in this population (i.e., the overall rates of screening opportunities and diagnostic interventions that come in consequence), then these women will experience increased harms of screening relative to the potential benefits.

Research priorities and recommendations

As of August-2011, considerable uncertainty exists about screening among vaccinated women. This uncertainty relates to age of screening onset, most appropriate screening technology, and screening interval. More evidence is needed to support changes in screening guidelines in a vaccinated population. Questions that need to be addressed include:

- **Effect of vaccination on HPV type distribution**: This information is required to estimate the incidence of non HPV 16/18 cervical lesions in vaccinated populations which will impact on optimal screening.[38, 39]
- **Performance of cytology and HPV DNA testing among vaccinated populations**: Documenting and understanding test performance among vaccinated women will determine which test to use and how frequently it should be repeated.[39] At present, modeling findings suggest the plausibility of a future decrease in screening performance due to the decrease in prevalence of CIN2+ post vaccination and that the effect on performance could differ by technology.[35]

- **Effect of vaccination on adherence with screening recommendations**: Should adherence to screening decrease in response to a greater sense of protection from vaccination, it may be necessary to devise methods that would increase understanding of need for continued screening and enhance participation.[40]
- **Duration of immunity conferred by vaccination**: More precise knowledge concerning the duration of immunity will allow for selection of age of onset and intervals for screening.[38, 39]

Although most of our knowledge to date on this subject has been achieved through mathematical modeling,[40] increasing uptake of the vaccine and collection of data since implementation of vaccine delivery will soon provide us with real, empirical findings. The questions could be examined through epidemiologic surveillance via linkage of vaccination registries with screening and HPV testing databases. This would permit comparison of HPV DNA types, screening behaviors, and differences in histopathologic outcomes between vaccinated and unvaccinated cohorts.[39] Special attention should be given to the age at diagnosis of precursor or invasive lesions and time elapsed since the last screening test, to determine any change in age of onset of screening and safe screening interval. Although some of these issues may be studied with clinical trials, others, such as adherence with screening recommendations, will require observational data from active epidemiologic surveillance. It is highly probable that the latter type of studies may represent the bulk of the scientific evidence to emerge in the future. Future policy decisions may not have the luxury of being informed via RCTs of the performance of screening in vaccinated populations, for purely economic reasons. With the expected 50% to 70% reduction in precancerous lesion prevalence after vaccination, the required sample sizes to attain adequate statistical power would become substantially larger, with an obvious escalation of costs. More subtle questions related to age of onset and screening interval, based on smaller effect sizes and acceptance of risk, would be impractical by today's standards of relevance-to-cost ratios that characterize much of publicly-funded health research today.

Finally, arguments about the impact of HPV vaccination on cervical screening practices may become moot if a second generation of HPV vaccines proves to be successful. The latter vaccines are either currently under evaluation in RCTs (e.g., a nonavalent HPV vaccine by one of the manufacturers) or will be soon (L2-based vaccines that confer broader protection). The extent of protection by these vaccines against cervical cancer will certainly take decades to be proven beyond doubt, but it is reasonable to assume that, if they are successful at the RCT stage, the risk reduction for CIN2/3 lesions will be much larger than that conferred by the first generation of HPV vaccines currently available. As the reduction of precancer lesion risk approaches 100%, the above discussion about the requirement for RCTs of screening in vaccinated populations to have very large sample sizes will be even more pertinent. This underscores the need for creating surveillance systems that merge vaccination and screening registries as the most likely source of empirical data to assist policymakers tasked with making cervical cancer prevention recommendations in the future.

If screening begins at a later age than currently recommended in the post-vaccination era, say at 25 years of age, we should expect that risk of CIN2 or greater at this age should be no greater than the risk for such lesions among 21 year olds who may not have the benefit of vaccination. This would provide a good benchmark for risk tolerance during the post-vaccination era that could assist in providing the basis for a change in screening age once HPV vaccination has the intended public health impact.

A difficulty with the above rationale is the requirement that epidemiologic surveillance be established early enough to permit real-time monitoring of incidence rates of cervical lesions in most American states. Luckily, surveillance mechanisms have been established by the CDC in sentinel sites and in New Mexico[41-44] to measure the rates of high grade lesions and correlate them with the history of HPV vaccination in these populations. Presumably, this will permit verification with ample reliability of the moment when rates in women aged 25 years have declined sufficiently to reach (or even be reduced to below that) the level of such lesions in women aged 21 years. This could serve as a trigger for the modifying guidelines for age to begin screening.

Can we recommend later age of onset for the individual vaccinated woman?

As discussed in the preceding sections, as of this writing there was no empirical evidence from randomized controlled trials to permit an unequivocal recommendation concerning practice guideline changes in the U.S. towards a later age of onset and less frequent cervical cancer screening for the population as a whole. Other important considerations that support maintaining the status quo are: (i) the low and socioeconomically dependent age-specific vaccination uptake in the U.S.; (ii) cervical cancer screening in the U.S. is entirely opportunistic, even in more controlled scenarios of managed care, and thus a call-recall system is not viable at present; (iii) vaccination registries are yet to become an established norm in this country, which precludes the possibility of allowing physicians to have access to reliable vaccination histories when deciding about the level of protection for an individual woman and (iv) duration of protection beyond 6 years has not been established. Children vaccinated at 11 years of age would need proven protection for at least 15-20 years to delay screening.

There is controversy whether the above is relevant to both population and individual recommendations. Many of the modeling studies discussed above are relevant to populations, and only a few are relevant to the individual woman. In addition, the RCT vaccine studies did not address age to screen nor interval. Based on expert opinion, some have discussed whether there should be an option of recommending a more liberal screening strategy based on self-reported vaccination histories. A woman who was fully vaccinated prior to the onset of sexual exposure is indeed substantially protected against cervical lesion development for at least the next decade of her life. Therefore, it stands to reason that in the future the provider will have the option of recommending for such a patient a later age of screening initiation and possibly a longer interval than are currently accepted as standard of practice. Currently, the evidence to delay screening in the individual woman is weak, specifically in regard to self-reported histories.

Before any such recommendation could be made, several key premises for assuming that the patient's risk is indeed minimal must be in place. First, the woman's vaccination history must be credible, preferably via medical chart or school records; self-reported histories would be largely unreliable. Second, the provider must ascertain that the full course of vaccination must have been taken prior to the onset of sexual activity, an assurance that is only reasonable if the record indicates that the woman received all doses during the pre-adolescence non-sexually active years. Third, the clinician must be reasonably certain that the patient will not miss the future appointment for a new, delayed age at onset of screening. The latter requirement is particularly difficult to guarantee if the present economic climate continues to prevail and the patient may lose health insurance. Fourth, the provider must have a frank discussion with the patient to assess her overall level of risk by considering her lifestyle, sexual behavior, and other characteristics that may expose her to HPV infection during the period preceding the first scheduled screen. Such risk must be judged as lower than average. Fifth, the first screen done at a later age must be via an acceptable technology that guarantees maximal sensitivity in detecting cervical lesions that would have been caused by HPV types other than 16/18 (cotesting via HR-HPV and cytology is presently the most sensitive approach that is approved in the U.S. today, as discussed elsewhere in the present guidelines). Sixth, an adolescent vaccinated at 11 years of age would not be screened for another 14 years. Data on efficacy of this duration will need to be established.

The above considerations are obviously intended to err in the side of caution. As the experience with the impact of vaccination increases and successive cohorts of vaccinated young women reach the age of screening, there will be better evidence and quantitatively more robust estimates of the reduction in risk post-vaccination. Although some key cohort studies have indicated that the natural history of non-16/18 lesions carries a better prognosis than those elicited by 16/18,[45] more evidence is needed with respect to the detectability of the former lesions via different screening methods. The accrued experience with molecular methods for cervical cancer screening may also provide additional insights to be used for future guideline modifications. Evidently, from a societal perspective, adding the costs of vaccination to an already expensive screening program will only increase health care costs. It is imperative that surveillance systems and vaccination registries be implemented for a rational combination of the two modalities of prevention. Optimal use of vaccination while tailoring screening strategies will likely lead to a substantial reduction of cervical cancer risk with potential savings to the health care system and reduced harm regarding obstetric outcomes.

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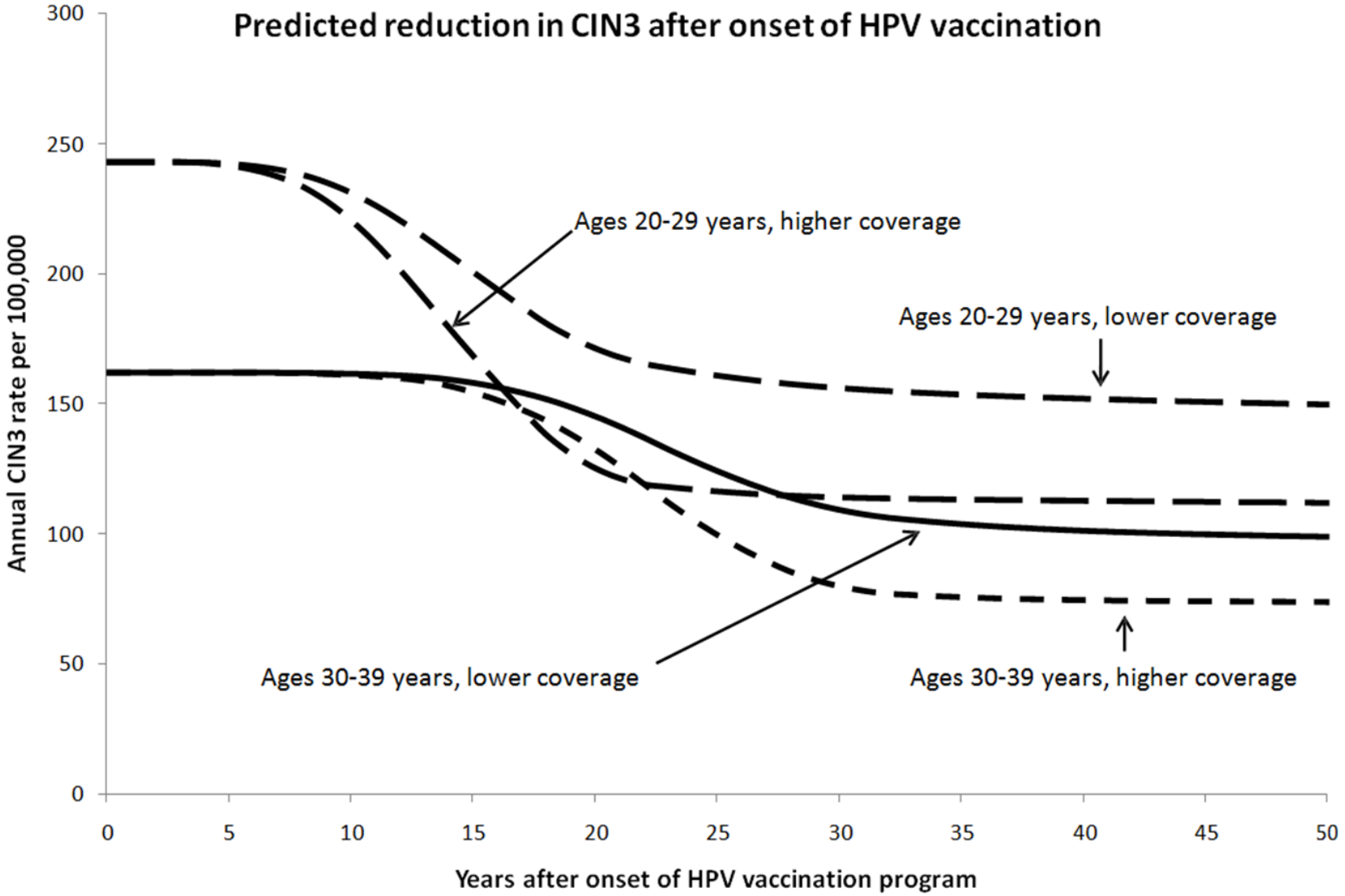
Predicted reduction in CIN3 after onset of HPV vaccination
Annual CIN3 rate per 100,000
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
45
50
Years after onset of HPV vaccination program
Ages 20-29 years, higher coverage
Ages 20-29 years, lower coverage
Ages 30-39 years, lower coverage
Ages 30-39 years, higher coverage

Working Group 6: Looking to the Future - Potential Impact of Molecular Screening

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Introduction

The fundamental goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer. The most successful screening strategy would identify those cervical cancer precursors that are likely to progress to invasive cancers and avoid detection of transient high-risk HPV infection and associated lesions. Screening strategies should optimize true disease detection while minimizing clinical harms that occur as a consequence of imperfect diagnostic and therapeutic processes. Since cytology testing and eradication of precursors exists as an effective screening strategy that has radically reduced cervical cancer incidence and mortality, new strategies should demonstrate either superior disease detection without increasing harms from the misidentification of self-limited lesions with minimal cancer risk or equivalent accuracy with longer screening intervals that might reduce harms associated with screening. The burden for a new strategy is therefore significant, given the substantial investment in cytology testing, the degree of patient and provider acceptability, and the low rate of cervical cancer in the population.

Current annual incidence of cervical cancer approaches 13,000 cases per year in the United States and approximately 4,000 deaths.[1] Since more than half of incident cases are in unscreened or under-screened women, technologic improvements in screening are unlikely to have a substantial impact on mortality if they do not reach this population. Given the low current burden of cancer, concerns about harms arising as a result of imperfect screening strategies that improve sensitivity while decreasing specificity, even marginally, become important considerations. Even small decrements in specificity dramatically increase the number of women with false positive tests requiring further testing for a small improvement in true positive results.

Primary HPV testing has been prospectively assessed in multiple cohorts as a replacement for current standard cytology testing. Randomized controlled trials (RCTs) of primary HPV testing have demonstrated that when compared to standard cytologic screening, HPV testing has increased sensitivity for detection of cervical cancer precursors after a single screening round. Greater sensitivity also means greater negative predictive value over a longer time period because the absence of HPV conveys a low future risk of developing CIN3+ over at least five years. Most studies have been restricted to women over the age of 30 years, based upon the generally observed decline in HPV prevalence around that age. If HPV testing is used as a primary screening test in women over 30, subsequent HPV screening intervals may be safely

extended to 5 years, which would reduce the burden of unnecessary screening procedures in these women.

Primary HPV testing for screening younger age groups is unlikely to be useful given the ubiquity of HPV infection, and relatively low prevalence of disease with invasive potential in this age group. In addition, the decreased positive predictive value of HPV relative to cervical cytology in a low cervical cancer prevalence population requires a secondary triage method to identify clinically significant disease prior to treatment. This is critical in order to minimize clinical harms that arise as a consequence of diagnostic and therapeutic procedures for lesions not destined to cause cancer. That optimal triage modality has yet to be defined.

Key Questions

1. **1.** Determine, based on the trade-offs between potential benefits and harms, whether a multi-society statement supporting the use of HPV DNA testing alone for women in the general population can be strongly or weakly recommended.

2. **2.** Should women who test HPV positive be triaged to cytology (or another triage strategy such as genotyping)?

3. **3.** For women with two or more consecutive negative HPV results, should the interval be increased further (e.g., to 150% or 200% of the initial interval)?

Recommendations

1. In most clinical settings in the United States, we recommend against the use of high risk HPV[*] testing as a primary screening strategy (even with defined follow up triage). (*weak recommendation)*

2. There is no evidence to support the superiority of any single testing method for the triage of women with a positive HPV test when used as a primary screening modality.

3. Screening intervals may be extended to 5 years if HPV testing is used for primary screening, among women ages 30 and older, when the HPV test results are negative.

Evidence Review

As described separately, a literature review was conducted to identify relevant articles published between January, 1995 and July, 2011. 399 articles were identified and 106 articles were included to inform this set of recommendations.

[*] HPV refers only to high-risk HPV as other HPV types are unrelated to cervical cancer and therefore should not be used in cervical cancer screening. Testing for low-risk HPV types has no clinical role in cervical cancer screening or evaluation of women with abnormal cytology

Rationale and Evidence

There is high-quality evidence to suggest a superior sensitivity of primary HPV screening; however data to assess the specificity and relative harms associated with this strategy are of low quality. Data are limited to women over the age of 30 years, and are derived primarily from studies conducted outside of the United States. HPV-based screening approaches may be most appropriate for countries with organized screening programs where women are invited periodically for screening and referred to specialized centers for evaluation, management, and treatment or alternatively in low resource settings where screening is likely to be a rare event.

HPV in Primary Screening

Despite its promise, the evidence for the effectiveness of a lifelong program based on HPV DNA testing alone is still too preliminary to recommend abandoning cytology in the U.S. And therefore, cotesting is a potentially transitional strategy. Nonetheless, the performance of HPV testing alone deserves further evaluation since HPV testing contributes most of the sensitivity of cotesting.

Cervical cancer screening is a decades-long, iterative process that should lead to the identification and treatment of pre-invasive lesions prior to development of invasive cancer, thereby reducing morbidity and mortality of cervical cancer. Identification of lesions that would not progress to cancer is not beneficial but in fact may harm women through needless anxiety, morbidity from procedures and treatments, relationship disruption, and cost. This Working Group reviewed randomized studies during its GRADE assessment process that attempted to approximate multi-event screening through use of two or more rounds of screening.[2] A sensitive test may front-load detection of cancer precursors ("lead-time detection"), but this is beneficial only if the lesions identified would have escaped detection in subsequent screening rounds prior to development of invasive cancer.

Based upon review using GRADE assessment, HPV DNA testing for primary screening appears promising in women aged 30 years and older, who may be at greatest risk for developing high grade cervical intraepithelial lesions and cancer.

In single round screening studies, HPV testing is more sensitive for detection of CIN2+ and/or CIN3+ than cytology alone or cytology in combination with HPV testing. HPV testing for primary screening is less specific in its performance and consequently more likely to identify clinically insignificant disease that will regress (functionally false positive results). Since high risk HPV is relatively prevalent and lesions destined to become invasive relatively uncommon, marginal declines in specificity may have an adverse impact on negative predictive value and increase the need for follow-up testing. For this reason if HPV testing is employed in a primary screening setting, triage with a secondary test is essential to avoid diagnostic (colposcopy) and therapeutic procedures for women with transient HPV-related lesions of negligible oncogenic

risk. The use of cytology and/or validated molecular markers of oncogenic risk for this purpose appears to be promising and deserves rigorous evaluation.

The evidence-based review commissioned by the Agency for Healthcare Research and Quality for the US Preventive Services Task Force has important implications for Key Question 1. Specifically it concludes that the use of the HC2 HPV test as a primary cervical cancer screening tool appears very promising in women aged 30 years and older.[2] Subsequently published first-round studies that have suggested utility of primary HPV screening are limited by lack of longer follow-up.[3,4] In the only study comparing standard cytology-based screening with HPV testing using 3 rounds of screening, (ARTISTIC) no differences in CIN3+ detection were identified; HPV testing led to more rapid detection of lesions, but cytology also found disease before development of invasive cancer.[5] A limitation for this trial in particular was the limited one-year follow-up of women who had HPV-positive, cytology-negative results, in whom the added sensitivity of HPV testing over cytology alone could have been observed.

Recent modeling analyses suggest that a strategy of HPV testing followed by cytology for high-risk HPV positive women, with referral to colposcopy if both tests are abnormal, is consistently identified as efficient, regardless of whether colposcopies or tests (screening and triage) are used to quantify burden.[6] It is also noteworthy that several recent analyses conclude that primary screening with cotesting (concurrent HPV and cytology testing) may offer little benefit over HPV testing alone.[2,7]

Post-HPV Screen Triage Strategies

Sensitivity—especially for surrogate endpoints--cannot be the sole criterion for a screening test. A strategy of immediate treatment of all HPV-positive women is generally considered unacceptable because of the consensus that the risks of harms, associated with treatment, outweigh potential benefits. Given this, a program of screening using primary HPV testing requires one or more triage tests in addition to a positive HPV DNA result before further work-up or treatment. As an apparent exception, Ronco *et al*. used colposcopy alone as the triage strategy after HPV was detected and showed a significant reduction in cervical cancers.[8] This is qualified by the fact that colposcopy for women who are HPV positive, cytology negative appears to have only 50% sensitivity for the detection of precancer.[9]

Other strategies have aimed to improve specificity and reduce harm by interposing another test between a positive HPV test and colposcopy; these include triage using cytology, HPV genotyping (with HPV 16 and/or 18), HPV mRNA testing, or other biomarkers (e.g. p16). These studies have not shown an improved sensitivity compared to standard cytology after multiple rounds, and specificity and consequent harms have not been well defined. In an HPV-based screening strategy, the rate of colposcopy may be expected to be twice that of cytology in women aged 35-60 years[8] due to the lower specificity in a single round of screening. Particularly in low-disease prevalence populations, this decreased specificity may lead to

increased follow up costs and potential harms, such as overtreatment of active HPV infections and related lesions of minimal oncogenic risk. However, it is unclear whether the cumulative harms after several rounds of screening would be higher if the frequency of screening (and thus frequency of false positive results) was reduced by extending screening intervals in a primary HPV testing strategy compared with cytology alone performed at more frequent intervals.

Currently there are no published completed large-scale or population based studies that have evaluated and compared triage strategies post HPV primary screening. However, because of the relatively high specificity of cytology in identifying true CIN2/3+, modeling analyses suggest improved positive predictive value using HPV testing followed by cytology.[10] Additionally, although a variety of markers of oncogenic potential have been developed and variably assessed, there are limited data regarding the test performance of these markers. Specifically, the cross-sectional and archival nature of most available studies of these molecular markers limits their usefulness for prospective screening strategies at this time. Moreover, prospective studies used a single round of testing to determine clinical performance, which may result in earlier diagnosis of CIN2+ that would have been found in subsequent rounds before progressing to cancer and therefore overestimating the long-term programmatic impact of such an approach. Finally, the inclusion of CIN2 in addition to CIN3+ as a primary endpoint may result in identification of lesions fated to regress spontaneously with no cancer prevention benefit.

The current limited U.S. data from small scale retrospective, cross sectional, and limited prospective studies provide an insufficient evidence base for alternative triage approaches to HPV population-based screening. Furthermore, there are no data or current trials that define the long-term impact of a primary HPV-based screening strategy with the necessary repeat interval testing and long-term follow up that would be necessary for the development of guidelines and clinical care algorithms in U.S.-based healthcare settings.

Interval Screening for Women with Consistently Negative HPV

While the increased sensitivity of HPV testing in a low prevalence population may result in overtreatment of clinically insignificant disease, the predictive value of a negative HPV result would safely allow lengthening of testing intervals. That in turn might reduce harms from false positive tests over time. The negative predictive value for CIN3+ of a single HPV test is over 99%. In the presence of a single negative HPV test at baseline, the percent of women 35-60 years old with CIN3+ detected by conventional cytology three years later is exceedingly low (0.02%).[8] Katki et al demonstrated that in HPV-negative women, the 5-year cumulative incidence of CIN3+ was 0.87% (95% CI, 0.62 to 1.12), a rate reported in other RCTs using primary HPV screening.[7] The interval of screening using HPV testing may be safely increased to approximately five years. One rather than two negative HPV tests (as proposed in the Key Question) may be sufficient to achieve this.[5,11] Additional studies are needed to determine the cost effectiveness of such a strategy and the impact of longer screening intervals on compliance in an opportunistic screening setting, such as what currently exists in the U.S. The goal should

be to reduce the screening burden for women who are at low risk in an effort to redirect resources for programs that reach unscreened and rarely screened populations or those who are at higher risk for cervical cancer

Considerations Regarding HPV Testing

Clearly, not all HPV tests are identical. While Hybrid Capture 2 is most often studied in the available well-designed population-based screening studies, a variety of other methods are in use or in development for use in the United States. In the context of these recommendations, HPV testing refers to any assay for the group of high-risk HPV genotypes used for cervical cancer screening or triage provided that any of those tests meets specific criteria for *clinical* performance and validity.[12-17] The clinical comparability of alternative HPV testing methods that do not meet these standards (including laboratory developed tests) are not well understood and need further evaluation before being applied to screening populations; excessive analytic sensitivity will be unlikely to improve clinical sensitivity for CIN3+ but will increase harms due to poorer specificity. Test performance characteristics vary between commercially available HPV tests, and comparability cannot be assumed.[16] In general, research studies often rely upon HPV testing performed at a single laboratory, and may not reflect the inter-laboratory variation that may arise when multiple laboratories are involved in the large scale HPV testing environment encountered in the current opportunistic testing programs of the United States.

HPV testing performed in research laboratories using some commercial tests has been shown to have good inter-laboratory reliability[17] but additional studies of inter-laboratory comparability of HPV testing in the clinical laboratory setting, and the consistency of results between laboratories, are needed. Laboratories testing for HPV should use FDA approved HPV diagnostic tests in the manner in which they are intended, must have a robust quality assurance program, and participate in inter-laboratory testing or proficiency testing that ensures quality laboratory results across laboratories.[18]

Research Priorities and Recommendations

- Large prospective studies are required to assess the utility, limitations, and variety of HPV testing strategies in a U.S. primary screening setting. Because results need to be generalized to lifetime serial testing, these trials should include results of first and subsequent rounds of screening, provide long-term follow up of enrolled women, define numbers of women referred to colposcopy and treated in each arm, and include CIN3+ as a primary outcome.
- The natural history of CIN2 is poorly understood. Factors including age at detection, HPV type, baseline cytologic findings, immune factor, reproducibility of the CIN2 histologic diagnosis and likelihood of regression or progression should be incorporated into prospective trials to help define clinically relevant screening programs.

- Hybrid Capture 2 is the most common HPV test used in population-based screening studies. While alternate testing methods may have been compared to HC2, the clinical comparability of alternative HPV testing methods (including HPV genotyping) is poorly understood at this time and deserves further study.
- The systematic assessment of strategies to manage women with an HPV positive screening test need to be conducted, and should include the assessment of cytology, genotyping, and a variety of biological markers of oncogenic potential. Ideally, comparative trials should be conducted.
- Clinical trials are needed to develop evidence-based approaches to the clinical management strategies for the HPV-positive, cytology-negative women.
- Consensus recommendations of clinical endpoints should be developed to ensure consistency across study populations including: clinically meaningful age stratification, length of follow up, histopathologic outcomes (CIN3 being a preferred end point) and other clinically relevant variables.
- Harms related to false positive test results should be quantified and the impact of lengthening screening intervals on these should be explored.
- Novel approaches (including self-collection, urine-based screening, and visual inspection) to unscreened or under-screened U.S. populations must be developed, evaluated, and, for those showing promise, scaled up in order to reach subpopulations of women not currently served by the existing screening programs and among whom half of all cervical cancer cases will occur.[19]
- If studies to address these research priorities are prohibitive in terms of cost and sample size, modeling is useful to evaluate relative benefit and harms of alternative strategies.

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