Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of the American Society of Cytopathology (2020) 9, 602–606

Available online at www.sciencedirect.com

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journal homepage: www.jascyto.org/

COMMENTARY

Are CIN3 risk or CIN3+ risk measures reliable surrogates for invasive cervical cancer risk?

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Received 2 May 2020; received in revised form 17 June 2020; accepted 6 July 2020

Risk-Based Management Consensus Guidelines have recently been published by the American Society for Colposcopy and Clinical Pathology (ASCCP).[1-3] These guidelines are an evolution of earlier 2012 guidelines[4] that were the first to be based on the so-called principle of equal management for equal risk, referring specifically to the risk of a patient developing invasive cervical cancer, "estimated by the surrogate endpoint of the 5-year-risk of cervical intraepithelial neoplasia (CIN) grade 3 (CIN3) or more severe diagnoses (CIN3+)."[1] Recently reviewed American Cancer Society (ACS) Guidelines for Cervical Cancer Screening—2020 similarly use CIN3 and CIN3+ as the "best surrogate measure of incident cervical cancer risk," given the absence of US clinical trial data sufficiently powered to evaluate cervical cancer risk.[5] We put the case forward here that CIN3 and CIN3+ are not reliable surrogate endpoints for invasive cervical cancer risk and that cervical screening guidelines based on these surrogate risk endpoints may therefore unexpectedly prove to be misleading.

Although histopathologic CIN3 is an important endpoint for widely used clinical management algotrithms,[6] there are reasons why CIN3 risk differs significantly from cervical cancer risk. Most importantly, the best available long-term natural history data indicates that only around 30% of CIN3 lesions will progress to cervical cancer in 30 years.[7,8] Therefore, measures of prevalent CIN3 lesions (detection sensitivity)[9,10] are inevitably dominated by detection of nonprogressive intraepithelial lesions which may either regress or persist in some form without ever developing into invasive cervical cancer.[11,12] Epidemiologists designate detection of such nonprogressive intraepithelial lesions as "overdiagnosis," because detection of such lesions leads to surgical procedures without lowering cancer risk.[9] The only method to measure the relative detection of progressive versus nonprogressive intraepithelial lesions is to specifically measure the number of interval cancer diagnoses made between 2 screens and the cancers detected by the subsequent screen, using the so-called interval cancer method.[9,13] The only randomized controlled clinical trial that has used this approach in comparing cytology and human papillomavirus

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https://doi.org/10.1016/j.jasc.2020.07.133

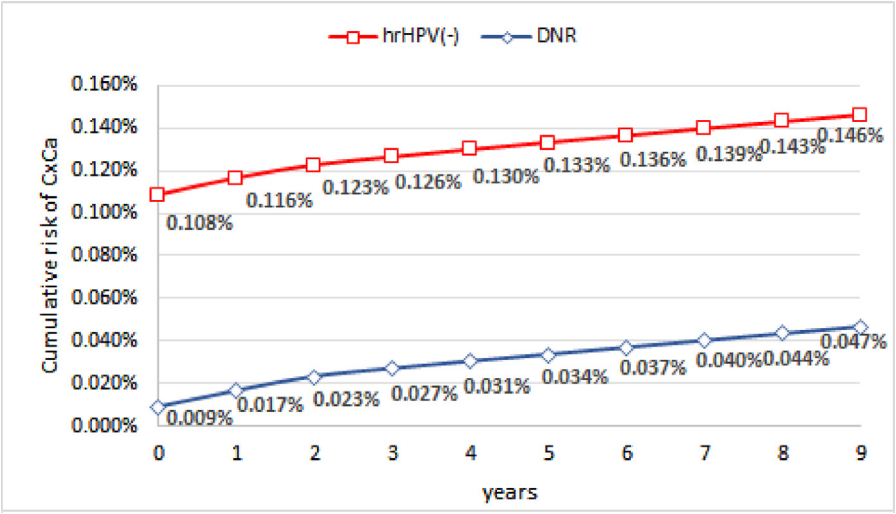

Figure 1 Pittsburgh Cervical Cancer Screening Model risk projections for histopathologic diagnosis of invasive cervical carcinoma with extended rescreening intervals. CxCa, cervical carcinoma; DNR, double negative results; hrHPV, high-risk human papillomavirus.

(HPV) screening has been a Finnish cervical screening study in which investigators concluded that the detection of progressive lesions using HPV testing was similar to that of Papanicolaou testing, but that HPV testing alone caused more detection of nonprogressive lesions;[13] HPV testing excelled disproportionately in detecting nonprogressive high-grade intraepithelial lesions.

Even the alternative histopathologic endpoint of CIN3+ (CIN3 and more severe lesions) in well-screened populations is inevitably dominated by nonprogressive intraepithelial lesions compared with a very limited number of diagnosed cervical cancers on which to base statistical measures of cancer risk.[14] The difference between CIN3 and invasive cervical cancer is also reflected in the differences in high-risk HPV genotype distribution between tested lesions; a few high-risk genotypes are significantly more likely to be detected in invasive cancers than in CIN3 tissue biopsies.[15] Because cervical cancers associated with HPV18 or HPV45 are significantly less likely to be detected in the precancerous phase, this cancer risk is significantly underestimated using the surrogate risk endpoint of CIN3 or even the CIN3-dominated surrogate risk endpoint of CIN3+.

Invasive cervical cancer risk and cancer-associated morbidity and mortality are widely acknowledged as the key measures of cervical screening effectiveness in health systems and can unfortunately only be measured based on

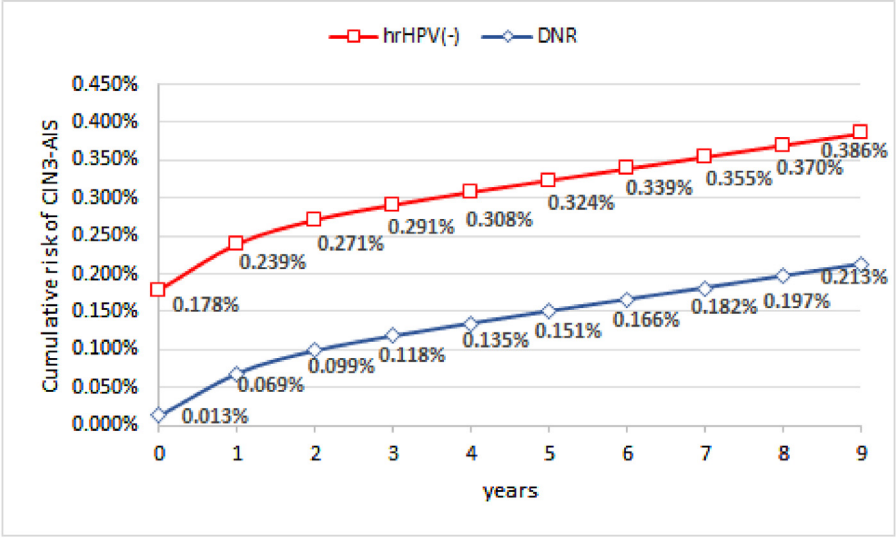

Figure 2 Pittsburgh Cervical Cancer Screening Model risk projections for histopathologic diagnosis of cervical precancer (CIN3-AIS) with extended rescreening intervals. AIS, adenocarcinoma-in-situ; CIN3, cervical intraepithelial neoplasia 3; DNR, double negative results; hrHPV, high-risk human papillomavirus.

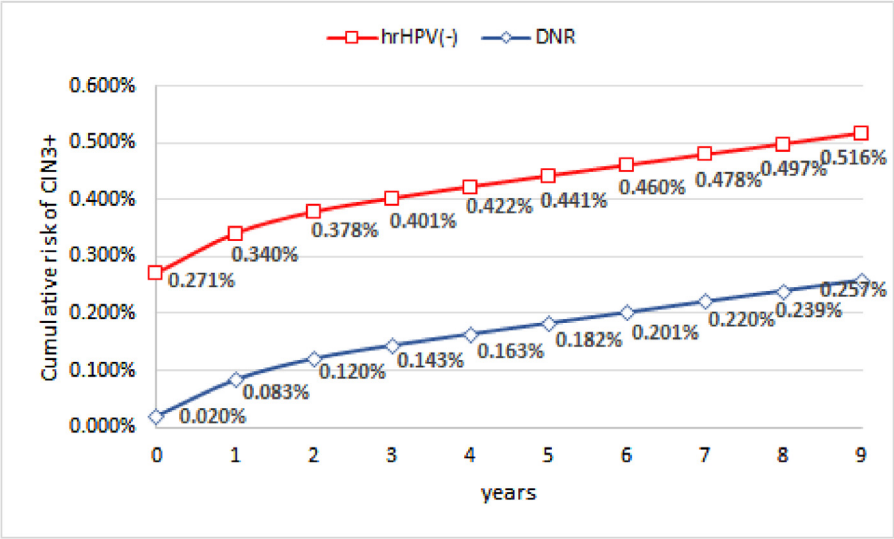

Figure 3 Pittsburgh Cervical Cancer Screening Model risk projections for histopathologic diagnosis of CIN3 and higher with extended rescreening intervals. CIN3, cervical intraepithelial neoplasia 3; DNR, double negative results; hrHPV, high-risk human papillomavirus.

data from long-term observational studies.[16-18] Numerous international long-term observational studies have clearly documented significant declines in cervical cancer incidence after the introduction of cytology in diverse health systems.[16] Studies from the United Kingdom (UK) have further documented that modern high-quality cytologic screening in the UK has prevented 70% of cervical cancer deaths in all age groups.[18] Recent long-term observational data from 3 large US systems has become available on the impact of cytology and HPV cotesting on cervical cancer diagnosis,[19-21] and interestingly all 3 studies show that abnormal cytology findings in cotesting are more likely before subsequent squamous carcinoma diagnoses than before subsequent CIN3 diagnoses; no data on death rates are reported. The most widely cited US projections of the possible impact of HPV and cytology cotesting or primary HPV screening on cervical cancer incidence and death rates have been based entirely on modeling.[22-24]

One major model relied upon in recent ACS and United States Preventive Services Task Force (USPSTF) guidelines is a Harvard model that relies exclusively on data on cervical screening and prevention of cervical squamous carcinoma.[22] This should be of concern, as modern hysterectomy-adjusted US data (1999-2015) indicates that overall cervical squamous cell carcinoma rates continue to decline while overall cervical adenocarcinoma rates continue to increase, leading the US Center for Disease Control (CDC) to conclude that current trends "underscore the importance of intensifying efforts to reverse increasing adenocarcinoma rates."[25] Furthermore, the latest models relied on by ASCCP predict, without explanation, very different benefits and harms with different cervical screening options than the earlier model utilized in 2012.[23,24] Also, the transparency of the current ASCCP modeling methods is quite limited. As repeatedly acknowledged by CDC experts during the current COVID-19 coronavirus pandemic, all models are estimates based on underlying assumptions.

Commentary by some recent guideline authors has also acknowledged that cervical cancer and cervical cancer risk are the most relevant clinical endpoints to patients and the paramount concern of both screened patients and providers.[26] We agree with this viewpoint. As noted by the USPSTF, "the degree of benefit in preventing invasive cancer cannot be determined from test performance studies alone. The cross-sectional data suffer from determining sensitivity, specificity, and related predictive values for a surrogate outcome (CIN2+) and not invasive cervical cancer."[27]

The Pittsburgh Cervical Cancer Screening Model (PCCSM) is a unique Bayesian decision science tool that allows for quantitative risk estimates from large complex data sets for rare clinical endpoints that are of special clinical concern, such as the development of invasive cervical cancer in screened populations.[20,28-34] PCCSM projections reported previously in the *Journal of the American Society of Cytopathology*[30] have shown that both invasive cervical cancer risk and CIN3-adenocarcinoma in situ (AIS) risk will increase over time as screening intervals are increased with either cytology and HPV cotesting or with HPV testing alone.[30] Lowest risk is consistently achieved with cytology and HPV cotesting compared with HPV testing alone.[30] Updated projections from our large integrated health care system, based on 2005−2018 data, are shown in Figs. 1−3. As anticipated, the projected risk of developing cervical cancer over varying screening intervals with similar screening methods is consistently much lower than the projected risk for histopathologic diagnoses of CIN3-AIS (Figs. 1 and 2), due to both the nonprogressive character

of most high-grade intraepithelial lesions as well as the effects of ablative treatments. The projected risk for CIN3+ is higher than the projected risk for invasive cervical cancer alone (Figs. 1 and 3), reflecting both the very small number of invasive cervical cancers in a well-screened population and the much larger number of prevalent and usually nonprogressive high-grade intraepithelial lesions.

It is not generally appreciated that the most widely cited models[22-24] and current risk-based consensus guidelines have largely relied on clinical trial data measuring prevalent CIN3 (detection sensitivity) and CIN3+ as the key endpoints measuring cervical screening test performance. This approach inevitably overestimates the cervical cancer risk-reducing benefit attributable to HPV testing, which excels disproportionately in detection of nonprogressive intraepithelial lesions.[13] This approach also exaggerates the lower risk and apparent safety of extended screening intervals.[20,21]

The advantage of Bayesian analysis in addressing uncertainty in large complex data sets remains underutilized in risk analysis, despite the success of Bayesian methods in more accurately predicting risk than classical statistical analysis in diverse areas,[35] including nuclear power plant accidents[36,37] as well as the current COVID-19 coronavirus outbreak.[38] A key advantage of Bayesian modeling over classical statistical approaches lies in its ability to handle incomplete data sets. With the Bayesian network modeling approach, not all information on a patient needs to be observed to calculate a risk value. This property distinguishes Bayesian network analysis from classical statistical approaches where no missing values among covariates are allowed.[31,32] Bayesian analysis is also able to assign personalized risk estimates for individual patients from health system data sets, taking into account complex long-term clinical, diagnostic, and treatment history.[33,34] It is our hope that the medical community will more carefully assess the limitations associated with using CIN3 or CIN3+ as the favored surrogate endpoints for cervical cancer risk and the related limitation of emphasizing these endpoints in widely used modelling approaches.

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