

RESEARCH ARTICLE

Population-Based Cervical Screening Outcomes in Turkey over a Period of Approximately Nine and a Half Years with Emphasis on Results for Women Aged 30-34

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Abstract

Purpose: To appraise the frequency of cervical cytological abnormalities in a population at normal risk via analysing the archive records of cytology for the period of approximately 9,5 years, comparing them with patient demographic characteristics, and discuss the results for women under age of 35. **Materials and Methods:** A total of 32,578 cases of Pap smears were retrieved and analysed from our archive included the Pap tests performed between January 2001 and April 2010 at the Early Cancer Screening, Diagnosing and Education Center by the consent of three pathologists via utilizing the Bethesda System Criteria 2001 and the results were compared with some demographical characteristics. **Results:** Our rate of the cervical cytological abnormality was 1.83%, with ASCUS in 1.18%, LSIL in 0.39, HSIL in 0.16%, AGUS in 0.07%, squamous cell carcinoma in 0.02%, and adenoarcinoma in 0.006%. Cytological abnormalities were detected mostly in those with higher age, lower parity, and premenopausal period whereas the smoking status was without influence. Bacterial vaginosis (5.6%) was the most frequent infectious finding (*Candida albicans* 2.7%; *Actinomyces* sp. 1.3%; and *Trichomonas vaginalis* 0.2%) detected on the smears. The rate of abnormal cervical cytology was 9.5% among the women aged between 30-34. **Conclusions:** Early detection of the cervical abnormalities by means of the regular cervical cancer screening programmes is useful to attenuate the incidence, mortality, and morbidity of cervical cancer. Our prevalence of the cytological abnormalities was much lower than the one in Western populations in general but very similar to those reported from other Islamic countries that may be explained by the conservative lifestyle and the lower prevalence of HPV in Turkey. A remarkable rate of abnormal cervical cytology of women aged 30-34 was pointed out in the present study.

Keywords: Papanicolaou smear - cancer screening - HPV - cervical cancer - liquid based cytology - prevention

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Introduction

Cervical cancer is one of the foremost public health. It is evidently known that Papanicolaou (Pap) smear-based cytology population screening programmes significantly attenuates both the incidence of and mortality from cervical cancer particularly in high-income countries. A survey of National Cancer Institute (NCI), had been performed between 1973-1995 revealed 43% reduction of the incidence of and 46% reduction of mortality from cervical cancer. However, aforementioned cancer still have been remaining a substantial challenge in low-income countries due to the shortage of these kind of programs (Quinn et al., 1999; Singh et al., 2003; Parkin et al., 2005; Peto et al., 2005; Waggoner et al., 2010).

World Health Organization (WHO) and The Turkish Ministry of Health propounded that a Pap test which would be performed for the women 35-40 years-old may

reduce the risk of invasive cancer (Tuncer, 2008). One emphasis is on improving attendance (Arabaci and Ozsoy, 2012; Karabulutlu, 2013). The goals of the present study were to evaluate the prevalence of the cervical cytological abnormalities in 32 578 women in Giresun, Turkey and to discuss the abnormal results of the women under 35 year-old on the basis of the revised standarts.

Materials and Methods

Participants

One of The Early Cancer Screening, Diagnosing and Education Center of The Turkish Ministry of Health has been active at Giresun Prof. Dr. A. İlhan Ozdemir State Hospital since March 1999. A total of 32,578 cases of Pap smears were retrieved and analysed from the Archive of The Department of Pathology which had been provided by the Pap tests, performed between January 2001 and April

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The sample collection and cytological assesment

All the samples had been obtained by rotating the device through 360° after the cervical area visualized. Then, all the materials had been spread on the appropriately labeled slides. Afterwards, they had been immediately sprayed with a fixative and all the slides had been evaluated at the Department of Pathology. The cytological abnormalities had been confirmed by the consent of three pathologist for each one. All performed via using the Bethesda System Criteria 2001. The reactive cytological changings, infectious findings and repeated Pap smears after the diagnosis of ASCUS/AGUS had not been included in the data of the present study.

The data collection

The data had been collected from The Archive of Department of Pathology via screening the period of 9.5 years. They had been obtained by examining the pathology/cytology reports and the request papers, made out by the Gynecology and Obstetrics Clinics, including the hospital records. The data of the demographical characteristics such as age, parity, usage of oral contraceptive, smoking status and smear status during the last 5 years had been attained from the mentioned papers/records.

The statistical analyses

The statistical evaluation was performed with software SPSS for Windows, version 21.0 (SPSS IBM, New York, USA) utilizing descriptive statistical methods. As the descriptive statistical behaviour of the data, the values of the mean, standard deviation, ratio, and frequency were assigned. The distribution of the variables were controlled exerting Kolmogrov-Smirnov test (K-S test). While Independent samples t-test had been using for the analyses of the qualitative data, χ^2 test had been using for the analyses of the quantitative data. The following results of the present study will be interpreted using $p < 0.05$ as the criterion for the statistical significance.

Results

A total of 32,578 women with the cervical cytology had been studied carefully utilizing the Pathology/Cytology reports and the request papers including the hospital records., made out by the Gynecology and Obstetrics Clinics that we derived them from The

Archive of Department of Pathology. The mean \pm SD of the participants in terms of the age was 42.4 \pm 13.2 (range, 18-84); the parity in women with normal cytology was 2.8 \pm 1.9 (0-6 range) and in women with abnormal cytology was 1.6 \pm 1.5 (range 0-6); and being a regular smoker (consuming more than 5 cigarettes per day) was 9.6% in women with normal cytology and 9.7% in women with abnormal cytology. While 10,095 women (31%) were postmenopozal, 22,483 (69%) were reproductive. Just 424 women (1.3%) had a report for the cervical cytology of the smear during the last 5 years and 5,819 (17.9%) had been using the oral contraceptive.

There were 1 401 (4.3%) unsatisfactory smears and 1,093 (78%) of them were belonging to the ones coming from the external centers that had been appealed to us during the period of 9 years and 4 months. Overall, our prevalence of the cytological abnormality was 1.83% (598), with ASCUS in 1.18% (386), LSIL in 0.39% (127), HSIL in 0.16% (53), AGUS in 0.07% (23), squamous cell carcinoma in 0.02% (7), and adenoarcoma in 0.006% (2). The number of the abnormal cervical cytology were 57 (9.5%) among the women aged between 30-34. (Table 1).

The distribution of the abnormal cervical cytology on the basis of the decades of cases were summarized in Table 2. The mean age \pm SD (41.3 \pm 13.2) of women having the normal cytological findings were significantly lower than the mean age \pm SD (45.3 \pm 12.5) of women having the abnormal cervical cytology ($p < 0.05$). 47.8% of the postmenopausal and 69.2% of the premenopausal women had the abnormal cytology with the statistical significance ($p < 0.05$). While the mean \pm SD parity of the women having the abnormal cervical cytology was 1.6 \pm 1.5, normal cervical cytology was 2.8 \pm 1.9 with the statistical significance ($p < 0.05$). There was no significant

Table 1. Distribution of the Abnormal Cytology among the Women Aged 30-34 and 18-84 and Their Percentages for the Appointed Group, Aged 30-34

	Aged 30-34	%*	Aged 18-84	%**
ASCUS	42	10.9	386	1.18
L-SIL	8	0.6	127	0.39
H-SIL	3	0.6	53	0.16
AGUS	3	1.3	23	0.07
CA	1	1.1	9	0.026
Total	57	9.5	598	1.83

*The percentages of abnormal cytology in the appointed group (aged 30-34);
**The percentages of abnormal cytology in the appointed group (aged 18-84)

Table 2. Distribution of the Cytological Results According to the Age Range

Age range	Unsatisfactory	Normal	Abnormal	ASCUS	L-SIL	H-SIL	SgCC	AGUS	AdenoCa
18-29	432	3190	94	75	12	5	0	2	0
30-39	301	9707	104	69	20	6	2	7	0
40-49	266	8275	114	72	22	14	2	3	1
50-59	183	9028	230	153	55	17	0	4	1
60-69	94	351	49	17	18	9	1	4	0
70-79	74	20	7	0	0	2	2	3	0
>80	51	8	0	0	0	0	0	0	0
Total (%)	1401 (4.3)	30579 (93.87)	598 (1.83)	386 (1.18)	127 (0.39)	53 (0.16)	7 (0.02)	23 (0.07)	2 (0.006)

*SgCC: Squamous cell carcinoma; AdenoCa: Adenocarcinoma

Table 3. Comparative Results of Women with Normal and Abnormal Cytology According to the Risk Factors

	Normal (n=30579)		Abnormal (n=598)		p
	Mean±SD	%	Mean±SD	%	
Menopausal status					
>50 age	9407	30.8	286	47.8	0.000
<50 age	21172	69.2	312	52.2	
Age	41.3±13.2		45.3±12.5		0.000
Parity	2.8±1.9		1.6±1.5		0.000
Smoking					
Present	2935	9.6	58	9.7	0.982
Absent	27644	90.4	540	90.3	

difference in smoking habit between the women with or without cytological abnormalities (Table 3).

Bacterial vaginosis (5.6%) was detected as the most frequent infectious finding on the Pap smears of the present study followed by *Candida albicans* (2.7%), *Actinomyces* sp. (1.3%), *Trichomonas vaginalis* (0.2%) that they all were constituting approximately 9.8% of the participants.

The histopathological evaluation after the colposcopic biopsy of the women having the abnormal cytology of 95 ASCUS and 15 AGUS for all that the repeated Pap tests were 5 LSIL and 1 adenocarcinoma respectively. The colposcopic histopathology of the women having the cytology of 86 LSIL were 73 LSIL, 2 HSIL, and 11 normal cytology. The same results were 49 HSIL, 3 LSIL, and 1 squamous cell carcinoma for the ones having the cytology of 53 HSIL.

Discussion

The small DNA viruses infecting the epithelia of mucosa and skin, called human papillomaviruses (HPVs) are known as having more than 170 types including 13 high-risk and 7 probably high-risk HPVs. Although there is some substantial differences between the continents, HPV is currently considered the most common sexually transmitted virus worldwide even that may be as high as 80% with a lifetime prevalence. A German virologist, Harald zur Hausen, first demonstrated the relationship between the genital infections and cervical cancer in the early 1980s. Now, it is known that the low-risk HPV types trigger the benign lesions, but the high-risk ones have been established as the etiological agents of cervical cancer (Zur Hausen 1988; Baseman and Koutsky 2005; Li et al., 2011; Tachezy et al., 2013). Specially, the five types of HPV were notified as the most prevalent regardless of the geographical distribution: HPV 16, 18, 52, 31, and 58 (Kahn, 2009; Bruni et al., 2010).

Today, HPV is accepted as an causative agent of cervical cancer and its precursors. So, oncogenic and non-oncogenic HPV viruses may lead to some viral cytopathic effect such as koilocytosis, with cellular enlargement, hyperchromasia, and irregularity of the nuclei which may be an alarming mark of cytological abnormality (Feichter et al., 2002; Castle et al., 2010; Zeferino et al., 2011).

Pap test for cervical cancer screening was introduced to practice in the United States in 1941 and led to the first systematic effort for cancer screening. After widely usage it has been associated with reduction in cervical cancer

incidence and mortality. The Pap smear has become a model for cancer screening. However, the effectiveness of Pap smear screening for cervical cancer has never been demonstrated in a randomized trial. There are observational studies about effectivity of Pap test. In a study, cure rates were higher for women with cervical cancer detected by screening than for women whose cervical cancer was diagnosed by symptoms (difference in cure rates of 26 percent, 95%CI 16-36 percent) (Andrae et al., 2012). Several studies demonstrated that cervical cancer screening by Pap test reduces mortality rates. (Nygard et al., 2002; Abed et al., 2006; Aklimunnessa et al., 2006; Taylor et al., 2006). Currently, there is no organized population-based screening program available for the whole World. Every country tries to evaluate their own screening programme. (Abdul Rashid et al., 2013; Demirtas, 2013). There are two different techniques for cervical cytology: manual liquid based cytology and conventional Pap staining. Manual liquid based cytology can be considered as one of the suitable technique for screening with the above-mentioned benefits. It provides better morphology with increased detection of abnormalities and preservation of specimen for cell block and ancillary studies like immunocytochemistry and HPV detection. (Nandini et al., 2012; Moosa et al., 2014).

Hitherto, different studies have exhibited the major and substantial variations considering the rates of ASCUS, LSIL, HSIL, AGUS, and cervical cancer (Forman 2003; Sanjose et al., 2003; Altaf 2006; Duggan et al., 2006; Turkish Cervical Cancer And Cervical Cytology Research Group, 2009; Castle et al., 2010; Kulig et al., 2010). In the present study, 1.83% of the Pap smears had the abnormal cytology, with ASCUS in 1.18%, LSIL in 0.39, HSIL in 0.16%, AGUS in 0.07%, squamous cell carcinoma in 0.02%, and adenoarcinoma in 0.006%. Turkish Cervical Cancer and Cervical Cytology Group performed an important study with the participation of 33 healthcare centers consisting of 22 university and 11 government hospital clinics and private healthcare centers including 140 334 women for evaluation of the prevalence of cervical cytological abnormalities in Turkey. Their overall prevalence of cytological abnormality was 1.8% and prevalence of ASCUS, LSIL, HSIL, and atypical glandular cells (AGC) was 1.07%, 0.3, 0.17% and 0.08%, respectively. Our prevalence rates were very similar to those reported in the study of Turkish Cervical Cancer and Cervical Cytology Group (Turkish Cervical Cancer And Cervical Cytology Research Group 2009), an extended investigation in Turkey. But, the rates of the present study were much lower than the ones reported for Western populations, in general (de Sanjose et al., 2003; Duggan et al., 2006; Kroupis et al., 2007; Kulig et al., 2010; Marques et al., 2011). However, our results were very similar to those reported from other Islamic countries like Saudi Arabia, Egypt, and Iran (Jamal et al., 2003; el-All et al., 2007; Nokiani et al., 2008) that may be ascribed to low prevalence of HPV (Tuncer et al., 2006; Ozalp et al., 2012), religion, or the conservative cultures, akin to Turkish population. Besides, the mentioned rates detected by cervical screening may also vary with the nature of populations screened. For instance, the rates were reported

as higher than the control groups at a clinic for sexually transmitted disease and among prostitutes/sex workers (Shlay et al., 1998; Nunez et al., 2002; Mak et al., 2004; International Collaboration of Epidemiological Studies of Cervical Cancer, 2007) posing the importance of early detection of cervical cytological abnormalities especially in the populations at high risk.

In the present study, we computed the rates of unsatisfactory smears as 4.3%. However, 78% of whole unsatisfactory smears were accounting for the ones coming from the external centers. So, it may also revealed the importance of the education and the training of midwives and nurses in Early Cancer Screening, Diagnosing and Education Centers. The ASCUS/SIL ratio has been used for evaluating the quality measurement tool in terms of intra- and inter-laboratory comparison. In USA, 1166 cytology laboratories had been analysed by a nationwide survey and 80% of them reported a ASCUS/SIL ratio between the range of 0.64 and 4.23. Finally, the median ratio was calculated as 2.0 in this survey (Davey et al., 2000; 2004). Our ASCUS/SIL ratio was 2.14, similar to the reported in USA, that may point out the quality of our laboratory may be comparable with the mentioned ones.

Smoking is conceded as a risk factor for squamous cancer and squamous intraepithelial lesions (International Collaboration of Epidemiological Studies of Cervical Cancer 2007). Contrarily, there was no significant difference in the rates of cervical cytological abnormalities between smokers and nonsmokers in the present study.

As is customary, the microorganisms, detected on the Pap smear were diagnosed in the present study. According to our results, the most frequent one was bacterial vaginosis (5.6%), followed by *Candida albicans* (2.7%), *Actinomyces* sp. (1.3%), *Trichomonas vaginalis* (0.2%). As a whole, the infectious findings on the Pap smears were constituting approximately 9.8% of the participants. Because of the production of microfloral carcinogenic nitrosamines, bacterial vaginosis has been insinuated in the progression of cervical dysplasia, as well as HPV (Pavic, 1984; Gillet et al., 2012; Jahic et al., 2013).

It is a remarkable point that the rate of abnormal cervical cytology of the women aged between 30 and 34 were constituting 9.5% of the whole abnormal cytologies among the population screened. The Turkish Ministry of Health, The Cancer Control Department declared "The National Standards for the Screening of Cervical Cancer" in 2007 in which cytology alone every 5 years was recommended for the women aged 35-65 (Tuncer 2007). Afterwards, The Cancer Control Department declared "The New National Standards for the Screening of Cervical Cancer" in December 2012 in which HPV test or cytology every 5 years was recommended for the women aged 30-65 (The National Standards for the Screening of Cervical Cancer in 2012a; 2012b). It means for the present study that our rate of abnormal cytology of the women aged between 30-34, constituting 9.5% of the whole abnormal result, would be excluded according to previous standards for the screening of cervical cancer. Besides, Saslow et al. (2012) offered no screening before aged 21; cytology alone every 3 year for aged between

21-29; HPV and cytology "cotesting" every 5 year (preferred), cytology alone every 3 year (acceptable) for aged between 30-65; no screening following adequate negative prior screening after aged 65 as a summary of recommendations of American Cancer Society (ACS); American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) screening guidelines for the prevention and early detection of cervical cancer.

So, our results were encouraging the national and international guidelines those accept the age of 30 as the starting point for the mentioned screenings.

Our limitations were not inquiring about the number of pregnancies and sexual partners, age at marriage, and not performing HPV testing those would have been utilized for the risk stratification from which some data about the mentioned risk factors may have been derived.

Conclusively, the incidence, mortality, and morbidity of cervical cancer have been reduced by means of early detection of the cervical abnormalities particularly in the high-income countries having the regular cervical cancer screening programmes. Cervical cancer screening remains an evolving field with new HPV DNA tests, and development of new technologies. However, Pap smear tests are cheap, easy to perform, and have been embraced as the effective population screening method extensively. In spite of our limitations and the limited number of the cases, the present study supply the data for the period of approximately a decade. Our rates of the cytological abnormalities were much lower than the ones in Western populations in general but very similar to those reported from other Islamic countries. Besides, it is pointed out in this study that the rate of abnormal cervical cytology of the women aged 30-34 could not be underestimated, so our results were supporting the screening guidelines starting from the age of 30. The further multicentered prospective high volumed studies including HPV vaccination and comparing the starting points in terms of age are required.

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