

PATHCHAT

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Cervical Cancer Screening: Role of HPV DNA-based Screening and Cytology

Natural history of genital HPV infections in women

Genital infection with human papillomavirus (HPV) is the most common sexually transmitted infection today, and persistent infection with high-risk genotypes is the cause of cervical cancer. Over 40 HPV genotypes infect mucosal surfaces, including the anogenital epithelium (e.g. cervix, vagina, vulva, rectum, urethra, penis and anus). Most genital HPV infections are transient and asymptomatic. Approximately 70% of women with genital infections become HPV DNA negative within one year, and approximately 91% within two years following the initial infection.

For most of these HPV genotypes, there is sufficient evidence to divide them into "high-risk" (i.e. oncogenic or cancer-associated) types and "low-risk" (i.e. non-oncogenic) types (Table 1). Persisting infections with high-risk HPV genotypes lead to precancerous lesions and ultimately cervical cancer.

Table 1: High- and low-risk HPV genotypes

High-risk types (oncogenic or cancer-associated)	Low-risk types (Non-oncogenic)
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82	6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81
Approximate contribution of genotypes in causing cervical cancer: HPV-16: ± 60% HPV-18: ±10% HPV-31: ±4% HPV-45 : ±4% HPV-33, 52 and 58 together: ±2%	These cause benign or low-grade lesions and genital warts

High-risk HPV DNA testing for preventing cervical cancer

In view of the fact that persistent infection with a high-risk HPV (hr-HPV) is necessary for the development of cervical carcinoma, high-risk HPV DNA testing, either alone or in combination with cytology, has become an integral part of cervical cancer screening, triage and follow-up of treated lesions.

Primary hr-HPV DNA screening has the following advantages:

- Approximately 30% more sensitive in detecting CIN2+ lesions compared to cytology
- Approximately 20% more sensitive in detecting CIN3+ lesions compared to cytology
- Provides 60-70% greater protection against invasive cervical cancer compared to cytology-based screening
- Allows an extension of the screening intervals to five years (if HPV negative) compared to the recommended three-yearly intervals for cytology

Hr-HPV DNA testing has the following limitations:

- HPV DNA assays, while highly sensitive for detecting HPV infections, are not able to distinguish an infection that will clear spontaneously from one that will become persistent and lead to precancerous lesions and ultimately cervical cancer (i.e. specificity is poor). For this reason, women who test hr-HPV positive require what is known as a "triage" test to determine whether they have an underlying precancerous lesion that requires treatment.

Practical issues: Which patient, which screening method? (Table 2)

Table 2: Current best-practice guidelines

Age (in years)	Screening method	Comments
21-30	Cytology	Do not use hr-HPV screening due to higher rates of HPV infection and the transient nature of these infections. Re-screen after three years if negative.
30 -65	hr-HPV DNA	Re-screen after five years if hr-HPV negative.
Older than 65	Stop screening	Stop only if there is no prior history of CIN and the last hr-HPV test was negative.
HIV-infected women of any age	Cytology annually	Utility of hr-HPV screening has not been determined.

Note:

- Co-testing (both cytology and hr-HPV), although still recommended in the USA, is not widely used elsewhere as it is more costly and has virtually no added value compared to hr-HPV screening alone.

Practical issues: How do I manage women with positive hr-HPV tests or abnormal cytology?

Figure 1 and 2 highlight the steps to follow when performing either hr-HPV or cytology screening.

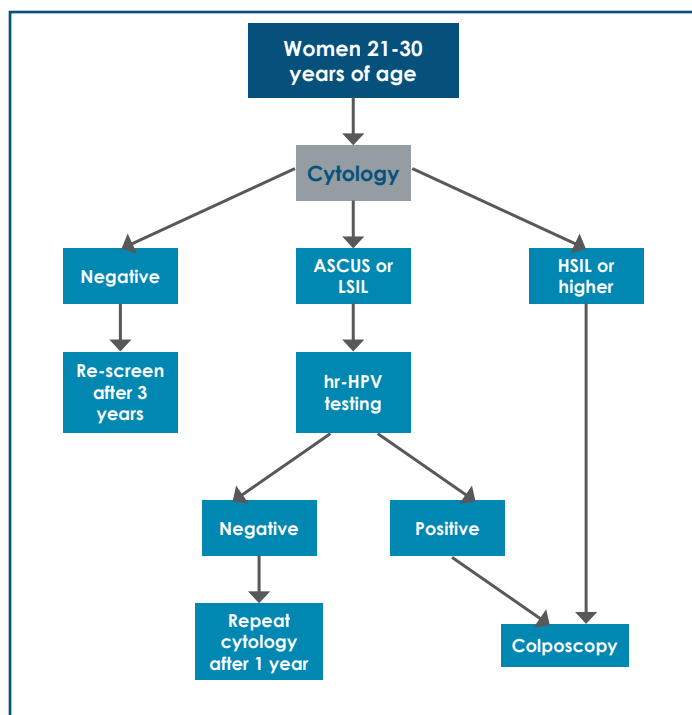


Figure 1

Key points:

- Primary hr-HPV DNA screening is evidence-based and should replace cytology-based screening programmes in women 30-65 years of age.
- Hr-HPV screening should start at the age of 30 with cytology alone used to screen women between 21 and 30 years of age due to the high prevalence and transient nature of the infection in young women.
- Screening can stop at the age of 65 provided there is no history of previous CIN and the last HPV test is negative.
- All HIV-infected women should be screened with cytology on an annual basis.
- Current re-screening intervals for hr-HPV DNA negative women are five years.
- Cytology should be used to triage hr-HPV positive women to determine the need for colposcopy. The triage test may change in future as other options are being investigated.
- A liquid-based cytology (LBC) sample should be used for hr-HPV requests, as well as cytology. This allows for the appropriate triage tests to be done on request (cytology if hr-HPV positive or hr-HPV if cytology shows ASCUS or LSIL).

References:

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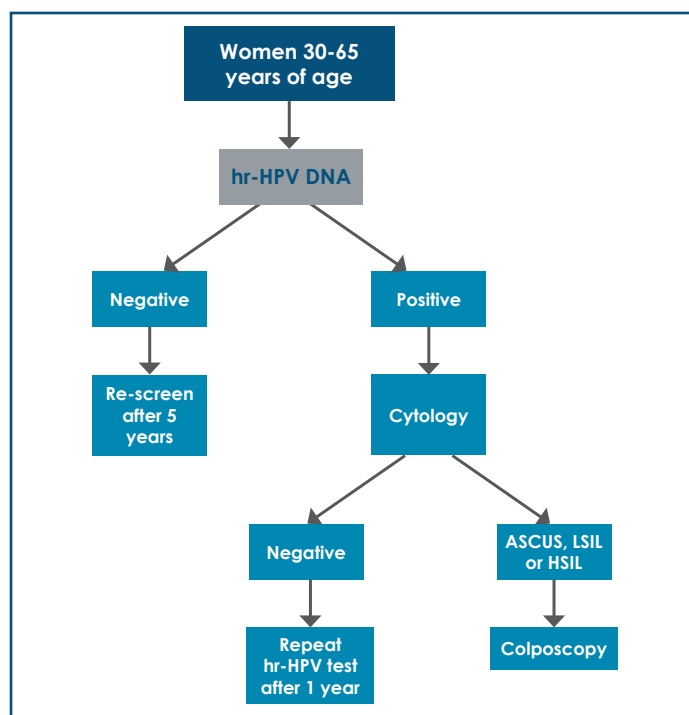


Figure 2