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It's time to re-evaluate cervical Cancer screening after age 65

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Abstract

Cervical cancer screening guidelines currently recommend cessation of cervical cancer screening after age 65, despite 20% of new cervical cancer cases occurring in this age group. The US population is aging, research methodology that examines cervical cancer incidence and mortality rates has changed, and sexual behaviors and the rates at which women have hysterectomies have changed over time. Current guidelines do not adequately address these changes, and may be missing significant opportunities to prevent cervical cancer cases and deaths in older women. Furthermore, racial disparities in cervical cancer outcomes may be exacerbated by not addressing the preventive health needs of older women through cervical cancer screening.

Keywords

Cervical cancer; Cervical cancer screening; Prevention; Over 65

An estimated 20% of all cervical cancer cases in the United States are diagnosed in women over age 65 [1–3]. Elderly women are more likely to be diagnosed with late stage cancer, resulting in worse outcomes and higher mortality rates [4]. Despite this, many women over age 65 are not being screened for cervical cancer because current screening guidelines intend to balance benefits and harms. The recommendation to stop routine cervical cancer screening at age 65 among "adequately screened" women has been in place since 2012 [5]. However, improved calculation of true cervical cancer incidence and mortality rates by age and race [6,7], changing population demographics and life expectancy, and evolving treatment and surgical practices require a careful reexamination of these recommendations and how they are broadly and faithfully implemented. We address the flaws with the current recommendations to stop screening in some women after 65 years of age with the concern

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that current recommendations may, in fact, increase the future burden of cervical cancer incidence and disparities.

Cervical pre-invasive disease and cancer remain significant public health problems both in the US and around the world despite the substantial decrease in cervical cancer incidence and mortality rates since the introduction of the Pap smear and organized screening. In 2020, there will be an estimated 13,800 new cases and 4290 deaths from cervical cancer, with an incidence of 7.6 per 100,000 women [8]. However, research has shown that cervical cancer incidence rates have been underestimated due to a lack of accounting for hysterectomy in population-level calculations [6,7,9]. Actual corrected incidence rates of cervical cancer are more than double those of previously uncorrected estimates, particularly in groups such as older women and older Black women, whose cervical cancer incidence rate of 53 per 100,000 women age 65–69 is 126% higher than the previously reported uncorrected rate. Notably, cervical cancer mortality rates in Black woman in the US equal or exceed those in many African countries that have organized screening programs, with Black women dying of cervical cancer at a rate of 10 per 100,000 women [7].

The American Cancer Society (ACS) and United States Preventive Services Task Force (USPSTF) recommend cessation of cervical cancer screening at age 65 for women who have been adequately screened and have no history of CIN 2 or greater in the preceding 20 years [10,11]. As defined by the ACS, adequate prior screening for a 65 year old woman is: two consecutive negative co-tests or primary HPV tests, or three consecutive negative cytology results within the past 10 years, with the most recent test occurring within the past 5 years [10]. This recommendation is based largely on theoretical modeling and expert opinion [10–12]. Many of these models focus on the impact of harm caused by increased colposcopies instead of the harm caused by missed cases of cervical cancer or other patient informed outcomes of harm. Specifically, the harms and costs associated with the treatment of advanced cancer, such as cold knife conization, radical hysterectomy, pelvic radiation therapy and chemotherapy, must also be considered. Additionally, it is important to note that qualitative data on women's perception of the benefits and harms of screening after age 65 are lacking and are therefore excluded from assessing the balance of benefits and harms [13]. Of note, the USPSTF gave the recommendation for screening cessation after age 65 a D grade ("There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits") instead of an I ("…the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined."). The USPSTF should consider changing this recommendation to an I grade, to recognize the insufficiency of evidence in support of screening cessation at age 65.

Proponents of the recommendation to exit women from screening at age 65 argue that the guidelines account for the importance of adequate prior screening before cessation of screening, as the majority of cervical cancer cases are diagnosed in women who have not been adequately screened. Dinkelspiel et al. estimate that in the Kaiser Permanente Northern California population, 75% of patients who developed cervical cancer after age 65 from 2003 to 2008 had not been adequately screened prior to diagnosis [14]. Hammer et al. also showed that 72% of women diagnosed with cervical cancer had not had adequate screening

prior to diagnosis. [15] However, they also showed that, of the women who developed *advanced* stage cervical cancer, there was not a statistically significant difference between women who had been adequately screened and those who had not. Other studies have shown that only 25–50% of women diagnosed with cervical cancer had "adequate prior screening" before their cancer diagnosis [16,17]. Unfortunately, the assumption of adequate prior screening relies on physicians' ability to determine accurate screening histories in the setting of disjointed and disconnected medical records, years of complicated guideline changes that are ongoing today, and patients who are often unaware of their own history. Furthermore, women diagnosed with CIN3 at age 50 or older are *seven* times more likely to develop cervical cancer than those diagnosed before age 50, underlining the importance of screening for cervical dysplasia at older ages and continued surveillance in patients who have cervical precancerous conditions [18].

The issue of potential missed screening in women over age 65 is further exaggerated given that the United States has an aging population. Data from the US Census Bureau indicate that adults over age 65 will account for over 20% of the nation's population by the year 2030 and will continue to do so until at least 2050 [19]. Some argue that this aging population is not likely to affect cervical cancer incidence, as older women may be less likely to be newly exposed to HPV with enough time to develop pre-invasive or invasive disease and therefore wouldn't benefit from cervical cancer screening [20]. However, it has been shown that lifetime number of sexual partners may be more important than recent new partners for HPV infection [21–23]. Paul, et al., recently demonstrated the rate of new high-risk HPV detection in women ages 30–60 was 5.0/1000 woman-months, and that only 19.4% of those new HPV detections were associated with new sexual partners [21]. These data indicate that the majority of "new" HPV infections are likely reactivation of previously acquired HPV. This study also found that the rate of new detection of high-risk HPV was highest in women who reported five or more lifetime sexual partners, regardless of recent partnerships. [21] These data are important as sexual behaviors have changed over time, and a cohort effect may be masking an increased risk for women who grew up during and after the sexual revolution and were not accounted for in previous studies of older women [13,24]. Finally, women are living longer - the average life expectancy at age 65 is greater than 15 years, and when caught early, cervical cancer deaths are preventable. While adequate negative screening at age 50–64 showed to be protective against cervical cancer, the magnitude of the protection steadily decreases after age 69 [16], warranting continued screening as life expectancy has increased by about 20 years for women age 65 [25].

Accounting for the rate of hysterectomy on cancer incidence has led to more accurate epidemiological assessment of current cervical and endometrial cancer trends in the population, with important age-related and racial disparities [6,7,26]. Possibly even more important, however, is the impact of hysterectomy on future targets of screening programs and cancer rates. Hysterectomy rates have changed significantly over time and continue to change, in part due to the increasing popularity of alternative treatments for common gynecologic complaints (i.e. progestin-containing intrauterine devices, endometrial ablation) and changing cultural norms and preferences around complete hysterectomy [27,28]. With fewer women having complete hysterectomies, more women will remain 'at risk" for cervical cancer across their lifetime [29]. Simms et al. modeled the impact that changing

rates of hysterectomy will have on cervical cancer rates out to 2035 [27]. They project that hysterectomy rates will decrease by about 32% from 2012 to 2035, and based on changes in hysterectomy rate alone, cervical cancer incidence will increase by 9% over the same time period. When considering the impact of HPV vaccination on cervical cancer rates, this rate is actually expected to increase by 16% in women not eligible for the vaccine based on age at the time of vaccine introduction, those aged 55–84 in 2035. Their model also projects that if race-related cervical cancer disparities persist, cervical cancer incidence will be 73% higher in Black compared to White women for women age 55 and over. These data further emphasize the increasing incidence of cervical cancer in older women that must be reflected by changes in screening guidelines in order to prevent set-backs in our progress towards a global and equitable reduction in cervical cancer.

With the knowledge that life expectancy is increasing and recent data predicting changing racial demographics, in particular an increase in the proportion of non-white women over age 65 [19], measures should be considered to improve health outcomes and equity for the growing population of older women. Some purport that screening is less reliable in older women because tissue atrophy impacts cytology results [30]. However, with organizations moving towards primary HPV screening, this argument is becoming obsolete. Within the current screening recommendations, novel methods that simplify screening or make it more accessible – such as HPV self-swabbing [31] – should be considered. This could capture patients who do not present for standard screening and who are at risk for developing cervical cancer at a later age. Furthermore, the risk difference between women who have been adequately screened and those who have not could be taken into consideration, as we know that women who have not had adequate screening prior to age 65 are more likely to be diagnosed with cancer [14,15]. Differential recommendations for those with well-documented and verifiable screening histories versus those without could be considered. Another novel approach could include a required “welcome to Medicare” screening test, which would capture all women at age 65.

Cervical cancer is not only a disease of younger women. More than 20% of women diagnosed with cervical cancer are age 65 or older, and population-based incidence rates increase with age when accounting for prevalence of hysterectomy, especially for Black women. Women are living longer, and the population of elderly women at risk for getting, and dying from, cervical cancer is growing. Current screening guidelines state that a patient can exit after age 65 if she has had adequate negative screening. However, does this practice make sense given the very compelling epidemiology, gaps in our knowledge, future trends, and difficulty in elucidating an accurate history? The authors express concern about the overall impact and practicality of this recommendation and believe the evidence-base supports a more conservative approach to cancer prevention in older women.

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HIGHLIGHTS

- Cervical cancer screening guidelines recommend screening stop after age 65 despite 20% of new cases occurring in this group
- Demographics, research methods and treatment paradigms are changing and guidelines may not adequately address these changes
- Racial disparities in cervical cancer may be exacerbated by not addressing the preventive health needs of older women