women were pooled to examine the long-term predictive values of HPV testing and cytology [22]. The 6-year risk of CIN3+ following a negative HPV test was 0.27%, compared to 0.28% among cotest negatives. By comparison, the 6-year risk of CIN3+ following a negative cytology alone was significantly greater at 0.97%. The authors also noted that the risk of CIN3+ at a 3-year screening interval, the most commonly used screening interval in Europe, after negative cytology was 0.51%. In a retrospective observational study of 330,000 women aged 30 years and older undergoing cotesting (at 3-year intervals) in routine clinical practice [74], the 3-year risk of CIN3+ following negative cytology alone (regardless of the HPV result) was 0.17%; the 5-year risk of CIN3+ following a negative HPV test alone (regardless of the cytology result) was 0.17%; and the 5-year risk of CIN3+ following a negative cotest was 0.16%, essentially comparable results across each testing strategy. Likewise, the risks of cancer also were comparable (0.018%, 0.019%, and 0.016%, respectively).

In the same analysis [74], women who cotested negative at the initial screening and HPV and/or cytology positive 3 years later were at a lower risk of CIN3+ or cancer than women with a positive HPV and/or cytology result at the initial screen. This lower risk associated with previously negative findings presumably is due to the prolonged period of HPV carriage (chronic infections) required for invasive cancer to develop. Taken together, these reports indicate that healthcare providers can rely on the negative predictive value of the HPV test to assure women who cotest negative that they are at very low risk for CIN3 and cancer for at least 5 years after negative cotesting.

### *Risks Associated With Screening at Different Intervals*

Modeling from several sources indicates that there is a dramatic increase in colposcopy rate with minimal change in invasive cancer incidence as screening intervals decrease below 3 years, regardless of the modality employed [63, 84, 85]. Despite differing assumptions, all three analyses indicated that the number of colposcopies more than tripled with annual cytology starting at age 21, in comparison to annual cytology for ages 21–29 and cotesting at 5-year intervals starting at age 30. The models also agreed that cotesting of women aged 30 and older at 5 years intervals involves fewer colposcopies with similar or slightly lower cancer risk compared with 3-year cytology.

### *Detection of Adenocarcinoma of the Cervix and Its Precursors*

Case control studies in Australia and Italy demonstrated that cytologic screening provides only modest protection against adenocarcinoma [86, 87]. More recently, the International Collaboration of Epidemiological Studies of Cervical Cancer Group pooled screening data from 12 studies involving 1374 women with adenocarcinoma and concluded that risk reduction of a preceding cytology test was greater for squamous cell carcinoma than for adenocarcinoma [88].

In Castellsague *et al.* [89], HPV was detected in 93% of 167 adenocarcinomas of the cervix (including 55 adenosquamous carcinomas). A case control study with these cases and 1881 controls was also reported. Testing HPV positive (vs. negative) was strongly associated (odds ratio = 81.3) with a diagnosis of cervical adenocarcinoma [89]. From Katki *et al.* [74], 63% of the adenocarcinomas diagnosed over a 5-year period followed an initial HPV-positive, cytology-negative cotest result.

## Management of Women with HPV Positive, Cytology Negative Cotests

***Recommendation.*** Women cotesting HPV positive, cytology negative should be followed with either (as noted in the interim ASCCP guidelines [78]: Option 1) repeat cotesting in 12 months, or Option 2) immediate HPV genotype-specific testing for HPV16 alone or for HPV16/18. If cotesting is repeated at 12 months, women testing positive on either test* should be referred to colposcopy; women testing negative on both tests** should return to routine screening. If immediate HPV genotype-specific testing is used, women testing HPV16 positive or HPV16/18 positive should be referred directly to colposcopy; women testing HPV16 negative or HPV16/18 negative should be cotested in 12 months, with management of results as described in option 1.

Women cotesting HPV positive, cytology negative should not be referred directly to colposcopy. Furthermore, they should not be tested for individual HPV genotypes other than HPV16/18. The use of HPV genotype-specific testing for HPV16 or HPV16/18 is recommended only for the management of HPV-positive, cytology-negative women. Currently, there is insufficient evidence to support the use of non-HPV biomarkers.

*HPV positive OR LSIL or more severe cytology
**HPV negative AND ASCUS or negative cytology