

The Trend of Abnormal Cervical Cytology Among Iranian Women During Recent Years from 2013 to 2016

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ABSTRACT

Background & Objective: Cervical cancer is one of the common cancers in developing countries, which has a high rate of mortality. This study aimed to evaluate the prevalence of abnormal cervical cytology among Iranian women.

Materials & Methods: In this cross-sectional study, cervical cytological results of 137,484 Iranian women, who were screened for cervical cancer in Tehran and 12 other provinces of Iran from 2013 to 2016, were investigated. The Pap smear was prepared by a liquid-based method and evaluated by a pathologist.

Results: The overall prevalence of abnormal cervical cytology in the studied population was 3%. The mean age of the population was 35.77 ± 9.6 . In this study, the prevalence of abnormal cytology in 2013, 2014, 2015, and 2016 was 2.10%, 2.68%, 3.47%, and 3.60%, respectively. The rate of the abnormal Pap smear has increased over the years, and this trend has been statistically significant ($P < 0.001$). In this population, atypical squamous cells of undetermined significance (ASCUS) cytology was the most common abnormal Pap smear (1.96%).

Conclusion: In this study, the prevalence of abnormal cervical cytology has been significantly increased in Iran in recent years. This increase requires careful monitoring of general education programs, strict cervical cancer screening, and routine vaccination against HPV infection.

Keywords: Pap smear, HPV vaccination, Cervical cancer screening



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Introduction

As a gynaecologic cancer, cervical cancer is the third common cancer and also the cause of cancer-related death in the United States (1). The prevalence and mortality rate due to the cervical cancer, depends on the availability of screening programs for detection precancerous lesions and vaccination against human papillomavirus (HPV), which are more accessible in developed countries comparing to developing countries. These interventions have led to a reduction of 75% in the prevalence and severity of this cancer in developed countries over the last

50 years (2,3). Unfortunately, in developing countries, cervical cancer, with over 85% of new cases, is one of the leading causes of cancer death, where the access for cervical cancer screening programs and HPV vaccination is limited (4-6). Evaluation of cervical cytology, with the introduction of Papanicolaou smear in 1941, is a standard method for screening cervical cancer and identifying premalignant lesions (7). According to Chaichian *et al.* study, the incidence of cervical cancer has been increasing in Iran during recent years. By some data (from the

National Cancer Registry and Center for Disease Control of the Ministry of Health, as well as Treatment and Medical Education), they showed that registered cancer cases increased approximately three-fold from 394 cases in 2003 to 907 in 2009. Their research indicated that the incidence rate of cervical cancer increased from 1.64 per 100,000 women in 2003 to 2.61 per 100,000 women in 2009 (8).

HPV plays a major role in developing cervical cancer and precancerous lesions (9-11) and can be detected in 99.7% of cervical cancers (9). Among all behavioral, sexual, and socioeconomic risk factors, the effect of HPV infection, in cervical neoplasia, is more critical than other ones, which are also dependent upon HPV infection (12). Recent studies have shown that the prevalence of HPV infection has increased in Iran in recent years (13). This suggests the possibility of an increase in abnormal cervical cytology and risk of cervical cancer in the coming years. The prevalence of abnormal cytology and premalignant lesions varies in different regions and changes over time. In the study by Afrakhteh, the prevalence of the abnormal Pap smear was 1.18% in Tehran in 2007 (14).

This study aimed to evaluate the prevalence of abnormal cervical cytology based on the 2001 Bethesda System and its changing trends in Iran in recent years.

Materials and Methods

Study Population

In this cross-sectional study, the results of Pap smears, from all subjects of NILOU Medical Laboratory, were reviewed from 2013 to 2016. Pap smear samples were taken by gynaecologists in public and private clinics in Tehran and 12 other cities (provinces) and then sent to the NILOU Laboratory (i.e., one of the most accredited laboratories in Iran). The information of the subjects was recorded by trained laboratory personnel.

Cytology Analysis

Slurries were stained based on liquid-based (using E-Prep, South Korea) and Thin Prep (using the Hologic

system, USA) methods via Papanicolaou staining, and checked out by verified cytoscreeners. It should be noted that 10% of normal slides (randomly) and all abnormal slides were reviewed by two pathologists and then the final results were reported. The results are classified according to the 2001 Bethesda System, which included negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells-cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), and squamous cell carcinoma (SCC).

Statistical Analysis

The quantitative data were reported by using mean and standard deviation, and the qualitative data were reported by using frequency and percentage. The estimated prevalence was reported by using a 95% confidence interval. Chi-square tests of trend were used for the data analysis. Statistical analyses were performed in R statistical software (version 3.1), and P-value<0.05 was considered statistically significant.

Results

In this study, the results of the Pap smears of 137,484 Iranian women aged between 17 and 82 years were studied. According to the Bethesda System, 99.6% of Pap smears were satisfactory for evaluation in the studied population. The mean age of the screened women was 35.77±9.6 years. The prevalence of abnormal cervical cytology in this study population was 3% (4,115 out of 137,025) according to the Bethesda System classification. The abnormal cytology of ASCUS is the most common type (64.8%) of the abnormal Pap smear. The prevalence of abnormal cytology is presented in [Table 1](#).

In this study, the largest screened age group was 30-39 years. The highest prevalence of abnormal cytology (4.12%) was significantly related to the age group of less than 25 years ($P<0.001$). The mean age of women with HSIL is 32.78±8.03 years. The prevalence of abnormal cytology, in relation to age, is presented in [Table 2](#).

Table 1. Prevalence of abnormalities

Abnormal Pap smear	Number (Percent of Total)	Prevalence (95%CI)
ASC-US	2667 (64.80%)	1.95% (1.87% - 2.02%)
ASC-H	637 (15.50%)	0.46% (0.43% - 0.50%)
LSIL	739 (18.00%)	0.54% (0.50% - 0.58%)
HSIL	60 (1.46%)	0.04% (0.03% - 0.06%)
AGC	12 (0.24%)	0.01% (0.01% - 0.04%)
TOTAL	4115	3% (2.91% - 3.10%)

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.

Table 2. The rate of abnormal Pap smear according to the age of the individual

Age category	Total number of participants	Number of abnormal Pap smear	Prevalence of abnormal Pap smear (95% CI)	P-value
<25 y	13,215	544	4.12% (3.79%-4.47%)	< 0.001
25-29 y	26,081	973	3.73% (3.51%-3.97%)	
>30 y	97,729	2598	2.66% (2.56%-2.76%)	
TOTAL	137,025	4115		

In this study, the prevalence of abnormal Pap smears increased from 2.10% (95% CI 1.94%-2.27%) in 2013 to 3.6% (95% CI 3.41%-3.79%) in 2016, and this difference is statistically significant ($P=0.001$). The prevalence of low-risk abnormal cytology increased from 1.76% in 2013 to 2.95% in 2016 with a statistically significant increasing trend during this period ($P<0.001$). Also, the prevalence

of high-risk abnormal cytology increased from 0.34% in 2013 to 0.65% in 2016 ($P<0.001$ for trend). The trend of the prevalence of abnormal cytology is presented in [Table 3](#).

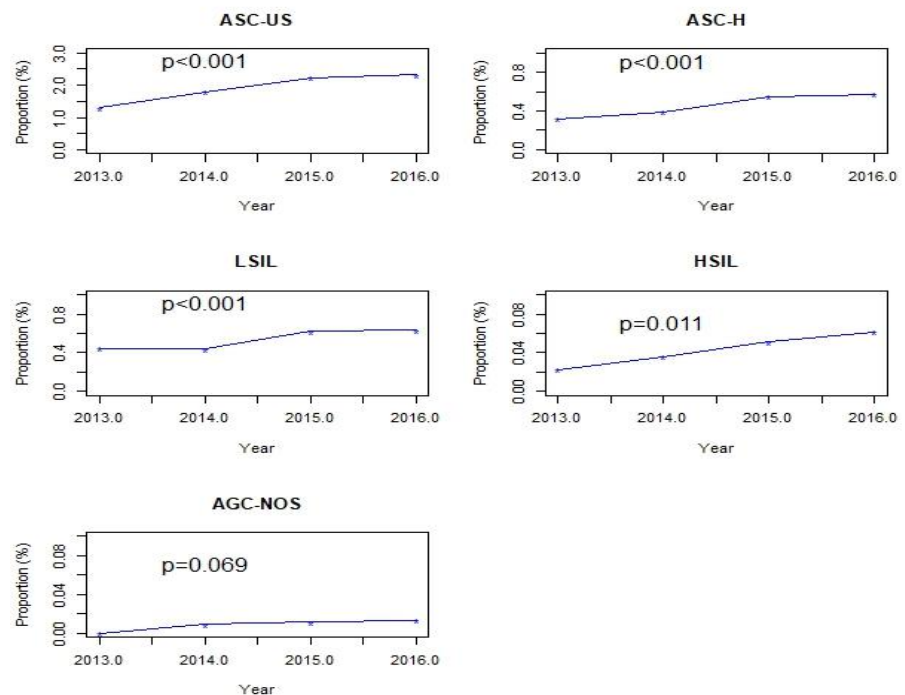
The incremental trend was observed from 2013 to 2016 in all kinds of abnormal cytology, except AGC. Data are represented in [Figure 1](#).

Table 3. Assessment of the prevalence of abnormal cytology during 2013-2016

Abnormality	Year				P-value*
	2013	2014	2015	2016	
Abnormal cytology	2.10% (1.94%-2.27%)	2.68% (2.51%-2.86%)	3.47% (3.28%-3.67%)	3.60% (3.41-3.79)	0.001
Low-risk Abnormal cytology	1.76% (1.61%-1.91%)	2.24% (2.09%-2.41%)	2.86% (2.69%-3.04%)	2.95% (2.78%-3.13%)	<0.001
High-risk Abnormal cytology	0.34% (0.28%-0.42%)	0.43% (0.37%-0.51%)	0.61% (0.53%-0.70%)	0.65% (0.57%-0.73%)	<0.001

Data are represented as a prevalence (95% CI). *P-value for trend. Low-risk Abnormal cytology: ASCUS and LSIL; High-risk Abnormal cytology: HSIL, ASC-H, and AGC.

Figure 1. The trend of a different kind of abnormal cytology during 2013-2016 (p-value in each box is related to the trend test). 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.



Discussion

Cervical cancer is considered as a preventable malignancy due to appropriate screening programs, HPV vaccination, its lengthy pervasive conditions, and effective treatments for a precancerous disease (15-17). The common types of cervical cancer start with precancerous changes, which can be detected in screening cervical cytology and led to early treatment (15).

Surprisingly, the prevalence of abnormal cervical cytology is different in other countries at different times. Based on the published studies, the rate of abnormal Pap smear showed a wide range of percentages from as low as 0.98% in Israeli Jewish women (18) to as high as 15.5% in a rural population of Zimbabwe (19).

In this study, the overall prevalence of abnormal Pap smears in the study population was 3% from 2012 to 2016, which was higher than previous studies in Iran (14,20-21). ASCUS was the most common type (1.95%) of abnormal cytology in the study population. In a similar study by Afrakhteh *et al.* (2007), the prevalence of the abnormal Pap smear was 1.18% in Tehran (14). ASCUS was the most common abnormal cervical pathology in their study too, and the prevalence of cervical cancer was 0.2% (14). In another study by Almassi Nokiani (2008), the prevalence of the abnormal Pap smear was only 0.3%. In their study, no cases of HSIL and cervical cancer were reported under the age of 35 years (20). Masoumi *et al.* (2016) reported that the prevalence of the abnormal Pap smear was 1.67% in Hamadan, Iran. The most-reported abnormal cytology was ASCUS, and the lowest was LSIL. (21). The percentage of the abnormal Pap smear in Iran is comparable to other countries in the middle-east region. The rate of abnormal cytology is reported to be 3.8% in Jordan (22), 4.3% in Kuwait (23), 4.89% in UAE (24), and 4.7% to 7.9% in different regions of Saudi Arabia (24,25). It is also comparable to some European countries, such as Turkey (2.8%) (26), Italy (2.4%) (27), and Belgium (3.7%) (28). However, the rate of cervical cytology abnormalities in Iran is lower than many countries around the world, such as Russia (9.8%) (29), Egypt (7.8%) (30), Romania (5.9%) (31) and India (6.3%) (32).

Although the total prevalence of the abnormal Pap smear is still low in Iran, in this study, we encountered a significant increase in both low-grade and high-grade cytological abnormalities from 2013 to 2016. The prevalence of cytological abnormalities in 2013, 2014, 2015, and 2016 was 2.10%, 2.68%, 3.47%, and 3.60%, respectively ($P < 0.001$), which is alarming. No consistent pattern emerges in other countries. For example, in UAE, 60% increase of cervical cytological abnormalities was

reported by Muna Al Zaabi *et al.* over the last 10 years (33). On the other hand, in the study by Massad LS *et al.* the prevalence of abnormal pap-smear have decreased in US women with HIV infection over the past two decades (34). Our finding suggest that the trend of abnormal cervical cytology was increasing during the period of 2013-2016 in Iran.

Over the past years, the prevalence of high-risk HPV infection has been increasing in Iran, which rose from 5% in 2012 to 10.3% in 2018 (13,35). This increase in the prevalence of high-risk HPV infection could lead to an increase of abnormal cervical cytology in future. Momenimovahed (2018) stated that despite the low incidence of cervical cancer in Iran, the risk factors associated with this cancer are not few, which may result in a higher incidence of cervical cancer in the future. Their findings demonstrated that some factors, such as marital status, marriage age and age of first pregnancy, smoking, consumption of oral contraceptive pills, multiple sexual partners, family history, and multiparty are associated with cervical cancer (36).

It was noticed that in the majority of studies, including ours, ASCUS had the highest prevalence among all cytological abnormalities (14,21,23,25-29,31, 33). In the present study, the mean age of the screened women was 35.77 ± 9.6 years, and the largest screened age group was 30-39 years.

In this study, the prevalence of cervical cytological abnormalities in women, younger than 25 years old, was significantly higher than those of older ages ($P < 0.001$). However, major lesions were low-grade lesions, such as ASCUS and LSIL in this age group, and the mean age of severe dysplasia and HSIL was 32.78 years. The higher rate of the low-grade lesion, among young women in this research, is comparable to the other studies and is due to the higher prevalence of HPV infection in this age group. However, it is not worrisome. Based on several researches, many of the cytological abnormalities, even high-grade lesions, regress spontaneously in this age group after disappearing HPV infection (37-39). These findings emphasize that there is a strong need for vaccination and regular screening of young women.

As mentioned earlier, the increase in the prevalence of high-risk HPV infection had many causes, which consequently has led to an increase of cervical cytological abnormalities and cervical cancer in Iran in recent years. Most of the Iranian population is young, and we have observed a change in the sexual behavior of adolescents in recent years, which emphasizes a need for training for this age group. Hookah smoking is a traditional type of smoking in Iran, which has become popular among

teenagers in recent years. Meanwhile, most people are unaware of the disadvantages of using this type of tobacco. According to the researches, Tobacco smoking is considered a potential risk factor for cervical cancer and also is associated with an increased risk of HPV infection and genital wart (40-41). Water pipe use is associated with higher CO₂, equal amount of nicotine and dramatically, more smoke exposure compared to cigarette smoking. Water pipe tobacco smoking exposes the people to some serious toxicants as cigarette smoking and associated with similar health risks (42).

On the other hand, vaccination against HPV virus in Iran is not routine, and insurance companies do not cover vaccination costs and especially HPV testing costs during cervical cancer screening programs. As it was found in the study of Staples *et al.*, educational interventions, focusing on the importance of HPV vaccination for parents with young children, have a positive effect on public health. This study also emphasizes that early prevention and diagnosis have a vital role in the reduction of inequalities in cervix cancer (43).

Limitation: Given the retrospective nature of the study, demographic data of patients were not complete, and studying the risk factors of abnormal cytology was not possible.

Conclusion

This study shows that in recent years the prevalence of the abnormal Pap smear has had an increasing trend in Iran, which may be alarming and need to assess the etiology. These findings emphasize that there is a strong need to routinize vaccination against HPV infection, cover HPV testing cost, properly implement the cervical cancer screening, and increase training in the society.

Ethics Approval and Consent to Participate

The study was approved by the Preventative Gynecology Research Center (PGRC), Shahid Beheshti University of Medical Sciences ethics committees. All study participants were informed about the study and signed the written consent form.

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Conflict of Interest

Authors declared no conflict of interests.

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