Better triage tests needed for HPV positive women. (Mini commentary on BJOG-20-0093.R1)

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Mini-commentary on BJOG-20-0093.R1: The impact of age and high risk human papillomavirus (hrHPV) status on the prevalence of high grade cervical intra-epithelial neoplasia (CIN2+) in women with persistent hrHPV positive, cytology negative screening samples: a prospective cohort study.

Better triage tests needed for HPV positive women

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Tidy *et al* showed that 1/3 of all referrals for colposcopy, in settings where primary high-risk HPV (HR-HPV) test is used for screening, are due to positive tests with a negative triage cytology (BJOG 2020 xxxx). These represent a significant burden of colposcopies but yield a relatively low number of cases of CIN2+ (7%), translating a low positive predictive value (PPV) of this approach.

Before generalizations of the results of this study can be made, some particularities of the English cervical cancer screening program must to be accounted for: 1) any HR-HPV positive test (including HPV16 and 18) is subjected to triage with cytology; 2) there is an ongoing organized screening program since 1988. In many countries, HPV16/18 positive women are directly referred for colposcopy. An organized screening, with a good coverage rate, even if cytology based, leads to a significant reduction in the prevalence of disease – the near absence of CIN2+ encountered in older women is not a reality for most countries.(Mendes D*et al. European Journal of Public Health* . 2018; 2:343–7) In its absence, the incidence of cervical cancer is bimodal, with the second peak at the age of 60-69.

The rate of CIN2+ decreased steadily, as age increased: from 14.2% in the group aged 25-34 years to absent in those >65 years. In the first group, most cases were due to HPV16, while it lost importance with increasing age. The PPV of colposcopy was lower in those positive for non 16 HR-HPV. Additionally, the rate of non-visualization of the squamo-colunar junction (SCJ) increased with age. Low rate of disease, dominance of non 16 HR-HPV genotypes and non-visualization of the SCJ contributed to a decline in the role and performance of colposcopy in older women (in this equation the poorer performance of cytology in older women is not being considered).

A minority of the women were likely to have been vaccinated against HPV. As vaccinated women enter screening, the rate of HPV16 and 18 will drop significantly in the younger cohorts. Putting in perspective: less HPV16/18 and less CIN2/3, that is, a scenario comparable to the one described in this paper for older

women. The remaining CIN2/3, even in younger women, will be attributable to genotypes of lower risk, thus less likely to progress.

We are reaching a point, in adequately vaccinated and screened populations, in which we must question ourselves whether we want to find all CIN2/3 or just the ones that are likely to progress. As HPV16 and 18 become rarer, this will be a more and more a burning question. Finding the right CIN2/3 is more important than finding all of them! The burden associated with colposcopies and treatments cannot be ignored.

HPV will maintain its role in screening (probably with more extended genotyping), as its sensitivity is unaffected by the decrease in prevalence of disease. Nevertheless, more specific tests, unaffected by the hormonal status or genotype, will be needed for triage (i.e. methylation markers). Until the day prevalence becomes so low that screening is not cost-effective...

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