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Concerns Over Impending Alterations in US Cervical Screening Policies: Is Less Frequent Screening Less Safe?

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Abstract

Several revisions in national cervical screening guidelines have been lately introduced worldwide, supported by accumulating evidence from meta-analyses and robust epidemiological studies. Pre-announced changes in US cervical screening policies are being eagerly anticipated, because of their global impact. We argue against the impending change in US cervical screening policy that will introduce increased intervals between consecutive rounds of cervical screening. Such a shift might decrease the level of protection against cervical pre-cancer achieved by current screening strategies, and it will influence cervical screening policies worldwide.

Keywords

Cervical screening; Cytology; Biomarkers; Cervical cancer; HPV vaccination; Colposcopy

Short Communication

Almost fifteen years following the launch of the first-generation prophylactic anti-HPV vaccines, primary cervical cancer prevention is progressively implemented worldwide with universal adoption of vaccination strategies and millions of vaccine doses administered. There is now ample epidemiological documentation for herd immunity development and considerable reductions in vaccine's effectiveness proxies such as in the prevalence of genital warts and dysplasias [1]. Lately it seems that the principle HPV vaccination endpoints have been achieved, with documented declines in cervical cancer rates observed in settings which pioneered anti-HPV vaccination [2].

However, although HPV vaccination has gained global acceptance, challenges remain in the field of secondary cervical cancer prevention strategies. In most settings, given the limited resources, funding of the ambitious vaccination programs and related infrastructure development often necessitates corresponding savings of scale in secondary prevention implementation. This dictates more cost-effective cervical screening strategies; a goal which can be achieved using more accurate screening modalities, less screening rounds, implementing fewer (stand-alone) tests, or cheaper screening tests.

Since the fall of 2017 the U.S. Preventive Services Task Force (USPTFS) has released a draft proposal on cervical screening policies [3], for which the opportunity for public input expired on October 13, 2017. Major changes for this late draft proposal in comparison with previous guidelines focus on abandoning the policy of co-testing with cervical cytology and high-risk human papillomavirus (hr-HPV) testing for the vast 30-65 y old age groups. Valid options will include either screening with cytology every 3 years or with hr-HPV testing every 5 years as stand-alone tests; the related evidence is rated as "grade of recommendation A".

Previous experience shows that the core points of this draft will be only slightly revised before being incorporated in the next ASCCP cervical screening guidelines due in late 2019. The standards posed by these guidelines will soon become global benchmarks for cervical screening practices. This is a cause for some serious concerns.

It is irrefutable that supporting evidence favoring biomarker-based molecular cervical screening is overwhelming. A recent study by Schiffman et al. examined the effectiveness of cervical precancer detection by co-testing compared with HPV testing alone within the Kaiser Permanente Northern California (KPNC) cohort [4]. In this study, which covers 1,208,710 women aged 30 years and older that have undergone triennial cervical co-testing since 2003 the contribution of cytology to screening translated to earlier detection of at most five cases per million women per year. This offers compelling evidence that the added sensitivity of co-testing vs. HPV alone for detection of treatable cancer affected extremely few women. This concurs with the findings of another recent study within the KPNC cohort that followed for a 3.5 year period 1,262,713 women combining cytology and HPV DNA co-testing [5]. In this study, HPV-negative HSIL+ represented only 0.01% of test results and the authors argue that HPV status was the most important test considered; cytologic results were of importance (only) when HPV status was positive. The findings of this publication are also in line with previous observations that one single positive HPV test was predicting elevated cervical cancer risk 18 years later in the Portland cohort [6]. Furthermore these findings challenge previous assumptions on co-testing performance, like the one suggesting that 5 years after a negative co-test the risk of CIN3+ is similar to the risk of CIN3+, 3 years after a negative cytology [7].

The majority of currently available robust epidemiological data originate from several studies conducted within the NCI cohorts, mainly the KPNC cohort. However, no study has ever proved in pragmatic terms the assumptions of the equal protective effect of the current screening strategies against cervical cancer with the efficacy of the long-used method of annual cytology. Indeed, as late as 2003 annual pap smears represented the recommended cervical screening policy, endorsed by most US scientific authorities [8]. This long-standing policy which started in the 60's paved the way to the vast reductions in the cervical cancer rates in US. Having been involved in the development of previous US cervical screening guidelines, Kinney et al. comment that the policy of annual cytology which benchmarked the acceptable level of protection from cervical cancer in the US represented also "a profoundly inefficient system" [9].

In the last decades, several aspects of the natural cycle of HPV have been elucidated. As Dinkelspiel and Kinney point out, the understanding of HPV's natural history with the rapid resolution of

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most cervical infections drove biomarker research to establish the most accurate test at the longest possible interval [10]. Subsequently, the FDA approval and ASCCP recommendation of pap plus HPV co-testing at 3 year intervals aimed to provide cancer protection similar to the previous performance of annual cytology, with fewer tests and visits. In the same paper the authors question the standard policy of judging on the efficacy of the various cervical cancer screening protocols using CIN3 as primary end-point; despite for obvious ethical reasons randomized controlled trials comparing the results of different screening strategies on the prevalence rates of cervical cancer are unfeasible and should not be anticipated [10]. However, from the patient's perspective, changes in these rates represent the most meaningful outcome. The authors stress that screening failures do not manifest themselves as cancer immediately (since only a fraction of untreated CIN3 might become cancer after several decades) and the consequences of screening indeed manifest and accrue over a woman's lifetime. In a later publication these authors together with other experts advocate that the transition to the molecular age of cervical screening should not be associated with a reduction in cancer protection [9].

In a most recent article, Kinney and Huh comment that newer cervical screening guidelines accept a possibly higher cancer risk in the interest of avoiding the harms and burdens of more frequent screening [11]. Justification for lengthened screening intervals is based on the principle of 'equal management for equal risk', introduced by Castle et al. [12]. Dinkelspiel and Kinney suggested that "the issue of screening intervals can be addressed if there is consensus on what level of cancer risk the population wishes to tolerate, and how much harm they are willing to endure and pay for that level of risk" [10]. The 'equal management for equal risk' paradigm stemming from the 2013 algorithms will inspire the anticipated next round of ASCCP-sponsored guidelines; new, tailored recommendations that will be fully risk-based are anticipated for each woman sub-group. Based on the level of risk of precancer/cancer, the guidelines might recommend that the clinician "should consider treatment", "should perform colposcopy and biopsy", "should retest in 1 year", "should rescreen routinely", or "should exit screening". As stated, this guideline's launch is scheduled sometime in 2019 [5].

Some authorities might advocate that in hindsight less frequent intervals of molecular cervical screening might not prove to have a detrimental effect on cervical cancer rates. Indeed, some over screened populations can tolerate less intense cervical screening. Vaster gains in reducing cervical cancer incidence and mortality will be most likely achieved by increasing screening rates among unscreened women, or those who have not been screened regularly, very likely in conjunction with self-sampling biomarker-based strategies [13].

A closely related issue that needs addressing within the core of the forthcoming guidelines is the frequency of cervical screening among vaccinated populations, or alternatively the launch of cervical screening policies which will be dependent on vaccination status. Some investigators consider that initiating screening in women at age 25 among individuals vaccinated before the onset of sexual activity represents a safe practice, while some others suggest alterations on screening frequency that will affect all age range groups [14,15]. Conversely, universal screening protocols independent from HPV vaccination status, justified by the low and variable rates of vaccination coverage as well as the fraction of cervical precancers attributable to hr-HPV genotypes that are left uncovered by the first generation HPV-vaccines might prove safer over time [14,16]. Numerous publications have been published so far to allow for safe mathematic simulation and decision models these screening strategies will almost certainly be molecular-based [17,18].

Conclusion

In conclusion, future cervical screening policies will be either based on HPV related biomarkers, cytology or their combinations depending on local infrastructures and resources. Molecular HPV screening indeed does offer greater reassurance, and therefore might be implemented in less frequent intervals [19]. Our concerns which are shared by other authors are that by introducing extended intervals there is an increased chance of women missing consecutive screening rounds, mainly attributed to failures in electronic medical record-keeping, poor compliance from screened individuals or other reasons. Furthermore, in settings or countries where cervical screening constitutes a part of a "well-woman visit", increases in the rates of other gynecologic neoplasms which will fail to be screened (breast, endometrium) could be anticipated if these policies are finally adopted.

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