Letter to the editor in response to the article: "*HPV screening, invasive cervical cancer and screening policy in Australia*" (Cox B & Sneyd MJ; J Am Soc Cytopathol doi: 10.1016/j.jasc.2018.07.003).

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We agree with Cox and Sneyd that cervical cancer incidence is expected to increase following the change in cervical screening policy in Australia. Our comprehensive modelled analysis predicted a transient effect of moving to a more sensitive test on increased early detection of cancer, but also predicted this would be followed by a longer term decline of 42-51% by 2035.[1] This is, however, the only point upon which we agree, because they have presented a flawed analysis based on cherry-picked data.

Cox and Sneyd's predictions use a highly simplified approach and rest entirely on the assumption that a negative HPV test provides the same protection over time as a negative cytology test. This is completely at odds with the evidence.[2, 3] HPV testing detects lesions earlier in their natural history,[3] providing much greater safety if a woman is HPV-negative and allowing the screening interval to be safely extended compared to cytology-based screening. This advantage is not trivial – fewer lifetime screens will greatly improve screening acceptability to women with a likely consequent improvement in participation. HPV-based screening also enables self-sampling which can provide screening to women who (whether for cultural reasons or related to previous sexual trauma) will never allow a speculum examination for screening.

Cox and Sneyd also fail to support, with evidence, their assumption that any diagnosis of high-grade cervical abnormalities (HGA) other than in the screening round immediately preceding cancer diagnosis represents 'over-diagnosis'. The objective of cervical screening is to detect and treat HGA. It is a fact that HGA can be detected with better sensitivity by HPV screening than by cytology screening. The specificity of HPV testing for HGA detection has been effectively addressed by: (1) setting an appropriate start age and screening interval for HPV screening; (2) using clinical HPV tests, which are (by design) not as sensitive to low viral loads; and (3) effective triaging of HPV-positive women.[2] Australia also has a sentinel screening cohort, via an ongoing large-scale randomised trial, Compass, and first results have demonstrated, as expected, increased detection in HPV-screened vs cytology-screened women.[4]

Cox and Sneyd acknowledge that their conclusions would not hold if disease that becomes invasive cancer was detected three or more years sooner by HPV testing than by cytology. This was already strongly suggested by trial data showing the benefit of HPV over cytology increased over time, and a recent study has demonstrated this clearly.[3] This study examined the longer-term screening history of 623 women diagnosed with cervical cancer (thus avoiding the known biases of studies which are restricted to test history in the year preceding diagnosis). HPV testing identified more women subsequently diagnosed with cancer than cytology, and did so sooner – even more than six years pre-diagnosis approximately half of the HPV tests were positive (versus approximately 20% of the cytology tests). This was not the case for cytology until approximately 6-12 months prior to diagnosis – at least five years later.

We believe that Cox and Sneyd fail to acknowledge the weight given to the extensive evidence review and public consultation in the decision-making process in Australia, which occurred alongside the extensive modelled analysis. The decision-making process took over three years,

and involved three expert committees. The modelled analysis has since been published in a major peer-reviewed journal.[5]

We are concerned that publication of their flawed study gives unwarranted credibility to spurious concerns based on simplistic modelling of non-representative data, potentially undermining public and provider confidence in a crucial cancer prevention policy.

References

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Declarations of interest: MAS, KTS and KC undertook the modelled analysis that formed part of the policy evaluation for the Australian Medical Services Advisory Committee (MSAC), were part of the technical team for the Cervical Cancer Screening Guidelines Working Party, and have performed other modelled analyses for the Australian Department of Health. IGH, LA and MS were invited to sit on expert advisory groups that supported the decision-making and policy implementation process around changes to cervical screening policy in Australia, as follows. IGH chaired the Renewal Steering Committee, the Steering Committee for the Renewal Implementation Project, and the Cervical Cancer Screening Guidelines Working Party. LA was a member of the Cervical Cancer Screening Guidelines Working Party and is the current Vice President of the Australian Society of Cytology. MS was a member of Renewal Steering Committee, the Steering Committee for the Renewal Implementation Project and was deputy chair of the Cervical Cancer Screening Guidelines Working Party. MS and KC are co-PIs of an investigator-initiated trial of cytology and primary HPV screening in Australia (`Compass'), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity. JMLB and MAS are on the Compass study team. MS and JMLB report that their institution, VCS Foundation, has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Roche Tissue Diagnostics, AZ USA. Neither KC not MAS nor their institution on their behalf (Cancer Council NSW) receive direct funding from industry for the Compass trial or any other project. KC sits on the Protocol Advisory Sub-Committee of MSAC.