Active surveillance of cervical intraepithelial neoplasia grade 2: 2025 British Society of Colposcopy and Cervical Pathology and European Society of Gynaecologic Oncology consensus statement

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Histological diagnosis of cervical intraepithelial neoplasia grade 2 (CIN2) has traditionally been the cutoff for local surgical treatment, due to a substantial risk of cancer development. However, evidence from the past decade suggests 50–60% of CIN2 lesions spontaneously regress, and active surveillance (or conservative management—ie, leaving the lesion untreated) might be justified in some cases. Active surveillance of CIN2 lesions is now practised widely, although clear recommendations on eligibility, frequency of surveillance, threshold for treatment, and criteria for return to routine recall are insufficient in most countries. In 2023, the cumulative risk of invasive cancer over 20 years was found to be substantially higher in patients under active surveillance when compared with patients who received immediate local treatment, with the greatest difference observed in women older than 30 years. This Policy Review and practice algorithm from the British Society of Colposcopy and Cervical Pathology and the European Society of Gynaecologic Oncology prevention committees aims to review existing evidence and present clear recommendations to assist clinical decision making. Active surveillance, rather than immediate treatment, might be reasonable in a carefully selected cohort of patients. The risk of progression, need for repeat visits, and cumulative risk of future invasion associated with active surveillance should be carefully balanced against the benefits of awaiting regression, including consideration of the woman's age, fertility wishes, additional risk factors, and likelihood of compliance to follow-up. Clinical audit and, ideally, prospective databases are required to monitor long-term outcomes and safety.

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Introduction

The introduction of systematic call and recall screening programmes over the past 20 years has resulted in substantial reductions to the incidence and mortality of invasive cervical cancer, as its precursors, cervical preinvasive lesions, can be detected and treated.[1,2]

Persistent infection by high-risk oncogenic human papillomavirus (HPV) subtypes is a necessary condition for the development of invasive cervical cancer, although only a small number of infections develop into cancer.[3] More than 70% of women (used throughout this Policy Review to refer to people who were born biologically female) who are sexually active become infected with HPV during their lifetime.[4] The majority of infections clear or become undetectable through an incompletely understood immune response within 12–24 months of detection.[5] The preinvasive precursor cervical intraepithelial neoplasia (CIN) has been traditionally categorised into 3 grades, 1 to 3, with no evidence of CIN or cancer classified as normal (ie, healthy).[6] CIN grade 1 (CIN1; also known as low-grade squamous intraepithelial lesion) is now recognised as a state of continuous viral replication rather than a true invasive precursor, and CIN grade 3 (CIN3) is a preinvasive lesion associated with more than 30% risk of disruption of the basal membrane and stromal invasion.[7] The biological behaviour and natural history of CIN grade 2 (CIN2) is not as well understood.

Traditionally, the diagnosis of CIN2 with histological biopsy has been considered the cutoff for local excision of the transformation zone. Meanwhile, local excision has been associated with an increased risk of reproductive morbidity in subsequent pregnancies.[8,9] A 2018 systematic review and meta-analysis by Tainio and colleagues[10] found a regression rate of CIN2 of 50% (95% CI 43–57), which was higher than previously recognised, especially in women younger than 30 years (60% [95% CI 57–63]).[10] This was later supported by a large cohort study of 11 056 women from Denmark by Lycke and colleagues[11] (table), which showed a CIN2 regression rate of 62·9% (95% CI 61·9–63·8), although the length of follow-up was short (24 months). As such, concerns were raised about potential overtreatment in a substantial number of women with CIN2 whose lesions would otherwise regress without intervention. However, in 2023, Lycke and colleagues published a nationwide, population-based, historical cohort study of 27 524 women in Denmark who were diagnosed with CIN2, a proportion of which were managed with active surveillance (also referred to as conservative management) from as early as 1998.[12] Active surveillance data were linked to cancer registries and suggested that the cumulative risk of invasive cervical cancer over 20 years was substantially higher in women who underwent active surveillance compared with those who received immediate local treatment; higher invasion rates and a greater risk difference were found in women older than 30 years compared with women aged 30 years or younger, which raises concerns about long-term safety.[12]

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See Online for appendix

The histological classification of CIN2 as a high-grade lesion might induce a tendency towards overtreatment, in our opinion. The current US national guidelines, the 2019 American Society of Colposcopy and Cervical Pathology (ASCCP) risk-based management consensus guidelines, developed through a consensus effort of 19 national organisations, recommended that histological high-grade lesions be classified as CIN2 or CIN3 to allow for the option of active surveillance of CIN2.[13] The ASCCP additionally proposed $p16^{INK4a}$ (p16) immunostaining as a marker to classify an equivocal CIN2 lesion into the low-grade or high-grade phenotype.[13,14] p16 immunostaining is widely used across Europe; however, no consensus is yet available on the exact clinical applications of this marker.

Although active surveillance of CIN2 lesions is sometimes practised in the UK and in other European countries, such as Finland and Denmark, clear and detailed guidelines on who to recommend for active surveillance and the exact management and follow-up protocol are either insufficient or unavailable, depending on the country. Eligibility for active surveillance, frequency of surveillance, threshold of treatment, and criteria for return to routine recall have not been previously adequately described. National screening guidelines (including UK Government guidance from National Health Service [NHS] England)[15] aim to outline best practice and can improve standardisation while allowing personalised treatment. This Policy Review aims to summarise existing evidence and present a consensus statement on the clinical course of CIN2, management and treatment options (panel), and an algorithm to support clinician decision making (figure 1). The consensus statement is based on a literature review and critical appraisal of the evidence by a group of experts from the British Society of Colposcopy and Cervical Pathology (BSCCP) and the European Society of Gynaecologic Oncology (ESGO) prevention committee.

Methods

BSCCP and ESGO prevention committee executive councils nominated specialists from their membership bodies who had well recognised expertise, clinical and research activity, and leadership in the field of colposcopy and management of cervical pathology.

We conducted a systematic literature review of MEDLINE for studies published between database inception and May 3, 2024. Search indexing terms and criteria are listed in the appendix (p 1). The literature search was limited to publications in English. Case reports, letters, and in vitro studies were excluded.

Data extraction and preparation was done by SJB and LBE for all articles dealing with active surveillance. Discrepancies were resolved with the involvement of MK.

Evidence-based consensus statements were developed on active surveillance of CIN2 and prepared into tabular format by SJB and LBE. The chair (MK) was responsible for drafting corresponding preliminary statements based on the review of the relevant literature. These preliminary statements were then sent to the group of selected specialists. After discussion, specialists were asked to vote for, vote against, or abstain from agreement on 28 statements. The chair then discussed the results of this first round of voting and revised the statements if necessary. The revised version of the statements was distributed again to all experts, who were given the opportunity to evaluate and revise the next version of the statements. The statements were finalised on the basis of the results of this second round of voting. The group reached consensus on all 28 statements.

Epidemiology and evidence on natural history of CIN2

Given that CIN2 preinvasive cervical lesions are not recorded in cancer registries, the true incidence of CIN2 is difficult to establish. Approximately 2–3% of women who are unvaccinated against HPV are estimated to be diagnosed with CIN2 or CIN3 in UK screening programmes annually, with the highest incidence (10%) among women aged 25–29 years.[16] In 2017, the incidence of CIN3 in women in the UK was estimated to be 75 per 100 000 women, and CIN2 rates are likely to be similar.[17] The latest NHS Digital data from 2022–23 suggest that 8755 (7·0%) of 124 839 patients referred by screening to colposcopy were diagnosed with CIN2 in England in 1 year.[18] Data collated in mostly unvaccinated cohorts suggest that the number of women in Europe with new CIN2 lesions or worse (ie, CIN3 or invasive disease) is approximately 500 000 each year.[19]

Accurate data from longitudinal studies on the clinical course of CIN2 lesions have been limited by both the equivocal histological diagnosis and the ethical dilemma of conservatively managing possible precancer, with most data coming from studies in adolescents and women younger than 25 years. Furthermore, the definition of regression varies between studies. The first report on the clinical course of CIN, published in 1984 by McIndoe and colleagues,[20] reported CIN3 progression to invasive cancer to be as high as 30%; progression of

	At risk (n)	Regression		Progression	
		Events (n)	Cumulative incidence function (95% CI)	Events (n)	Cumulative incidence function (95% CI)
6 months since CIN2 diagnosis	11 056	3070	27·9% (27·0–28·7)	1658	15·1% (14·4–15·7)
12 months since CIN2 diagnosis	6269	2994	55·4% (54·5–56·3)	1546	29·3% (28·4–30·1)
18 months since CIN2 diagnosis	1617	558	60·9% (60·0–61·9)	281	32·1% (31·2–33·0)
24 months since CIN2 diagnosis	614	145	62·9% (61·9–63·8)	95	33·3% (32·4–34·2)

Reproduced from Lycke et al.[11] CIN2=cervical intraepithelial neoplasia grade 2.

Table: **Regression and progression rates of CIN2**

***Panel*: Recommendations for the active surveillance of women with cervical intraepithelial neoplasia grade 2**

Case selection

- Active surveillance of cervical intraepithelial neoplasia (CIN) grade 2 lesions is an option for carefully selected patients.
- In women younger than 25 years with CIN grade 2 (CIN2), active surveillance is preferred, although treatment is acceptable.
- In women aged 25 years and older, active surveillance is an acceptable management option. There is no upper age limit for active surveillance if other criteria as described in this panel are met, although the risks and benefits should be discussed in the context of the low, long-term risk of invasion that is associated with active surveillance, particularly in women older than 30 years.
- Active surveillance of CIN2 lesions should only be offered to women who are willing and likely to comply with intensive monitoring visits.
- All women considered for active surveillance should have histological confirmation at baseline and additional histological confirmation in case of worsening or persistent lesions or at least once every 12 months, until negative for high-risk HPV (human papillomavirus) or the decision to treat is made.
- All cases of CIN2 that are proposed for active surveillance should be discussed in multidisciplinary meetings or equivalent panels, with expert review of the cytology, colposcopic impression, and biopsy.
- The squamocolumnar junction and the upper limit of the lesion or lesions should be visible in order to consider active surveillance of CIN.
- Women with immunosuppression should not be offered active surveillance and should instead be treated.
- Women with previous treatment should not be offered active surveillance and should instead be treated.
- The screening history, age, HPV vaccination history, likelihood of compliance with intense surveillance, and patient's fertility wishes should be carefully considered during decision making.
- Factors such as large lesion size, the number of involved quadrants being more than 2, presence of expansile CIN, crypt involvement, HPV-16 or HPV-18 genotypes (if available), and high-grade index cytology might increase the risk of progression and should be carefully considered during decision making.
- No evidence supports recommending endocervical curettage in women with CIN2.
- Women of reproductive age should be counselled that their risk of preterm birth is lower if the lesion regresses but higher if the lesion progresses and treatment is performed at a later date.
- Patients with cytological or histological abnormalities in the glandular epithelium are excluded from this algorithm and should be managed as per existing guidelines.

Active surveillance and management

- Active surveillance should include co-testing or repeat testing for high-risk HPV with reflex cytology if positive, and colposcopic assessment at least once every 6 months. Histological biopsy should be done at least every 6 months if presumed persistent or progressive disease is suspected on the basis of colposcopy and cytology. In the presence of high-risk HPV positivity and evidence of regression on cytology and colposcopy (to low-grade or healthy status), histological biopsy should be done at least every 12 months.
- If there is evidence of a progressive lesion, it should be treated with local excision of the transformation zone.
- Local excisional treatment should be offered at 24 months of active surveillance if CIN2 persists, unless there is histological confirmation of regressive disease to CIN grade 1 (CIN1) or normal grade cytology. 90% of lesions that progress or regress do so within 12 months.[11]
- If low-grade disease is persistent after 24 months of active surveillance, local treatment could be considered at the discretion of the clinician and patient.
- Women on active surveillance that become pregnant should be managed as per current guidelines on management of high-grade CIN during pregnancy. The aim of surveillance during pregnancy is to rule out invasion and defer biopsy or excision treatment until after delivery, unless invasive disease is suspected.

Follow-up after active surveillance

- Two consecutive high-risk HPV negative tests 12 months apart are required to discharge a woman back to a 3-year recall. If high-risk HPV testing is negative at 3 years after discharge, the woman can return to routine recall which could include extended 5-yearly screening intervals until the usual exit screening round.
- If a high-risk HPV screening test is positive at any stage in women who were previously managed with active surveillance and regressed without local treatment, immediate referral to colposcopy is recommended irrespective of triage cytology.

Use of biomarkers

- Genotyping for HPV-16 and HPV-18, DNA methylation testing, or a combination of these are not practised in all settings and cannot be routinely used to triage women for treatment during follow-up or at the end of 2 years of surveillance, but might support clinical decision making where available. HPV-16 positivity is associated with risk in terms of persistence and progression of CIN compared with other HPV genotypes.
- $p16^{INK4a}$ (p16) staining in histological samples cannot replace conventional grading. Although not routinely practised in all settings, p16 staining should not be used to upgrade a histological lesion from CIN1 to CIN2; however, absence of

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staining could be useful as a negative predictor of high-grade disease in equivocal cases.

Risk of developing invasion

- The risk of invasive disease (3 in 1000) and the risk of glandular disease (5 in 1000) during follow-up are low but not absent.[10,12] Counselling women on the importance of attending their follow-up is important.
- The absolute cumulative risk for invasion at 20 years after either immediate surgical excision or successful active surveillance of CIN2 is low overall, but higher in the active surveillance group (2·65% [95% CI 2·07–3·23]) in comparison with the immediate surgical excision group (0·76% [0·58–0·95]).[12] This risk is also higher in women who had histological regression during active surveillance (3·83% [3·24–4·42]) than in the immediate treatment group (0·69% [0·46–0·93]),[12] which emphasises the importance of follow-up and the low threshold for future colposcopy or treatment in those managed with active surveillance.

Administration

- A patient information sheet should be provided that emphasises the importance of compliance with intensive active surveillance.
- The discussion on risks and benefits and mutual agreement of the plan for active surveillance and importance of compliance with follow-up should be clearly documented in the medical notes.
- Patients under active CIN2 surveillance should be regularly audited for outcomes and ideally recorded on prospective national screening databases.

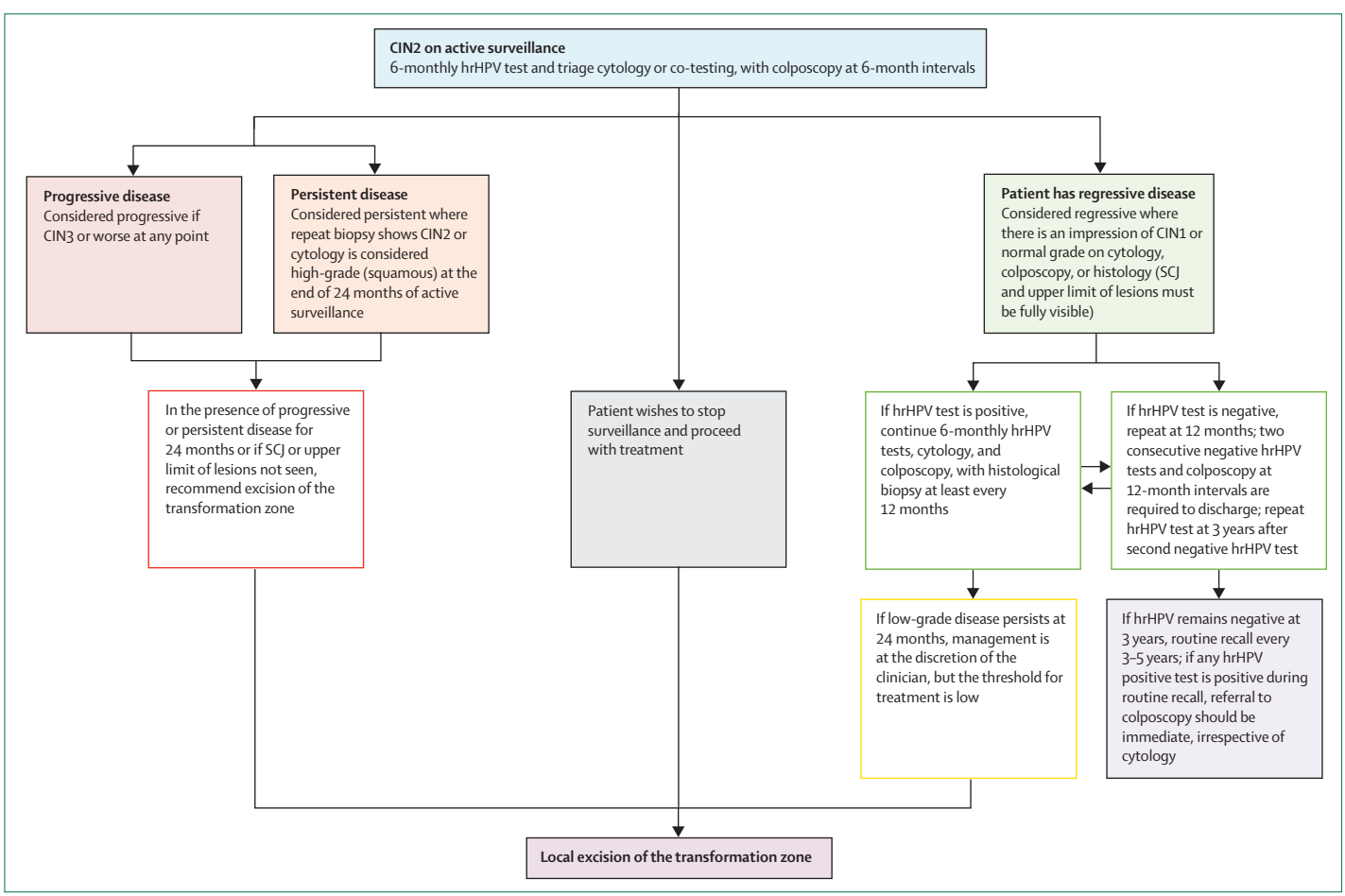


Figure 1: **British Society of Colposcopy and Cervical Pathology and European Society of Gynaecologic Oncology Clinical Guidelines algorithm for active surveillance of CIN2**
CIN1=cervical intraepithelial neoplasia grade 1. CIN2=cervical intraepithelial neoplasia grade 2. CIN3=cervical intraepithelial neoplasia grade 3. hrHPV=high-risk human papillomavirus. SCJ=squamocolumnar junction.

CIN2 was not studied. The most-cited report by Ostör[21] documents a 35% CIN2 persistence, a 22% rate of progression from CIN2 to CIN3, a 5% rate of progression from CIN2 to invasive disease, and a 40% regression rate when averaging across 12 studies published from 1955 to 1990 including a total of 2247 women. These data have some inherent limitations. A definition of regression was not included, and different studies have been included in the estimated proportion for each outcome. Other potential biases are the inclusion of studies from 1955 where cytological classification differed to current practice, follow-up durations as short as 4 months, the inclusion of small cohorts, varying inclusion criteria, and a paucity of advanced statistical techniques with no adjustment for sample size or estimates of heterogeneity. A 2010 prospective cohort study of 95 women aged 18–23 years with CIN2 reported regression in 68% (95% CI 57–78), with only 15% (9–26) showing progression to CIN3 in 3 years.[22] Another prospective cohort of 397 women with CIN2 aged 18–62 years reported that more than 40% of CIN2 lesions regressed within 2 years.[23] A 2016 retrospective review of 319 women younger than 25 years with CIN2 that was managed with active surveillance found that 150 (71%) lesions regressed completely.[24]

Tainio and colleagues included 36 studies of more than 3160 women with histologically confirmed, untreated CIN2 managed with active surveillance in their systematic review and meta-analysis[10] and reported that after 2 years, 50% (95% CI 43–57) of CIN2 lesions regressed to CIN1, atypical squamous cells of undetermined significance, or healthy tissue; 32% (23–42) persisted; and 18% (11–27) progressed. In a subgroup analysis of 1069 women younger than 30 years, the rates of regression were higher, with 60% (57–63) of lesions regressing, 23% (20–26) persisting, and 11% (5–19) progressing. In 2021, a meta-analysis of 42 studies on CIN2 found that the rate of regression to CIN1 or a less severe condition was 55% (50–60), the rate of persistence was 23% (19–28), and the rate of progression was 19% (15–23).[25] In summary, these studies estimate that approximately half of untreated CIN2 lesions will regress after 2 years, approximately a fifth will progress, and 5 in 1000 will develop into invasive cervical cancer.

Denmark is one of the first countries to have introduced guidelines regarding active surveillance of CIN2, with active surveillance being practised in regions of Denmark from as early as 1995 based on local guidelines. National guidance introduced in 2012 recommended consideration of active surveillance of CIN2 in women of reproductive age, with monitoring every 6 months up to 2 years.[26] A nationwide, register-based cohort study of women aged 18–44 years comparing outcomes in those who had active surveillance for histologically confirmed CIN2 (6721 in 2008–11 and 6399 in 2014–17) showed that the implementation of the Danish national guidance in 2012 led to an increase in active surveillance from 29·6% to 53·3% and an increase in regression rates from 41·8% to 46·7%.[27] A 2023 study using Danish national registries data of 11056 patients with CIN2 managed with active surveillance between 1998 and 2020 showed progression rates to be 33·3% (95% CI 32·4–34·2) and regression to CIN1 or normal-grade cytology to be 62·9% (61·9–63·8) within 2 years of diagnosis. However, only half of these lesions regressed to normal-grade cytology; 90% of those that progressed or regressed did so within 12 months of diagnosis.[11]

Eligibility criteria for active surveillance vary substantially globally. Although English guidelines suggest active surveillance should be an option only for small lesions (ie, involving no more than two quadrants of the cervix),[28] Denmark currently has no restrictions on what makes a CIN2 lesion eligible for active surveillance, except that the patient should be of reproductive age.[26] 13 (36%) of the 36 studies included by Tainio and colleagues did not have robust inclusion and exclusion criteria.[10] Thus, a proportion of the variation in the reported clinical course of CIN2 could be due to the heterogeneity in the included populations, and given the absence of restriction, the Danish cohort data are likely to represent higher absolute risk of progression than populations that have been more narrowly selected.

Risk factors

Risk factors proposed to affect chances of progression or regression during the 2-year surveillance period include age, immunosuppression, HPV-16 or HPV-18 positivity, HPV vaccination (received before age 15 years),[29] high-grade index cytology, crypt involvement, expansile CIN at histology, and possibly DNA methylation positivity. One of the most important predictors of progression or regression appears to be age. Although Tainio and colleagues found a higher rate of regression over 2 years since diagnosis in women 30 years or younger (60%) than in the whole population (50%), Lycke and colleagues showed similar progression rates (to CIN3 or worse) among women aged 30–40 years (35·2%) and women aged 23–29 years (33·9%). The progression rate among 1161 women aged 18–22 years was substantially lower (25·1%). Women with CIN2 who are younger than 25 years are highly likely to have lesion regression; one small study of 34 women based in Germany found regression in 30 (88%).[30]

Subgroup analysis by Tainio and colleagues[10] revealed that across three studies, the risk of progression was lower in women who tested negative for any high-risk HPV type (3%) at the time of CIN2 diagnosis than in women who tested positive for any high-risk HPV type (25%). Similarly, across two studies, risk of progression was lower in women who tested negative for HPV-16 or HPV-18 (5%) than in women who tested positive for HPV-16 or HPV-18 (21%). One prospective cohort study of 95 women aged 18–23 years with CIN2[22] showed a 68% regression rate within 3 years of diagnosis; progression

was higher in women with HPV persistence of any type or with hormonal contraceptive use, and marginally higher in women who tested positive for HPV-16 or HPV-18. In a study based in New Zealand and Australia of 201 women aged younger than 25 years who had active surveillance of CIN2, regression was observed in 146 (73%) women who tested negative for HPV-16 and HPV-18 at CIN2 diagnosis.[31] In this same study, 30 (45%) of 66 women who tested positive for HPV-16 had lesions that regressed, and 14 (61%) of 23 who tested positive for HPV-18 had lesions that regressed.[31] A 2023 study of 455 women aged 23–40 years under active surveillance for CIN2 showed a marked difference in absolute risk of persistence and progression by HPV type, with a risk of 71% in those with HPV-16, 48% in those with HPV-18, and 32% in those with HPV-51.[32] These findings are in line with those from a 2024 Danish cohort study in which the authors investigated how the risk of progression in women under active surveillance for CIN2 was affected by previous HPV vaccination status.[29] This study found that women who had received the quadrivalent HPV vaccine before age 15 years had a 35% lower risk of progression compared with unvaccinated individuals (adjusted relative risk [RR] 0·65 [95% CI 0·57–0·75]), but no difference in risk was observed between women who had received the quadrivalent HPV vaccine at age 20 years or older and unvaccinated women (adjusted RR 1·02 [0·79–0·95]).[29]

In a prospective cohort study of 149 women with CIN2 managed with active surveillance, 88 (59%) had lesions that regressed, 36 (24%) had lesions that persisted as CIN1 or CIN2, and 25 (17%) had lesions that progressed to CIN3 or worse. In this cohort, a combination of a positive DNA methylation test and cytology of high-grade squamous intraepithelial lesions or worse provided an area under the curve of 0·735 in predicting progression versus regression.[33] In a second cohort of 93 women with CIN2 or CIN3 tested for FAM19A4/miR124-2 methylation, women with a negative methylation test at baseline showed more clinical regression (74·7% [95% CI 65·7–81·7]) than those with a positive methylation test at baseline (51·4% [34·6–65·9; p=5·013).[34]

In a similar way to HPV genotyping and DNA methylation, a high-grade index cytology might confer a high risk of progression during the 2-year active surveillance period. The 2023 Danish cohort study of 11 056 women reported that 5125 women (46·4%) who had a high-grade cytology at the time of CIN2 diagnosis had a 60% higher risk of progression compared with 1258 women (11·4%) with normal index cytology (adjusted RR 1·58).[11] In a US study of 2417 women aged 21–39 years who were managed with active surveillance for CIN1 and CIN2, CIN2, or CIN2 and CIN3, women referred with high-grade cytology were more likely to receive treatment (202 [37%] of 544 women) irrespective of the baseline histology than women with low-grade cytology (228 [27·7%] of 824 women).[35]

In addition to a high-grade cytology at baseline, the presence of expansile CIN at histology (a feature of CIN that involves the endocervical crypts and is associated with high-grade CIN) and a greater number of involved cervical quadrants at colposcopic examination could be associated with a reduced chance of CIN2 regression.[36] In a 2011 study of 42 women with CIN2, lesions involving only one quadrant were 6·5 times more likely to regress than those extending beyond one quadrant in the first 3 months of follow-up, although by 12 months, no statistically significant difference in regression was observed according to number of affected quadrants (odds ratio 2·40 [95% CI 0·46–12·7]).[37] The Swede scoring system has shown that lesions occupying multiple cervical quadrants are more likely to be high-grade disease than lesions occupying a single quadrant.[38]

Given that many countries have transitioned to primary HPV screening (with most using cytology triage), the importance of using HPV assays that enable partial or extended genotyping could be useful in stratifying the risk of disease progression. For example, information on HPV genotype, particularly the presence of HPV-16[39,40] in combination with associated cytology and lesion size,[37] could be useful for shared decision making in people diagnosed with CIN2.

CIN is difficult to diagnose and treat in patients with previous local excision[41] and in patients without a fully visible squamous columnar junction; therefore, active surveillance cannot be recommended in these groups. Immunosuppression from HIV or systemic immunosuppressive treatments increases HPV persistence and risk of CIN, cervical cancer,[42] and treatment failure.[43] Although treatment of HIV with antiretroviral treatment might increase likelihood of regression of CIN,[44,45] the safety in these groups is unknown, and active surveillance therefore cannot be recommended at present.

Adherence with follow-up

Likelihood of compliance with surveillance is important in deciding management. Tainio and colleagues[10] found the rate of non-compliance at 6–24 months of follow-up in prospective studies was approximately 10%, which was more than twice as high as the 4·7% rate reported by Lycke and colleagues.[12] External factors, such as pregnancy, might delay repeat colposcopy (eg, in Denmark, repeat colposcopy was performed at 8 weeks postpartum).[26] A high adherence to follow-up is important for shared decision making between physician and patient for active surveillance versus immediate treatment. Additionally, robust systems with a high level of quality assurance that minimise the number of errors in patient recall and an assessment of affordability of care as a barrier to long-term follow-up are needed when implementing surveillance programmes.

Missing invasive and glandular disease

One of the major concerns in the management of CIN2 is the risk of missing prevalent invasive disease. Tainio and colleagues[10] reported a total of 15 (0·5%) cases of invasive disease (median follow-up 16 months [IQR 7·6–27·4]) among 3160 women included in their meta-analysis. 13 (87%) of these 15 cases were stage 1A1, and two (13%) were of more advanced invasive disease (one stage 1B1 and one of unspecified stage). 11 (73%) of the 15 invasive cases were reported in a single study from Japan[46] that lacked histological confirmation of CIN2 at baseline and had a median follow-up of persistent CIN2 beyond 24 months.

In the Danish cohort study, 33 (0·3%) of 11056 women were diagnosed with invasive disease during a 2-year follow-up period, with 12 (60%) of 21 women with available stage data being diagnosed at International Federation of Gynaecology and Obstetrics stage 1A1.[11] In Lycke and colleagues'[12] analysis of 27524 women aged 18–40 years who were diagnosed with CIN2 in 1998–2020, 12483 (45·4%) were treated with active surveillance and 15041 (54·6%) were treated with immediate large loop excision of transformation zone (LLETZ). No difference was found in the cumulative risk of invasion during the 2 years of follow-up (adjusted cumulative risk of invasion 0·56% [95% CI 0·40–0·71] after active surveillance *vs* 0·37% [0·31–0·44%] after immediate LLETZ).[12] However, the cumulative risk for invasion at 20 years follow-up was higher in the active surveillance group (2·65% [2·07–3·23]) than in the immediate surgical excision group (0·76% [0·58–0·95]),[12] which emphasises the importance of continuing follow-up and the low threshold for future colposcopy or treatment in those who are managed with active surveillance (figure 2).

Tainio and colleagues[10] also reported a high incidence of invasive disease in women older than 40 years. Lycke and colleagues[12] reported that 68% of cervical cancers identified during follow-up in their study were diagnosed in women who were older than 30 years at CIN2 diagnosis. Thus, the 20-year risk of cancer was substantially higher in women aged 30 years or older at CIN2 diagnosis compared with those younger than 30 years at diagnosis (5·30% [95% CI 3·91–6·69] *vs* 1·52% [0·92–2·12]).

Although glandular disease is excluded from most active surveillance protocols, among 3160 patients, Tainio and colleagues[10] found 15 cases of cervical glandular intraepithelial neoplasia or adenocarcinoma in situ during the follow-up period. These findings highlight the value of histological confirmation of CIN2 at baseline, including evaluation for cervical glandular intraepithelial neoplasia or adenocarcinoma in situ, and the need for local excision if CIN2 persists after 24 months.

Recurrence, reproduction, and long-term risk of cancer

When managing CIN2, the harms of immediate local excision should be balanced against the potential harms of the number of repeat visits, delayed treatment, the risk of non-compliance, rates of recurrence, and the possible increased long-term risk of cancer associated with active surveillance. Although local surgical excision increases the risk of preterm birth, especially when repeated,[8,47–50] a 2024 cohort of 10537 women with CIN2 and a subsequent singleton birth found that the risk of preterm birth was similar between active surveillance and immediate LLETZ (RR 1·03; 95% CI 0·90–1·18).[51] However, the risk of preterm birth for women who received delayed LLETZ after active surveillance (1539 [35%] of 4430 in the active surveillance group) was 30% higher than for women who received immediate LLETZ (RR 1·29; 95% CI 1·08–1·55). The risk of preterm birth was slightly lower in women with lesions that regressed (RR 0·88; 95% CI 0·74–1·04;[51] figure 3). As the authors were unable to retrieve information on cone size, whether the observed increased risk was due to a combined effect of the HPV infection, disease, and larger excision volume was unclear. Nevertheless, the findings suggested that risk stratification at CIN2 diagnosis is important to identify women with an increased risk of needing delayed LLETZ after a period of active surveillance. Recurrence rates after lesion regression should also be considered. Wilkinson and colleagues[52] identified 683 women younger than 25 years with CIN (405 with CIN2 and 278 with CIN1) who were managed with active surveillance from the New Zealand national screening programme. Of the 405 women with untreated CIN2, 106 (26%) had spontaneous regression of CIN2 within 2 years of surveillance and 299 (74%) women were treated. After a median follow-up of 4 years, 18 (17%) of the 106 women who had CIN2 regression during active surveillance later developed a recurrent high-grade lesion, a rate that was found to be statistically significantly higher when compared with the 13 (4%) women who had a recurrence among the 299 who were immediately treated for CIN2 (p=0·01). Comparatively, progression to a high-grade lesion was observed in 32 (12%) of 278 women with

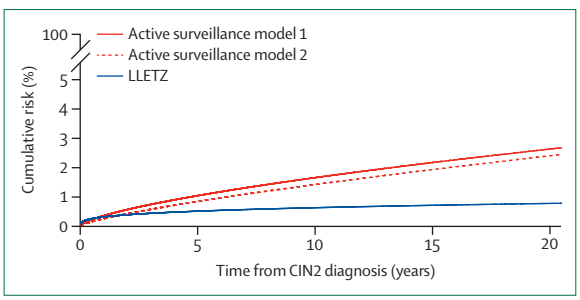
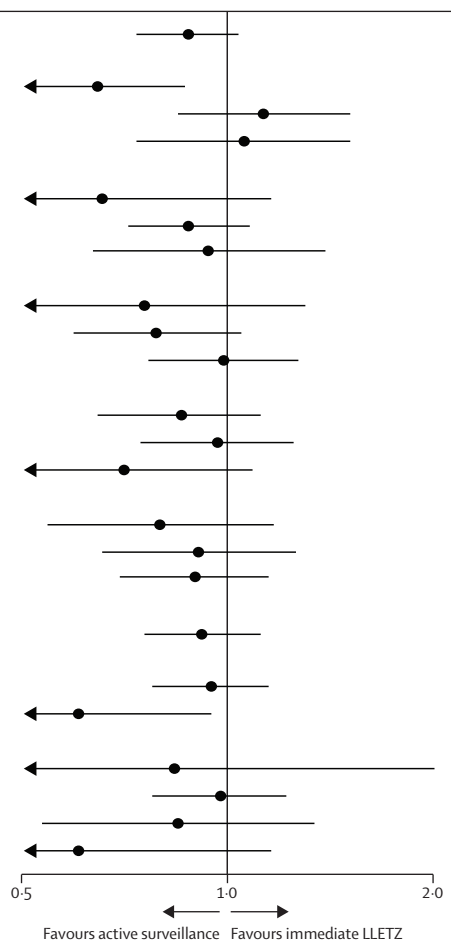


Figure 2: **Cumulative risk of cervical cancer among women with CIN2 who have active surveillance or immediate LLETZ**
Model 1 refers to the follow-up from date of CIN2 diagnosis. Model 2 refers to the follow-up from the date of CIN2 diagnosis, with women in the active surveillance group who were treated with LLETZ within 28 months of follow-up, censored at date of LLETZ. CIN2=cervical intraepithelial neoplasia grade 2. LLETZ=large loop excision of transformation zone. Reproduced from Lycke et al[12] by permission of BMJ.

A

	Active surveillance without LLETZ, n (%)	LLETZ, n (%)	Adjusted RR (95% CI)
Overall	**202 (7·0)**	**501 (8·2)**	**0·88 (0·74–1·04)**
Time since CIN2 diagnosis			
0–2 years	78 (5·6)	237 (8·6)	0·65 (0·49–0·87)
3–5 years	81 (8·2)	151 (7·4)	1·13 (0·85–1·51)
>5 years	43 (8·6)	113 (8·7)	1·06 (0·74–1·51)
Age at CIN2 diagnosis			
18–22 years	18 (5·5)	43 (9·0)	0·66 (0·37–1·16)
23–29 years	146 (7·2)	317 (8·1)	0·88 (0·72–1·08)
30–40 years	38 (7·2)	141 (8·2)	0·94 (0·64–1·39)
Index cytology			
Typical	22 (6·4)	35 (8·6)	0·76 (0·44–1·30)
Low-grade	79 (7·0)	170 (8·8)	0·79 (0·60–1·05)
High-grade	87 (7·1)	261 (7·9)	0·99 (0·77–1·27)
Calendar year of CIN2 diagnosis			
1998–2006	67 (7·7)	266 (8·9)	0·86 (0·65–1·12)
2007–12	86 (7·3)	202 (7·6)	0·97 (0·75–1·25)
2013–18	49 (5·8)	33 (7·2)	0·71 (0·46–1·09)
Calendar year of birth			
1998–2006	36 (7·5)	115 (8·9)	0·80 (0·55–1·17)
2007–12	45 (7·2)	212 (8·4)	0·91 (0·66–1·26)
2013–18	121 (6·8)	174 (7·6)	0·90 (0·70–1·15)
Parity			
Nulli	171 (7·6)	370 (8·6)	0·92 (0·76–1·12)
Smoking status			
Non-smoker	167 (6·8)	360 (7·4)	0·95 (0·78–1·15)
Smoker	27 (7·0)	128 (11·4)	0·61 (0·39–0·95)
BMI			
<18·5 kg/m²	7 (6·9)	21 (10·3)	0·84 (0·35–2·00)
18·5–24·9 kg/m²	130 (7·1)	275 (7·3)	0·98 (0·78–1·22)
25–29·9 kg/m²	29 (6·5)	88 (8·7)	0·85 (0·54–1·34)
≥30 kg/m²	14 (6·4)	47 (9·8)	0·61 (0·32–1·16)



(Figure 3 continues on next page)

untreated CIN1. The study was not powered to assess for risk of invasive disease. Lycke and colleagues[12] reported an increase in the 15-year cumulative risk of cervical cancer from 0·69% in women who had immediate excisional treatment to 3·83% in women who had active surveillance and histological regression with no treatment during the 2-year surveillance period. These factors, together with the likelihood of an individual's adherence to follow-up, are therefore important to consider during the shared decision making for active surveillance versus immediate treatment.

Histological assessment and p16 immunostaining

Integral to a successful active surveillance programme is the quality of colposcopy practice and histopathology reporting. Even in the best performing screening programmes and research studies, interobserver variability in histological classification is well documented, and histopathology is subject to less quality control than other areas of screening programmes, such as the strict quality control processes for cytology.[53] In a 2023 review of 455 cases of conservatively managed CIN2 in Denmark, 56 (12%) were upgraded to CIN3, and 121 (27%) were downgraded to CIN1 or normal grade upon expert review.[32] A similar study in the USA examined 2295 samples classed as CIN2 by community pathologists, and after expert pathology review, 990 (43·1%) were downgraded to CIN1 or normal grade and 433 (18·9%) were upgraded to either CIN3 or adenocarcinoma in situ.[54] Multidisciplinary meetings offer the chance to review cases of discordant cytology and histology and reduce misclassification. Furthermore, molecular markers have the potential to reduce misclassification by uncovering carcinogenic progression before macroscopic changes visible at colposcopy or histopathology. Such markers could be a particularly relevant tool in active surveillance pathways. Although

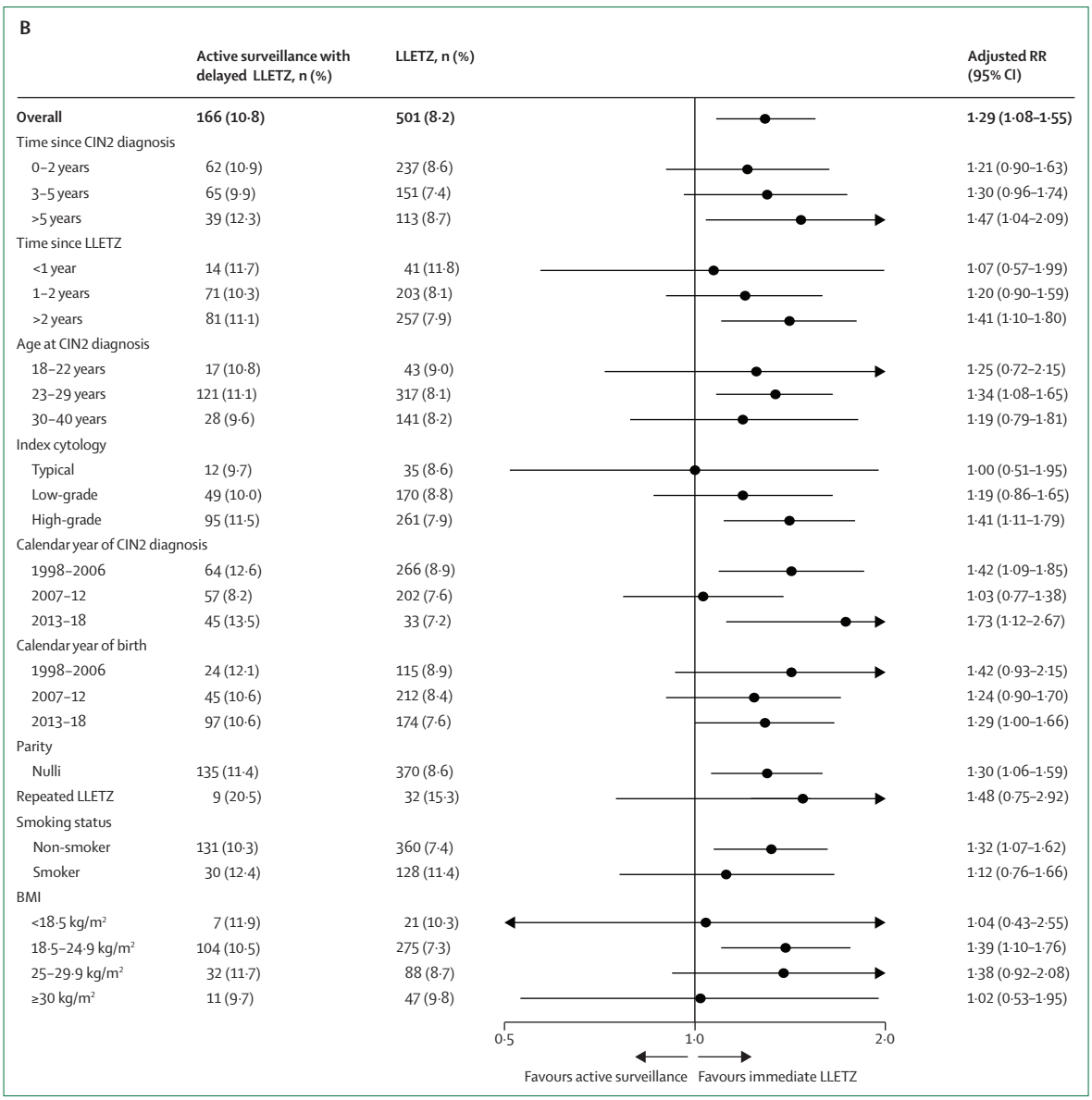


Figure 3: **Risk of preterm birth in women with CIN2 undergoing active surveillance alone versus immediate LLETZ (A) and those undergoing active surveillance with delayed LLETZ versus immediate LLETZ (B)**
Reproduced from Lycke et al.[51] CIN2=cervical intraepithelial neoplasia grade 2. LLETZ=large loop excision of transformation zone. RR=relative risk.

several molecular markers are under investigation (eg, E6 and E7 proteins, HPV mRNA, and methylation), p16 protein immunostaining is the only marker with current use in clinical practice worldwide. High-grade histology samples were shown to be more likely to stain positive for p16 protein in a meta-analysis[55] and have been suggested as a useful adjunct to prevent misclassification between CIN1 and CIN2 in cases where morphology is uncertain. The 2019 ASCCP guidelines recommend p16 immunohistochemistry to support the diagnosis of histological CIN2 or worse if morphological assessment on the haematoxylin and eosin slide is consistent with CIN2 or CIN3, with the caveat that p16 should not be used to upgrade a histological lesion from CIN1 to CIN2 where p16 is positive, as this has the potential to overestimate the grade of the disease.[13] However, studies have reported conflicting evidence on the diagnostic accuracy of p16 expression to improve the accuracy of CIN grading.[56] Although some studies report an improvement in diagnostic accuracy for CIN2 or worse when p16 is used,[57,58] other studies did not find it to be a clinically useful marker for detection of all high-grade lesions.[59] Evidence from one study suggested that p16-positive CIN2 lesions have a low chance of being upgraded to CIN3 on expert review and are not likely to have antecedent high-grade cytology, and therefore

should not be used as a triage for active surveillance, particularly in women younger than 30 years.[60] The performance of E4 and p16 is currently under investigation in a historical cohort study of 500 women with CIN2 who had active surveillance.[61] The British Association of Gynaecological Pathologists guidance from 2022 on interpretation of p16 immunohistochemistry reports that up to 50% of CIN1 might be p16-positive, and that p16 is therefore not diagnostic of high-grade CIN.[62] Although p16 has potential as a negative predictor of high-grade disease in equivocal cases,[63] the additional training and cost-effectiveness of this testing,[59] in balance with any possible benefit it could offer, needs to be taken into consideration before p16 can be recommended routinely.

2025 BSCCP ESGO recommendations

The 2019 ASCCP[13] risk-based management consensus guidelines outline options for active surveillance of CIN2 lesions in women younger than 25 years and in women 25 years or older (appendix p 2). In the UK, screening does not commence until the age of 25 years. In other European countries, the age of initiation of screening varies; primary high-risk HPV testing is commonly offered after the age of 30 years and cytology is the screening test of choice in younger women.[64] The BSCCP ESGO 2025 recommendations, made after assessment of the existing evidence, are summarised in the panel.

Conclusion

This Policy Review adds to an increasing body of evidence that active surveillance of CIN2, rather than immediate treatment, might be reasonable for a carefully selected cohort of patients. When considering active surveillance, the risk of missed or future invasive disease should be balanced against the benefits of awaiting regression, age, fertility wishes, the impact and cost of repeat visits, and the possibility of only delaying treatment. Patients should be informed that the cumulative risk of invasion within 20 years is low overall, but substantially higher when compared with immediate excision. Prospective databases are required to monitor long-term outcomes and safety in those who are managed with active surveillance, for future appropriate risk stratification. Continued research into biomarkers that could differentiate those at higher risk of progression from those likely to regress will also be highly valuable.

Contributors

This Policy Review was conceived by PM-H and MK. MK and SJB wrote the first draft. All authors contributed to regular consensus statement meeting and proposed recommendations. All authors reviewed the manuscript.

Declaration of interests

MK received funding from the European Society of Gynaecological Oncology for this work. MK received honoraria from Hologic unrelated to this work. SJB has received funding from the National Institute of Health and Care Research and a Wellcome Trust Clinician Scientist 4i Fellowship, unrelated to this work. AH has received an honorarium from Exeltis and equipment from Roche Diagnostics, unrelated to this work. DL is the president of the British Society of Colposcopy and Cervical Pathology. TF-W has received travel funding from the Chinese Colposcopy Society, unrelated to this work, and she is the past president of the British Society of Colposcopy and Cervical Pathology and president elect of the International Federation for Colposcopy and Cervical Pathology. IK has received funding from the Finnish Research Council, Finnish Medical Foundation, Sigrid Juselius Foundation, and Finnish State Research Funding, unrelated to this work. All other authors declare no competing interests.

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References

1 Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol* 2012; **137:** 516–42.

2 Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999; **318:** 904–08.

3 Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189:** 12–19.

4 Bosch FX, de Sanjosé S. Chapter 1: human papillomavirus and cervical cancer—burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003; **31:** 3–13.

5 Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998; **338:** 423–28.

6 WHO. Comprehensive cervical cancer control: a guide to essential practice, 2nd edn. 2014. https://iris.who.int/bitstream/handle/10665/144785/9789241548953_eng.pdf;jsessionid=3B73F6B9B409B5C26AE45BC3C135D19D?sequence=1 (accessed Feb 7, 2025).

7 Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol* 2006; **2006** (suppl)**:** 40470.

8 Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006; **367:** 489–98.

9 Kyrgiou M, Athanasiou A, Paraskevaidi M, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 2016; **354:** i3633.

10 Tainio K, Athanasiou A, Tikkinen KAO, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ* 2018; **360:** k499–99.

11 Lycke KD, Kahlert J, Damgaard RK, et al. Clinical course of cervical intraepithelial neoplasia grade 2: a population-based cohort study. *Am J Obstet Gynecol* 2023; **229:** 656.e1–15.

12 Lycke KD, Kahlert J, Petersen LK, et al. Untreated cervical intraepithelial neoplasia grade 2 and subsequent risk of cervical cancer: population based cohort study. *BMJ* 2023; **383:** e075925.

13 Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2020; **24:** 102–31.

14 Waxman AG, Chelmow D, Darragh TM, Lawson H, Moscicki AB. Revised terminology for cervical histopathology and its implications for management of high-grade squamous intraepithelial lesions of the cervix. *Obstet Gynecol* 2012; **120:** 1465–71.

15 National Health Service England. Cervical screening: programme and colposcopy management. May 3, 2010. https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management (accessed Jan 24, 2025).

16 Rebolj M, Rimmer J, Denton K, et al. Primary cervical screening with high risk human papillomavirus testing: observational study. *BMJ* 2019; **364:** l240.

17 NHS England. Cancer registration statistics, England 2019. Oct 21, 2021. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2019 (accessed Jan 26, 2025).

18 NHS Digital. Cervical screening programme, England - 2022-2023 [NS]. Nov 23, 2023. https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/england-2022-2023 (accessed Jan 24, 2025).

19 Hartwig S, Baldauf J-J, Dominiak-Felden G, et al. Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines. *Papillomavirus Res* 2015; **1:** 90–100.

20 McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol* 1984; **64:** 451–58.

21 Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993; **12:** 186–92.

22 Moscicki AB, Ma Y, Wibbelsman C, et al. Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. *Obstet Gynecol* 2010; **116:** 1373–80.

23 Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol* 2009; **113:** 18–25.

24 Loopik DL, Doucette S, Bekkers RLM, Bentley JR. Regression and progression predictors of CIN2 in women younger than 25 years. *J Low Genit Tract Dis* 2016; **20:** 213–17.

25 Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RLM, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. *J Low Genit Tract Dis* 2021; **25:** 221–31.

26 Bchtawi AK, Lauridsen AH, Winter A, et al. Forebyggelse, udredning og behandling af dysplasi på cervix. September, 2021. https://static1.squarespace.com/static/5467abcce4b056d72594db79/t/61385d27aefc071b368483cf/1631083828420/Cervix+dysplasi+guideline.pdf (accessed Jan 26, 2025).

27 Skorstengaard M, Lynge E, Suhr J, Napolitano G. Conservative management of women with cervical intraepithelial neoplasia grade 2 in Denmark: a cohort study. *BJOG* 2020; **127:** 729–36.

28 NHS England. Guidance: colposcopic diagnosis, treatment and follow up. Sept 27, 2024. https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management/3-colposcopic-diagnosis-treatment-and-follow-up (accessed Jan 26, 2025).

29 Krog L, Lycke KD, Kahlert J, et al. Risk of progression of cervical intraepithelial neoplasia grade 2 in human papillomavirus-vaccinated and unvaccinated women: a population-based cohort study. *Am J Obstet Gynecol* 2024; **230:** 430.e1–11.

30 Ehret A, Bark VN, Mondal A, Fehm TN, Hampl M. Regression rate of high-grade cervical intraepithelial lesions in women younger than 25 years. *Arch Gynecol Obstet* 2023; **307:** 981–90.

31 Sykes PH, Simcock BJ, Innes CR, et al. Predicting regression of cervical intraepithelial neoplasia grade 2 in women under 25 years. *Am J Obstet Gynecol* 2022; **226:** 222.e1–13.

32 Damgaard RK, Jenkins D, Stoler MH, et al. High prevalence of HPV16 and high-grade cytology in women undergoing active surveillance for cervical intraepithelial neoplasia grade 2. *Acta Obstet Gynecol Scand* 2023; **102:** 1227–35.

33 Louvanto K, Aro K, Nedjai B, et al. Methylation in predicting progression of untreated high-grade cervical intraepithelial neoplasia. *Clin Infect Dis* 2020; **70:** 2582–90.

34 Kremer WW, Dick S, Heideman DAM, et al. Clinical regression of high-grade cervical intraepithelial neoplasia is associated with absence of *FAM19A4/miR124-2* DNA methylation (CONCERVE study). *J Clin Oncol* 2022; **40:** 3037–46.

35 Silver MI, Gage JC, Schiffman M, et al. Clinical outcomes after conservative management of cervical intraepithelial neoplasia grade 2 (CIN2) in women ages 21–39 years. *Cancer Prev Res* 2018; **11:** 165–70.

36 Papoutsis D, Underwood M, Williams J, Parry-Smith W, Panikkar J. Expansile endocervical crypt involvement by CIN2-3 as a risk factor for high grade cytology recurrence after cold coagulation cervical treatment. *Geburtshilfe Frauenheilkd* 2020; **80:** 941–48.

37 Discacciati MG, de Souza CA, d'Otavianno MG, et al. Outcome of expectant management of cervical intraepithelial neoplasia grade 2 in women followed for 12 months. *Eur J Obstet Gynecol Reprod Biol* 2011; **155:** 204–08.

38 Bowring J, Strander B, Young M, Evans H, Walker P. The Swede score: evaluation of a scoring system designed to improve the predictive value of colposcopy. *J Low Genit Tract Dis* 2010; **14:** 301–05.

39 Damgaard RK, Jenkins D, Stoler MH, et al. Human papillomavirus genotypes and risk of persistence and progression in women undergoing active surveillance for cervical intraepithelial neoplasia grade 2. *Am J Obstet Gynecol* 2024; **230:** 655.e1–10.

40 Kylebäck K, Ekeryd-Andalen A, Greppe C, Björkenfeldt Havel C, Zhang C, Strander B. Active expectancy as alternative to treatment for cervical intraepithelial neoplasia grade 2 in women aged 25 to 30 years: ExCIN2-a prospective clinical multicenter cohort study. *Am J Obstet Gynecol* 2022; **227:** 742.e1–11.

41 Rebolj M, Helmerhorst T, Habbema D, et al. Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study. *BMJ* 2012; **345:** e6855.

42 Looker KJ, Rönn MM, Brock PM, et al. Evidence of synergistic relationships between HIV and human papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *J Int AIDS Soc* 2018; **21:** e25110.

43 Debeaudrap P, Sobngwi J, Tebeu P-M, Clifford GM. Residual or recurrent precancerous lesions after treatment of cervical lesions in human immunodeficiency virus-infected women: a systematic review and meta-analysis of treatment failure. *Clin Infect Dis* 2019; **69:** 1555–65.

44 Liu G, Sharma M, Tan N, Barnabus RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS* 2018; **32:** 795–808.

45 Kelly H, Weiss HA, Benavente Y, de Sanjose S, Mayaud P, ART and HPV Review Group. Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. *Lancet HIV* 2018; **5:** e45–58.

46 Hosaka M, Fujita H, Hanley SJ, et al. Incidence risk of cervical intraepithelial neoplasia 3 or more severe lesions is a function of human papillomavirus genotypes and severity of cytological and histological abnormalities in adult Japanese women. *Int J Cancer* 2013; **132:** 327–34.

47 Kyrgiou M, Arbyn M, Martin-Hirsch P, Paraskevaidis E. Increased risk of preterm birth after treatment for CIN. *BMJ* 2012; **345:** e5847.

48 Kyrgiou M, Mitra A, Arbyn M, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. *BMJ* 2014; **349:** g6192.

49 Kyrgiou M, Athanasiou A, Kalliala IEJ, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. *Cochrane Database Syst Rev* 2017; **11:** CD012847.

50 Athanasiou A, Veroniki AA, Efthimiou O, et al. Comparative effectiveness and risk of preterm birth of local treatments for cervical intraepithelial neoplasia and stage IA1 cervical cancer: a systematic review and network meta-analysis. *Lancet Oncol* 2022; **23:** 1097–108.

51 Lycke KD, Kahlert J, Eriksen DO, et al. Preterm birth following active surveillance vs loop excision for cervical intraepithelial neoplasia grade 2. *JAMA Netw Open* 2024; **7:** e242309.

52 Wilkinson TM, Sykes PH, Simcock B, Petrich S. Recurrence of high-grade cervical abnormalities following conservative management of cervical intraepithelial neoplasia grade 2. *Am J Obstet Gynecol* 2015; **212:** 769.e1–7.

53 Kitchener HC, Castle PE, Cox JT. Chapter 7: achievements and limitations of cervical cytology screening. *Vaccine* 2006; **24** (suppl 3)**:** 63–70.

54 Stoler MH, Ronnett BM, Joste NE, Hunt WC, Cuzick J, Wheeler CM. The interpretive variability of cervical biopsies and its relationship to HPV status. *Am J Surg Pathol* 2015; **39:** 729–36.

55 Tsoumpou I, Arbyn M, Kyrgiou M, et al. p16(INK4a) immunostaining in cytological and histological specimens from the uterine cervix: a systematic review and meta-analysis. *Cancer Treat Rev* 2009; **35:** 210–20.

56 Zhong P, Li J, Gu Y, et al. P16 and Ki-67 expression improves the diagnostic accuracy of cervical lesions but not predict persistent high risk human papillomavirus infection with CIN1. *Int J Clin Exp Pathol* 2015; **8:** 2979–86.

57 Bergeron C, Ordi J, Schmidt D, et al. Conjunctive p16INK4a testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. *Am J Clin Pathol* 2010; **133:** 395–406.

58 Magkana M, Mentzelopoulou P, Magkana E, et al. The p16/ki-67 assay is a safe, effective and rapid approach to triage women with mild cervical lesions. *PLoS One* 2021; **16:** e0253045.

59 Wentzensen N, Fetterman B, Castle PE, et al. p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. *J Natl Cancer Inst* 2015; **107:** djv257.

60 Castle PE, Adcock R, Cuzick J, et al. Relationships of p16 immunohistochemistry and other biomarkers with diagnoses of cervical abnormalities: implications for LAST terminology. *Arch Pathol Lab Med* 2020; **144:** 725–34.

61 Damgaard RK, Jenkins D, de Koning MN, et al. Performance of HPV E4 and p16INK4a biomarkers in predicting regression of cervical intraepithelial neoplasia grade 2 (CIN2): protocol for a historical cohort study. *BMJ Open* 2022; **12:** e059593.

62 Singh N, Gilks BC, Wing-Cheuk Wong R, et al. Interpretation of p16 immunohistochemistry in lower anogenital tract neoplasia. August 12, 2022. https://www.thebagp.org/download/interpretation-of-p16-immunohistochemistry-in-lower-anogenital-tract-neoplasia/ (accessed March 27, 2023).

63 Maniar KP, Sanchez B, Paintal A, Gursel DB, Nayar R. Role of the biomarker p16 in downgrading -IN 2 diagnoses and predicting higher-grade lesion. *Am J Surg Pathol* 2015; **39:** 1708–18.

64 Kyrgiou M, Arbyn M, Bergeron C, et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). *Br J Cancer* 2020; **123:** 510–17.