ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2025;(2):182-192 // 10.5505/amj.2025.37891

IS IT TIME TO REVISE CERVICAL CANCER SCREENING GUIDELINES?

Celal Akdemir[1], Mücahit Furkan Balcı[2], Mustafa Şanlı[3], Abdulmecit Öktem[2], Ali Onur Arzık[1], Yasemin Alan[4], Özgür Erdoğan[1], Murat Alan[2], Muzaffer Sancı[1]

[1]Department of Gynecologic Oncology, University of Health Sciences İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
[2]Department of Gynecology and Obstetrics, University of Health Sciences İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
[3]Department of Gynecology and Obstetrics, Sivas Yıldızeli State Hospital, Sivas, Türkiye
[4]Department of Gynecology and Obstetrics, İzmir Metropolitan Municipality Eşrefpaşa Hospital, İzmir, Türkiye

Correspondence:
Murat Alan (e-mail: gozdealan@hotmail.com)

Submitted: 04.11.2024 // Accepted: 21.05.2025

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: In our retrospective study, we tried to determine whether cervical smear screening is necessary in patients over 65 years of age by comparing the cytological and histological results of patients over 65 years of age.

Materials and Methods: A retrospective review of the cytological and histological results of 3465 patients over the age of 65 who underwent cervical cytology between September 2017 and September 2022 was conducted.

Results: It was established that 547 of the 3,361 patients with normal Pap smear results had irregular screening follow-ups, while 2,814 patients were undergoing regular follow-ups following the screening program. Of the 104 patients with abnormal Pap smear results, 54 had irregular follow-ups and 50 had regular screening. Among the 601 patients aged 65 and above who did not undergo regular cervical screening, 8.98% exhibited abnormal smear results and 3.16% displayed abnormal histological findings. When abnormal Pap-Smear results and abnormal biopsy results were analyzed, it was found to be significantly higher in women over 65 years of age without regular follow-up. ($p<0.001$),($p<0.05$)

Conclusion: Significant differences were observed in the frequency of abnormal smear results and the severity of diagnosis in women over 65 years of age who were followed up irregularly in line with the cervical cancer screening program compared to those who were followed up regularly. The results of our study indicate that the screening cut-off age should be revised for patients with irregular cervical screening to reduce the incidence of cervical cancer and precursor lesions.

Keywords: Pap smear, cervical cancer, HPV.

Introduction

Cervical cancer remains a significant public health concern, despite a decline in its prevalence due to screening and prophylactic vaccination. According to the 2020 global estimates, it is the fourth most common cancer in women and a leading cause of cancer-related mortality. The majority of cervical cancer cases are attributed to persistent infections with high-risk oncogenic types of sexually transmitted human papillomavirus.[1]

Cervical cancers are largely preventable through three main avenues: primary prevention with HPV vaccination, secondary prevention with cervical screening and treatment of precancerous lesions, and tertiary prevention with early diagnosis and treatment of cancer. The most effective methods for reducing the incidence of cervical cancer and associated mortality are primary prevention and screening. The high cost of the HPV vaccine, the failure of most countries to implement a free vaccine program, and the lack of compliance with screening programs present significant challenges to the effective prevention and control of cervical cancer.

According to the National Cancer Screening Program of the Ministry of Health of Turkey, women between the ages of 30 and 65 are advised to undergo a smear and HPV-DNA test every five years to detect cervical cancer. This recommendation is based on the evidence that cervical cancer is most prevalent in women in this age range and that regular screening can facilitate early detection and improve outcomes. Despite current screening guidelines, opportunistic cervical smears are frequently performed in older women during routine gynecological visits, especially in the absence of reliable screening history documentation.

The growing proportion of older people in the global population is influencing the development of new research methods for analyzing the incidence of cervical cancer and cancer-related mortality. The current guidelines may be insufficient in anticipating these changes. They may be failing to identify crucial opportunities for the prevention of cervical cancer incidence and mortality in women over the age of 65.

According to national and international guidelines, the patient's screening history should be taken into account when deciding whether to discontinue cervical smear screenings. It is obligatory that the patient has undergone at least two negative tests in the preceding five years and has no prior history of preinvasive neoplastic disease. The proposal to cease routine cervical cancer screening at the age of 65 among women who have undergone regular and adequate screening has been put forth since 2012.[2]

According to the American College of Obstetricians and Gynaecologists (ACOG), a woman aged 65 years or older is considered to be adequately screened if she has had three or more consecutive negative cytology tests or two consecutive negative test results within the last ten years, with the most recent test being within the last five years. In the present study, the retrospective results were analyzed, with patients who met the specified

conditions deemed to have been adequately screened. Conversely, patients who did not meet these conditions were considered to have been inadequately and irregularly screened. Patients classified as having regular screening had a documented history of normal cytology or test results and no prior diagnosis of abnormal smear or preinvasive cervical lesions.

The objective of our study was to investigate the frequency of abnormal cytology in women over the age of 65 whose previous follow-ups were classified as either "regular, adequate" or "inadequate, irregular" by the established recommendations.

Materials and Methods

This study was conducted by the ethical principles set forth in the Declaration of Helsinki. The data for our single-center retrospective study were obtained from the archives of SBÜ İzmir Tepecik Training Research Hospital. The study commenced after obtaining approval from the SBÜ İzmir Tepecik Training Research Hospital Ethics Committee with approval number 2023/01-21.

A retrospective review of the files of 3465 patients who had undergone a Pap smear test between September 2017 and September 2022 and met the inclusion criteria was conducted. The histological results of patients who underwent biopsy were duly recorded in the case report form. Only asymptomatic women undergoing routine gynecologic care were included. No smear was obtained based on a suspicious clinical finding.

Inclusion criteria for patients: individuals aged 65 years and above, patients with adequate cervical cytology, and patients without pathologically confirmed preinvasive cervical lesions. Patients who are excluded from the study are those under the age of 65, those with inadequate cervical cytology, those with a history of preinvasive lesions, those with a pathologically confirmed history of gynecological malignancy, and patients who have undergone hysterectomy for non-malignant reasons.

The data were analyzed using IBM Statistics 21.0. Comparisons between groups were performed using the chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate associations. A p-value < 0.05 was considered statistically significant. The strength of the association was evaluated using the odds ratio (OR) with a 95% confidence interval (CI). The data were expressed as absolute (n) and relative (%) frequencies to assess the relationship between the diagnostic categories. A significance level of 5% was deemed appropriate for this study.

Results

The mean age of the 3,361 patients with normal Pap smear results was 69.9 years, while the mean age of the 104 patients with abnormal Pap smear results was 70.1 years. No statistically significant difference was observed in the mean age between the two groups.

A total of 547 patients out of 3,361 whose Pap smear results were reported as normal were found to have undergone an 'irregular, inadequate' follow-up, while 2,814 patients had received 'regular, adequate' follow-up by the national cancer screening program. It was established that 54 of the 104 patients who had been identified with abnormal Pap smear results were monitored in an "irregular and inadequate" manner, whereas 50 patients were monitored "regularly and adequately" by the national cancer screening program.

It was established that the prevalence of abnormal Pap smear results in patients aged 65 and above was markedly elevated in those who were monitored irregularly in comparison to those who were monitored regularly within the framework of the national cancer screening program. ($p < 0.001$). Among the 601 patients aged 65 and above who did not undergo regular cervical screening, 8.98% exhibited abnormal smear results and 3.16% displayed abnormal histological findings. Of the 104 patients with abnormal smear results, 61 were diagnosed with ASCUS (58.6%), 16 with ASC-H (15.3%), 8 with LGSIL (7.7%), 7 with HGSIL (6.7%), and 12 with AGC (11.5%). At follow-up, 60 patients (57.6%) underwent repeat cytology, 36 (34.6%) underwent colposcopy and 64 (61.4%) underwent diagnostic biopsy. Table 1 presents the distribution of abnormal cytology and the rate of repeated cytology, colposcopy, biopsy, and abnormal biopsy rates.

Table 1: The distribution of abnormal cytology, along with the rates of repeat cytology, colposcopy, biopsy, and abnormal biopsy, is presented according to the types involved.

First Cytology Results	n (%)	Repeat Cytology	Colposcopy	Abnormal Colposcopy	Biopsy	Abnormal Biopsy
ASCUS	61 (58.6%)	55 (90.1%)	14 (22.9%)	11 (18.0%)	28 (45.9%)	10 (16.4%)
ASC-H	16 (15.3%)	0	9 (56.2%)	6 (37.5%)	16 (100%)	7 (43.7%)
LSIL	8 (7.7%)	3 (37.5%)	1 (12.5%)	0	3 (37.5%)	0
HSIL	7 (6.7%)	2 (28.5%)	4 (57.1%)	2 (28.5%)	7 (100%)	4 (57.1%)
AGC	12 (11.5%)	0	4 (33.3%)	2 (16.6%)	10 (83.3%)	5 (41.6%)
Total	**104**	**60 (57.6%)**	**36 (34.6%)**	**21 (20.1%)**	**64 (61.4%)**	**26 (25.0%)**

Abbreviations: ASCUS, Atypical Squamous Cells of Undetermined Significance; ASC-H, Atypical Squamous Cells-cannot exclude HSIL; LSIL, Low-grade Squamous Intraepithelial Lesion; HSIL, High-grade Squamous Intraepithelial Lesion; AGC, Atypical Glandular Cells.

An abnormal biopsy result was observed in 26 of the 64 patients. It was determined that 7 of the 26 patients who underwent biopsy and were followed up due to abnormal biopsy results were under regular follow-up and 19 were under irregular follow-up. Abnormal biopsy results were observed in seven of the 27 patients with abnormal smear results and regular follow-up, and 19 of the 37 patients with abnormal smear results and irregular follow-up. Although statistical significance was not reached in odds ratio analysis (OR: 3.02, $p = 0.070$), the frequency of abnormal cytology and biopsy findings was significantly higher in the irregular screening group ($p < 0.05$). This trend suggests a potential association that warrants further investigation in larger cohorts.

Amongst the cohort of patients who were monitored regularly, one patient was diagnosed with cervical intraepithelial neoplasia I (CIN), three patients with CIN III, one patient with squamous cell carcinoma, and two patients with endometrial adenocarcinoma. In the irregularly followed-up patient group, eight patients were diagnosed with cervical intraepithelial neoplasia I (CIN), two with CIN II, one with CIN III, five with squamous cell carcinoma, and three with endometrial adenocarcinoma. Table 2 presents the abnormal biopsy rates observed in patients with regular and irregular follow-up.

Table 2: Abnormal biopsy rates in patients with regular and irregular follow-up.

	Abnormal Biopsy Results	
	Regular Follow-up	**Irregular Follow-up**
ASCUS (n:28)	CIN I (n:1) CIN III (n:2)	CIN I (n:3) CIN II (n:2) SCC (n:2)
ASC-H (n:16)	CIN III (n:1) SCC (n:1)	CIN I (n:2) EA (n:1) SCC (n:2)
LGSIL (n:3)	0	0
HGSIL (n:7)	0	CIN I (n:2) CIN III (n:1) SCC (n:1)
AGC (n:10)	EA (n:2)	EA (n:2) CIN I (n:1)
Total (n:64)	**7**	**19**

Abbreviations: CIN, Cervical Intraepithelial Neoplasia; EA, Endometrial Adenocarcinoma; SCC, Squamous Cell Carcinoma.

A total of six patients diagnosed with squamous cell carcinoma were examined. Staging was performed using the FIGO 2018 classification system. One patient was classified as Stage 1A2, while the remaining five patients were categorized as Stage IIB or higher. The remaining five patients exhibited advanced-stage cervical cancer, classified as Stage IIB or above. A review of medical records revealed that all patients with advanced-stage cervical cancer had been irregularly followed up. One patient was recommended for radical hysterectomy, while five patients were advised to undergo concomitant chemoradiotherapy and brachytherapy. The stages of patients diagnosed with squamous cell carcinoma (SCC) were classified according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system and are presented in Table 3.

Table 3: The distribution of patients with squamous cell carcinoma (SCC) according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system.

	Regular Follow-up	**Irregular Follow-up**
SCC	Stage 1A2 (n) 1	Stage IIB ≥ (n) 5

SCC, Squamous Cell Carcinoma

Discussion

There is currently no definitive evidence regarding the optimal age and population for cessation of cervical cancer screening.[4] Approximately 20% of cases of cervical cancer are diagnosed in women over the age of 65. Although the diagnosis is made at a more advanced stage in older women, this results in a worse prognosis and a higher cancer-related mortality rate.[5,6,7]

However, current screening guidelines recommend stopping routine cervical cancer screening at age 65 in "adequately screened, regularly screened" women, and aim to balance the benefits, harms, and costs for women over 65.[2] Nevertheless, a growing number of studies suggest that screening also reduces cancer incidence and mortality in women aged 65 and older.[8,9]

Most cervical cancers and pre-cancerous lesions are known to result from persistent human papillomavirus (HPV) infection. One of the hypotheses put forward to justify the cessation of screening in women over 65 years of age is the age-related decline in the prevalence of HPV.

Furthermore, the incidence of cervical cancer is relatively low in older women with a history of negative screening results. Castanon et al. demonstrated that it may be safe for women with three negative tests after

the age of 50 to undergo cervical screening at the age of 65.[10] The American Cancer Society (ACS) advises that individuals aged 65 years and over with no history of grade 2 or more severe cervical intraepithelial neoplasia within the past 25 years and documented adequate negative screening results within the previous 10 years should cease cervical cancer screening.[11] These recommendations are predominantly founded upon theoretical modeling and the opinions of experts in the field. Nevertheless, the majority of modeling exercises concentrate on the influence of expenses and detriments resulting from augmented screening and colposcopies, as opposed to the harm caused by the consequences of unidentified cervical cancer cases.

Nevertheless, evidence indicates that the risk of developing cervical cancer following multiple consecutive negative screening results is comparable between women aged 50 and younger.[12] Consequently, a history of negative results at older ages may not be a sufficient rationale for discontinuing screening.

In the present study, 8.98% of 601 patients aged 65 and above who had not undergone regular cervical screening exhibited abnormal smear results, while 3.16% displayed abnormal histological results. Furthermore, the decline in participation in screening programs with increasing age contributes to the higher incidence of cervical cancer observed in older women.[13]

The decline in screening participation with increasing age also contributes to the higher incidence of cervical cancer observed in older women, particularly in settings where screening programs are opportunistic. These same explanations have also been put forward to explain the frequency of abnormal tests in older women with inadequate screening histories in Australia and Finland.

The persistence of cervical cancer diagnoses in patients aged 65 and above, despite the availability of effective preliminary screening, may be attributed to the diminished sensitivity of these screening methods and the age-related decline in the efficacy of colposcopic examination. Cytological tests may become less sensitive because of recession, vulvovaginal atrophy, and cervical atrophy of the squamocolumnar junction that occurs after menopause.[14,15]

Population aging and increasing life expectancy are likely to influence the future prevalence of cervical cancer in older women. Cervical cancer is more severe and has a worse prognosis in older patients than in younger patients.[7] In our study, five patients whose diagnosis of cervical cancer was confirmed by biopsy results were diagnosed with advanced-stage cervical cancer (Stage IIB and above).

Some studies in the literature posit that the aging population will not impact the incidence of cervical cancer. The aforementioned studies posit that older women are less likely to be exposed to new HPV infections, do not have sufficient time to develop pre-invasive or invasive disease, and therefore will not benefit from cervical cancer screening.[16] However, it has been shown that the number of lifetime sexual partners may be more

important for HPV infection than recent new partners.[17] The results of these studies indicate that a significant proportion of new HPV infections are the result of reactivation of previously acquired HPV infections.

In women aged 65 years, the average life expectancy is more than 15 years. Consequently, early diagnosis of cervical cancer can prevent cervical cancer-related deaths. Although adequate negative screening between 50 and 64 years of age has been demonstrated to be protective against cervical cancer, the effectiveness of this protection gradually decreases after 69 years of age.[18] This evidence indicates that screening should be maintained, given that life expectancy for women aged 65 and above has increased by approximately 20 years.

Cervical premalignant lesions and cervical cancer are not exclusive to young women. Notably, more than 20% of women diagnosed with cervical cancer are aged 65 or above. As the population continues to age, the prevalence of HPV infection and associated cervical lesions in older women will undoubtedly remain a significant challenge for the prevention and control of cervical cancer. It is therefore beneficial to diagnose cancer in the elderly population at an early stage, as this will help to reduce the disease burden and mortality.

The most significant limitation of our study is the absence of integration between smear results and HPV DNA results, as well as the lack of evaluation of abnormal smear results in conjunction with HPV results. Three options are available for the screening of cervical cancer in individuals between the ages of 30 and 65. These include primary HPV testing every five years, cervical cytology alone every three years, or co-testing with a combination of cytology and HPV testing every five years.[19] While all three screening strategies have demonstrated efficacy, with a reasonable balance of benefits and potential harms, HPV DNA testing is strongly recommended, particularly for new or changing partners. One of the main limitations of our study is the absence of HPV DNA results due to the lack of systematic HPV testing in our center during the study period.

A further limitation of this study is that the results were derived from a single center, which may not be representative of the general population. However, our center is in one of the most populous cities in our country, and our current study demonstrates the prevalence of abnormal cervical smear results in individuals aged 65 and above in our population.

Consequently, the rise in the average life expectancy of women has resulted in an increase in the population of older women at risk of developing cervical cancer and dying from this disease The findings of our study indicate that the detection rates for premalignant and invasive neoplasms were significantly higher in women who did not undergo regular follow-up compared to those who did.

In conclusion, the current screening guidelines stipulate that a patient who has undergone adequate screening and has received a negative result may opt out of further screening after reaching the age of 65. These findings highlight the potential clinical benefit of extending cervical cancer screening beyond the age of 65 in women

without an adequate screening history. Revising current guidelines considering increased life expectancy and inconsistent follow-up records may reduce the burden of undiagnosed cervical cancer in the elderly population.

Ethical Considerations: The study was approved by SBÜ İzmir Tepecik Training Research Hospital Ethics Committee with the date and approval number 07.02.2023-2023/01-21

Conflict of Interest: The authors declare no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-49.
2. Massad LS, Einstein MH, Huh WK, et al.; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S1-S27.
3. American College of Obstetricians and Gynecologists (ACOG). Updated cervical cancer screening guidelines. 2021. [Internet] https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines (Accessed: 12.04.2021)
4. Arbyn M, Anttila A, Jordan J, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition summary document. Ann Oncol. 2010 Mar;21(3):448-58.
5. Fox KV, Shah CA, Swisher EM, et al. An evaluation of cervical cancer in women age sixty and over. Gynecol Oncol. 2008 Apr;109(1):53-8.
6. Dilley S, Huh W, Blechter B, Rositch AF. It's time to re-evaluate cervical Cancer screening after age 65. Gynecol Oncol. 2021 Jul;162(1):200-02.
7. Darlin L, Borgfeldt C, Widén E, Kannisto P. Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. Anticancer Res. 2014 Sep;34(9):5147-51.
8. Rustagi AS, Kamineni A, Weinmann S, Reed SD, Newcomb P, Weiss NS. Cervical screening and cervical cancer death among older women: a population-based, case-control study. Am J Epidemiol. 2014 May 1;179(9):1107-14.
9. Vicus D, Sutradhar R, Lu Y, Elit L, Kupets R, Paszat L. Investigators of the Ontario Cancer Screening Research Network. The association between cervical cancer screening and mortality from cervical cancer: a population based case-control study. Gynecol Oncol. 2014 May;133(2):167-71.
10. Castanon A, Green LI, Sasieni P. Impact of screening between the ages of 60 and 64 on cumulative rates of cervical cancer to age 84y by screening history at ages 50 to 59: A population-based case-control study. Prev Med. 2021 Aug;149:106625.
11. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020 Sep;70(5):321-46.
12. Rebolj M, van Ballegooijen M, Lynge E, et al. Incidence of cervical cancer after several negative smear results by age 50: prospective observational study. BMJ. 2009 Apr 24;338:b1354.
13. Zhang W, Gao K, Fowkes FJI, et al. Associated factors and global adherence of cervical cancer screening in 2019: a systematic analysis and modelling study. Global Health. 2022 Dec 9;18(1):101.

14. Gustafson LW, Petersen LK, Bor P, Andersen B, Hammer A. Cervical cancer prevention among older women - challenges in screening, diagnostic workup and treatment. Acta Obstet Gynecol Scand. 2021 Aug;100(8):1364-8.
15. Huiyun J, Yuebo Y, Xiaomao L. Prevalence of human papillomavirus and cervical lesions among elderly women: an unignored challenge to cervical cancer prevention. Ann Med. 2024 Dec;56(1):2404548.
16. Rodríguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. J Natl Cancer Inst. 2010 Mar 3;102(5):315-24.
17. Paul P, Hammer A, Rositch AF, 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 Apr 23;223(8):1423-32.
18. 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 Jan;11(1):e1001585.
19. Curry SJ, Krist AH, Owens DK, Barry MJ, et al. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018 Aug 21;320(7):674-86.