

RESEARCH COMMUNICATION

Cost - Effectiveness of Pap Smear in Kermanshah, Iran

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Abstract

Objective: To determine the incidence of pre invasive and invasive cervical lesions and also cost- effectiveness of Pap smears in Kermanshah, Iran (2004-2007). **Methods:** A descriptive, cross sectional study was performed between March 2004-March 2007 with all cytological smears analyzed according to the Bethesda II system. Efficacy was estimated as the ratio of HSIL and invasive carcinomas detected to all Pap smears. Data were analyzed with SPSS software and mean \pm SD for cost in each age. **Results:** 148,472 smears were analyzed of which 99.7 % were negative, only 0.3% having cytological abnormalities. ASCUS, LSIL, HSIL and carcinoma positive rates were 205.4, 73.4, 21.6 and 5.4 per 100,000 Pap smears respectively. The incidence of HSIL and carcinoma in total was 26.9 per 100,000 women. Before age 35 there were no such lesions so that the effectiveness of Pap smear before age 35 was zero. The cost for one smear was 5 Euros and the cost for detection per HSIL or carcinoma was 18,559 Euros. The mean age of women for HSIL was 52.0 \pm 10.7 and for carcinoma 48.1 \pm 1.81 years. **Conclusions:** Since no HSIL or carcinomas were detected before age 35, and since for changing one LSIL to HSIL or carcinoma should take more than 5 years, the results of this study suggest that Pap smears before 35 years old is not effective and we suggest commencement of Pap smear in Iran from age 30.

Key Words: Cervical carcinoma - HSIL - pap smear - cost – effectiveness

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Introduction

Cervical cancer is a serious public health problem, given the morbidity and mortality among women. Survival rate for cancer of the uterine cervix have improved over the last 50 years largely, because of the impact of measures such as Pap smear. Pap smear has been one of the most widely accepted screening procedures for cervical cancer. Pap smear is easy to perform, well tolerated, and relatively inexpensive. The ability to screen and treat women for preinvasive disease, cervical dysplasia, is the key factor leading to the reduction in the incidence of invasive cervical cancer (Shingleton et al., 1995; O' Meara, 2002), but cervical cancer continues to be a leading cause of cancer death in women. About 80% of cervical cancers occur in less developed countries (Suba et al., 2001; Jeanne et al., 2002; Le Van Xuan and Le Truong Giang, 2006).

Prior to introduction of Pap smear screening, the incidence of death attributable to cervical cancer in the United States was 25 in 100,000 women, which is remarkably similar to current cervical cancer incidence rates in some developing nations. Today the estimated death from cervical cancer in Vietnam is at least 13.5 per 100,000 women and its incidence is 26 per 100,000 women (Suba et al., 2001). For comparison in the United States, the current rate of cervical cancer is 5 per 100,000 women (Ilana et al., 2007). Mexico as a developing country has

the highest cervical cancer mortality rate in the world and has ranked first in cervical cancer mortality for Latin America. Incidence of invasive cervical cancer in Mexico, 1997, is estimated 50 new cases per 100,000. In Mexico the average age at death from cervical cancer is 45 years and 74% of those deaths occur in the 30-64 age group (Flores et al., 2003).

The screening recommendations and official policies in different countries and regions show considerable variation. For example in Netherlands and Finland, the recommended number of Pap smears during a woman's life time is seven, whereas in Germany and Australia, the recommended number is more than 25. In addition in the Netherlands, and England the recommended time interval between screening examinations is 5 years and in Australia it is 2 years and in Germany it is 1 year. There are also alterations in the target age range. For example, in the Netherlands, screening is offered between the age 30-60 years (before 1996, screening was offered between 35-53), whereas in Australia screening is recommended 18 - 70 years (van den Akker-van Marle et al., 2002).

These different policies is dependent to the cost effectiveness of the test in different countries. In one study in Italy the cost per examined woman was 24.6 \$, whereas per CIN2 or more severe lesion detected was 13,600 \$. In that study although the cost for a single procedure is low, the cost per detected lesion is quite remarkable due to

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low detection rate in populations screened (Zappa et al., 1998).

The purpose of this study was to identify and report the incidence of pre invasive and invasive cervical lesions and the cost – effectiveness of Pap smear test in a developing country such as Iran, according to age group 15-74, 20-74, 25-74, ... 70-74 years, and to detect the most effective target age range in Kermanshah, Iran.

Materials and Methods

For this cross-sectional descriptive study the cytological findings of all Pap smears recorded in all laboratories in Kermanshah province (private laboratories and laboratories of governmental family planning clinics) from March 2004 to March 2007 were collected (n=148,472). The cytological smears were analyzed according to the Bethesda II system by cytopathologists or cytotechnologists. The cost for each Pap smear test (excluding all gynecology related costs) is estimated 5 Euros.

Non medical costs have not been addressed by any of the published models. Relatively small costs related to time lost from work, child care, transportation, etc, born by the majority of the population may counterweight the larger costs associated with cancer. Effectiveness was estimated as ratio of number of HSIL and invasive carcinoma detected to all smears.

Data were analyzed with SPSS software and cross tabulation tables and central tendency and dispersion indices, such as, mean and standard deviation for cost in each group.

Results

Between March 2004 to March 2007, 148,472 Pap smears were performed. The age of women was 15-74 years. Mean age was 34.2±10.9. Many of the women were under 25 years old (20.4%). 99.9% of smears were satisfactory and 0.1% were unsatisfactory (n=125). All of the unsatisfactory samples were negative. The great majority of examinations had a negative result (99.7%). Only 0.3% had cytological abnormalities (Table 1).

Incidence of HSIL was 4 times to carcinoma. The lowest mean age was in negative group and highest mean age was in group HSIL. Incidence of LSIL under 25 years was 36.3 per 100,000 (n=11). Age specific incidence rates and frequency of diagnosis per 100,000 are shown in Table 2. 83321 smears were conducted for people under 35 years old but no HSIL or carcinoma were found under age 35. The incidence of HSIL and carcinoma totally was 26.9 per 100,000. All of invasive carcinoma and HSIL was found in 35-71 years and total incidence for HSIL and carcinoma in this age group was 61.4 per 100,000. 99.9% of smears less than 25 years were negative. Minimum percent of negative was in age group 70-74 and 60-64 years (98.7%). Least incidence for carcinoma was in the age group under 45 (n=0).

The incidence of carcinoma above 55 years was zero. But HSIL above 55 was 172.8 per 100,000. Under age 35, we have not found HSIL or carcinoma. So the rate of

Table 1. Incidence Rate of Abnormalities in Pap Smears, Kermanshah, Iran (2004-2007)

Diagnosis	Number	per 100,000	Mean age	SD	age range
Negative	14,8018	99,694.2	34.1	10.8	15-74
ASCUS	305	205.4	41.2	11.9	16-73
LSIL	109	73.4	41.5	12.1	17-72
HSIL	32	21.6	52.0	10.7	35-71
Carcinoma	8	5.4	48.1	1.8	45-50
Total	148,472	100	34.17	10.86	15-74

HSIL or carcinoma to all smears was zero , so Pap smear was not cost- effective before age 35 in this study. The cost for finding 40 cases of HSIL and carcinoma was 742,360 Euros. The cost for finding one HSIL or carcinoma was estimated 18,559 Euros (Table 4).

Discussion

Pap smear for cervical screening has been around for over 50 years , but there is still world wide variation regarding screening age limits and intervals. The Pap test has been successful in reducing the incidence of cervical cancer by 79% and the mortality by 70% since the 1950’s (Ilana et al., 2007). A rational approach to determining screening policy should take into account the underlying rate of cervical cancer, the absolute difference in effectiveness of screening at different intervals, and the costs of screening. Effectiveness of Pap smear in Kermanshah, (Iran) before age 35 was zero in the present study.

In a cost-effective model in a developing country (Parana in Brazil), the great majority of examinations had

Table 2. Age Specific Incidence Rates and Frequency of Diagnosis per 100,000 Pap Smears

Age	Negative	ASCUS	LSIL	HSIL	Carcinoma	Total
15-19	6,737	6	3	0	0	6,746
		(88.9)	(44.5)	(0)	(0)	
20-24	23,508	12	8	0	0	23,528
		(51)	(34)	(0)	(0)	
25-29	26,507	31	5	0	0	26,543
		(116.8)	(18.8)	(0)	(0)	
30-34	26,446	42	16	0	0	26,504
		(158.5)	(60.4)	(0)	(0)	
35-39	21,669	51	12	7	0	21739
		(234.6)	(55.2)	(32.2)	(0)	
40-44	17,174	53	21	1	0	17,249
		(307.3)	(121.7)	(5.8)	(0)	
45-49	11,389	34	20	7	6	11,456
		(296.8)	(174.6)	(61.1)	(52.4)	
50-54	7,713	33	9	5	2	7,762
		(425.1)	(115.9)	(64.4)	(25.8)	
55-59	3,150	19	3	4	0	3,176
		(598.2)	(94.5)	(125.9)	(0)	
60-64	1,786	12	8	3	0	1,809
		(663.5)	(442.2)	(165.8)	(0)	
65-69	1,118	6	2	2	0	1,128
		(531.9)	(177.3)	(177.3)	(0)	
70-74	821	6	2	3	0	832
		(721.2)	(240.4)	(360.6)	(0)	
Total	148,018	305	109	32	8	148,472
		(205.4)	(73.4)	(21.6)	(5.4)	

Table 3. Cost Distribution of Diagnosis of HSIL and Carcinoma by Age Groups

Age group	Total Cost (Euros)	Number of HSIL or carcinoma	Cost per HSI or carcinoma
15-19	33,730	0	*
20-24	117,640	0	*
25-29	132,715	0	*
30-34	132,520	0	*
35-39	108,690	7	15,527
40-44	86,250	1	86,250
45-49	57,280	13	4,406
50-54	38,810	7	5,542
55-59	15,880	4	3,970
60-64	9,045	3	3,015
65-69	5,640	2	2,820
70-74	4,160	3	1,386
Total	742,360	40	18,559

*Number of HSIL or Carcinoma equal zero.

a negative result (98%), only two percent of examinations had cytological abnormalities, LSIL predominated in women age 15-30 years, HSIL was more common at 25-45 years and women older than 40 years had the greatest incidence of invasive cancer (Bleggi Torres et al., 2003). In a survey in USA for screening 5100 women for cervical cancer using liquid-based cytology found 3.3% HSIL, 4.3% LSIL, 9.7% ASCUS (Mao et al., 2005).

Candidates for Pap smear screening include women between the age of onset of sexual activity and the age of 85. The American Cancer Society suggests pap smear from age 21 or 3 years after commencing vaginal sex with no upper limit (Ilana et al., 2007). The age for beginning screening is 30 years of age for Finland, the Netherlands and Japan, and 25 years of age for most other countries. In 2003, England changed its screening policy to offer 3 yearly screening from 25 - 49 years of age and then 5 yearly screening for women age 50-54. In England the incidence of cervical cancer in women under 25 years of age is low (2.5 per 100,000 women per years (Sasieni and Castanon, 2006). Under age 35 we had 109.2 ASCUS per 100,000. ASCUS is the most common abnormal cytological report on Papanicolaou smears (3-5%) (Ilana et al., 2007). Every year approximately 2 million US women are diagnosed as having a cervical cytological result of ASCUS but this is associated with only a 10-20% incidence of CIN1 and 3-5% risk for CIN2 or 3. It has become apparent that CIN1 is most often a benign HPV infection and will regress spontaneously in more than 60% of cases (Ilana et al., 2007).

In a 3 year study of population of Southampton there were 10 times as many cases of CIN3, compared with invasive squamous cell carcinoma (Herbert and Smith, 1999). The peak age incidence of CIN was in those aged 25-29 years, which was 20 years earlier than the peak age incidence of invasive cervical carcinoma. But in Kermanshah HSIL was 4 times compared with invasive cervical carcinoma. In England in women aged 50 years the rate of CIN3 is 2.5 times that cervical cancer (Sasieni and Castanon, 2006). In Southampton 90% of CIN3 was diagnosed in women less than 50 years. The results of this study suggest that the best opportunity preventing invasive squamous cell carcinoma lies in the screening

women age 20-39 years, when the incidence of CIN2 in the screened population is highest and before the peak incidence of invasive disease (Herbert and Smith, 1999).

In another survey in Aten on 31,409 smears the frequency of CIN3 was 12 per 100,000 and invasive cancer 3.2. The mean age of CIN3 was 37 (Oncins et al., 2001). In Iran frequency of HSIL was 21.6 per 100,000 and invasive carcinoma 5.4 per 100,000. The mean age for HSIL was 52.03 years.

In England the commencement of screening at the later age of 25 is suggested (Moban and Ind, 2004). In Netherlands before 1996 screening was offered between age 35-53 and now is offered between 30-60 years, but in Australia screening is recommended between age 18-70 (van den Akker-van Marle et al., 2002). We had not any HSIL or carcinoma under age 35. We had 16 case of LSIL under age 30, that it can occasionally progress to HSIL during 10-15 years (Sasieni and Castanon, 2006). So we don't suggest conventional Pap smear with this quality before age 30, and smear before age 35 is not cost effective. So we can reach to this point that the age for commencement of Pap smear in Iran can be higher than other reports. In Vietnam invasive cervical cancer rarely occurs in women before age 30 or in post menopausal women who have had a history of negative Pap smear. The five years time interval is chosen in order to decrease costs. The mean progression rate of a squamous intra epithelial lesion (SIL) even a high risk one, to invasive cervical cancer is longer than five years. Therefore a 5 years screening interval detect the majority of high risk SILS before they progress (Le van Xuan and Le Truong Giang, 2006). The time of progression from CIN to CIS is estimated to be 10-15 years creating a lengthy lead time during which the disease may be identified (Cervical cancer prevention: Cost – effective screening).

In Sweden of 1998, the screening guide lines are 3-yearly tests between 23 and 50 of age and 5 years tests between 50 and 60 years of age (Dillner, 2000). In one study from Carolina screening every 1 or 2 years compared with every 3 years improved the effectiveness by less than 5%, so screening is recommended at least every 3 years from about age 20 to about age 65 years (Eddy, 1990).

Result of one study in Netherlands is that in the case of limited resources, the program should use a five years interval and concentrate on the age range 25-60 years, with special attention to women who have never been screened or screened >10 years previously (Hanselaar, 2002). In a cost – effectiveness survey of cervical cancer screening in five developing countries (India, Kenya, Peru, South Africa, and Thailand), visual inspection of the cervix with acetic acid or DNA testing for HPV in one or two clinical visits was cost- effective alternatives to conventional cytology – based screening and the two visits for the test is suggested at 35 and 40 years of age (Sue et al., 2005). In India it is suggested that alternative methods like visual inspection methods could be more feasible for organized population based screening in a low resource country (Patro and Nongkynrih, 2007).

Low incidence of epithelial cell abnormalities in this study, really may be due to lower incidence of the disease and lower incidence of human papilloma virus (HPV)

infection or due to high false negative rate of pap smear due to sampling errors and misinterpretation of smears. False negative rate of pap smear in U.S.A is 51% (6). The sensitivity of a single pap smear is poor and is between 30-87% (Moban and Ind, 2004). Approximately 30% of new cancer cases each year result from women who have undergone pap testing, but errors of sampling, fixation or interpretation occur (Ilana et al., 2007). In Iran if pap smear will be done with this quality, is not cost effective before age 35, because we had not HSIL or cervical cancer under age 35. Thus we must not only increase the quality of sampling but also we must use the newer methods with higher sensitivity, like liquid based pap smear (80% sensitivity), and if with increasing quality of sampling and using more sensitive methods, we would have low epithelial cell abnormalities, we can reach to this point that the incidence of disease in Iran is lower than west. We must have a survey on the incidence of high risk HPV. In western countries the incidence of HPV in genital tract is high and 90% of cervical intraepithelial neoplasia is attributable to HPV, thus we see cervical epithelial abnormalities in lower age group and with higher incidence (Sasieni and Castanon, 2006; Ilana et al., 2007). In our study the highest incidence of ASCUS is in age 70-74, and is perhaps due to cervical atrophy in this age group and perhaps this is the reason, the mean age of LSIL and HSIL was lower than ASCUS. In Iran the cost for one smear was 5 Euros and the cost for finding one HSIL or carcinoma was 18,559 Euros. In one survey in Portugal the average cost for carcinoma detected was 1199 Euros with Pap screening (Boronow, 1998). In another survey in Tunisia Pap smear for 40-64 years every 5 years had the highest cost – effectiveness ratio (Novoa Vazquez, 2004).

In 1986 with the data from 8 countries it was found that the highest impact on incidence rates comes from screening every 3-5 years between the age of 35 and 64 years (Sasieni and Castanon, 2006). From our data we believe that the same or starting at 30 can be recommended in Iran.

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