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Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test☆

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HIGHLIGHTS

- A negative HPV results at baseline predicts one-half the risk of CIN3+ over 3 years than a negative cytology result.
- HPV primary screening with triage using 16/18 genotyping and cytology increases sensitivity to detect CIN3+ 28% over cytology.
- Cytology failed to detect approximately 50% of CIN3+ in women 25–29 years.

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ABSTRACT

Objectives. ATHENA evaluated the cobas HPV Test as the primary screen for cervical cancer in women ≥25 years. This reports the 3-year end-of-study results comparing the performance of HPV primary screening to different screening and triage combinations.

Methods. 42,209 women ≥25 years were enrolled and had cytology and hrHPV testing. Women with abnormal cytology (≥atypical squamous cells of undetermined significance) and those HPV positive were referred to colposcopy. Women not reaching the study endpoint of CIN2+ entered the 3-year follow-up phase.

Results. 3-year CIR of CIN3+ in cytology-negative women was 0.8% (95% CI; 0.5–1.1%), 0.3% (95% CI 0.1–0.7%) in HPV-negative women, and 0.3% (95% CI; 0.1–0.6%) in cytology and HPV negative women. The sensitivity for CIN3+ of cytology was 47.8% (95% CI; 41.6–54.1%) compared to 61.7% (95% CI; 56.0–67.5%) for the *hybrid strategy* (cytology if 25–29 years and cotesting with cytology and HPV if ≥30 years) and 76.1% (95% CI; 70.3–81.8%) for *HPV primary*. The specificity for CIN3+ was 97.1% (95% CI; 96.9–97.2%), 94.6% (95% CI; 94.4–94.8%), and 93.5% (95% CI; 93.3–93.8%) for *cytology*, *hybrid strategy*, and *HPV primary*, respectively. Although *HPV primary* detects significantly more cases of CIN3+ in women ≥25 years than either *cytology* or *hybrid strategy*, it requires significantly more colposcopies. However, the number of colposcopies required to detect a single CIN3+ is the same as for the *hybrid strategy*.

Conclusions. HPV primary screening in women ≥25 years is as effective as a hybrid screening strategy that uses cytology if 25–29 years and cotesting if ≥30 years. However, HPV primary screening requires less screening tests.

Introduction

Persistent infection with a high-risk human papillomavirus (HPV) genotype is required for the development of high-grade cervical neoplasia (cervical intraepithelial neoplasia [CIN] grade 3, adenocarcinoma in-situ, and invasive cervical cancer (CIN3+) [1]. Molecular tests that detect HPV demonstrate increased sensitivity but lower specificity than cytology for detecting women with CIN3+ [2]. Currently in the United States (U.S.) HPV testing is recommended to triage women with atypical squamous cells of undetermined significance (ASC-US) and as an adjunct to cytology when screening women ≥30 years (i.e., "cotesting") [3–5]. In Europe, guidelines recommend the use of HPV testing to triage women with ASC-US, for surveillance after treatment of CIN, and as a stand-alone primary screening test without cytology

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for cervical cancer screening (HPV primary screening) [6]. Several countries including Australia and the Netherlands have now adopted HPV primary screening for their national screening programs [7,8]. HPV primary screening could reduce both the complexities and resource expenditure inherent in cotesting while maintaining a high sensitivity. Longitudinal follow-up studies and randomized trials have shown that HPV primary screening is more sensitive than cytology and identifies CIN3+ earlier [2,9]. As a result, fewer cases of cervical cancer or CIN3 are identified on subsequent rounds of screening [10,11]. Despite the attractiveness of HPV primary screening, there remain several unresolved issues. These include developing an effective strategy to determine which HPV-positive women should be referred to colposcopy and how HPV primary screening performs in the U.S.

In 2008, the 3-year prospective ATHENA (Addressing the Need for Advanced HPV Diagnostics) study was initiated in the U.S. [12]. This study was specifically designed to evaluate primary screening with the cobas HPV test in women ≥25 years in the U.S. as well as to evaluate different triage strategies for HPV-positive women. End-of-study results from ATHENA are presented in this manuscript.

Materials and methods

Study patients

Nonpregnant U.S. women ≥21 years presenting for routine cervical cancer screening (n = 47,208) were enrolled in this observational study between May 2008 and August 2009. Study inclusion and exclusion criteria have been previously described and are provided in detail in the Supplemental appendix together with an in-depth description of study procedures [12–14]. Since current U.S. management guidelines recommend against HPV testing for any reason below the age of 25 years, only women ≥25 years were included in the 3-year follow-up phase and in this subanalysis (n = 41,955) [5]. The study protocol was approved by institutional review boards of all study sites, and written informed consent was obtained. This study is registered with ClinicalTrials.gov (NCT00709891) and was completed in December 2012.

Design and study interventions

Baseline phase

After a brief medical history, a cervical sample was collected and placed into a PreservCyt vial (Hologic, Inc.). Prior to processing for cytology (ThinPrep; Hologic, Inc), a 4-mL aliquot was removed for HPV testing using the cobas HPV Test (Roche Molecular Systems) that provides three HPV positive/negative results: HPV 16, HPV 18, and 12 other HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 66, pooled). Samples were also tested using the AMPLICOR and LINEAR ARRAY HPV Genotyping Test (Roche Molecular Systems) which are research tests with high analytic sensitivities. Cytology and HPV testing were conducted in the U.S. at 4 clinical laboratories and Roche Molecular Systems served as a fifth site for HPV testing. Bethesda System terminology was used for reporting cytology results [15]. Prior to reporting to the sites, test results were entered into a randomization database that selected women for colposcopy based on age, cytology and AMPLICOR/LINEAR ARRAY HPV test results. This included all women with abnormal cytology and HPV positivity, as well as a random subset of HPV and cytology-negative women that was required for verification bias adjustment of the performance of the screening tests.

Colposcopy with biopsy and in some patients endocervical curettage (ECC) was completed within 12 weeks of the initial visit (see Supplemental appendix for complete details). Both the colposcopist and patients were masked to the screening test results until after the colposcopy visit. Biopsies and ECCs were reviewed by a panel of 3 pathologists who were masked to patient information and screening test results. Standard CIN terminology was used for reporting the histology results [16]. Women with CIN2+ exited the study for appropriate management.

Follow-up phase

All women who underwent colposcopy in the baseline phase and who did not have CIN2+ were eligible for the 3-year follow-up phase. During follow-up, women had annual examinations with collection of a cervical specimen for both cytology and HPV testing. Women with abnormal cervical cytology (≥ASC-US) underwent colposcopy with biopsies and ECCs that were reviewed as in the baseline phase. Women diagnosed with CIN2+ during follow-up exited the study. At year 3, patients were invited to have an "exit colposcopy" (see Supplemental appendix for complete details). Women who declined the exit colposcopy (319 of 4663) had a cervical specimen collected for cytology and HPV testing.

Primary and secondary outcomes

The follow-up phase of ATHENA was designed to document the safety of the cobas HPV Test both when used for cotesting in women ≥30 years as well as when used for HPV primary screening in U.S. women ≥25 years. With respect to primary HPV screening in women ≥25 years, the 3-year follow-up phase had two secondary objectives. The first was to compare the 3-year cumulative risk of CIN2+ in women with different baseline HPV results (stratified by HPV negative, pooled 14 high-risk HPV positive, HPV 16/18 positive, and HPV 12 "other" positive). The second objective was to compare the 3-year cumulative incidence rate of CIN2+ in women with a negative HPV test at baseline and those with a negative cytology. After analyzing the performance of different screening strategies incorporating HPV testing alone and in combination with cytology for the detection of CIN2+ using data from the baseline phase, we decided to perform a post hoc analysis of the performance of these strategies over the full 3 years of the study. This was indicated because all of the strategies incorporate retesting of selected women at 12 months and it was important to include the results of this retesting to fully understand how the strategies would perform in a screening setting [5,17].

Screening strategies

We calculated the performance of three screening strategies for women enrolled in ATHENA over a 3-year period using the dataset created by the study. One strategy was cytology with HPV testing performed only for ASC-US (*cytology*). The second was a *hybrid strategy* that uses the *cytology* strategy for women 25–29 years of age and cotesting with both cytology and HPV (pooled 14 genotypes) in women ≥30 years. The *hybrid strategy* mimics current U.S. screening recommendations [3,4]. With cotesting, HPV-positive women with negative cytology are retested with both tests in 1 year and undergo colposcopy if either is abnormal. We compared these strategies with a *HPV primary* strategy in which HPV-negative women are rescreened in 3 years, HPV16/18-positive women receive colposcopy, and women positive for the 12 other HPV genotypes have reflex cytology with colposcopy if the cytology is ≥ASC-US. If the cytology is negative women are rescreened with HPV and cytology in 1 year. In all strategies, women who were referred to colposcopy and found to not have CIN2+ are rescreened with both tests in 1 year and referred to colposcopy if ≥ASC-US or persistently HPV-positive. More complete details of the screening strategies are provided in the Supplemental appendix.

Statistical analysis

Verification bias adjusted (VBA) estimates of absolute risk of CIN2+ or CIN3+ for each year were obtained by estimating the likely cases of CIN2+ and <CIN2 for each year as previously described [13,14]. Cumulative risk over 3 years was obtained by using the Kaplan–Meier method and the VBA risk estimates for each year. Confidence intervals for the

cumulative risk were estimated using the bootstrap method [18]. An in-depth description of how the calculations were adjusted for selection bias and loss to follow-up is included in the Supplemental appendix.

Calculating 3-year performance of screening strategies

Because cytology and HPV testing were performed each year during the study, we could determine HPV persistence, repeat cytology results, and loss to follow-up rates annually. This allowed calculation of how specific screening strategies would perform over the course of 3 years, as well as the utilization of clinical resources to include number of tests, colposcopies and number of colposcopies required to detect one case of CIN2+.

Since all women who were HPV-positive or had ≥ASC-US at baseline underwent colposcopy and exited the study if they had CIN2+, calculating how individual screening strategies would perform over a 3-year screening cycle required 3 assumptions. One was that CIN2+ lesions identified at the baseline colposcopy but missed by a specific screening strategy would persist until the Year 1 visit and be detected if the woman was referred to colposcopy based on the Year 1 cytology and HPV results. The second was that HPV-positive CIN2+ lesions at baseline would be persistently HPV positive at Year 1. Finally, we assumed that any woman who returned for follow-up and had an abnormal test result underwent colposcopy. A more detailed description of how the calculations were adjusted for selection bias and loss to follow-up is included in the Supplemental appendix.

Results

From May 2008 to August 2009, 42,209 women ≥25 years were enrolled in ATHENA, of whom 41,955 (99%) met the eligibility criteria. The baseline demographic characteristics of this population have been previously described and are provided in Supplemental appendix [13]. A total of 1054 women had missing or invalid test results at enrollment, leaving 40,901 women evaluable for this analysis. After the enrollment visit, 9353 women were selected for colposcopy, of whom 8067 had the procedure (Fig. 1A). This included 892 randomly assigned women who were both HPV and cytology-negative allowing for adjustment of verification bias. The follow-up rates were 81%, 84% and 90% for years 1, 2 and 3, respectively (Fig. 1B). During the course of the 3-year study a total of 240 CIN2, 319 CIN3, 20 adenocarcinoma in-situ, and 8 invasive cervical cancer cases were detected, Supplemental appendix.

3-year cumulative risk of CIN3+ (or CIN2+)

At baseline 10.5% (4275 of 40,901) of women were HPV-positive and 6.4% (2617 of 40,901) had cytology of ≥ASC-US. 164 of 347 (47.3%) of CIN3+ identified during the 3-year study occurred in women with negative baseline cytology, Supplemental appendix. In contrast, 34 (9.8%) occurred in women high risk HPV negative at baseline ($p < 0.001$). Similar results were observed using a CIN2+ endpoint. All of the invasive cervical cancers (8 of 8) were HPV-positive at baseline, and 7 of 8 (87.5%) had ≥ASC-US cytology. 6 of 8 (75%) cervical cancers were identified at the baseline colposcopy and 2 (25%) at Year 1 colposcopy. Of 20 cases of adenocarcinoma in-situ, 17 (85.0%) were HPV-positive at baseline and 13 (65.0%) had ≥ASC-US.

HPV genotype status at baseline was predictive for CIN3+ (or CIN2+) during the course of the study (Fig. 2). CIN3+ was identified at baseline in 17.8% (95% CI, 14.8–20.7%) of HPV16 positive women and after 3 years the cumulative incidence rate (CIR) was 25.2% (95% CI, 21.7–28.7%). In contrast, the 3-year CIR of CIN3+ was 5.4% (95% CI, 4.5–6.3%) in women with HPV genotypes other than 16/18. HPV18 positive women had a 3-year CIR that was intermediate between women with HPV16 and women with 12 other genotypes. Similar results were observed using a CIN2+ endpoint. Fig. 3 presents the VBA 3-year CIR for all of the different combinations of baseline screening test results. The 3-year CIR for CIN3+ was lower in HPV-negative women (0.3%; 95% CI, 0.1–0.7%) than in cytology-negative women (0.8%; 95% CI, 0.5–1.1%) with a CIR ratio of 0.38 (95% CI 0.19–0.6). When a negative cytology result was added to a negative HPV result, the 3-year CIR for CIN3+ (0.3%; 95% CI, 0.1–0.6%) was identical to that in HPV negative women.

Detection of disease in women of different ages

To determine the impact of initiating HPV screening at different ages, we compared the prevalence of HPV positivity and cytological abnormalities, as well as the 3-year cumulative detection rate of CIN3+ (or CIN2+) by age group, Table 1. The prevalence of HPV positivity (14 pooled genotypes) was almost twice as high in women 25–29 years (21.1%; 95% CI: 20.1–22.1%) as in women 30–39 years (11.6%; 95% CI: 11.0–12.2%). HPV16/18 positivity and cytological abnormalities were also highest in women 25–29 years. Although women 25–29 years accounted for only 16.3% of all study subjects, 35.8% (95% CI; 31.9–39.8%) and 34.3% (95% CI; 29.3–39.6%) of CIN2+ and CIN3+, respectively, occurred in this age group. More cases were identified in women 25–29 years than in women ≥40 years. In the 25–29 year age group more than half of women with CIN2+ (or CIN3+) had a negative cytology result.

Comparing different screening strategies

Of the three screening strategies that were evaluated, *HPV primary* in women ≥25 years had the highest adjusted sensitivity over 3 years (76.1%; 95% CI: 70.3–81.8%) for the detection of CIN3+, Table 2. For comparison, the adjusted sensitivity of *cytology* for CIN3+ was 47.8% (95% CI; 41.6–54.1%) and that of the *hybrid strategy* was 61.7% (95% CI: 56.0–67.5%). In women ≥25 years, *cytology* had the highest specificity for CIN3+ (97.1%; 95% CI: 96.9–97.2%) and *HPV primary* had the lowest specificity (93.5%; 95% CI: 93.3–93.8%). The *hybrid strategy* had a specificity intermediate between the other two strategies. Similar results were found using a CIN2+ endpoint. In women ≥30 years the *hybrid strategy* and *HPV primary* had similar sensitivities and both were higher than *cytology* for the detection of CIN3+ (or CIN2+). In women ≥30 years *cytology* had a higher specificity for CIN2+ or CIN3+ than did either the *hybrid strategy* or *HPV primary*, which had similar specificities. Positive and negative predictive values, as well as positive and negative likelihood ratios are also shown in Table 2. Of note, *HPV primary* had a significantly higher negative predictive value (NPV) than cytology.

In women ≥25 years *cytology* detected 179 (95% CI: 152–206) cases of CIN3+: 143 (95% CI: 119–167) at baseline and 36 (95% CI: 25–49) during follow-up, Table 3. *Cytology* required the fewest colposcopies overall and the fewest colposcopies to detect a single case of CIN3+. The *hybrid strategy* required almost twice the number of screening tests as *cytology*, but detected 61 more cases of CIN3+ because HPV-positive, cytology-negative women were retested in 1 year and referred to colposcopy if either test was abnormal. At year 1, 50% of HPV-positive, cytology-negative women had an abnormal test result and underwent colposcopy. The *hybrid strategy* resulted in an increase in the number of colposcopies (60.1% compared to *cytology*) and an increase in the number of colposcopies per case of CIN3+ detected to 12.9 (95% CI: 11.5-14.8). Similar results were seen using CIN2+ as the endpoint.

In women ≥25 years *HPV primary* detected more CIN3+ than either of the other strategies, including the *hybrid strategy*. It detected 37.8% more cases of CIN3+ (197; 95% CI: 169–226) at baseline compared with either *cytology* or *hybrid strategy* (143; 95% CI: 119–167 for both). In total, *HPV primary* identified 64.2% more CIN3+ (294; 95% CI: 260–325) than *cytology* (179; 95% CI: 152–206) and 22.5% more CIN3+ than the *hybrid strategy* (240; 95% CI; 2069–270). *HPV primary* resulted in an increase in the number of colposcopies compared with the *hybrid strategy*, but the number of colposcopies per case of CIN3+

was similar. Comparable results were seen using a CIN2+ endpoint. In women ≥30 years, the differences between *cytology* and *HPV primary* observed in women ≥25 years remained, but many of the differences between the *hybrid strategy* and *HPV primary* were diminished. Both the *hybrid strategy* and *HPV primary* identified almost the same total number of CIN3+ in women ≥30 years and required a similar number of colposcopies. However the increase in the number of cases of CIN3+ identified at baseline by *primary HPV* and the higher number of screening tests with the *hybrid strategy* persisted.

Discussion

Numerous cross-sectional and prospective screening trials have documented that cervical cancer screening strategies incorporating molecular testing for HPV are more sensitive than cytological screening [2,9]. There are three ways that HPV testing can be incorporated into screening: as a triage for ASC-US cytology, testing all women with both HPV and cervical cytology (e.g., "cotesting"), and HPV primary screening in which HPV is utilized alone [3,5,9,19]. Cotesting requires more screening tests than HPV primary screening and interpretation of screening results is also somewhat more complicated since all women have two test results that must be taken into account. Recently a number of prospective randomized screening trials, primarily from Europe, have shown that cotesting offers minimal increased protection against the subsequent development of cervical disease compared to HPV primary screening [9,10,20,21]. Similar conclusions have been reached in long-term follow-up studies of women enrolled in Kaiser Permanente of Portland, Oregon and Northern California [22,23]. After 5 years of follow-up, the cumulative probability of CIN3+ was 0.17% (95% CI; 0.11–0.28%) in HPV-negative women and 0.16% (95% CI; 0.06–0.39%) in women with negative results for both cytology and HPV in Kaiser Permanente, Northern California [23]. Based on these studies and cost-effectiveness modeling analyses, both Australia and the Netherlands have decided to adopt HPV primary screening for their national cervical cancer prevention programs. [7,8]

ATHENA is the first large, U.S. prospective screening study of HPV primary screening and the results confirm both that HPV primary screening increases sensitivity when compared to cytology and that

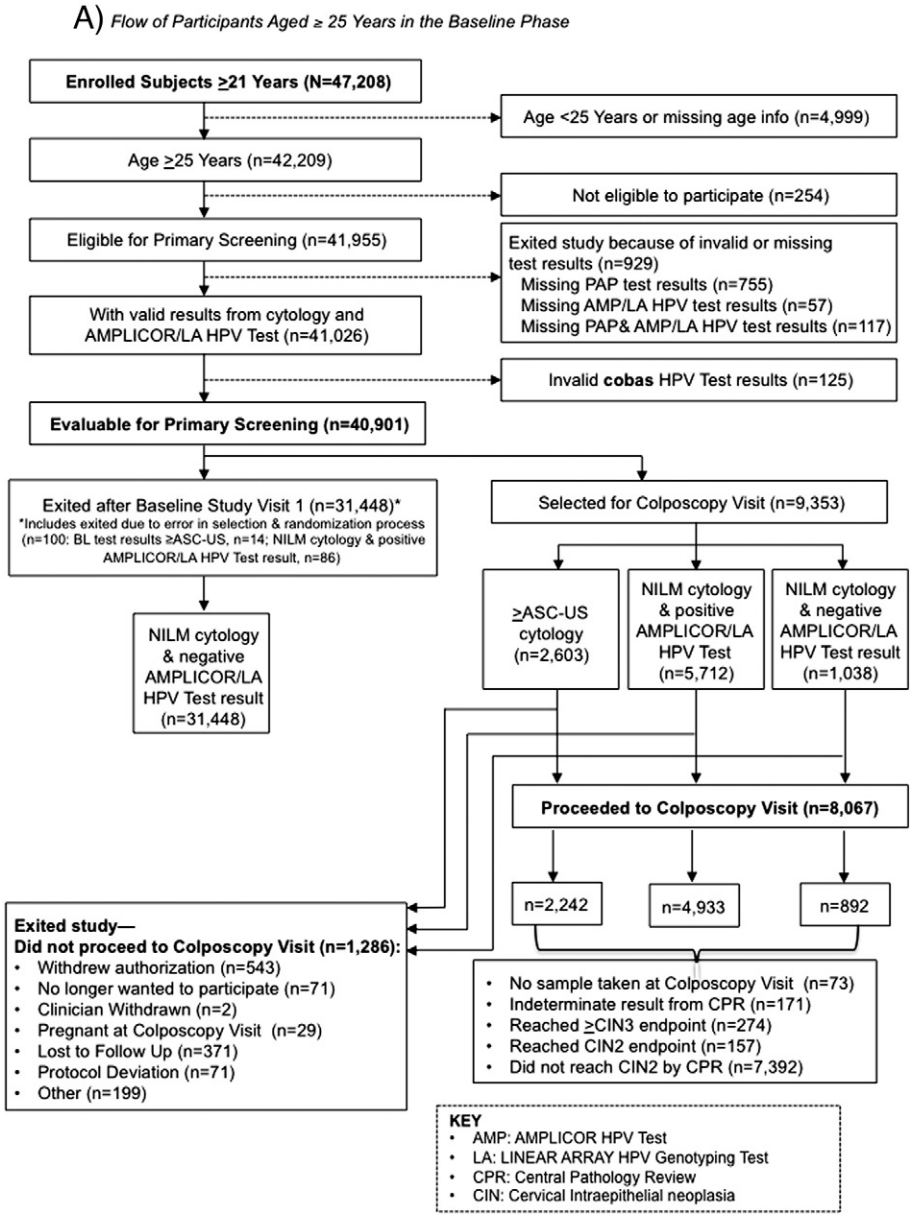

Fig. 1. A: CONSORT Diagram of flow of patients through the study. B: CONSORT Diagram showing at what point patients were diagnosed with CIN2+.

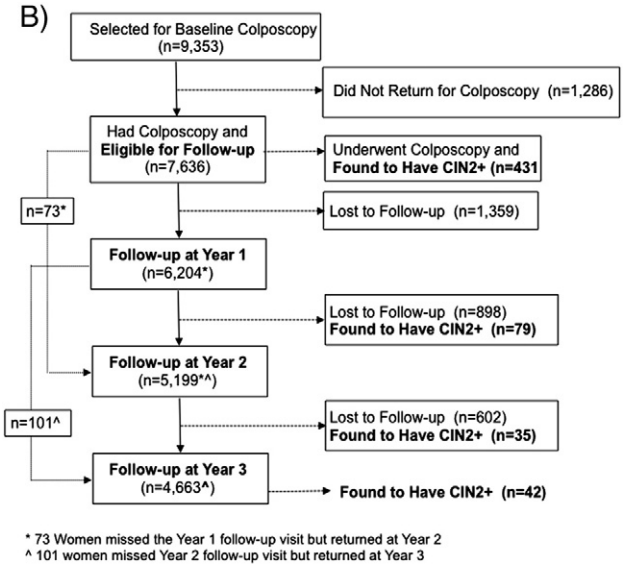

Fig. 1 *(continued).*

cotesting provides minimal increased protection against the development of CIN2+ or CIN3+ compared to HPV primary screening. The results of the current analyses showed that *HPV primary* screening, compared to *cytology*, provided a 28.3% increase in sensitivity for CIN3+ in women ≥25 years and a 24.3% increase in women ≥30 years. After 3 years of follow-up, the CIR of CIN3+ in cytology-negative women was more than twice that of HPV-negative women and the CIR in HPV-negative women was comparable to those who were both HPV and cytology-negative.

In the current study, the reason why *HPV primary* detected more CIN3+ in women ≥25 years is that with the *hybrid strategy* women 25–29 years were screened using *cytology* and only women ≥30 years had the added sensitivity of HPV testing. In addition, about half of all CIN3+ lesions were HPV16/18 positive and would be referred to colposcopy with *HPV primary*. However, with the *hybrid strategy*, HPV16/18 positive women do not undergo immediate colposcopy and are deferred to cotesting in 12 months allowing a substantial number to be lost to follow up. It should be emphasized that current U.S. screening recommendations do not endorse cotesting in women 25–29 years. This is because guideline groups were concerned that the high prevalence of HPV in this age group would result in unnecessary colposcopies and the detection of clinically unimportant CIN2 lesions. However, we found both a substantial burden of CIN3+ in women 25–29 years and also, as previously reported from the United Kingdom, that cytology was insensitive in this age group [24]. Additional studies have shown that the relative sensitivity of HPV testing versus cytology is higher in women younger than 30 or 35 years compared to older women [25–27].

Screening guidelines attempt to balance the benefits of detecting CIN3+ with the "harms" of overscreening [3,28]. A potential harm of overscreening is the detection of transient HPV infections that can result in patient anxiety and unnecessary colposcopies [3,19,28]. In ATHENA 10.5% of women ≥25 years were HPV-positive. This means that the benefits of using HPV would be outweighed by excess colposcopies unless some form of triage is used to reduce the number of women with clinically unimportant HPV infections referred to colposcopy. The most obvious triage approaches are cytology and HPV16/18 genotyping, both of which have been discussed widely in the literature and incorporated into U.S. guidelines for cotesting [3,5,9,21,25]. Our *HPV primary* strategy incorporates both genotyping for HPV16/18 and reflex cytology for women positive for other HPV genotypes to determine who needs colposcopy. Although *HPV primary* reduces the number of women undergoing colposcopy compared to performing colposcopy in all HPV-positive women, it still results in a significant increase in the number of colposcopies compared to either *cytology* or the *hybrid strategy*. Compared to *cytology*, *HPV primary* almost doubles the number of colposcopies that would be performed in women ≥25 years and it also significantly increases the number compared to the *hybrid strategy* in women ≥25 years but not ≥30 years. However, because *HPV primary* detects significantly more CIN3+ (and CIN2+) than *cytology*, the number of colposcopies required to detect a single CIN3+ only increases from 10.1 (95% CI; 8.6–12.2%) to 13.1 (95% CI; 11.5–15.2%). The number of colposcopies required to detect a single case of CIN3+ with *HPV primary* is not increased compared to the *hybrid strategy*, which is the preferred screening approach in the U.S. [3,28].

ATHENA has both strengths and limitations. Strengths include number of participants, rigorous disease ascertainment, and verification bias adjustment. Limitations include only 3 years of follow-up with a relatively high loss to follow-up rate and with a study design that exited women with CIN2+ at baseline. Therefore the outcome if these CIN2+ had not been treated is unknown. Other studies have found that approximately 20% of untreated CIN2 regresses after one year and 60% after three years [29,30]. However, CIN3 infrequently regresses in this time frame which is why we have focused on the CIN3+ data [21]. Other limitations are that the study had organized follow-up and it is unclear how the screening strategies would perform in the U.S. where screening is opportunistic, that only one type of HPV test was evaluated, and that the study is underpowered to use cervical cancer as an endpoint. We also are unable to tell what proportion of CIN3+ detected during follow-up was missed by baseline colposcopy and what proportion represents incident lesions.

In summary, ATHENA is the first prospective U.S. screening study to evaluate the performance of HPV primary screening. The results support the use of HPV primary screening with triage of HPV-positive women using a combination of genotyping for HPV 16/18 and reflex cytology beginning at age 25 years. Screening with *HPV primary* in women ≥25 years is significantly more sensitive for the detection of CIN3+ than either *cytology* or the *hybrid strategy*, the two strategies supported by current guidelines. The increase in sensitivity is associated with a significant increase in the number of colposcopies compared to either *cytology* or the *hybrid strategy* but the number of colposcopies required to detect a case of CIN3+ is the same as with the *hybrid strategy*.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2014.11.076.

Author contributions

Dr. Thomas Wright had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Wright and Behrens contributed equally to the manuscript. Drs. Stoler, Sharma, Zhang and Teresa Wright provided critical guidance for the manuscript development.

Study concept and design: Thomas Wright, Mark Stoler, Catherine Behrens, Teresa Wright.

Acquisition of data: Thomas Wright, Mark Stoler, Catherine Behrens.

Analysis and interpretation of data: Catherine Behrens, Abha Sharma, Guili Zhang, Thomas Wright.

Drafting of the manuscript: Thomas Wright, Catherine Behrens.

Critical revision of the manuscript for important intellectual content: Thomas Wright, Catherine Behrens, Teresa Wright.

Statistical analysis: Abha Sharma, Guili Zhang.

Administrative, technical, and material support: Roche Molecular Systems.

Conflict of interest statement

Dr. Thomas C. Wright, Jr is a consultant and speaker for Roche Molecular Systems, BD Diagnostics, and GenProbe-Hologic. He is a consultant to Cepheid. Dr. Mark H. Stoler is a consultant and speaker for Roche Molecular Systems and GenProbe-Hologic. He is a consultant to BD Diagnostics and Cepheid. Drs. Behrens, Sharma, Zhang are employed by Roche Molecular Systems. Dr. Teresa Wright is employed by Genentech.

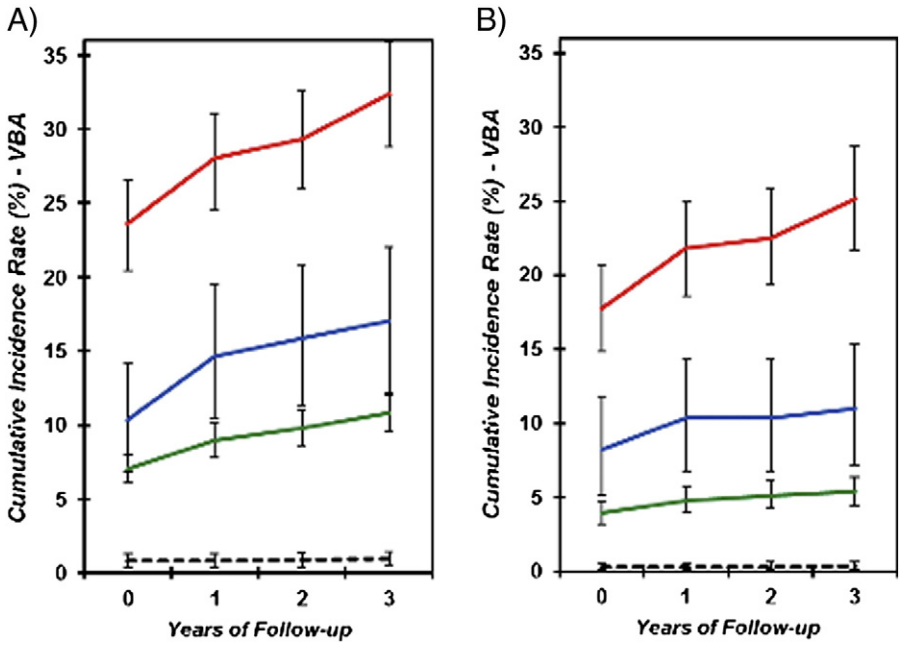

Fig. 2. Verification bias-adjusted (VBA) cumulative incidence of consensus pathology cervical intraepithelial neoplasia 2+ (CIN2+) (A) and CIN3+ (B) during 3 years of follow-up stratified by baseline human papillomavirus (HPV) status. Red solid line, HPV-16 positive; blue solid line, HPV-18 positive; green solid line, 12 other HPV genotypes positive; black dotted line, HPV-negative.

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Role of the sponsor

Roche Molecular Systems, Pleasanton, CA was involved in all aspects of the design and conduct of the study; collection, management, analysis, and interpretation of the data. Catherine Behrens and Abha Sharma who are Roche employees were integral to the preparation of the manuscript and the sponsor reviewed the final manuscript.

Previous presentations of parts of the data

Society of Gynecologic Oncology Annual Meeting, March 2013, Los Angeles, CA; EUROGIN, November 2013, Florence, Italy; Society of Gynecologic Oncology Annual Meeting, March 2014, Tampa, FL.

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Laboratory testing sites

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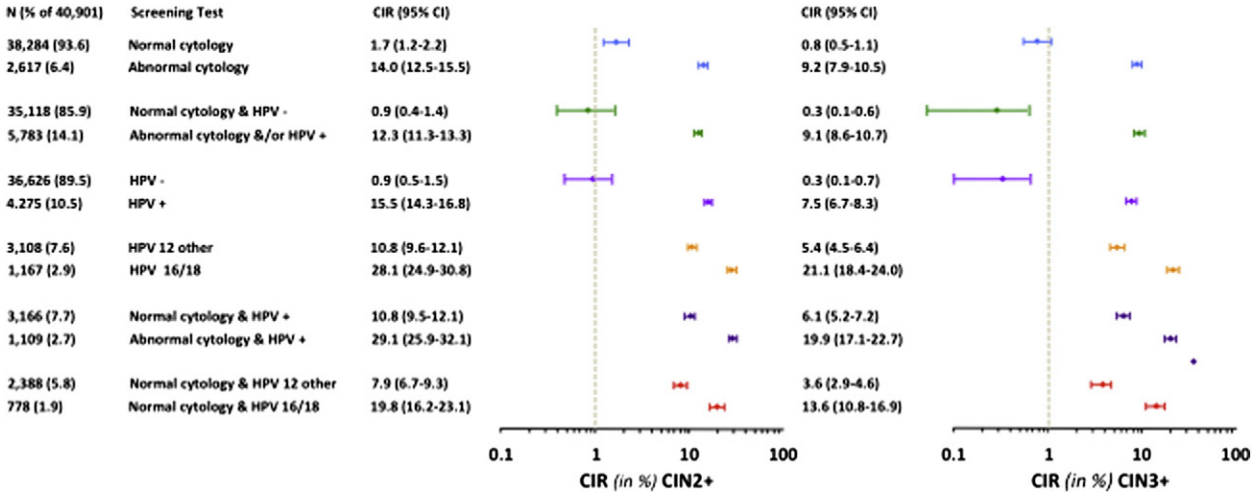

Fig. 3. Verification bias-adjusted (VBA) 3-year cumulative incidence rates of consensus pathology cervical intraepithelial neoplasia 2+ (CIN2+) and CIN3+ stratified by different combinations of baseline cervical cytology and HPV results. Note the x-axis is logarithmic.

Table 1
Impact of age on HPV status and CIN2+ and CIN3+.

	25–29 years	30–39 years	40–49 years	≥50 years	Total
Baseline result					
Number	*6647*	*12,248*	*11,689*	*10,317*	40,901
(% of row; 95% CI)	(16.3%; 15.9–16.6%)	(29.9%; 29.5–30.4%)	(28.6%; 28.1–29.0%)	(25.2%; 24.8–25.6%)	
hrHPV (+)	*1403*	*1419*	*830*	*623*	4275
(% of age group; 95% CI)	(21.1%; 20.1–22.1%)	(11.6%; 11.0–12.2%)	(7.1%; 6.–7.6%)	(6.0%; 5.6–6.5%)	
HPV 16/18 (+)	*464*	*401*	*181*	*121*	1167
(% of age group; 95% CI)	(7.0%; 6.4–7.6%)	(3.3%; 3.0–3.6%)	(1.5%; 1.3–1.8%)	(1.2%; 1.0–1.4%)	
Cytology ≥ ASCUS	*651*	*849*	*727*	*390*	2617
(% of age group; 95% CI)	(9.8%; 9.1–10.5%)	(6.9%; 6.5–7.4%)	(6.2%; 5.8–6.7%)	(3.8%; 3.4–4.2%)	
Cumulative detection of cervical disease at baseline and through year 3					
Number *CIN2*	*91*	*85*	*44*	*20*	240
(% of row; 95% CI)	(37.9%; 31.8–44.4%)	(35.4%; 29.4–41.8%)	(18.3%; 13.6–23.8%)	(8.3%; 5.2–12.6%)	
Number *CIN2+*	*210*	*225*	*101*	*51*	587
(% of row; 95% CI)	(35.8%; 31.9–39.8%)	(38.3%; 34.4–42.4%)	(17.2%; 14.2–20.5%)	(8.7%; 6.5–11.3%)	
% Cytology ≥ ASCUS	*42.9%* (36.1–49.8%)	*49.3%*	*59.4%*	*47.1%*	
(95% CI) in *CIN2+*		(42.6–56.1%)	(49.2–69.1%)	(32.9–61.5%)	
% 16/18 HPV (+)	*47.6%*	*47.1%*	*30.7%*	*29.4%*	
(95% CI) in *CIN2+*	(40.7–54.6%)	(40.4–53.9%)	(21.9–40.7%)	(17.5–43.8%)	
Number *CIN3+*	*119*	*140*	*57*	*31*	347
(% of row; 95% CI)	(34.3%; 29.3–39.6%)	(40.3%; 35.1–45.7%)	(16.4%; 12.7–20.8%)	(8.9%; 6.2–12.4%)	
% Cytology ≥ ASCUS	*43.7%*	*55.0%*	*59.6%*	*64.5%*	
(95% CI) in CIN3+	(34.6–53.1%)	(46.4–63.4%)	(45.8–72.4%)	(45.4–80.8%)	
% 16/18 HPV (+)	*57.1%*	*56.4%*	*43.9%*	*45.2%*	
(95% CI) in CIN3+	(47.7–66.2%)	(47.8–64.8%)	(30.7–57.6%)	(27.3–64.0%)	

The confidence interval calculation is based on exact confidence interval for proportion.

Collection sites

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Table 2
Adjusted performance of different screening strategies for the detection of cervical disease at baseline and through Year 3.

Strategy	Performance measure (95% CI)	CIN2+	CIN3+
Women ≥25 years			
Cytology	Sensitivity	40.6 (36.1–45.1)	47.8 (41.6–54.1)
	Specificity	97.3 (97.1–97.5)	97.1 (96.9–97.2)
	Positive Predictive Value	24.8 (22.3–27.4)	17.0 (14.7–19.2)
	Negative Predictive Value	98.7 (98.5–98.9)	99.3 (99.2–99.5)
	Positive Likelihood Ratio	15.1 (13.7–16.7)	16.3 (14.6–18.1)
	Negative Likelihood Ratio	0.6 (0.6–0.6)	0.5 (0.5–0.6)
Hybrid strategy	Sensitivity	55.5 (50.4–60.5)	61.7 (56.0–67.5)
	Specificity	95.0 (94.8–95.2)	94.6 (94.4–94.8)
	Positive Predictive Value	19.5 (17.6–21.4)	12.6 (11.2–13.9)
	Negative Predictive Value	99.0 (98.8–99.2)	99.5 (99.4–99.6)
	Positive Likelihood Ratio	11.1 (10.3–11.9)	11.4 (10.6–12.4)
	Negative Likelihood Ratio	0.5 (0.4–0.5)	0.4 (0.4–0.5)
HPV primary	Sensitivity	69.1 (63.7–74.4)	76.1 (70.3–81.8)
	Specificity	94.0 (93.8–94.3)	93.5 (93.3–93.8)
	Positive Predictive Value	20.2 (18.3–22.0)	12.9 (11.6–14.2)
	Negative Predictive Value	99.3 (99.1–99.5)	99.7 (99.6–99.8)
	Positive Likelihood Ratio	11.5 (10.9–12.2)	11.8 (11.1–12.5)
	Negative Likelihood Ratio	0.3 (0.3–0.4)	0.3 (0.2–0.3)
Women ≥30 years			
Cytology	Sensitivity	40.3 (34.6–46.0)	48.0 (40.6–55.4)
	Specificity	97.9 (97.7–98.0)	97.7 (97.5–97.8)
	Positive Predictive Value	23.9 (21.0–26.8)	16.7 (13.9–19.5)
	Negative Predictive Value	99.0 (98.8–99.2)	99.5 (99.4–99.6)
	Positive Likelihood Ratio	18.8 (16.6–21.2)	20.6 (18.0–23.5)
	Negative Likelihood Ratio	0.6 (0.6–0.7)	0.5 (0.5–0.6)
Hybrid strategy	Sensitivity	63.4 (56.7–70.1)	69.3 (61.7–76.9)
	Specificity	95.1 (94.8–95.3)	94.7 (94.5–95.0)
	Positive Predictive Value	17.8 (15.8–19.8)	11.4 (9.8–13.0)
	Negative Predictive Value	99.4 (99.2–99.5)	99.7 (99.6–99.8)
	Positive Likelihood Ratio	12.9 (11.9–14.0)	13.2 (12.1–14.4)
	Negative Likelihood Ratio	0.4 (0.4–0.4)	0.3 (0.3–0.4)
HPV primary	Sensitivity	64.8 (58.4–71.1)	72.3 (65.0–79.6)
	Specificity	95.2 (95.0–95.5)	94.9 (94.6–95.1)
	Positive Predictive Value	18.5 (16.4–20.6)	12.1 (10.4–13.8)
	Negative Predictive Value	99.4 (99.2–99.5)	99.7 (99.6–99.8)
	Positive Likelihood Ratio	13.5 (12.5–14.6)	14.1 (13.0–15.3)
	Negative Likelihood Ratio	0.4 (0.3–0.4)	0.3 (0.3–0.4)

Table 3
Detection of cervical disease using different screening strategies and the number of screening tests and colposcopies that each strategy requires.

	Strategy	Number of detected cases[a] (95% CI)			No. missed cases	No. screening tests (95% CI)	No. colposcopies (95% CI)	No. colposcopies to detect 1 case (95% CI)
		Total	Detected at baseline	Detected years 1–3				
≥25 years								
CIN2+	*Cytology*	*270* (239–303)	*215* (187–245)	*55* (41–70)	*317* (282–350)	*45,166* (44,931–45,392)	*1934* (1809–2061)	*7.1* (6.4–8.0)
	Hybrid strategy	*384* (347–421)	*215* (187–245)	*169* (145–193)	*203* (178–230)	*82,994* (82,634–83,397)	*3097* (2948–3264)	*8.1* (7.4–8.9)
	HPV primary	*471*[b,c] (430–514)	*283*[b,c] (250–318)	*188* (164–215)	*116*[d,e] (97–136)	*52,651*[b,e] (52,249–53,111)	*3767*[b,c] (3617–3962)	*8.0*[b] (7.4–8.8)
CIN3+	*Cytology*	*179* (152–206)	*143* (119–167)	*36* (25–49)	*168* (144–194)	*45,166* (44,931–45,392)	*1934* (1809–2061)	*10.8* (9.4–12.6)
	Hybrid strategy	*240* (209–270)	*143* (119–167)	*97* (79–115)	*107* (89–126)	*82,994* (82,634–83,397)	*3097* (2948–3264)	*12.9* (11.5–14.8)
	HPV primary	*294*[b,c] (260–325)	*197*[b,c] (169–226)	*97* (78–115)	*53*[d,e] (42–66)	*52,651*[b,e] (52,249–53,111)	*3769*[b,c] (3617–3962)	*12.8*[b] (11.7–14.5)
≥30 years								
CIN2+	*Cytology*	*185* (158–213)	*144* (121–168)	*41* (29–54)	*192* (164–221)	*37,312* (37,077–37,574)	*1294* (1197–1390)	*7.0* (6.1–8.1)
	Hybrid strategy	*299* (267–331)	*144* (121–168)	*155* (133–178)	*78* (64–94)	*75,140* (74,684–75,614)	*2457* (2316–2607)	*8.2* (7.4–9.2)
	Primary HPV	*299*[b] (266–332)	*178*[b,c] (152–205)	*121* (101–143)	*78*[d] (63–94)	*42,425*[b,e] (42,030–42,847)	*2522*[b,c] (2376–2667)	*8.4*[b] (7.6–9.4)
CIN3+	*Cytology*	*128* (105–152)	*106* (87–127)	*22* (13–31)	*100* (82–121)	*37,321* (37,077–37,574)	*1294* (1197–1390)	*10.1* (8.6–12.2)
	Hybrid strategy	*189* (163–215)	*106* (87–127)	*83* (67–99)	*39* (30–49)	*75,140* (74,684–75,614)	*2457* (2316–2607)	*13.0* (11.5–15.0)
	Primary HPV	*192*[b] (165–218)	*136*[b,c] (113–160)	*56* (42–71)	*36*[d] (27–48)	*42,425*[b,e] (42,030–42,847)	*2522*[b,c] (2376–2667)	*13.1*[b] (11.5–15.2)

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.
[a] This analysis utilizes crude numbers of detected cases as opposed to verification bias adjusted numbers.
[b] Significantly higher than *Cytology only* ($p < 0.05$).
[c] Significantly higher than *Hybrid strategy* ($p < 0.05$).
[d] Significantly lower than *Cytology only* ($p < 0.05$).
[e] Significantly lower than *Hybrid strategy* ($p < 0.05$).

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