

## Cervical Pap screening among Israeli women, 2005–2010

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### Abstract

**Purpose** This study describes the distribution and the trends of cervical abnormalities in Israel, based on Pap smear results.

**Methods** A retrospective analysis of cervical smears received by the Central Pathology Laboratory of Maccabi Healthcare Services between January 2005 and December 2010.

**Results** In total, 711,541 Pap smears were screened in the study period. Cytological abnormalities were observed in 4.78 % of the total smears screened. An increase was

observed in the rate of positive results from 2.63 % in 2005 to 6.78 % in 2010 ( $p = 0.0026$ ). The cervical abnormalities in the study period distributed as follows: atypical squamous cell (ASC)—2.72 %, low-grade squamous intraepithelial lesion (LSIL)—1.54 %, high-grade squamous intraepithelial lesion (HSIL)—0.34 %, squamous cell carcinoma—0.01 %, atypical glandular cells (AGC)—0.10 %, adenocarcinoma in situ (AIS)—0.06 % and invasive adenocarcinoma—0.01 %. The increase was statistically significant for ASC ( $p = 0.0028$ ), LSIL ( $p = 0.0069$ ) and for HSIL ( $p = 0.0260$ ). The mean ages at diagnosis of women with ASCUS, LSIL, HSIL, squamous cell carcinoma, AGC, AIS and adenocarcinoma were 37.8, 33.2, 38.6, 55.4, 41.1, 49.9 and 57.1 years, respectively.

**Conclusions** The increase in the rate of squamous cell abnormalities demonstrated in this study emphasizes the need of implementing an education and a screening program among Israeli women. HPV vaccine, sexual behavior, cytology performance and HPV test are primary and secondary prevention tools which may reduce morbidity and mortality in the future. In addition, based on the age at diagnosis of the different pathologies, the age group in which Pap test is performed in Israel should be expanded from 35–54 to 25–65 years.

**Keywords** Pap test · Cytological abnormalities · Cervix · Israel

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### Introduction

Cervical cancer is a major public health problem and was ranked in 2008 as the second most frequent cancer among women worldwide with an age standardized rate of 15.2 per 100,000 and high mortality rate of 7.8 per 100,000 [1].

Cervical cancer is highly associated with Human Papilloma Virus (HPV) infection (99.7 % of all cases) [2] and is an example of neoplastic progression in which the epithelium produces a precursor lesion which, if left untreated, has the potential to progress to invasive carcinoma [3]. The precursor can be readily detected by a painless, reproducible and reasonably accurate test, the Pap smear [4].

The use of Pap smear as a screening tool for the early detection of cancer of the cervix in the last 50 years had lead to a significant decrease in death rate from this disease, the decrease being as high as 70 % in some countries [3]. The decline in cervical cancer incidence was also achieved by increased public awareness for sexual transmitted diseases (STDs) and safe sexual behavior. It has been noted, though, that the Pap test is not a diagnostic but rather a screening test that filters out those in need of further assessment [3]. An abnormal Pap smear should be followed up or further checked by other diagnostic technologies [3].

Screening guidelines vary from country to country. According to “The American College of Obstetricians and Gynecologists” (ACOG), screening should start at the age of 21 and continues until about the age of 65 or 70 [5].

In Israel, the age-adjusted incidence rate of cervical cancer is 5.4 per 100,000 [6]. Pap test is recommended, and fully covered by the National Health Insurance Law, every 3 years for women aged 35–54. The Israeli Gynecological Society recommends performing Pap smear as a screening test every 3 years between the ages 25 and 60 years [7] but no national screening program has been implemented and the screening is opportunistic.

The purpose of this study is to report the distribution of the cervical abnormalities in Israel and to assess the trends of cervical abnormalities in the last half decade in Israel, by year, age group and district.

## Methods

This is a retrospective survey based on Pap test results from the central pathological laboratory in the “Maccabi Healthcare Services” (MHS).

Health care in Israel is delivered in a universal fashion, thanks to the National Health Insurance Law and participation in a medical insurance plan is compulsory. There are four Health Maintenance Organizations (HMO's) in Israel which cover the total population. MHS is the second largest one, covering, in average, 24.5 % of the population between 2005 and 2010.

Data were collected for the period of January 2005 through December 2010 from the computerized system of the MHS central laboratory. The pathological data included

all Pap smears with positive cytological findings according to the Bethesda system.

The Bethesda system (2001) allows the classification of the Pap test results into two major groups of abnormalities [8]:

1. Squamous cell abnormalities:
  - 1.1 Atypical squamous cells (ASC): atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells—cannot exclude HSIL (ASC-H)
  - 1.2 Low-grade squamous intraepithelial lesion (LSIL)
  - 1.3 High-grade squamous intraepithelial lesion (HSIL)
  - 1.4 Squamous cell carcinoma.
2. Glandular cell abnormalities:
  - 2.1 Atypical glandular cells (AGC): atypical glandular cells not otherwise specified (AGC-NOS) and atypical glandular cells, suspicious for AIS or cancer (AGC-neoplastic)
  - 2.2 Adenocarcinoma in situ (AIS)
  - 2.3 Adenocarcinoma.

We have implemented a text search in the MHS laboratory database, using the following combinations: “Atypical squamous cells of undetermined significance”, “Atypical squamous cells of undetermined significance cannot exclude HSIL”, “Low grade squamous intraepithelial lesion”, “High grade squamous intraepithelial lesion”, “Squamous cell carcinoma”, “Atypical glandular cells favor endocervical origin”, “Atypical glandular cells favor endometrial origin”, “Atypical glandular cells not otherwise specified”, “Atypical glandular cells suspicious for malignancy”, “Atypical glandular cells, suspicious for endocervical adenocarcinoma in situ”, “Endocervical adenocarcinoma in situ”, “Adenocarcinoma favor endocervical origin”, “Adenocarcinoma favor endometrial origin”, “Adenocarcinoma not otherwise specified”, and abbreviations.

Between January 2005 and July 2009, Pap test was done in MHS using the conventional method, in which samples are smeared directly onto a microscope slide after collection. In August 2009, MHS began performing liquid-based cervical cytology with computer assisted screening (Thin-prep Imaging System) where the sample is collected from the cervix by a soft brush, transferred to a preservative solution and sent to the pathology laboratory for slide preparation and analysis. The new technology was fully implemented in 2010. For a single follow-up of an abnormal smear, the sensitivity of the conventional Pap test is 61.0 % [9]. The sensitivity of the Thin-Prep imaging system is 73.4 % [10].

Using the total number of positive cases, including repeated tests, we calculated the total outcome proportion and the proportion by year.

The incidence data, referred only to new positive cases in the study period, excluding all repeated test results. Data on the population size for incidence rates calculations were achieved by social security publications on the HMOs in Israel, including the distribution of the insured population by years, age groups and districts [11]. Data on the reason for performing the test (screening/diagnostic) were regrettably unavailable and we assumed that repeated tests were carried out because of a medical indication. In order to avoid high rates in 2005, we used an evaluation of 6.5 % of the total Pap tests performed in MHS are done because of a medical indication (personal communication—Dr. Schejter) and this proportion was deleted randomly.

The data retrieved by the laboratory did not include the exact home address of the participants; thus, resolution of geographical distribution is limited to the district level only, based on the location of the clinic from which the specimen was collected, assuming the women live in the vicinity of the clinic.

The study was approved by the Institutional Review Board at MHS.

#### Data analysis

The rate of positive specimens was calculated by dividing the number of positive test results by the number of Pap tests performed in a specific year. Incidence rates were calculated by dividing the number of new cases by population size, in total, and per age groups, multiplied by 100,000.  $p$  for trend was calculated using linear regression.  $p$ -value  $< 0.05$  was considered as statistically significant. Data were analyzed using the SAS software (version 9.1.3).

#### Results

Between 2005 and 2010, a total of 711,541 pap smears were performed among MHS insurers. The number of Pap tests executed increased annually (from 101,582 in 2005 to 135,819 in 2010).

Between 2005 and 2010, 33,991 Pap smears with pathological findings were observed, which consisted 4.78 % of the smears screened. The rate of positive specimens increased from 2.63 % in 2005, to 3.35 % in 2006, 4.97 % in 2007, 4.91 % in 2008, 5.12 % in 2009 and 6.87 % in 2010.

The overall distribution of the Pap tests results was 95.22 % negative, 4.61 % were squamous cells abnormalities (2.72 % were ASC, 1.54 % were LSIL, 0.34 % were HSIL and 0.01 % were squamous cell carcinoma) and 0.16 %

glandular cell abnormalities (0.10 % were AGC, 0.06 % were AIS and 0.01 % were adenocarcinoma) (Table 1). A significant, but not stable increase between 2005 and 2010 was observed in squamous cell abnormalities: ASC ( $p = 0.0028$ ), LSIL ( $p = 0.0069$ ) and HSIL ( $p = 0.0260$ ) (Table 1).

Between 2005 and 2010, 22,752 new cases of abnormalities were observed.

The highest number of positive Pap tests was observed in the year of 2010 (27.6 %), 34.6 % of the abnormal smears were observed in women in the age group of 25–34 years and 38.8 % of the smears were performed in women from the Tel Aviv district (Table 2).

The total crude incidence rate in the years 2005–2010 of any cervical abnormalities was 412.0 per 100,000. The age-adjusted incidence rate of cervical abnormalities increased from 220.4 per 100,000 in 2005 to 708.3 per 100,000 in 2010 (Fig. 1). The crude incidence rates of squamous cell abnormalities and glandular cell abnormalities were 404.4 and 7.6 per 100,000, respectively. The age-adjusted incidence rate of squamous cell abnormalities increased from 212.2 per 100,000 in 2005 to 702.8 per 100,000 in 2010 (Fig. 2). The age-adjusted incidence rate of glandular cell abnormalities decreased from 8.2 per 100,000 in 2005 to 5.5 per 100,000 in 2010 (Fig. 2). The early stages of squamous cell abnormalities contributed mostly to the increase in the age-adjusted incidence rate: ASC increased from 134.2 per 100,000 in 2005 to 485.8 per 100,000 in 2010 (the first steepest increase is from 2006 (201.3 per 100,000) to 2007 (344.4 per 100,000) and the second, from 2009 (338.1 per 100,000) to 2010. LSIL increased from 60.4 per 100,000 in 2005 to 182.1 per 100,000 in 2010 and HSIL increased from 17.3 per 100,000 in 2005 to 34.9 per 100,000 in 2010.

The average age of women with squamous cell abnormalities was 36.9 years (Standard Error = 0.1, Min = 15.4, Max = 87.7) while for women with glandular cell abnormalities the corresponding value was 43.0 years (Standard Error = 0.6, Min = 23.2, Max = 96.3). The difference between the two groups was statistically significant ( $p$ -value  $< 0.0001$ ).

The highest incidence rates were demonstrated for the squamous cell abnormalities in the 25–34 years age group (901.4 per 100,000) and for the glandular cell abnormalities in the 35–44 years (19.2 per 100,000). For ASC, LSIL and HSIL, the highest incidence rate was in the age group of 25–34 years, with 599.4, 254.4 and 47.3 per 100,000, respectively (Table 3). For squamous cell carcinoma, the highest incidence rate was observed in the 75+ age group with 1.6 per 100,000 (Table 3). For AGC, AIS and Adenocarcinoma, the highest incidence rates were observed in 35–44, 45–54 and 65–74 age groups, respectively (Table 3). The age-adjusted incidence rates of any cervical abnormalities were higher in Haifa and Tel Aviv districts but increased along the study period in all districts (Fig. 1).

**Table 1** Pap tests results distribution in Maccabi Healthcare Services, 2005–2010

	2005 (%)	2006 (%)	2007 (%)	2008 (%)	2009 (%)	2010 (%)	Total	<i>p</i> for trend
Squamous cell abnormalities (Total <i>N</i> = 32,824)								
ASC	1.25	1.83	2.92	2.93	2.93	3.96	2.72	0.0028
LSIL	0.91	1.06	1.46	1.50	1.58	2.45	1.54	0.0069
HSIL	0.25	0.23	0.36	0.32	0.48	0.37	0.34	0.0260
Squamous cell carcinoma	0.01	0.00	0.01	0.01	0.01	0.00	0.01	0.6162
Glandular cell abnormalities (Total <i>N</i> = 1,167)								
AGC	0.12	0.14	0.13	0.08	0.07	0.08	0.10	0.1555
AIS	0.08	0.08	0.09	0.05	0.05	0.01	0.06	0.0763
Adenocarcinoma	0.00	0.00	0.01	0.01	0.01	0.00	0.01	0.4998
Normal (Total <i>N</i> = 677,550)								
Normal	97.37	96.65	95.03	95.09	94.88	93.13	95.22	0.0004
Total (Total <i>N</i> = 711,541)								
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	

ASC atypical squamous cell, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion, *AGC* atypical glandular cells, *AIS* endocervical adenocarcinoma in situ

**Table 2** Characteristics of pathological Pap smears in Maccabi Healthcare Services, 2005–2010

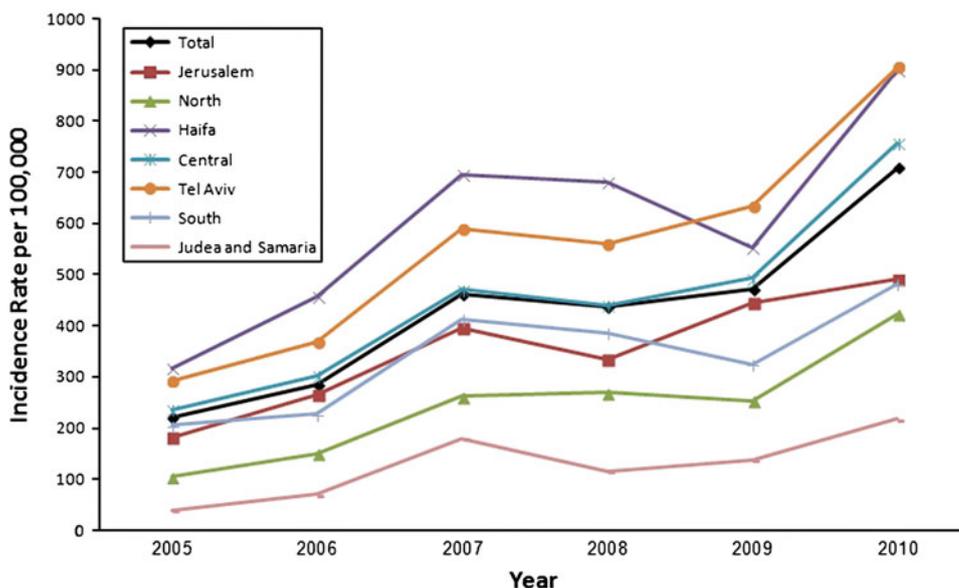
	<i>N</i>	%
Year		
2005	1,881	8.3
2006	2,452	10.8
2007	4,026	17.7
2008	3,882	17.1
2009	4,222	18.6
2010	6,289	27.6
Total	22,752	100.0
Age group (years)		
15–24	2,809	12.4
25–34	7,874	34.6
35–44	7,077	31.1
45–54	3,704	16.3
55–64	1,019	4.5
65–74	223	1.0
+75	46	0.2
Total	22,752	100.0
District		
Jerusalem	798	3.5
North	993	4.4
Haifa	3,266	14.4
Central	6,397	28.3
Tel Aviv	8,764	38.8
South	2,216	9.8
Judea and Samaria	176	0.8
Total	22,610	100.0

The increases in the incidence rates from 2005 to 2007 and from 2009 to 2010 were consistent in all districts (Fig. 1). The highest incidence rates of squamous cell abnormalities, by district, were documented in Haifa (511.0 per 100,000) and Tel Aviv (506.2 per 100,000) and for glandular cell abnormalities, 9.9 per 100,000 in Haifa and 8.4 per 100,000 in Tel Aviv.

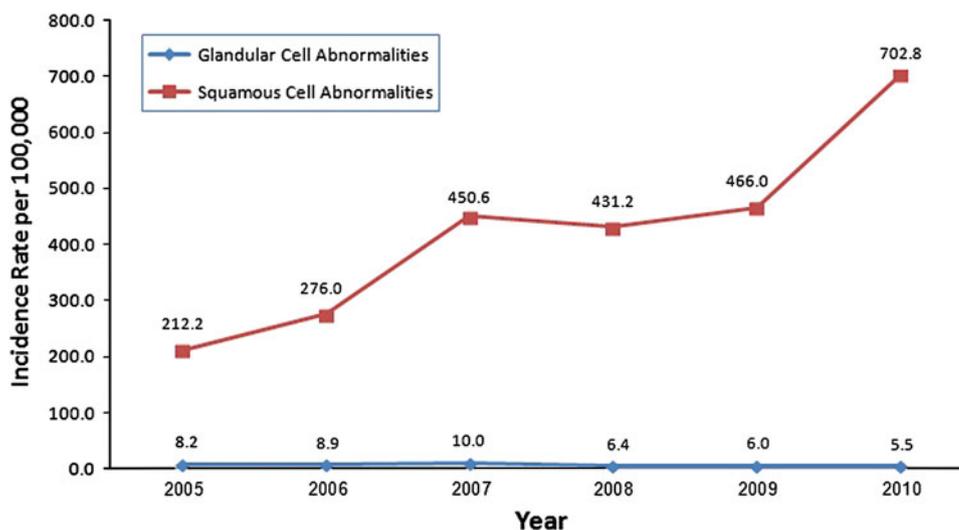
## Discussion

In this study we aimed to summarize the distribution and time trends of Pap smear results in Israeli women in 2005 through 2010. A significant increase in the rate of positive results was observed, from 2.63 % of the total smears performed in 2005 to 6.87 % in 2010. The increase was mostly due to an increase in the incidence of ASC and LSIL. These findings are in accordance with previous report [12]. An increase in the rate of positive results was observed in England, mostly due to an increase in ASCUS rates [12]. The increase was explained by the fact that the area examined had the fastest growing population in Britain, which is most pronounced in the 15–39 years age group, the women with the greatest increase in abnormal smears [12]. Yet, the principal conclusion of the study in England was that the increased pick up rates of abnormal cervical smears in the district reflected a true increase [12]. The increase observed in the current study apparently also reflects the reality. During the study period there were no changes in screening policy. The change from conventional Pap smear to the automated liquid-based cytology took

**Fig. 1** Incidence rate of Pap positive results, total and by district, per 100,000, age-adjusted, Maccabi Healthcare Services, 2005–2010



**Fig. 2** Incidence rate of Pap tests results by cell type per 100,000, age-adjusted, Maccabi Healthcare Services, 2005–2010



**Table 3** Age-specific incidence rate of Pap tests results per 100,000, Maccabi Healthcare Services, 2005–2010

ASC atypical squamous cell, LSIL low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesion, AGC atypical glandular cells, AIS endocervical adenocarcinoma in situ

	ASC	LSIL	HSIL	Squamous cell carcinoma	AGC	AIS	Adenocarcinoma
15–24	272.1	135.5	8.6	0.0	0.7	0.0	0.0
25–34	599.4	254.4	47.3	0.3	10.4	0.8	0.2
35–44	595.2	137.8	41.6	0.3	17.5	1.0	0.7
45–54	485.4	69.2	27.5	0.2	11.1	2.3	0.6
55–64	176.0	18.8	11.7	1.0	4.0	0.6	1.0
65–74	64.1	5.9	7.9	0.8	4.7	2.0	2.4
+75	15.1	1.1	2.7	1.6	1.1	1.1	2.2
Total	296.2	88.2	19.7	0.3	6.4	0.7	0.5

place at MHS in 2009 through 2010 and can only partially explain the increasing incidence trends, since the sensitivity improvement associated with the new technology is 12 % [9, 10] while the increase in the incidence rate of

squamous cell abnormalities was by 66 %. This leads us to conclude that the incidence genuinely increased. The increase reported in the current study may be explained by an increase in the awareness of cervical cancer prevention

and due to a propaganda done in the media, especially after the introduction of the HPV vaccines in the world. In the last 2 years of the study period we observe stability in the incidence rate, which may or may not continue. Only a future study will clarify this point.

The rate of positive Pap results in the current study was 4.78 %. Studies from Iran, Turkey, California, Italy and India demonstrated positive rates of 0.3–5 % [13–17]. Studies from the United States and Bangladesh reported 5.5–8.2 % positive rates [18, 19] and studies from Saudi Arabia and South Africa demonstrated high positive rates of 17.3 and 43.2 %, respectively [20, 21]. The distribution of the positive results was, by descending order, ASCUS, LSIL, HSIL and carcinoma and changed according to the proportion of positive results [16, 18, 20, 21]. We found that LSIL and HSIL accounted for 1.54 % and 0.34 % of the total Pap tests performed, respectively, but a previous analysis conducted in Israel between 1991 and 1999 found lower rates of LSIL and HSIL, 0.65 % and 0.29 %, respectively, with no increase during the study period [22].

The distribution of the cervical abnormalities shown in our study reflects the natural behavior of cervical disease. The risk to develop cervical cancer decreases with time since regression may occur in pre-malignant cervical lesions and in most women the immune system naturally removes these lesions from the cervix.

The increase in the squamous cell abnormalities and not in glandular cell abnormalities may be explained by the difficulty of finding abnormal glandular cells that are anatomically situated further inside the uterus than squamous cells, and by the higher exposure of squamous cells to HPV, again, as a result of the anatomical structure.

The mean ages of the patients diagnosed with ASC, LSIL, HSIL, squamous cell carcinoma, AGC, AIS and adenocarcinoma were 37.8, 33.2, 38.6, 55.4, 41.1, 49.9 and 57.5 years, respectively. Other studies demonstrated the same age trends [13, 17]. In India, the mean ages of patients diagnosed with LSIL, HSIL and invasive cancer were 32.3, 40.5 and 57.0 years, respectively [17]. In Iran, the mean ages of women with ASCUS, LSIL, HSIL and carcinoma were 41.2, 41.5, 52.0 and 48.1 years, respectively [13]. A previous study performed in Israel between 1991 and 1999 demonstrated that the highest incidence of LSIL was observed in women in the age group of 20–24 years and HSIL was most likely to be diagnosed in women in the age group of 30–39 years [22]. The mean ages at diagnosis reflect the natural history of the disease and the way it progresses with time. After infection with the human papillomavirus (HPV), which is the main risk factor for cervical lesions transmitted through sexual relations, ASCUS develops, with mild inflammation or irritation around the cervix. This causes the cells to appear slightly abnormal. Within several months, the lesion may

progress to LSIL, and in case of persistent high risk HPV infection, may lead to HSIL after months/years. Progression to cervical cancer takes years and occurs when abnormal cells cross the basal membrane of the epithelial layer and invade the stroma (the underlying supportive tissue of the cervix).

In our study we found cytologic changes suspicious of squamous cell carcinoma in women in the age group of 25–34 years. The high rates in young women may reflect an early exposure to HPV as a result of early sexual activity. High rates were also found among women older than 55 years which may be associated with age-related weakened immune system following HPV exposure. Positive cytology in women aged >25 and >55 years highlights the need to expand the recommended age range for cervical screening in Israel (currently 35–54 years) to a wider range of 25–65 years.

The highest incidence rates of cervical abnormalities by district were documented in Haifa and Tel Aviv. In Israel, the total incidence rates of cancerous diseases overall are higher in the Tel Aviv and Haifa districts compared to other districts [23]. The high rates may be explained by over representation of residence in Tel Aviv and Haifa districts among the MHS insured women in our study, with an average of 44.2 and 30.6 % of the total MHS population residing in the Tel Aviv and Haifa sub-districts, respectively, compared to an average of 24.5 % in the total Israeli population. The geographical differences may also be explained by differences in sexual behavior habits in these regions, mental barriers within specific groups, access to health care services and the awareness of the physicians. An association between air pollution and cervical abnormalities has not been documented but high rates of environmental pollutants in these highly industrialized districts may also contribute to these geographical differences.

The low sensitivity of the Pap test [9] is a major public health problem and routine, consistent follow-up is thus essential. Efforts should be made to reach unscreened populations and to train new gynecologists with appropriate collection and handling of the specimens. Continuing medical education and training of cytotechnologists and cytopathologists are also needed [3].

One of the main considerations taken into account in implementing a national screening and prevention program is its cost-effectiveness [16]. Since vaccination and performing of Pap tests are much cheaper than treating cervical pre-cancerous lesions and cervical cancer, substituting the opportunistic screening plan in Israel with a constructed national program should be considered. Implementation of routine screening programs in different countries all over the world decreased the incidence of cervical cancer by 50–85 % [24]. We recommend to consider the application of a national screening program that

will be based on “The American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology” recommendations from March 2012 which includes [25]: Age 21–29 years—Screening with cytology alone every 3 years. Age 30–65 years—Screening with cytology and HPV testing every 5 years or cytology alone every 3 years. Age older than 65 years—Women with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened. Following hysterectomy (due to a non-cervical disease) which includes removal of the cervix—no further screening is needed. HPV vaccinated—recommended screening practices should not change on the basis of HPV vaccination status. In light of the relatively low incidence rates of cervical cancer in Israel, these recommendations may need certain modifications and adjustments but they do serve as guidelines.

It is also important to address the main factors which, according to the scientific evidence, affect women’s unwillingness to perform a Pap test, i.e., lower socioeconomic status (including lower education, lower income and being single) [26–30], older age [29, 30], the belief that cervical cancer has symptoms [27] and the patient–doctor interaction [30]. According to a previous study in Israel, 46 % of the Israeli women aged 21–59 years who were insured by MHS, had a Pap smear during 2006–2008 [31]. This low rate strengthens the need for a national screening program, as currently the screening plan in Israel is opportunistic and may not cover the population most needing it.

This study has several strengths: First, we investigated a large group of women which included the total “Maccabi Healthcare Services” population, an HMO that covers around a quarter of the total Israeli population. Second, all of the smears were examined in one laboratory, which strengthen the reliability of the results.

This study has several limitations: First, the study included data from only one health service provider in Israel and not the total Israeli population. Second, the data are based on opportunistic screening and not on a massive, organized screening program. Thus, the women included in this study may be a selective group of women with high health awareness who understand the importance of Pap tests. Third, in August 2009, MHS has started using the Thin-Prep method, which provides decreased numbers of unsatisfactory samples and an increased sensitivity for the detection of cytological abnormalities [32]. The new technology was fully available during 2010 and was partially associated with the dramatic increase in 2010. Fourth, the database did not include the test indication, screening or diagnostic, and we had to eliminate a random number of women for the incidence analyses to avoid a selection bias.

Fifth, the study is based only on cytological data, without correlation to biopsy findings.

In conclusion, based on the results of the current survey, we recommend that an organized screening program will be implemented in Israel. Women who never performed a Pap test should be identified by their HMOs and should be urged to perform one. A public awareness program should also be implemented to publicize the importance of cervical cancer prevention and its precursors. The increasing prevalence of cervical pathologies calls for improved health education programs with respect to sexually transmitted disease and safe sex [33]. Based on the age at diagnosis of the different pathologies, the age group in which Pap test is performed in Israel should be expanded from 35–54 to 25–65 years.

**Conflict of interest** We declare that we have no conflict of interest.

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