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The awareness of Cervical Cancer Screening among Appalachian Women: Review Article

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

There is a long tradition of negative experiences with cancer among Appalachian women that manifests as avoidance behaviors in seeking screening and follow up because of fear of a cancer diagnosis. The avoidance is usually seen as 'passive refusal,' but also occurs in an active form as refusal to obtain services even when offered. This problem is compounded by poverty, which influences many parts of life and is associated with lack of transportation, child care, and exclusive

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reliance on public health departments and other safety net health care providers to seek cancer screening. Pap tests have reduced the annual incidence cervical cancers.
The study aims to overview cervical cancer methods and recommendations among women in reproductive age.

Keywords: Cervical cancer; cancer screening; cancer diagnosis.

1. INTRODUCTION

Cervical cancer (CC) is the third most common cancer in women, and the seventh of overall cancers worldwide. It has been estimated that more than 87% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers [1]. From 2009 to 2018, the pace of decline in the death rate decreased to less than 1% per year. In the United States in 2021, it is estimated that 14,480 cases of invasive cervical cancer will be diagnosed and that 4,290 women will die of the disease. These rates have been improving steadily. Incidence rates have stabilized in the most recent decade [2].

There are two major histologic types of cervical cancer, squamous cell carcinoma (about 75%) which mostly starts at the transformation zone of the ectocervix and adenocarcinoma (about 25%) which arises in the glandular columnar layer of the endocervix. The human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7% of cervical cancers. It is mostly caused by chronic infection with high-risk strains of HPV. The HPV subtypes associated with squamous cancer are different from those associated with adenocarcinoma.

Cervical cancer mortality, usually occurring among unscreened women, increases with age, with the maximum mortality for White women between the ages of 45 years and 70 years, and for Black women in their 70s [3]. In the case of cervical cancer, for every eligible woman, there is a specific and recommended process of screening and rescreening at specific intervals over a long period of time. However, it is well recognized that low socioeconomic status, specific ethnicity, rural location, and various fears and beliefs about cancer and health services dissuade women from seeking regular preventive services including Pap smears [4].

Cervical screening targets healthy populations to identify individuals with early changes to their cervical cells. It is now known that infection with the Human Papilloma Virus (HPV) is the cause for malignant change for almost all cases of cervical cancer. Subsequent monitoring and treatment prevent 8 out of 10 cervical cancers from developing. Without treatment, cells can potentially develop into cancer [4].

Preventive health care delivered by primary care providers is most effective when a combination of understanding and motivation from the patient, easy access to care, clinical skill, good communication by the provider, and financial resources to cover the costs of screening are all present. The patient must understand the reason for regular screening, identify with a source of care, receive and understand timely results, and be aware of treatment choices [5].

Substantial reduction in cervical cancer will only be realized if sustainable cervical cancer screening programs are implemented on a global scale to assure early detection and treatment of precancerous lesions. Effective programs must meet three targets: at least 70% of the targeted population should be screened at least once in a lifetime; screening assays and diagnostic tests must be reproducible and sufficiently sensitive; and specificity for the detection of high-grade precursor lesions and effective treatment must be provided [6].

2. TARGET POPULATION FOR SCREENING

Cervical cancer is more common among groups of women who are less likely to have access to screening for cervical cancer. Those populations are more likely to include Black women, Hispanic women, American Indian women, and women from low-income households [7].

ASCO recommends that all women receive at least 1 HPV test to screen for cervical cancer in their lifetime. The American Cancer Society recommends that women ages 25 to 65 should receive an HPV test once every 5 years. Women 65 and older or women who have had a hysterectomy may stop screening if their HPV test results have been mostly negative over the previous 15 years. Sometimes, women who are

65 and older and who have tested positive for HPV may continue screening until they are 70 [3,8].

Immunosuppression is another risk factor for cervical cancer; for example, coinfection with human immunodeficiency virus may lead to long-term persistence of viral infection (i.e., failure to clear). Once HPV infection occurs, several additional risk factors are associated with a higher risk of the eventual development of cervical cancer. These include high parity, long-term use of oral contraceptives, and active and passive cigarette smoking. The risk increases with longer duration and intensity of smoking. Diethylstilbestrol (DES) exposure *in utero* is also associated with an increased risk of developing cervical dysplasia [9].

In women between 21- 29 years, who have had two or more consecutive negative cytology results, data are not adequate to assert larger interval time between screening (>3 years). The HPV test should be used in these ages only after Pap test abnormal findings. Women between 30-65 years should be screened with both Pap test and HPV test (co-testing) every 5 years. This type of screening is preferable, but the continuing of Pap test screening every 3 years is also acceptable. Data is inadequate to support longer interval time between tests in this age group after a number of negative tests [9].

Infection of the uterine cervix with the high-risk types of HPV is necessary for the development of cervical cancer, although the HPV infection alone is usually not sufficient to cause cancer. The presence of additional co- factors is required. Most high-risk HPV infections clear spontaneously but in a small proportion of women the infection persists. It is these women who are at risk of developing high- grade cervical intraepithelial neoplasia (CIN) grades 2 or 3 and adenocarcinoma in situ, which are cancer precursors. CIN 2 and 3 can be effectively treated by excision or ablation of the lesion. Over a period of 30 years, untreated CIN 3 has a risk of progressing to invasive disease in approximately 25% to 30% of cases [10].

In high-income countries, the incidence of and mortality from cervical cancer appears to be falling, particularly in countries with systematic screening programmers. Despite this trend, cervical cancer remains the second most common cancer in women in high- income countries under 45 years of age [11].

Historically, visual inspection of the cervix without magnification was the first method of screening of the cervix. Currently, three different types of tests are promoted:

- Conventional Pap smear (or cytology) and liquid-based cytology
- Visual inspection with Acetic Acid (VIA) or with lugol iodine (VILI)
- HPV testing for high risk HPV types (e.g., types 16 and 18).

3. CYTOLOGY SCREENING

Screening for cancerous or precancerous changes of the cervix has traditionally been performed by scraping cells from the cervix and fixing them to a glass slide in a method developed by Papanicolaou called the Pap smear. The Pap smear is a cytologic screening test used to detect CIN and early cervical cancer so that these conditions can be managed or treated to prevent disease progression due to invasive cancer. Cervical cytology results are not diagnostic of CIN or cancer, as biopsy and histologic confirmation are required for diagnosis. While the incidence of SCC of the cervix has declined significantly since the introduction of the Pap smear, the incidence of adenocarcinoma has risen, leaving the optimal method of screening to detect adenocarcinoma of the cervix uncertain [12].

This technique has led to effective reduction in the incidence and mortality from CC in many developed countries. CC screening is one of the most successful disease-prevention programs. However, this approach has failed to attain the same results in developing areas. A cytology-based screening program requires repeat testing and visits to identify women who need treatment. Besides a cytopathologist, a colposcopy specialist and a pathologist should also be involved. To guarantee the success of a screening program, training and continuing education are essential [13].

The overall sensitivity of the Pap test in detecting a high-grade squamous intraepithelial lesion (HSIL) is 70.80%. A Pap screening done in association with an HPV DNA test increases the sensitivity for early detection of precancerous lesions [14].

4. HPV Testing For Primary Screening*

HPV is the major risk factor for the development of cervical cancer and can be directly detected with diagnostic tests that detect the presence of the virus. HPV tests can be used alone, administered at the same time as cytology testing (co-testing), or sequentially with one or more triage tests [15].

Approximately 40 HPV genotypes are known to be involved in genital HPV infections, 13 of which have been designated as high-risk HPV types due to their strong oncogenic potential. The strong causal link between HPV infection and cervical cancer provided the impetus for evaluating the use of HPV testing in screening for squamous intraepithelial lesions and invasive cancer. Genetic HPV tests detect the presence of HPV DNA or RNA in a sample of cervical cells, with a positive result indicating an HPV infection [16].

Current HPV tests are able to detect the presence of viral markers by signal amplification techniques, such as the Digene Hybrid Capture® II assay or by amplification of nucleic acid with polymerase chain reaction. When combined with Pap smears, HPV tests can achieve nearly 100% sensitivity and a specificity of 93% in women aged 30 years and older, with a negative predictive value of almost 100% [17]. Several studies support that HPV testing is feasible in low-resource settings and appears to be the best strategy for CC in this context [18]. Until recently, the greatest limitations of HPV testing were the need for expensive laboratory infrastructure and the 4-7 h time to process the test. The development of rapid molecular methods for detecting HPV DNA (e.g., care HPV® - Qiagen, GeneXpert® - Cepheid) for screening or other POC type of tests is a milestone in CC screening in low-resource settings [19].

5. VISUAL INSPECTION TESTS

Visual inspection of the cervix has reemerged as a screening tool for low-resource settings, despite its limited specificity, since it is economical and provides immediate results. Visual inspection is indicated for patients for whom cervical cancer screening is recommended and for whom these methods are the best screening option (ie, patients who do not have access to cervical cytology and human papillomavirus [HPV] testing). Visual inspection can be performed with acetic acid (VIA) or Lugol's iodine (VILI) [11].

The visible changes that occur in the cervix after application of acetic acid are immediate, and can be categorized as negative or positive for cervical neoplasia. These immediate results facilitate a same-day screen and management strategy. Therefore, this allows most of the eligible women to participate in the program by minimizing repeat visits. Evidence shows that this single-visit approach leads to the most significant decrease in high-grade cervical intraepithelial neoplasia (CIN) and it is regarded safe, acceptable and fairly effective [20,21].

VIA and VILI also have some drawbacks that need to be addressed. Interpretation of a visual test of the cervix has limited value in older women because of degenerating cervical epithelium and partial or lack of visibility of the transition zone with ageing. Indeed, studies have shown that VIA sensitivity declines substantially in women aged 40 years or older. VIA-based screening is also healthcare provider dependent and lacks reliable quality assurance control. As a consequence, and to maintain high quality, implementation of VIA screening at primary and secondary facilities would require close supervision, which is difficult to attain at a national level [22].

6. ROLE OF PRIMARY CARE

Among the most common are health service access barriers, culturally related fear and fatalism, a lack of confidence in cancer screening, and limited awareness of variation in successful treatment. For many Appalachians, cancer is believed to be one disease that is universally fatal and therefore early detection through screening provides little if any added value to the life of the patient or their family. These beliefs added to access barriers are clearly associated with low rates of screening and low rates of obtaining recommended diagnostic procedures [23].

Numerous epidemiological studies have consistently documented that in countries where the resources exist to ensure high-quality and good coverage of the population, cytology screening contributes to decreasing the incidence of advanced-stage cancers and mortality associated with cervical cancer [24].

A cross-sectional study of 934 asymptomatic women in primary health care in Sudan determined the feasibility of visual inspection as alternative to the Pap smear showed that VIA has higher sensitivity and lower specificity compared to Pap smear, but a combination of both tests has greater sensitivity and specificity than each test independently. It indicates that VIA is useful for screening of cervical cancer in the primary health care setting in Sudan, but positive results need to be confirmed by colposcopy and biopsy [25].

A study in USA in primary care settings estimated that primary hrHPV screening may represent a reasonable balance of harms and benefits when performed every 5 years. Switching from cytology to hrHPV testing at age 30 years yielded the most efficient harm to benefit ratio when using colposcopy as a proxy for harms [26].

A Randomized controlled study in India to investigate the efficacy of visual inspection with acetic acid (VIA) performed by primary health workers in reducing cervical cancer mortality reported that VIA screening by primary health workers statistically significantly reduced cervical cancer mortality. Our study demonstrates the efficacy of an easily implementable strategy that could prevent 22000 cervical cancer deaths in India and 72600 deaths in resource-poor countries annually [27].
A cross-sectional study of 300 women attending primary health care centres in Bahrain to explore the knowledge, attitudes, and practices of women for cervical cancer screening demonstrated a wide range of knowledge and attitudes towards cervical cancer screening. However, the majority demonstrated positive attitudes towards the HPV vaccine [28].

In Oman; a cross-sectional study assessed knowledge, attitudes, and practices regarding cervical cancer, cervical cancer screening, and Papanicolaou (Pap) smear testing among Omani women attending primary healthcare centers reported that knowledge regarding cervical cancer and Pap smear testing was suboptimal among a cohort of Omani women attending primary healthcare centers in Oman. This may be a factor behind the increased number of cervical cancer cases in Oman; as such, a well-structured awareness and educational program is needed to address this issue [29].

Cross-sectional interview-based study in Qatar in primary healthcare centers reported good level of knowledge as over 85% had heard of cervical cancer and 76% had heard about the Pap smear. Knowledge of cervical cancer was significantly greater among women aged 30-49 years, and those employed, married for > 15 years, with a university degree, or who had had 4 births or 3 miscarriages. Almost 40% had had a Pap smear test at least once and 85.5% of the rest would have a test if they were told that the procedure was painless and simple [30].

Another study in Sudan investigated the knowledge, attitudes and practices (KAP) of Sudanese women with regard to the Pap smear test and cervical cancer and found that less than half of participants had accurate knowledge about cervical cancer, HPV, and cervical cancer screening [31].

A screening test followed in the same visit by treatment of positive results is referred to as a ‘screen and treat’ or ‘see and treat’ protocol. This approach is only possible with screening tests that produce immediate results (e.g., visual inspection, rapid-result HPV testing). The treatment methods mostly used are cryotherapy, loop electrosurgical excision procedure or cold-knife conization [24].

There are also ‘Two-visit protocols’ which typically include a first visit with cervical cytology followed by a second visit with colposcopy and treatment based on the colposcope examination. Two-visit protocols should not be used in populations where patients cannot afford (e.g., for economic or logistic reasons) more than one visit to outpatient clinics [24].

7. RECOMMENDATIONS FOR SCREEN-ING

Cervical cancer screening has successfully decreased cervical cancer incidence and mortality. The ACS Guideline for the Early Detection of Cervical Cancer was last reviewed and updated in 2002; for the first time, those recommendations incorporated human papillomavirus (HPV) DNA testing. [32].

Since that time, numerous studies have been published that support changes to recommended age-appropriate screening as well as the management of abnormal screening results, as summarized in [33] Table 1.

Cervical cancer screening should begin at age 21 years. Women under the age of 21 should not be screened regardless of the age of sexual initiation or other risk factors. Cervical cancer is rare in adolescents and young women [34] and may not be prevented by cytology screening. [35]. The incidence of cervical cancer in this age group has not changed with increased screening. [34]. Screening adolescents leads to unnecessary evaluation and potentially to treatment of pre-invasive cervical lesions that have a high probability of regressing spontaneously. This overtreatment, and subsequent increased risk of reproductive problems, represents a net harm. [36]. Over time, growing evidence and the improved understanding of the natural history of cervical cancer have led to growing recognition that earlier recommendations for annual screening were excessive and led to an increased rate of harms. For women 21-29 years of age, screening with cytology alone every 3 years is recommended. For women 21-29 years of age with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e. >3 years). HPV testing should not be used to screen women in this age group, either as a stand-alone test or as a cotest with cytology. Women ages 30-65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable). There is insufficient evidence to change screening intervals in this age group following a history of negative screens.

Table 1. Summary of Recommendations

Population	Recommended Screening Method**	Management of Screen Results
< 21 Years	**No Screening**	
21-29 Years	Cytology alone every 3 years	HPV-Positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP Guidelines[2]
		Cytology Negative or HPV-Negative ASC-US*: Rescreen with cytology in 3 years
30-65 Years	HPV and Cytology "Cotesting" every 5 years **(Preferred)**	HPV-Positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP Guidelines[2]
		HPV Positive, Cytology Negative: Option 1 -- 12-month follow-up with cotesting Option 2 -- Test for HPV16 or HPV16/18 Genotyping if HPV16 or HPV16/18 positive: refer to colposcopy if HPV16 or HPV16/18 negative: 12-month follow-up with cotesting
		Cotest Negative or HPV-Negative ASC-US: Rescreen with cotesting in 5 years
	Cytology alone every 3 years (Acceptable)	HPV-Positive ASC-US* or cytology of LSIL or more severe: Refer to ASCCP Guidelines [2]
		Cytology Negative or HPV-Negative ASC-US*: Rescreen with cytology in 3 years
>65 Years	**No Screening** following adequate negative prior screening	

8. CONCLUSION

Health education about cervical cancer, HPV and sexually transmitted infections and the role of cervical cancer screening tests in prevention are crucial when designing interventions aimed at improving cervical cancer screening for women.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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