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The challenges of cervical cancer screening for women aged over 65 years

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The guidelines from the American College of Obstetricians and Gynecologists,[1] the American Cancer Society[2] and the United States Preventive Services Task Force[3] recommend that women aged >65 years discontinue cervical cancer screening if (a) they have had three consecutive negative cytology tests in the past 10 years or two recent consecutive negative HPV tests, and (b) they have not been diagnosed with cervical intraepithelial neoplasia grade 2 or more severe disease in the past 25 years. The recommendation is founded on the consideration that the benefits of ongoing screening for women aged >65 years who receive regular screenings are outweighed by potential harms, which include discomfort during sampling, false positives and potentially unnecessary treatment. Nevertheless, as the incidence of cervical cancer rises with age, it prompts a discussion on the appropriate age to discontinue cervical cancer screening.

Worldwide data from the International Agency for Research on Cancer indicate that 22% (n=132 471) of new cases of cervical cancer and 33% (n=113 271) of deaths occur in women aged >65 years.[4] Additionally, mortality rates for cervical cancer are highest in this age group.[4 5] Cooley *et al* analysed cervical cancer stage at diagnosis and survival among women aged ≥65 years using California Cancer Registry data, which included 12 442 patients aged ≥21 years diagnosed with primary cervical cancer during 2009–2018.[6] Almost one-fifth of the patients with cervical cancer (n=2171, 17.4%) were aged ≥65 years. A significant majority of women aged ≥65 years (71%) presented with late-stage disease and had lower 5-year relative survival rates for both early- and late-stage diagnoses compared with patients aged <65 years.[6] Studies from Germany and Korea also show similarly high incidence rates of cervical cancer in women aged ≥65 years, with rates of 27.6% and 29.6%, respectively.[7 8] These findings underscore a substantial burden of advanced cervical cancer in women aged ≥65 years. As life expectancy increases and hysterectomy rates decline, the incidence of cervical cancer in this age group is likely to rise even further.

A study by Andersen *et al* from Denmark suggests that the risk of acquiring a new human papilloma virus (HPV) infection in women aged ≥65 years is lower compared with younger age groups, which partly explains why some countries have adopted HPV testing as an opt-out test.[9] However, new or reactivated latent HPV infections have been documented in the older population.[10] HPV latent infection, also known as immunologically controlled HPV infection, refers to a phase in which the virus is present in the body but is not actively causing symptoms or visible signs of infection. It is challenging to detect because routine clinical tests often lack sensitivity due to the absence of viral replication and shedding of viral particles. The findings of the study by Hammer *et al* indicate that more than two-thirds of women in Denmark with any history of abnormalities harbour HPV infection, with the majority (57.9%) only exhibiting latent infection.[11] Considering that HPV latency is reversible, there is a possibility of viral reactivation and subsequent development of cervical pre-cancer, particularly with aging-related immunosenescence, increasing comorbidities, and medication use in older women. This suggests the need to include pre-existing low-grade disease as a screening exit criterion and to employ a more sensitive HPV test for safe screening cessation. Besides, from a clinical perspective, screening older women presents unique challenges compared with younger patients. With respect to morphologic interpretation, samples from older women can be easily mistaken for dysplasia, leading to overdiagnosis and unnecessary colposcopy. Moreover, the atrophy of the cervical epithelium and hormonal changes in older women often result in reduced or virtually invisible cervical

lesions during colposcopy. The incidence of invasive vulvar squamous cell carcinoma and the average annual percentage changes (AAPC) decreased significantly among 20–44-year-old women (AAPC 0.8) but significantly increased among those aged 45–64 years (AAPC 2.3) and 65+ years (AAPC 1.2) in the USA, providing evidence that HPV vaccinations likely contributed to a decrease in the incidence of invasive vulvar carcinoma among women aged 20–44 years.[12] The lack of HPV vaccination in older women may indicate the relatively higher incidence of cervical cancer in women aged >65 years.

There are other issues that may compromise the effectiveness of cervical cancer screening. One such issue is the participation rate, which is notably lower among older women. This may be attributed to the misconception that they have a reduced risk of cervical cancer due to decreased sexual activity.[13] Furthermore, women who discontinue cervical cancer screening are less likely to visit gynaecologists.[14] Another challenge lies in obtaining comprehensive medical histories spanning up to 10 years before cessation of screening, especially in regions lacking well-established pathology registries. Relying on women to recall previous screening results is unreliable.

Indeed, several studies have demonstrated the effectiveness of screening women aged ≥65 years in preventing advanced cervical cancer.[15 16] Currently, there is a lack of uniform guidelines for cervical cancer screening across different countries. Most European countries, the USA and China recommend discontinuing screening at ages 60 or 65 years.[2 17 18] In contrast, Canada continues screening until age 70, while Korea and Australia extend screening until age 74 years.[19–21]

The current guidelines for discontinuation of cervical smears in women aged >65 years have strict criteria given that the risk of cervical cancer is relatively high in this patient population. Of course, the main drawback of this approach is that these guidelines would apply only to a limited patient population and, by its strict nature, would disqualify other patients who may not necessarily benefit from additional HPV screening, especially in the context of newly adopted HPV vaccination practices. For this reason, sole usage of these guidelines is potentially limited in scope and applicability, so clinical providers should be encouraged to consider a more personalised approach by evaluating the specific needs of each individual with regard to cervical cancer screening as clinically indicated.

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