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SPECIAL ARTICLE

Cervical Cancer Screening in Elderly Women

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ABSTRACT

Cervical cancer (CC) is the one of the leading causes of cancer death among women worldwide. Globally, with the current projections for increases in life expectancy, the prevalence of CC in elderly women is expected to rise, increasing the desirability of CC screening to detect the disease at an earlier stage in this group. However, making the decision to screen for CC in elderly women is often difficult and complex. The decision needs to be made using the best available evidence and a personalized assessment that integrates factors unique to elderly women with the aim to weigh the risks and benefits for each woman. The recent 2020 United States guideline update from the American Cancer Society recommends against cervical screening beyond age 65 in women who have had adequate negative screening results. Despite the evidence cited for this recommendation, implementation in a clinical practice guideline can be challenging, with resistance from elderly women and clinicians. Following is a brief review of current knowledge concerning the CC screening in elderly women. We also review the benefits and risks of CC screening in women older than 65 years.

Keywords: cervical cancer, screening, elderly women, guideline.

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Introduction

Cervical cancer (CC) is one of the most burdensome cancers worldwide and the fourth most common cancer among Thai women, ranking after breast, lung, and liver and intrahepatic bile duct cancers[1,2]. Persistent infection with human papillomavirus (HPV), especially the high-risk type, is the major risk factor for CC[2]. The age distribution of CC incidence is bimodal, with the first peak at around 40 years of age with a secondary peak at around 60 years of age[3]. While scientific evidence supports CC screening programs such as cytology alone (liquid-based or conventional), primary HPV testing, or co-testing (HPV testing and cytology) for early detection and treatment of CC, thus reducing CC incidence, mortality and treatment-related morbidity, there are few studies which have focused on the benefits of such programs in elderly women[4].

With the ever-increasing age of the world's population, the number of cancers in the elderly will proportionally increase[3, 5]. In the United States (USA), the American Cancer Society (ACS) (2018) reported that more than 15% of CC patients were diagnosed in women aged > 65 years[6]. Recently, data from the Massachusetts Cancer Registry reported that nearly one-in-four (23.6%) women with CC are diagnosed at > 65 years[7]. Other studies have reported that elderly women were more frequently diagnosed with advanced stage CC and oncological outcomes worsened with increasing age and stage of diagnosis[3, 8]. A previous population-based study from Japan reported that relative 5-year overall survival for CC patients decreased with age (88.6% in patients < 30 years, 78.1% in 30-54 years, 67.7% in 55-64 years and 54.4% in 65+ years)[9]. There is also some evidence that older age at diagnosis is related with advanced stage of CC, probably because of the late presentation among patients[9, 10].

Several studies have reported that elderly women often do not get CC screening tests[11, 12]. There are several possible explanations for these lower rates of CC screening in older women[13]. First, many CC screening guidelines recommend that women at low risk can stop screening at age 65[4, 14, 15]. Second, life expectancy among elderly women decreases with increasing age, and the utility of CC screening decreases proportionately. And, as such, many elderly women and clinicians may be unwilling to continue with CC screening as women age into their seventh decade and more. Third, in elderly women, there is a lack of knowledge on the prevalence and natural history of HPV, and HPV-related cervical dysplasia/cancer. Finally, regarding anatomical and hormonal changes, and musculoskeletal disorders in elderly women, there may be perceptions that these changes such as vaginal atrophy may cause screening examinations to be painful and burdensome.

As reviewed below, determining the optimal CC screening regime for elderly women is considerably complex. To better understand this topic, this article will briefly review the current knowledge on CC screening, especially in elderly women. We also review the benefits and risks of CC screening in women older than 65 years.

Current cervical cancer screening recommendations

CC screening guidelines differ among countries with established national screening programs and even professional organizations (Table 1.)[4, 14, 15]. These differences include type of screening test, screening intervals, and the age at which women should start/stop having CC screening. Most of the disagreements stem from the type of screening test that each country/professional organization uses to formulate their recommendations, their interpretations of the evidence, and considerations about the balance between benefits, costs, and risks. The guidelines vary in the ages at which they recommend beginning (20-25 years) and ending (65-70 years) screening.

Table 1. Comparison of selected cervical cancer screening guidelines.

	ACS[14]	ACS[14]	RTCOG[4]	Australia[15]	Japan[15]
Published	- 2012	- 2020	- 2021	- 2017	- 2010
Age start	- 21 years	- 25 years	- 25 years with a history of sexual intercourse - 30 years without a history of sexual intercourse	- 25 years	- 20 years
Age stop	- 65 years	- 65 years	- 65 years	- 70 years	- No end date included
Test and interval	- 21-29 years; every 3 years with cytology - 30-65 years; every 3 years with cytology or co-testing - Primary HPV testing alone not recommended	- Every 5 years with primary HPV testing alone or co-testing or - Every 3 years with cytology	- Every 2 years with cytology or - Every 5 years with co-testing	- Every 5 years with primary HPV testing alone or co-testing	- Every 2 years with cytology
Post-hysterectomy	- Not recommended for women with no history of serious precancer of cervix or more lesions.	- Not recommended for women with no history of CIN2 or more lesions.	- Omit screening if hysterectomy was done for benign condition.	- Omit screening if no evidence of cervical pathology was detected on the hysterectomy specimen.	- Not mentioned.

ACS: American Cancer Society, RTCOG: The Royal Thai College of Obstetricians and Gynaecologists, CIN: cervical intraepithelial neoplasia

The 2020 guideline update from the ACS recommends that CC screening should start at age 25 years and then the woman should undergo primary HPV testing every 5 years until age 65 years. In a setting in which primary HPV testing is not available, then women aged 25-65 years should be screened with co-testing every 5 years or by cervical cytology alone every 3 years. This guideline recommends that women aged > 65 years who have no history of cervical intraepithelial neoplasia (CIN) II or more severe lesions in the past 25 years, and who have documented adequate negative prior screening results in the previous 10 years, discontinue all CC screening[14].

Adequate negative prior screening is described as 2 sequential negative primary HPV testing results, or 2 sequential negative co-testing results, or 3 sequential negative cytology results in the past 10 years, with the most recent test occurring within the past 3-5 years, depending on the screening test used. This guideline still suggests that women aged > 65 years

without conditions restricting life expectancy for whom adequate documentation of prior screening is not available should be screened until the criteria for screening cessation are met. CC screening may be ceased in women of any age with restricted life expectancy[14].

A strong evidence base has been compiled in recent years from the integration of good randomized controlled studies and population-based observational studies to inform recommendations for both type of CC screening test and screening interval time, although there are still gaps concerning the specific age at which testing should be started or the age and conditions under which women can safely exit CC screening. And due to this quite serious knowledge gap, recommendations concerning CC screening guidelines in these areas are force to depend on mathematical model studies and expert opinion[16].

Benefits and risks of cervical cancer screening in women older than 65 years

The benefits and risks of CC screening in women aged > 65 years are less well established and require further study before firm guidelines. Many of the physiological changes in older women are associated with low levels of estrogen, which results in narrowing of the cervical os and a reduction in the thickness of the cervical epithelium and stromal vascularity, making the cervix more difficult to expose, and thus the transformation zone where CCs are most likely to arise, making it more difficult to obtain an adequate cervical cytology sample and tissue sample, thus lowering the chance of both adequate cervical smears and a successful morphologic diagnosis by cytology and histopathology[17]. Older women have a higher false positive rate from cervical cytology, increasing the risk of further unnecessary investigations (such as repeat cytology, colposcopy, or biopsy) and overtreatment (such as conization). They can also experience pain or distress during or after CC screening[16-19]. Many mathematical model studies have concentrated on the harms of CC screening in women aged > 65 years caused by increased numbers of unnecessary investigations and overtreatments rather than the harms caused by missed CC cases, and such harms and the costs associated with unnecessary investigations and treatments of missed CC cases must also be considered[18]. There are also a lack of qualitative data examining older women's perceptions of the benefits and risks of CC screening, a critical omission in the consideration of the balance of benefits and risks of this procedure[16].

Women who have had a hysterectomy are no longer at risk of CC. Data from five nationwide registers in Denmark reported a high prevalence of hysterectomy in estimating population-based rates of CC at older women[20]. Failure to remove these elderly women who have had a hysterectomy from the population at risk leads to an underestimating of CC incidence rates in older women[18-19]. For example, in the USA from 2000 to 2009, the hysterectomy adjusted incidence rate of CC was 18.6 per 100,000, nearly 60% higher than the unadjusted rate of 11.7 per 100,000[21]. Therefore, some data behind the guidelines that recommend against CC screening in women aged > 65 years might underestimate their CC risk.

Again, the proper age at which we can safely say a woman has had adequate testing to safely discontinue further CC screening is still undecided. One population-based study from Kaiser Permanente Northern California reported that 75% of the women who were diagnosed with CC after age 65 years had not had adequate negative screening prior to the diagnosis[22]. A recent national cohort study from Denmark also reported that 80% of CC women who were diagnosed at age 60 years and older had insufficient screening including never screened. The same study also found that sufficiently screened women were significantly less likely to be diagnosed with advanced stage CC compared to never-screened women. Insufficiently screened women were more likely to be diagnosed with advanced stage CC compared to sufficiently screened women, but the difference was not significant[23]. A study by Yost and Hoekstra found that half of the women who developed CC after age 65 had had adequate screening prior to being diagnosed[24]. Interestingly, one population-based study from England and Wales found that the protective strength of previous negative

screening results for women from CC diminished with time; there were twice as many CC cases which had stopped screening at 65 years old as those at 75 years old[25]. These data suggest that we should consider extending the age of termination of CC screening even in women with a history of adequate negative prior screening.

Another important point of concern is the durability of protection in women aged > 65 years with adequate negative prior screening based on the role of HPV reactivation after latency in the cervix, as well as the risk conferred by newly acquired HPV infections from a new sexual partner. A recent study reported that the rate of new high-risk HPV detection among women aged 30-60 years was 5.0 per 1,000 woman-months. Reporting a new sexual partner was associated with higher HPV detection rates (adjusted hazard ratio, 8.1), but accounted for only 19.4% of all new detections[26]. Based on these findings, we can infer that the most of new HPV infections are probably reactivation of a prior HPV infection. However, as life expectancy increases around the world, many women aged > 65 years are still healthy and have an active sex life, and some of them will have newly acquired HPV infection. One large study from China reported that the risk of high-risk HPV infection in women aged 40 years to menopause is relatively low, but the infection rate increases after 65 years[27]. Moreover, several studies have found that primary HPV testing, whether clinician-collected or self-collected, is more sensitive for detecting precancerous and cancerous cervical lesions than cytology, especially in older women[28-30]. Therefore, women who have a history of multiple sexual partners and an active sex life after 65 years should continue routine CC screening after age 65 years, and use primary HPV testing as the primary screening test.

Conclusion

Decisions about CC screening in elderly women are often difficult, complex, and challenging. Despite the 2020 guideline update from the ACS recommending against CC screening beyond age 65 in women who have had adequate negative screening, nearly one-fourth of women diagnosed with CC are over 65 years of age. As life expectancy increases, older women are an increasingly healthy population. Therefore, the decision regarding when to stop CC screening should not be based on age and previous CC screening history alone. The decision requires a personalized assessment of health status, comorbidities, life expectancy, and cancer risk. It is important to consider the benefits and risks of continued CC screening. Primary HPV testing does seem to be a good method for CC screening in elderly women.

Potential conflicts of interest

The author declares no conflicts of interest.

References

1. Cancer IAfRo. Cancer incidence in five continents time trends. https://ci5.iarc.fr/CI5plus/Pages/online.aspx. Accessed 20 Sep 2022.
2. Chittithaworn S, Hanprasertpong J, Tungsinmunkong K, Geater A. Association between prognostic factors and disease-free survival of cervical cancer stage IB1 patients undergoing radical hysterectomy. Asian Pac J Cancer Prev 2007;8:530-4.
3. Tangkananan A, Thongkhao P, Janmunee N, Hanprasertpong J. Impact of chemotherapy cycles on oncological outcomes in elders with locally advanced cervical cancer treated with concurrent chemoradiotherapy. J Med Imaging Radiat Oncol 2022;66:1014-21.
4. Chittithaworn S, Charakorn C, Kongsawatvorakul C. Cervical cancer screening guidelines: An updated review. Thai J Obstet Gynaecol 2021;29:186-90.
5. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet 2017;389:1323-35.
6. Hou P, Hsieh C, Wei M, Hsiao S, Shueng P. Differences in treatment outcomes and prognosis between elderly and younger patients receiving definitive radiotherapy for cervical cancer. Int J Environ Res Public Health 2020;17:4510.
7. Feldman S, Cook E, Davis M, Gershman ST, Hanchate A, Haas JS, et al. Cervical cancer incidence among elderly women in Massachusetts compared with younger women. J Low Genit Tract Dis 2018;22:314-7.
8. Quinn BA, Deng X, Colton A, Bandyopadhyay D, Carter JS, Fields EC. Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment

and overall survival. Brachytherapy 2019;18:29-37.
9. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of age on cervical cancer survival in Japan. Jpn J Clin Oncol 2005;35:464-9.
10. Eggemann H, Ignatov T, Geyken CH, Seitz S, Ignatov A. Management of elderly women with cervical cancer. J Cancer Res Clin Oncol 2018;144:961-7.
11. Sawaya GF, Brown AD, Washington AE, Garber AM. Clinical practice. Current approaches to cervical-cancer screening. N Engl J Med 2001;344:1603-7.
12. Dinkelspiel H, Fetterman B, Poitras N, Kinney W, Cox JT, Lorey T, et al. Screening history preceding a diagnosis of cervical cancer in women age 65 and older. Gynecol Oncol 2012;126:203-6.
13. Alibhai SMH, Horgan AM. Cancer screening in older adults: What to do when we don't know? J Geriatr Oncol 2011;2:149-60.
14. Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020;70:321-46.
15. Wang W, Arcà E, Sinha A, Hartl K, Houwing N, Kothari S. Cervical cancer screening guidelines and screening practices in 11 countries: A systematic literature review. Prev Med Rep 2022;28:101813.
16. Gravitt PE, Landy R, Schiffman M. How confident can we be in the current guidelines for exiting cervical screening? Prev Med 2018;114:188-92.
17. Mossa MA, Carter PG, Barton DP, Young MP. Cervical intraepithelial neoplasia in postmenopausal women: difficulties in cytology, colposcopy and treatment. The Obstetrician & Gynaecologist 2001;3:8-12.
18. Dilley S, Huh W, Blechter B, Rositch AF. It's time to re-evaluate cervical cancer screening after age 65. Gynecol Oncol 2021;162:200-2.
19. Rositch AF, Silver MI, Gravitt PE. Cervical cancer screening in older women: new evidence and knowledge gaps. PLoS Med 2014;11:e1001586.
20. Lam JU, Lynge E, Njor SH, Rebolj M. Hysterectomy and its impact on the calculated incidence of cervical cancer and screening coverage in Denmark. Acta Oncol 2015;54:1136-43.
21. Rositch AF, Nowak RG, Gravitt PE. Increased age and race-specific incidence of cervical cancer after correction for hysterectomy prevalence in the United States from 2000 to 2009. Cancer 2014;120:2032-8.
22. Dinkelspiel H, Fetterman B, Poitras N, Kinney W, Cox JT, Lorey T, et al. Screening history preceding a diagnosis of cervical cancer in women age 65 and older. Gynecol Oncol 2012;126:203-6.
23. Hammer A, Soegaard V, Maimburg RD, Blaakaer J. Cervical cancer screening history prior to a diagnosis of cervical cancer in Danish women aged 60 years and older-A national cohort study. Cancer Med 2019;8:418-27.
24. Yost S, Hoekstra A. Cervical cancer in women over 65: An analysis of screening. Gynecol Oncol Rep 2018;25:48-51.
25. Castañón A, Landy R, Cuzick J, Sasieni P. Cervical screening at age 50-64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. PLoS Med 2014;11:e1001585.
26. Paul P, Hammer A, Rositch AF, Burke AE, Viscidi RP, Silver MI, et al. Rates of new human papillomavirus detection and loss of detection in middle-aged women by recent and past sexual behavior. J Infect Dis 2021;223:1423-32.
27. Shen Y, Xia J, Li H, Xu Y, Xu S. Human papillomavirus infection rate, distribution characteristics, and risk of age in pre- and postmenopausal women. BMC Womens Health 2021;21:80.
28. Eun TJ, Perkins RB. Screening for cervical cancer. Med Clin North Am 2020;104:1063-78.
29. Gilham C, Crosbie EJ, Peto J. Cervical cancer screening in older women. BMJ 2021;372:n280.
30. Lindström AK, Hermansson RS, Gustavsson I, Hedlund Lindberg J, Gyllensten U, Olovsson M. Cervical dysplasia in elderly women performing repeated self-sampling for HPV testing. PLoS One 2018;13:e0207714.