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Risk-based cervical screening guidelines should utilize large diverse national database and specifically measure invasive cancer risk of screened patients

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Risk-Based Management Consensus Guidelines have been published in 2020 in the United States (US) by the American Society for Colposcopy and Clinical Pathology (ASCCP) [1–3]. These US guidelines evolved from earlier 2012 guidelines [4] which were the first to be based on the principle of "equal management for equal risk." This referred specifically to the risk of a patient developing invasive cervical cancer, "estimated by the surrogate end-point of the 5-year-risk of cervical intraepithelial neoplasia (CIN) grade 3 (CIN3) or more severe diagnoses (CIN3+)" [1]. Still more recently released 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 have argued that neither CIN3 nor CIN3+ are equivalent and reliable surrogate end-points for invasive cervical cancer risk. This means that cervical screening guidelines based on these surrogate risk end-points could prove to be significantly misleading [6]. As other countries consider updating their approaches to cervical screening, we believe they should consider utilizing diverse nationwide datasets from their own systems and measure directly the quantitative relationship between nationwide cervical screening results and the follow-up risk of patients diagnosed in the same system with the crucial relevant endpoint of invasive cervical cancer. This approach optimally will utilize large nationwide databases. China, with its large population, expanding cervical screening, widespread use of new screening technologies, and rapidly modernizing data collection system, is in an excellent position to be the first to take this more accurate approach [7–11].

Though CIN3 is an important histopathologic endpoint for widely employed clinical management algorithms [12], there are widely overlooked reasons why CIN3 risk differs significantly from invasive cervical cancer risk. The most important reason is that the best available long term natural history data, from New Zealand, indicates that progression of CIN3 lesions to cervical cancer within 30 years will occur in only around 30% of cases [13,14]. Therefore, detection sensitivity of prevalent CIN3 lesions [15,16] is inevitably dominated by non-progressive intraepithelial lesions. These may either regress or persist in some form without ever developing into invasive cervical cancer [17,18]. Since detection of such lesions leads to surgical procedures without lowering cancer risk, epidemiologists designate detection of such non-progressive intraepithelial lesions as "over diagnosis" [15]. In order to measure the relative detection of progressive versus non-progressive intraepithelial lesions, it is necessary to specifically measure the number of interval cancer diagnoses made between two screens and the cancers detected by the subsequent screen. This is accomplished using the so-called interval cancer method [15,19].

The only randomized controlled clinical trial that using this approach to compare modern cytology and HPV screening has been a cervical screening study in Finland. The investigators in the Finnish study concluded that the detection of progressive lesions using HPV testing was similar to that of Pap testing, but that HPV testing alone caused more detection of non-progressive lesions [19]. It is not widely recognized that available randomized clinical trial data indicates that HPV testing excels disproportionately in detecting non-progressive high grade intraepithelial lesions.

The alternative histopathologic endpoint of CIN3+ is also inevitably dominated in well-screened populations by non-progressive intraepithelial lesions compared to a very limited number of diagnosed cervical cancers on which to base statistical measures of cancer risk [20]. There are also differences in high risk HPV genotype distribution between CIN3 and invasive cervical cancer. A few high-risk genotypes are significantly more likely to be detected in invasive cancers than in CIN3 tissue biopsies [21]. Some cervical cancers are significantly less likely to be detected by screening during their precancerous phase. Cervical cancers associated

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with genotypes HPV18 or HPV45 are among those that are less likely to be detected in their precancerous phase. Therefore, cancer risk due to these HPV genotypes is significantly underestimated using the surrogate risk end-point of CIN3 or even the CIN3-dominated surrogate risk end-point of CIN3+. These surrogate endpoints also exaggerate the safety of extended screening intervals.

It is widely acknowledged that invasive cervical cancer risk and cancer-associated morbidity and mortality are the key measures of cervical screening effectiveness in health systems. Unfortunately, these can only be measured based on data from long-term observational studies [22–24]. Several international long-term observational studies in diverse health systems have clearly documented significant declines in cervical cancer incidence after the introduction of cytology [22]. Studies from the United Kingdom (UK) have further shown that modern high quality cytologic screening has prevented 70% of cervical cancer deaths in all age groups [24]. No similar large-scale observational data is yet available to document the contribution of HPV testing to the lowering of cervical cancer incidence and cervical cancer morbidity and mortality. Long-term observational data from three large United States (US) systems has become available on the impact of cytology and HPV co-testing on US cervical cancer diagnoses [25–27]. It is notalble that all three co-testing studies show that abnormal cytology findings are more likely than abnormal HPV test results before subsequent squamous carcinoma diagnoses. Furthermore, these studies document that misleading HPV-negative results occur in over a third of developing invasive cervical cancer cases when HPV testing is performed more than 12 months before cancer diagnosis [25–27]. This data has been overlooked in recommendations supporting extended screening intervals. These large US co-testing studies also suggest that modern liquid-based cytology contributes more within the context of co-testing to detection of developing cervical cancers than does the conventional Pap smear.

The most widely cited US projections of the possible impact of cytology and HPV co-testing or of primary HPV screening on cervical cancer incidence and death rates have been based entirely on statistical modeling [28–30]. In contrast, US Bayesian modeling studies indicate that co-testing utilizing modern liquid-based cytology consistently detects more cervical cancers than either cytology or HPV testing alone [31]. One major statistical model relied upon in recent American Cancer Society (ACS) and United States Preventive Services Task Force (USPSTF) guidelines is the Harvard model. It which relies exclusively on data on cervical screening and prevention of cervical squamous carcinoma, excluding adenocarcinomas [28]. This is concerning, 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. This has led the US Center for Disease Control (CDC) to conclude that current trends "underscore the importance of intensifying efforts to reverse increasing adenocarcinoma rates" [32]. The latest US models relied on by ASCCP further predict, without explanation, very different benefits and harms with different cervical screening options than the earlier model utilized in 2012 [29,30]. It is also concerning that the transparency of the current ASCCP modeling methods is very limited. In the end, it must be kept in mind that all models are estimates based on underlying assumptions. In our opinion, these limitations of modeling emphasize the importance of direct analysis of large diverse observational national datasets.

Cervical cancer and cervical cancer risk are the most relevant clinical endpoints to patients and the paramount concern of both screened patients and providers, as has been acknowledged by recent US guideline authors [33]. We agree with this viewpoint. It has been noted by the USPSTF that "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" [34].

It is not generally appreciated that the most widely cited models [27–29] and current US risk-based consensus guidelines are based on clinical trial data that measure potentially misleading prevalent CIN3 (detection sensitivity) and CIN3+ as the key endpoints for measuring cervical screening test performance. It is inevitable that this approach will overestimate the cervical cancer risk-reducing benefit attributable to HPV testing, which disproportionately excels in detection of non-progressive intraepithelial lesions [19]. This approach also inadvertently exaggerates the lower risk and apparent safety of extended screening intervals [26,27]. The limitations of current US risk-based cervical screening guidelines approaches can be addressed in several ways. Most importantly, large nationwide datasets of sufficient size, such as datasets available in China, should be able to capture sufficient numbers of invasive cervical cancer cases to focus on this crucial endpoint in risk measurements rather than the misleading surrogate endpoints of CIN3 or CIN3+. Bayesian analysis is another underutilized approach which can be useful in addressing uncertainty in large complex datasets. A key advantage of Bayesian modeling as compared to classical statistical approaches is its ability to handle incomplete datasets. To calculate a risk value with the Bayesian network modeling approach, not all information on a patient needs to be observed. This property of Bayesian network analysis distinguishes it from classical statistical approaches for which no missing values among covariates are allowed [35]. Bayesian analysis can also be used to assign personalized risk estimates for individual patients from health system datasets, taking into account complex long term clinical, diagnostic, and treatment history [36,37]. It is our hope that China will consider these opportunities to further update and optimize its own risk-based cervical screening guidelines.

Conflict of interest

The authors declare that they have no conflict of interest.

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