

# CERVICAL CANCER SCREENING

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## 4. PREVENTIVE AND ADVERSE EFFECTS OF CERVICAL CANCER SCREENING

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### 4.1 Methodological issues

#### 4.1.1 Considerations about beneficial effects of cervical screening

##### (a) General principles

This section considers the benefits of cervical screening, the accuracy of methods used for cervical screening and management, and the types of studies and data used to evaluate cervical screening and the related metrics to evaluate the benefits of screening.

The main goal of cervical screening is the prevention of invasive cervical cancer by the detection and treatment of intraepithelial precancer (see Section 1.2). This needs to be distinguished from downstaging, which is the early detection and treatment of already invasive cancer to improve the chance of a cure; downstaging is the main goal of screening for cancer types that lack well-defined, treatable precancerous precursors. Successful detection and treatment of precancers should lead to a reduction in cervical cancer incidence and mortality. Successful stage shift should lead to a reduction in cervical cancer mortality.

The theoretical maximum possible benefit of cervical screening in a population is the complete secondary prevention of invasive cancer by detecting and treating all cervical precancers that would progress to invasive cancer. The

cumulative lifetime incidence of cervical cancer ranges from 1% to 5% of all women; for the other women, cervical cancer screening does not bring any benefits on a personal basis because they will never have the disease in any case, and thus it is essential to pay attention to its possible harms.

The use of cervical cancer screening with Pap cytology became widespread in many high-income countries during the late 1960s and the 1970s, before randomized trials became the standard for evaluating the efficacy of preventive interventions. Because of this, the initial evidence on the efficacy of cervical cancer screening was derived from ecological or surveillance data, cohort studies, and case-control studies (for details, see Section 4.3.2).

##### (b) Diagnostic accuracy

For a screening test to be accurate, it must, as a primary requirement, yield approximately the same result when repeated in the same and different test settings. Some tests are inherently subjective and often yield non-reproducible results in the case of minor cytological or minor visual abnormalities. Such tests are bound to be inaccurate.

Whatever type of cervical test is being evaluated, the same statistical analyses are applied to assess accuracy. Continuous or ordinal measurements (e.g. the viral load measured by a human papillomavirus [HPV] test or the

grades of cytological abnormality) are typically combined into a few categories before analysis (e.g. positive/negative or abnormal/normal). The accuracy of a screening test is measured as a trade-off between sensitivity and specificity, which are the well-known measures of test performance given outcome category (sensitivity is test positivity among precancers; specificity is test negativity given the absence of precancer or cancer). Sensitivity and specificity can be estimated with any major study design, including the common case–control study. An important derivative statistic that is based on sensitivity and specificity is the area under the curve (AUC) of a receiver operating characteristic (ROC) curve, which evaluates sensitivity and specificity over a wide range of cut-off values.

For the evaluation of screening tests, we distinguish between analytical accuracy and clinical accuracy. Analytical accuracy relates to the target of detection (e.g. HPV DNA), whereas clinical accuracy relates to the detection of cervical precancer. Achieving maximal analytical sensitivity is not the primary goal of cervical screening tests. HPV infection and its associated microscopic and visual abnormalities are common and are typically benign. The prevalence of HPV varies greatly by age and population and can be very high in some settings. A positive HPV test result (or low-grade squamous intraepithelial lesion [LSIL] cytology or visual impression of acetowhitening), which accurately detects infection with a carcinogenic HPV type, is, in the context of risk of precancer, a false-positive result, because most infections resolve or become undetectable without intervention. Unlike the situation for other infectious agents, considering all positive analytical test results to indicate a positive cervical screening result leads to poor specificity and low positive predictive value (PPV) in screening for cervical precancer. The challenge of cervical screening is to choose tests and thresholds that maximize accuracy for

diagnosis of precancer as distinct from benign HPV effects.

Evaluating the accuracy of screening tests typically involves testing followed by the systematic application of the reference standard test, traditionally colposcopy-directed biopsy of all acetowhite lesions ([Wentzensen et al., 2015](#)), to all women enrolled in a relevant study population. All tests, including the reference standard, should be performed independently and within a very short time period. The principles and reporting standards for diagnostic accuracy studies are summarized by the Standards for Reporting of Diagnostic Accuracy Studies (STARD) criteria ([Bossuyt et al., 2015](#)). The quality of diagnostic accuracy studies included in a meta-analysis can be assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist ([Clarke et al., 2020](#)).

It is not feasible or economically viable to apply the reference standard test to large populations of women attending cervical cancer screening; this would also be unethical, because it would result in a large number of women with a very low likelihood of having precancer undergoing colposcopy and biopsy. Clinical practice in cervical cancer screening usually involves a screening test, sometimes followed by triage; triage-positive or screen-positive women are referred for colposcopy and biopsy. Therefore, real-life screening data may suffer from partial and differential verification bias when absolute accuracy is estimated. When the screening test (e.g. visual inspection with acetic acid [VIA] or visual inspection with Lugol's iodine [VILI]) and the reference standard test (e.g. colposcopy) are subjective and correlated, this can lead to severely biased estimates ([Arbyn et al., 2008a](#)), unless intrinsic correlation is accounted for statistically ([Leeftang & Reitsma, 2018](#)). However, the risk of a cancer or even a precancer in women with a negative HPV test result is so low that it is not necessary to refer a fraction of HPV-negative women for further verification when a well-validated HPV

DNA test is used for primary screening. In fact, adjustment for verification bias in HPV-negative women can lead to substantial distortions in the estimates of test accuracy ([Castle et al., 2020](#)). Verification bias is usually a minor issue when relative accuracy (comparing one test directly with another) is assessed.

The design and evaluation of screening approaches depend on precise definition of the screening target. Precancer is the causal surrogate for cancer risk in this context; if defined formally, a reduction in precancer should translate into the same proportional reduction in cancer. However, there are no markers that accurately identify the lesions that would progress to cancer. Cervical cancer screening studies are usually based on cervical intraepithelial neoplasia grade 2 or worse (CIN2+) or CIN grade 3 or worse (CIN3+) as end-points. CIN3+ is a more reliable outcome, because this diagnosis is more reproducible and is more strongly associated with progression to cancer. If precancer is defined too broadly (e.g. including a subset of CIN2 caused by HPV types that are almost never found in cancer), tests evaluated against this inflated standard will have distorted evaluations. For example, an HPV test that correctly targets only the truly carcinogenic types would be incorrectly criticized for lack of sensitivity rather than being recognized for increased specificity. Although it is preferable to use CIN3/adenocarcinoma in situ (AIS) as the end-point in screening evaluations, treatment of CIN2 can lead to underestimation of risk of CIN3 because some of the treated CIN2 would progress to CIN3. This does not affect CIN3+ end-points in cross-sectional studies of previously unscreened individuals.

### (c) *Randomized screening trials*

To study the health effects of a new screening technology in real-world screening settings, randomized screening trials have been conducted in several countries. Screening trials are pragmatic trials ([Schwartz & Lellouch, 1967](#),

[2009](#)) embedded in routine screening with few additional inclusion criteria, and with realistic triage and management of surveillance. The intervention effect measured in such pragmatic trials will be close to the effect observed when implementing the new technology in the real world, and its interpretation will not be limited to the study trial.

The ultimate goal of cancer screening is the reduction of cancer mortality, but the effect on cancer mortality is very difficult to measure in countries with screening in place, and it has only been assessed in a previously unscreened population ([Sankaranarayanan et al., 2009](#)). The same limitations exist for the end-point cancer, which has only been studied in a pooled analysis of European screening trials ([Ronco et al., 2014](#)). Other screening trials have CIN3+ or CIN2+ as the primary end-point.

Randomized screening trials aim to directly estimate the effect of switching technology on the detection of CIN3+ and CIN2+ over one or two screening rounds. Results in the first round can also be studied by a prospective study, where the new and conventional technologies are used in parallel and women are managed on the basis of the results of all tests. However, the randomized trial and the combined testing design may give different results when the results from the new and conventional technologies are dependent for reasons unrelated to the development of cervical cancer. This is illustrated by two examples. The first example is a study in which primary HPV testing with cytological testing on HPV-positive samples is compared with cytology alone. The performance of cytology may be influenced by knowledge of the HPV status. A valid estimate of the effect of HPV testing on CIN3+ detection can be obtained through a randomized trial in which cytotechnicians in the intervention group are informed about the HPV status of the samples ([Leinonen et al., 2012](#)). The second example is a study in which liquid-based cytology is compared with conventional cytology. With the combined

testing design, the sampling procedure may place the second test at a disadvantage because cells for diagnosis have been removed by the first sample. This potential sampling effect can be avoided by randomizing women to one of the two test types ([Ronco et al., 2007](#)).

In most cervical cancer screening trials, participants are followed up for more than one screening round. Because the purpose of screening is to prevent cancer through the detection of precancer, the main aim of trials with CIN2+ or CIN3+ as end-points is to show that the new technology increases the lead-time gain from screening. This can be done by showing that increased detection of CIN2+ and CIN3+ in the first round of screening is followed by decreased detection in the second round.

Randomized screening trials vary in how they define the second round. Some trials categorize all CIN2+ and CIN3+ detected beyond a certain time point as in the second round ([Rijkaart et al., 2012](#); [Ogilvie et al., 2018](#)). The strength of this approach is that a decreased detection of CIN2+ or CIN3+ in the second round can be explained by earlier detection, because randomization ensures that the risks of precancer at baseline are equal in the two study arms. The approach works well when the screening interval is long enough to ensure that all women in the comparison group have completed the first round. Otherwise, it may be better to select women for whom completion of the first round can be confirmed. To minimize the chance that the impact on lead-time gain is distorted by baseline differences between subgroups in the risk of precancer, the second round should include not only follow-up of women with a negative screening test result at baseline but also follow-up of screen-positive women with a negative test result at short-term repeat testing ([Chan et al., 2020](#)) and follow-up of women who underwent surveillance after colposcopy ([Ronco et al., 2010](#)).

Randomized screening trials also vary with respect to the choice of technology in the second round. Some trials use only the conventional technology in both arms ([Naucler et al., 2007](#); [Ronco et al., 2010](#)), whereas others use the new technology in both arms ([Rijkaart et al., 2012](#); [Ogilvie et al., 2018](#)) or retain separate screening strategies in the two arms ([Kitchener et al., 2009](#)). This may influence the trial results. For example, some of the precancers may remain undetected in women who are offered conventional technology in the first and second round, in particular when the difference in lead-time gain between the two technologies is large.

#### (d) *Observational studies*

Observational data play an important role in evaluating and improving cervical cancer screening programmes. Observational data range from ecological studies involving cancer registries to specific cohort studies that directly compare screening tests and strategies.

Cytology screening was introduced without evidence from randomized trials. Large decreases in the incidence of cervical cancer after the rapid implementation of cervical screening in some populations provided evidence of the effectiveness of cervical screening even from study designs that are typically not considered to be sufficient to prove causal associations between an intervention and a health effect. For example, large reductions in the incidence of cervical cancer were seen in Finland, Slovenia, and the United Kingdom after the implementation of national call–recall organized programmes ([Quinn et al., 1999](#); [Anttila, 2007](#); [ZORA, 2018](#)). Furthermore, the implementation of organized programmes in European countries, including Denmark, Finland, Italy, the Netherlands, Sweden, and the United Kingdom ([Anttila et al., 2009](#)), and integrated health systems in the USA, including Kaiser Permanente Northern California ([Castle et al., 2018](#)), as well as experiences with opportunistic screening in the Republic of Korea

([Odongua et al., 2007](#)) and the USA ([Landy et al., 2020](#)), have led to the development of an infrastructure for the systematic collection of routine data on screening tests, results, and outcomes from screening and pathology registries. Many screening programmes continue to provide insights into the effectiveness of different screening protocols ([Rebolj et al., 2008](#); [Briët et al., 2010](#)) and new technologies ([Akamatsu et al., 2012](#); [Rebolj et al., 2015](#); [Rozemeijer et al., 2017](#); [Forslund et al., 2019](#); [Zorzi et al., 2020](#)).

One of the strengths of these population-based studies is that, given the implementation of a programme that targets an entire population, it is possible to evaluate intention-to-treat approaches in cohort studies (e.g. [Ronco et al., 2005](#)), which reduces bias related to indication. When historical or geographical controls are used, the comparability of populations, even in the absence of indication bias, is a concern, particularly when two screened populations are compared to evaluate different protocols or technologies. In fact, two main determinants of cervical disease outcomes – the screening history ([Maggino et al., 2016](#); [Castle et al., 2019](#)) and the prevalence of HPV ([Bray et al., 2005](#); [Sander et al., 2014](#)) – can change rapidly over time and vary by geographical region.

Retrospective cohort studies examining sensitivity and efficacy against cancer have been used to compare screening tests; however, this study design has important methodological issues, which can lead to severely biased estimates when they are not properly accounted for. For example, studies that use a cancer diagnosis or the detection of a high-grade precursor lesion as a starting point and retrospectively select on previous screening results may be biased in favour of cytology when the management is differential between cytology and other tests and the screening history is limited ([Blatt et al., 2015](#); [Castle, 2015](#); [Giorgi Rossi et al., 2016](#); [Kaufman et al., 2020](#); [Schiffman & Wentzensen, 2021](#)). The choice of end-point is also meaningful in

retrospective studies examining the performance of screening tests, and relates to the timing of previous testing. Most screening tests performed within a short time of cancer diagnosis are part of the clinical workup ([Andrae et al., 2008](#); [Castanon et al., 2013](#)) or represent detection of an advanced, symptomatic cancer. This study design cannot capture the screening performance of these tests as an instrument to prevent cancer by detecting precancer ([Ronco & Franceschi, 2018](#)).

Well-designed observational studies have become important pillars of regulatory evaluations of cervical screening tests. For example, recent United States Food and Drug Administration (FDA) approvals of HPV tests for primary screening, either alone or in combination with cytology, were based not on randomized trials but on prospective cohort studies in which all comparator tests were conducted in the entire population and positive results from any test led to referral for colposcopy ([FDA, 2019](#)). These studies enable the efficient comparison of disease detection for different assays in the first screening round, but because the management is not differential for different test results, they do not enable the evaluation of disease outcomes by test result in subsequent screening rounds.

#### (e) *Risk-based screening and management*

Test sensitivity and specificity do not directly inform health decisions, which require knowledge of risk (i.e. the measures of outcome based on test result). Risk is measured over a defined time period (cross-sectional or, ideally, prospective). When population data are available, optimally cohort data from an observational study or trial, health decisions about screening can be made by answering practical questions about absolute risk: What is the (pre-test) risk of developing this cancer? (This informs whether screening is worth doing.) What is the risk of developing this cancer if the test result is positive, and what should be done next? How reassuring is a negative

test result, and when should a participant with a negative test result come back for another screen?

An accurate screening test will divide the population pre-test risk (i.e. the population prevalence of precancer) into substantially higher risk (PPV defined as a function of time from screening) when a test result is positive, or lower risk ( $1 - \text{negative predictive value [NPV]}$ ) when a test result is negative. Risk stratification alone (i.e. the difference in post-test risk between those with a positive test result and those with a negative test result) is not meaningful without the context of clinical action thresholds. Meaningful risk stratification implies that the post-test risk for at least one of the groups (those with a positive test result or those with a negative test result) leads to different clinical management.

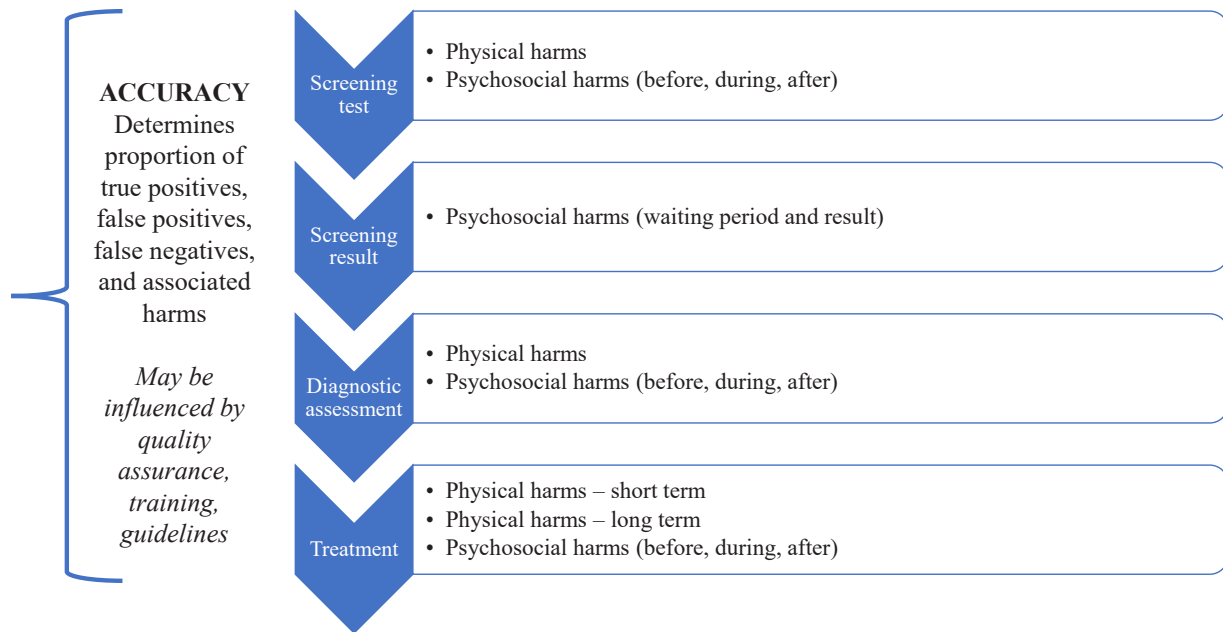
No single available cervical screening test has both very high PPV and very high NPV; therefore, a second, complementary triage test is generally used, which, in combination with the first test, provides a finer and more individually accurate level of risk discrimination. When the primary screening test is sensitive (e.g. in HPV testing), it is often reasonable to use the second test only to confirm the positive result from the first test, and to save the resources that would be required to co-test everyone. The combined results of screening and triage tests are grouped into categories, and the sensitivity/specificity or predictive values/risks of the combined strategy are assessed similarly as for a single test.

The same approach applies to screening, triage, post-colposcopy management, and post-treatment management. A risk-based approach may enable practice to be unified independent of the underlying tests. The 2019 update of the consensus guidelines for management of cervical cancer screening abnormalities ([Perkins et al., 2020](#)) adopted this principle as the foundation of the clinical guidelines. It is important to evaluate whether absolute risk estimates are portable between different populations. Even if the risk estimates apply across different populations, the

decision thresholds may be adapted to clinical and societal preferences in different settings.

#### 4.1.2 Considerations about harms of cervical screening

All cancer screening programmes involve potential harms, which individuals must balance against the potential benefits in deciding whether to participate in screening. Potential physical and psychological harms are considered in detail for each screening intervention or diagnostic step reviewed in this *Handbook*. Social and economic harms are generally not considered. Physical harms (e.g. pain, bleeding, and discharge) include those experienced because of the application of the initial screening test, as a consequence of follow-up, confirmatory, or diagnostic tests for women who receive a positive test result, or during or after treatment for screen-detected lesions. Psychological harms (e.g. anxiety and distress) may occur before, during, or after screening and may relate to the screening experience itself or to the receipt of the results and the perceived implications for the individual who has undergone a screening test, diagnostic test, or treatment procedures. Some harms, for example those that occur because of a false-positive test result, come about as a result of test characteristics or the screening system itself, and may not be observable directly by women or their clinicians. These harms may have effects at the population level; for example, false-positive screening test results may lead to unnecessary examinations and treatments, which, consequently, cause harm to women and waste medical resources. When policy-makers decide whether to implement a population-based screening programme, they must explicitly weigh the balance of potential benefits against potential harms at the population level (see Section 2.3). [Fig. 4.1](#) presents a schematic overview of the potential harms associated with the cervical screening pathway.

**Fig. 4.1 Potential harms associated with the cervical screening pathway**

Created by the Working Group.

Harms pertaining to any screening technique are presented in this section. Evidence relating to potential harms specific to a technique, including their nature and rates of occurrence as observed during screening, is provided by technique in the relevant sections of this *Handbook* for screening by visual inspection (see Section 4.2.3), cytology (see Section 4.3.5), HPV testing (see Section 4.4.8), colposcopy (see Section 4.5), and treatment (see Section 1.2.5).

Ideally, a screening test to be used in a population will have a high NPV, which enables most women at risk of cervical cancer to be identified and the women with a negative test result to be correctly reassured that they are at low risk until the next screening test is due. The number of women potentially harmed can be measured as  $1/PPV$ , which is the number of positive screening test results needed to confirm one precancer. Because of the natural history of HPV infection and disease (see Sections 1.2.1 and 1.2.2),

the choice of screening interval, as well as the specificity of the test itself, will influence the rate of false-positive test results. Given the transient nature of most HPV infections, screening very frequently, either for HPV infection or for the cellular or visual changes associated with it, will be more likely to identify acute infection or disease with no potential for malignancy, thus increasing the proportion and number of false-positive test results and the potential harms.

Some of the concepts relevant to the monitoring of harms in cervical cancer screening programmes are discussed here.

#### (a) *Overscreening*

Cervical cancer screening that is carried out more frequently than is recommended in the current guidelines or that is used in a wider target age range or after hysterectomy can be called overscreening. The results from a decision analysis suggested that a short screening



**Table 4.1 Harms associated with cervical cancer screening and management of screen-positive women in the USA and the Netherlands in 2007<sup>a</sup>**

Event	Events per 1000 women		USA:Netherlands ratio
	USA	Netherlands	
<i>Pap test</i>			
Number	394	164	2.4
Symptoms <sup>b</sup> for at least 2–7 days	51	21	2.4
<i>Abnormal test results</i>			
Number	25	9	2.8
Anxiety for at least 12 weeks	9	3	3.0
<i>Punch biopsy</i>			
Number	16.9	4.3	3.9
Light <sup>c</sup> symptoms	19	5	3.8
Moderate or strong <sup>c</sup> symptoms	11	3	3.7
<i>Treatment</i>			
Number	3.0	1.8	1.7
Light <sup>c</sup> symptoms	2.4	1.4	1.7
Moderate or strong <sup>c</sup> symptoms	3.8	2.3	1.7

<sup>a</sup> Data were standardized to the female population of the USA aged 21–65 years in 2007.

<sup>b</sup> Lower abdominal pain, urinary discomfort, feeling sick, feeling dizzy, and/or painful sexual activity.

<sup>c</sup> Light refers to very light or light pain, bleeding, or discharge; moderate or strong refers to moderate, severe, or very severe pain, bleeding, or discharge.

Reproduced from [Habbema et al. \(2017\)](#). Copyright 2017, John Wiley & Sons.

interval and the use of HPV screening in women younger than 30 years will lead to an increase in the number of unnecessary colposcopies ([Kim et al., 2018](#)). Based on a systematic review, the main types of overscreening are screening that is too frequent (more frequent than the guideline recommendation), screening after hysterectomy, screening started before the recommended age, and screening after the recommended age at which screening should be stopped ([Alber et al., 2018](#); [Kim et al., 2018](#)). A study in France reviewed outcomes for 63 821 women aged 25–65 years screened for up to 9 years, 37% of whom underwent cervical cancer screening at the recommended interval (every 3 years) and 63% more frequently. Overscreened women were more than twice as likely to have a CIN1 lesion diagnosed (age-adjusted relative risk, 2.09; 95% confidence interval [CI], 1.76–2.51) ([Thiery et al., 2017](#)).

Before the introduction of HPV testing, different screening intervals and ages were recommended in the USA and the Netherlands. [Habbema et al. \(2017\)](#) studied harms associated with cervical cancer screening and management of screen-positive women in the USA and the Netherlands. They included data on the number of Pap tests, abnormal test results, punch biopsies, treatments, and adverse effects of treatment ([Table 4.1](#)). The more intensive screening in the USA led to substantially higher rates of harms, with similar effects of screening on cervical cancer incidence and mortality in the two countries.

#### (b) *Overdiagnosis and overtreatment*

The target lesion for detection in cervical screening is the precursor lesions (high-grade squamous intraepithelial lesion [HSIL]/AIS), and the preventive effect on cervical cancer incidence is through treatment of these lesions.

Downstaging of cervical cancers discovered via screening is a secondary benefit that may also contribute to reductions in cervical cancer mortality achieved through screening (see Section 4.1.1). Overdiagnosis is defined as the diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if screening had not taken place. Harms related to overdiagnosis are caused both by the physical harms associated with treatment and by the psychosocial consequences of a cancer diagnosis. Some authors have argued that because not all CIN3 lesions will result in cancer in a woman's lifetime if left untreated, the diagnosis of CIN3 itself should be described as overdiagnosis ([Malila et al., 2013](#); [Hakama et al., 2015](#); [van Luijt et al., 2016](#)). However, because a significant proportion of CIN3 lesions will progress to invasive cancer ([Braun et al., 2011](#)) and it is not possible to know which lesions may be safely left untreated, the use of the term overdiagnosis in this context might have unintended effects and lead to a reduction in the treatment of women with CIN3 lesions, followed by a concomitant rise in cervical cancer rates ([Paul et al., 2018](#)).

Overtreatment is defined as the treatment of a lesion that would never have progressed to be clinically recognized during a woman's lifetime. In relation to cervical screening, precancerous lesions are asymptomatic and are only detected through screening or incidentally in the investigation of other gynaecological conditions. In cervical cancer screening, there is a potential for overtreatment because of false-positive results, misdiagnosis, and conservative overclassification of histopathology of a lower grade. Overtreatment also occurs when lesions with no malignant potential are identified as precancers (HSIL/AIS) that require treatment. HSIL encompasses both CIN2 and CIN3. Whereas CIN3 reliably represents transforming infection with malignant potential, CIN2 includes a mixture of lesions that indicate both florid productive infection and true transforming infection. Because of

an inability to reliably distinguish CIN2 lesions with true malignant potential from other lesions, most guidelines have recommended that CIN2 is also included as a treatment target ([Arbyn et al., 2008b](#); [Saslow et al., 2012](#); [WHO, 2013](#); [Jeronimo et al., 2016](#)). However, the likelihood of progression from CIN2 to invasive cancer is lower than that of CIN3. The clinical course of untreated CIN2 at 24 months is 50% regression, 32% persistence, and 18% progression to CIN3 ([Tainio et al., 2018](#)). Methods of refining the diagnosis of CIN2 lesions so that the potential for progression can be better understood (e.g. through genotyping or molecular markers) may be strategies to reduce overtreatment. Age may also be a significant predictor of the likelihood of HSIL regression, because older women are less likely to experience regression of screen-detected lesions ([Bekos et al., 2018](#)). As described in Sections 1.2.1 and 1.2.2, the likelihood of a given lesion progressing to cancer will also be influenced by factors such as the causal HPV type, the woman's HIV status, and immunosuppression.

Overtreatment of CIN at grades below the accepted treatment thresholds may occur after referral due to abnormal cytology as part of the diagnostic process (e.g. via cone biopsy) or despite the availability of treatment guidelines ([Volante et al., 2012](#); [Nowakowski et al., 2016](#); [Aitken et al., 2019](#)).

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