

### **Question 16**

For women who have been treated for a high grade precancerous squamous lesion what is the safety and effectiveness of testing with HPV test and cytology at 12 months after treatment and discharging if double-negative compared with testing at 12 and 24 months and discharging if double-negative at both 12 and 24 months?

**Search terms:** cervical intraepithelial neoplasia, CIN, recurrent, test of cure, surveillance, post-treatment, HPV, human papillomavirus, papillomavirus infections. Searches were limited to the English language and conducted from 2004 to current.

<b>Author</b>	<b>Country</b>	<b>Study type</b>	<b>Subjects/Methods</b>	<b>Findings</b>
Morrell et al, 2014	Australia	Retrospective cohort	<p>Women with CIN2+ diagnosed in NSW during 2006-2010 who also had HPV testing after treatment.</p> <p>N = 11,521</p> <p>Women who underwent co-testing at 12 and annually thereafter until 2 consecutive negative co-tests as per NHMRC 2005 follow-up guidelines</p> <p>N = 2,948</p> <p>Authors suggest that there may be some selection bias ie possible that HPV testing more likely to be recommended if women judged by clinician to be at higher risk of treatment failure</p>	<p>No follow-up of post-treatment histology results Deemed cured if 2 negative consecutive annual co-tests</p> <p>In the <math>\geq 2</math>-years after treatment, 75% of women who had <math>\geq 2</math> FU HPV and cytology tests according to NHMRC guidelines were cured (2,210/2,948 women). Cure rates were lowest in those aged <math>&lt;30</math> (71%) and highest in women 30-49 (80%). 68% were cured by the 2nd HPV test, 21% by the 3rd, and 11% at the 4th or later HPV test (up to 7 HPV FU tests).</p> <p>9.7% of those with negative co-test at 12 months had positive co-test at 24 months 14% of those with negative co-test at 3-7 months (n = 794) had positive co-test at 12 months</p> <p>Examining couplets of annual co-tests For women eventually cured (2 consecutive negative annual co-tests) , 88.5% were all negative on both testing occasions; 2.9% were HPV +/ cytology- followed by both negative; 2.7% were HPV-/ cytology+ followed by both negative; and 1.9% were both negative followed by HPV-/ cytology+. For non-cured women, 20.6% had HPV+/ cytology- followed by both tests being negative, 19.5% had both tests negative followed by HPV+/ cytology- and 16.2% had HPV+ / cytology- results on both occasions and 1.1% had HPV-/ cytology+ results on both occasions.</p>
Katki et al,	US	Retrospective	3273 women aged $\geq 25$ y treated	The more negative follow-up tests, the (non-significantly) lower was the subsequent 5-year CIN2+ risk. Following a negative initial cotest the risk

2013			<p>for biopsy-confirmed CIN2, CIN3, or AIS between 2003 and 2010 at Kaiser Permanente Northern California (KPNC)</p> <p>At KPNC:</p> <p>Women with negative cytology on screening were recalled for screening 3 years later</p> <p>Women with negative cytology and HPV status were recalled for screening 5 years later</p>	<p>was 2.4%, following consecutive negative initial and second cotests the risk was 1.5% (p = 0.8)</p> <p>After 2 negative cotests, the 1.5% (95%CI 0.3%-7.2%) risk approached the threshold for a 3-year return to screening (0.68% for a negative Pap test). However, even after 2 negative cotest results following treatment, this risk was higher than the threshold of 0.27% for a return to 5-year routine screening of . The authors concluded that it is difficult to justify return to routine, long-interval (i.e., 5-year) screening for a woman after she has been treated for CIN2. It will require longer follow-up of women with 3 or more repeated negative cotests to document whether and how soon their risk returns to "normal."</p>
<b>Author</b>	<b>Country</b>	<b>Study type</b>	<b>Subjects/Methods</b>	<b>Findings</b>
Uijterwaal et al, 2014 and Kocken et al, 2011 (combined results presented as studies were based on the same cohort)	Netherlands	Prospective follow-up study	435 women from 3 studies who were treated for CIN2/3 (399/435 had CIN3) in 1988-2004 and were FU by cytology and HPV testing at 6,12 and 24m after treatment and subsequent cytology screening every 5y. (results presented from 2 combined papers)	<p>76/435 (17%) developed post-treatment CIN2 or CIN2+ and 39 CIN3/CIN3+.</p> <p>If <u>contesting is negative for both tests at 6m</u> → 5-year risk of CIN2/CIN2+: 3% (95% CI 1.4–6.1) and for CIN3/CIN3+: 1.1% (95% CI 0.0–3.4)</p> <p>If <u>co-testing at both 6m and 24m are negative for both tests</u> -&gt; 5y risk of CIN2/CIN2+: 1.0% (95% CI 0.2-4.6) and for CIN3/CIN3+: 0.0 (0.0-2.9).</p> <p>The CIN2+ risk after 3 consecutive negative cytologic tests was with 2.9% (95% CI = 1.2%-7.0%) similar to the risk after 1 negative cotesting result at 6 months. The authors concluded that the 5-year risk of post-treatment CIN2 or CIN2+ in women with negative co-testing for cytology and hrHPV at 6 and 24 months was similar to that of women with normal cytology in population-based screening and therefore justifies their return to regular screening every 5 years</p>
Kitchener et al, 2008	UK	Prospective study	917 women (<35 years) treated for CIN recruited at the 6m FU visit. Of these 365 had CIN3, 326 had CIN2, 217 had CIN1 and 9 had cervical glandular intraepithelial neoplasia. 64% clear margins Cytology and HPV testing was carried out at 6 and 12m. At 24m	<p>The detected CIN2+ rate in this group was 12/917 (1.3% including 2 VAIN) at 6m, 6/778 (0.77%) at 12m and 8/707 (1.1% including 1 VAIN) at 24m. In this cohort 12 (1.3%) women with CIN2, 9 (1.0%) with CIN3, 1 (0.1%) with CGIN, 1 (0.1%) with cancer and 3 (0.3%) with VAIN were identified over 24m.</p> <p>Of the 744 women who were cytology negative/HPV negative at baseline, 2 women were diagnosed with CIN2 at 12 months, and 1 woman was diagnosed with CIN3, 1 woman with adenocarcinoma and 1 woman with VAIN, 1 with CIN3, 1 with cancer and 1 with VAIN1 were identified at 24</p>

			cytology alone was performed. Colposcopy if abnormal cytology or HPV positive and according to local practice if normal cytology and HPV negative	months follow-up. 9/10 cases of CIN3/CGIN occurred in HPV-positive women. At 23 m, cancer was identified in a woman treated for CGIN with clear resection margins, who had been cytology negative/HPV negative at both 6 and 12 months. That authors concluded that based on their study data the cumulative risk of residual disease is so low after 24m of FU that a women who are cytology negative and HPV negative at 6 months after treatment for CIN can safely be returned to 3-year recall.
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**Abbreviations:** GCIN: cervical glandular intraepithelial neoplasia; FU: follow-up; VAIN: vaginal intraepithelial neoplasia

### Possible useful information

Based on an updated meta-analysis of studies (Arbyn et al, 2012) the rate of residual or recurrent high-grade CIN, evaluated over 2 years or less, varied in the 15 included studies from 4–18%, with an average of 8%. Pooled long-term follow-up data indicate that women having been treated for CIN are still at increased risk for subsequent invasive cervical cancer compared to the general population, during at least 10 years and maybe up to 20 years after treatment (Soutter et al, 2005) .

### References

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