

THE STATE OF CERVICAL CANCER IN TURKEY AND CERVICAL CANCER SCREENING STUDIES

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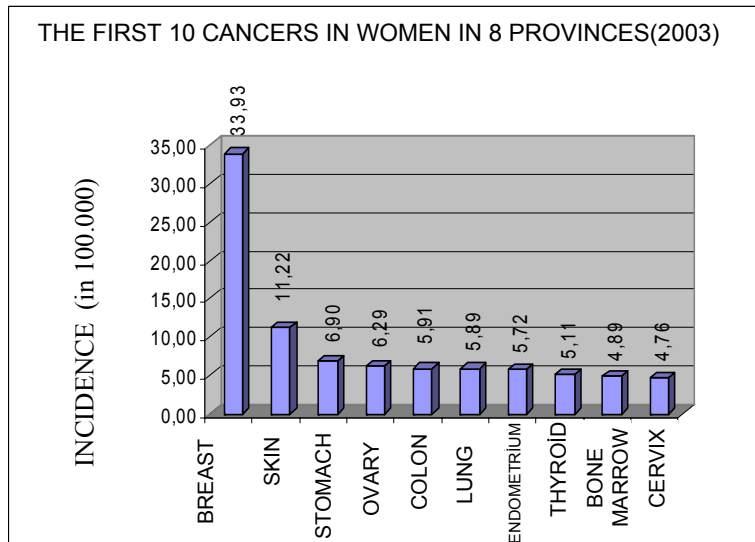
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Cervical cancer is the third most common cancer worldwide after breast and rectum cancers. While it is the second most common cancer in the developing countries, it falls down to the 6th or even 10th rank owing to the successful application of screening programs in the developed countries. While every year about 400,000-500,000 new cases of cervical cancer are detected in the world, of these 190.000 die from this illness and 78% of these deaths are in the developing countries. These figures show the importance of screening programs in decreasing the number of cervical cancer frequency and the mortality rate of this type of cancer (1, 2).

According to the data of the Ministry of Health of the Turkish Republic, while in 1996 623 cervical cancer cases were registered, placing cervical cancer on the 7th rank; in 2002, although the number of cases was found to be 708, it ranked the 10th among all women's cancers. In 2003 data, the number of cervical cancer cases increased to 763 and it ranked the 9th among all women's cancers. According to the GLOBOCAN study made by the International Agency for Research on Cancer in 2002, the cervical cancer incidence rate in Turkey is 4,5 in a hundred thousand, it is estimated to encounter 1364 new cervical cancer cases and 726 death cases associated with cervical cancer in the same year.

In 2003, studies made by the Ministry of Health, Department of Cancer Control in 8 cities, which are thought to represent Turkey, were published. The provinces selected for this study are Ankara, Antalya, Edirne, Erzurum, Eskişehir, İzmir, Samsun and Trabzon which constitute 19.71 % of Turkey's total population, and 36.82 % of all cancer cases are registered in these cities. Thus, this study made in 8 cities is representative of Turkey. The result of this study is that cervical cancer ranks the 10th among all women's cancers and its incidence rate is 4.76 per hundred thousand. (see Graph 1)

Graph 1



These figures suggest that the incidence of cervical cancer in Turkey is well below that of many of the world's developed countries which have national screening programs and which execute these programs successfully.

Since cervix is an easily reachable organ, the cancers in this organ can be diagnosed early thanks to Pap smear and prognosis is ameliorated significantly. The average diagnosing age for patients with cervical cancer is 51. There are two peaks in this disease, the first one is around the ages 35-59 and the second one around 60-64. The risk of cervical cancer for a woman who does not have any Papanicolau (Pap) smear test done throughout her life is 1/100.

In the USA, where the statistical information is most strictly collected, approximately 16.000 new cases of invasive cervical cancer are diagnosed every year and 5.000 deaths from these cases are expected. Thanks largely to the success of screening programs, the expected number of new cases has declined to 9710 and the expected death rate from this cancer has declined to 3700. (3)

The greatest risk in cervical cancer is never to have Pap smear test done. While 85% of all women in developed countries such as the USA have their Pap smear tests done at least once in their lives, this rate is only 5% in underdeveloped countries. (4)

Cytology and colposcopy and HPV DNA test which have gained importance in recent years are valuable means.

Etiology and Epidemiology

The cause of cervical cancer seems to be associated with continuing multiple damages and injuries. This type of cancer is more frequent in women in low socioeconomic groups and is connected with engaging in first coitus at early ages and with having multiple sexual partners. Today the Human Papilloma Virus (HPV) infection plays an important role in the etiology of cervical cancer. It is evidenced that this oncogenic virus that is spread by contagion via sexual intercourse causes frequently persistent subdural infection of the metaplastic epithelium in the cervical transformation zone.

95% of the cancers with squamous cell, and 90 % of the adenocarcinomas were found HPV DNA positive. As it was indicated in the preinvasive lesions, HPV 16, which is one of the high-risk oncogenic HPV types, is responsible mainly for carcinomas with squamous cell and HPV 18 for adenocarcinomas. (5)

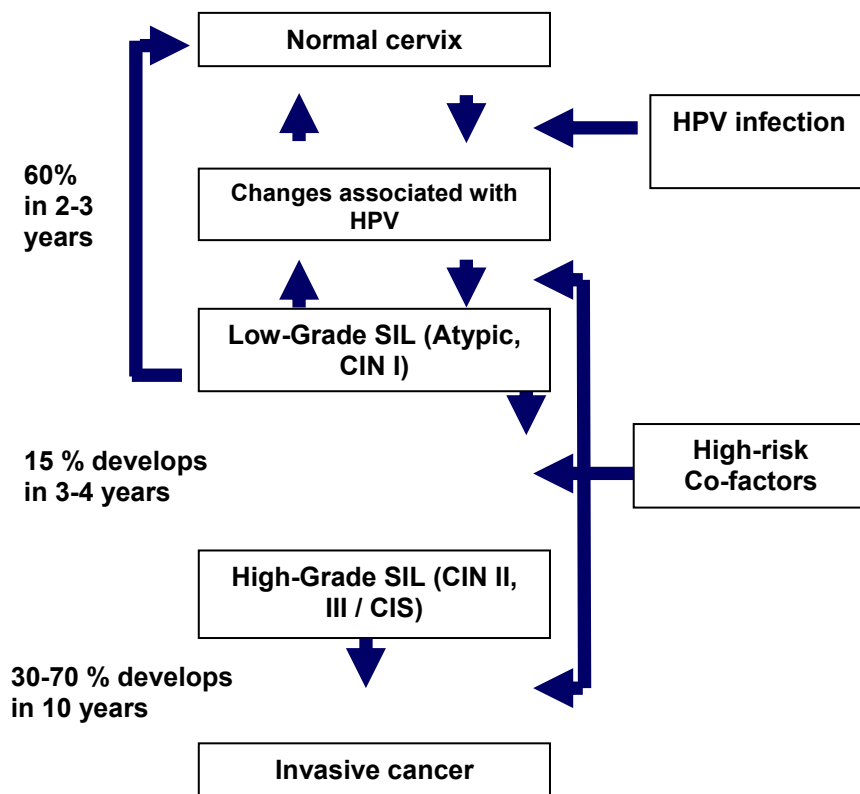
Risk Factors for Cervical Cancer

- HPV infection
- First coitus at an early age (before 16)
- Multi sexual partners
- Smoking (active or passive) (a correlation was found out between the habit of smoking and sexual behavior in many populations. In addition chemical substances related with cigarette were detected in the cervical mucus, it is thought that these substances are effective in the development of cervical cancer by causing DNA damages in the cervical cells)
- Nutrition (if there exists malnutrition and, the consumption rate of fruit and vegetable is insufficient in the nutrition program, the risk of cervical cancer increases)
 - Race
 - High parity
 - Low socioeconomic level (if getting medical services is low, the rate of attendance to routine screening services as well as the curability of the preinvasive lesions effectively will be respectively low. Moreover, generally malnutrition exists)
- Use of oral contraceptive (especially use of more than 5 years) (the use of these pills is also associated with sexual behavior)

Pathogenesis and History

After having a normal cervical HPV infection, first infectious changes caused by this infection are observed. These changes may either return to spontaneous normal or transform into low grade cervical intraepithelial lesion (LGSIL). 60% of the LGSIL cases may go back to its normal condition spontaneously within 2-3 years. However, 15% of them, affected by co-carcinogens, may develop within 3-4 years and may transform into high grade cervical intraepithelial lesion (HGSIL). If 30-70 % of HGSILs are not treated, they may eventually turn into invasive cancer within 10 years. The natural course of HPV infection is summarized in Figure 1

Figure 1: Natural Course of HPV infection



Screening and Protection

Only one negative Pap smear decreases the risk of the development of cervical cancer by 45%. 9 pap smear test made during whole life

decreases this risk by up to 99%. Therefore particularly the advanced countries have developed their own screening programs in accordance with their health policies.

According to the recommendations of the American Cancer Society (ACS) and the American College of Obstetricians and Gynecologists (ACOG), the age to begin screening is 3 years after starting to have sexual relations or at 21 at the latest (6). According to ACS, screening intervals, should be performed **annually** if by conventional cytology and **every two years** if with liquid-based Pap smear; and according to ACOG, **once a year**, whatever the technique may be. In the presence of a documented and technically satisfactory negative smear taken by using any technique or over the age of 30, screening should be made every **2 or 3 years**. In cases diagnosed with HIV infection and / or undergoing immunosuppressive treatment, it should be screened **two times for the first year**, and it should be **annually**, if the results are negative.

In the presence of **3** or more documented and technically satisfactory **negative smear** and in the absence of abnormal / positive cytology in the last decade, the screening activity should be ended at the **age of 70** according to ACS, and at **65** according to ACOG,. For those who had been exposed to DES in utero and / or undergoing immunosuppressive treatment (including HIV positive cases) the screening should be continued annually **until good health conditions are reached**.

Screening with vaginal cytology is not indicated in women who have undergone total hysterectomy due to benign gynecological reasons (CIN II and III are not considered to be benign).

In cases that have undergone hysterectomy due to CIN II and III, screening should be stopped in the presence of **3** documented and technically satisfactory negative cytology and in the absence of **abnormal / positive cytology in the last decade**.

Regarding protection, taking measures against diseases which are transmitted through sexual relations, quitting smoking, effective follow-up and treatment of pre-malign lesions are important. It seems as if the vaccinations developed against HPV in recent years will have an important role in protection from this disease.

Cervical Screening Programs in Turkey: Experiences in Şanlıurfa and Van

• Project for “Reproductive Health Education and Cervical Cancer Screening Among Women in Şanlıurfa”

Until today the most important society-based screening program in Turkey has been carried out in the province of Şanlıurfa. “Project for Reproductive Health Education and Cervical Cancer Screening Among Women in Şanlıurfa” is a program financed by the European Union and participated by the Ankara Middle East Lions Club as a non-governmental organization, and is a part of the “Reproductive Health

Program in Turkey” of the Ministry of Health of the Turkish Republic. The gynecologists and obstetricians from the Ankara Etlik Maternity and Gynecology Training and Research Hospital of the Ministry of Health of the Turkish Republic participated in every phase of the program. The project was carried out between January 2005 and January 2007 and completed.

The aim of the project was to raise awareness among people in the province of Şanlıurfa about reproductive health and cervical cancer, to launch a promotion campaign, to conduct cervical cancer screening, to ensure early diagnosis and treatment of cervical cancer; and to contribute in reducing the number of deaths from this cancer.

The project period was planned to be 2 years and to that end 50.000 persons in the city of Şanlıurfa was given training for two years. Smears were taken from 10000 women for early diagnosis of cervical cancer. These women were also subjected to Visual Inspection of Acetic Acid (VIA) and Visual Inspection of Lugol Iodine (VILI), which are two other cervical screening methods practiced in developing countries. Direct visual inspection of the cervix after 3.5% acetic acid and Lugol solution application was taught to the nurses working in the region through a short-term training program. This theoretical and practical training was given in the accompaniment of experienced physicians. The patients underwent abdominal and pelvic examinations, speculums were inserted and lesions that are related with cervical cancer are taught. Then after applying dilute acetic acid and waiting for about 1 minute, the cervix was inspected under light. The nurses were taught to be sure of seeing the entire transformation zone. According to the findings observed, the patients are evaluated as VIA negative or positive or VILI negative or positive.

All patients who were examined in this way and who were found to be positive in their tests, were subjected to colposcopy and if necessary to colposcopy-directed biopsy as an advanced examination.

The project was executed with wide participation of the Şanlıurfa Governorship and Municipality, Provincial Health Directorate, Şanlıurfa Directorate of National Education, Office of Mufti in Şanlıurfa, Association in Support of Contemporary Living, Turkish Confederation of Craftsmen and Artisans, Union of Chamber of Tradesmen and Craftsmen (TESK), Multi Purpose Community Centers (ÇATOM), Ankara Etlik Maternity and Gynecology Training and Research Hospital, ODTÜ Sociology Department and Sociology Department of Harran University.

In the promotion of the project, the prominent actresses of Turkey Hülya Koçyiğit and Selda Alkor contributed to the project by taking part in spot films free of charge. These short films were broadcasted in the regional televisions and TRT from time to time.

We encountered many problems during the execution of the project. These were gaining the trust of the regional people, increasing the presentations to the hospital, struggling against hot air conditions, challenges of transportation to the villages that are remote from the city

center and the difficulty of the public in understanding why the physicians from Ankara have come their area to serve free of charge.

After all, thanks to the self-sacrificing efforts of the project team and the physicians, nurses and midwives working in the local health care centers, women's smears were taken and they were sent to Ankara for analyses. 2500 women whose samples were suspected to be positive were reexamined and biopsies were taken and they were treated free of charge. The percentage of cervical cancers detected during the project was below those of Europe's. This suggests that cervical cancer in Turkey is below the expected level. This project was the first of its kind in Turkey and an important one worldwide. In addition, the support provided by the Department of Cancer Control of the Ministry of Health of the Turkish Republic during this project was at a significant level.

The reason for choosing cervical cancer in the project was the fact that cervical cancer cases appear frequently in this region, that this type of cancer is generally diagnosed in its later phases, that cervical cancer is the easiest and cheapest cancer to diagnose early, and that the frequency and rate of mortality of this cancer is reduced significantly through smear screening in the world.

According to the statistics of the State Institute of Statistics (DİE) and the Ministry of Health, Şanlıurfa is one of the cities socioeconomic condition of which is the worst. This region is highly below Turkey's average in benefiting health services and is the most underdeveloped. In this region, the number of physicians per 10000 patients is 4 (for Turkey it is 13 per 10000) and the number of beds per 10000 patients is 9.33 (23.04 per 10000 for Turkey), population growth rate is 36.5 per thousand (18.3 per thousand for Turkey), and the average rate of literacy is 70% and 55% for women (87% for Turkey).

The main owner of the project was the Ankara Middle East Lions Club and the physicians of the Gynecological Oncology Clinic of the Ankara Etlik Maternity and Gynecology Training and Research Hospital of the Ministry of Health.

Ankara Middle East Lions Club undertook the non-governmental organization part of the project and contributed about 50.000€ to the project which cost 538.000€ in total. The physicians and experts of the Gynecological Oncology Clinic of the Ankara Etlik Maternity and Gynecology Training and Research Hospital assumed all medical screening and treatment part of the project.

In the project totally 380 midwives-nurses, 120 medical practitioners, 250 teachers, 450 imams, 80 village headmen, and 70 volunteers working in several non-governmental organizations were trained. The screenings of 10,000 women were completed in the project. Approximately 50,000 women were trained and joint studies were carried out with the non-governmental organizations in the region. These were the teachers in the Community Training Centers, volunteers working in the Association in Support of Contemporary Living, teachers in the Multi Purpose Community Centers (ÇATOM) and the teachers, imams and village headmen in the region.

After the project was over, the Cancer Early Diagnosis and Screening Center (KETEM) founded in Şanlıurfa has been continuing to manage campaigns to ensure public awareness of such a project. The patients are presenting to health care centers and mother and child health care polyclinics and having their smears taken. The smears received are forwarded to the Şanlıurfa State Hospital for inspection. The patients with suspected pre-cancer findings in their smears are referred to Colposcopy Polyclinic of the Şanlıurfa Maternity Hospital and biopsies are taken. The conditions for cooperation of this center with the community leaders and non-governmental organizations has been established.

During the project, totally 9079 smears were taken. Of these, ASC-US were detected in 144 cases (1.6%), ASC-H in 6 of them (0.06%), AGC in 5 of them, LGSIL in 7 of them (0.07%) and HGSIL in 2 of them (0.02%). Squamous cell cancer was detected only in one patient and the incidence was determined to be 0.01%. The histopathological examination of these patients revealed 49 HPV infections, 27 CIN 1 infections, 5 CIN 2 infections, 5 CIN 3 infections, 1 microinvasive cervical cancer case and 1 endometrium cancer case. In 2 more patients referred by a gynecologist, squamous cell cervical cancer was identified.

Since the statistical studies of the date of this project are currently underway, it is impossible for now to provide more detailed information.

• **Project on “Early Diagnosis and Prevention of Cervical Cancer in the Province of Van”:**

The second broad ongoing project on this subject is called the “Project on Early Diagnosis and Prevention of Cervical Cancer in the Province of Van”, which is also financed by the European Union. It is a program mutually participated by the Ministry of Health of the Turkish Republic as the part of the “Reproductive Health Program in Turkey” as well as Hope in Health Foundation and Public Research Foundation as the non-governmental organizations. The project was launched in August 2006 and will be finished in August 2007.

The aim of the project is to increase and raise public awareness for early diagnosis and prevention of cervical cancer. With the same project, evolution of a social consciousness about sexual and reproductive health will be provided. The project will reach a total of 20000 (twenty-thousand) women between the ages of 20-49 in the province of Van. With a view to introducing the people and teaching them the measures to prevent cervical cancer, verbal, written and visual communication means will be used intensively. Department of Cancer Control of the Ministry of Health of the Turkish Republic and the Provincial Governorship has provided support for the project. The staff who will be employed in the training of the target group and the community leaders will be subjected to trainer orientation courses about cervical cancer and sexual and reproductive health. In the second phase, in accordance with a

predetermined content, the trainers will provide the target group identified in the province of Van awareness and consciousness-raising training, some of the participants (5000 women) will have Pap smear tests done and for those who are in need, family planning services will be provided. The studies will be promoted extensively and in the third phase the increase in the level of awareness and the increase of demand for medical services in comparison with former years will be measured. The experiences and accumulation of knowledge obtained through the project will be forwarded to the Center for the Early Diagnosis, and Detection of Cancer planned to be established in the region, and thus contribute to the sustainability of the project. The local administrators and politicians of the province will be informed of the scope of the project and their attention will be drawn to the issue. The budget of the project is 156.990 €, 10% of which is borne by non-governmental organizations.

Van Governorship and Municipality, Van Health Department, Gynecology and Maternity Department and the Pathology Department of Yüzüncü Yıl University in Van and experts and obstetricians from the Gynecological Oncology Clinic of the Ankara Etlik Maternity and Gynecology Training and Research Hospital of the Ministry of Health of the Turkish Republic took part in the project. In addition Turkish Republic Ministry of Health, Department of Cancer Control renders full support for this project.

Sharing the results will be possible following the completion of the project and evaluation of the obtained data.

How should the cervical cancer screening program be in Turkey?

In accordance with the **National Standards for Screening in Cervical Cancer** issued by the Ministry of Health Department of Cancer Control on May 29, 2007, the framework for the community-based screening program to be sustained for cervical cancer was defined. Upon the realization of this program, Turkey will both launch a national screening program and carry out successfully such a great organization.

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