Cervical Neoplasia in Israeli Jewish Women: Characteristics in a Low Risk Population

Joseph Menczer MD

Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Wolfson Medical Center, Holon, Israel

ABSTRACT: The incidence of invasive uterine cervical cancer in Israeli Jewish women is persistently lower than in many other countries, although the frequency of premalignant lesions is similar to that in other populations. Most characteristics, except certain traditional habits, are similar to those in other populations. The incidence among women born in North Africa and their Israeli born descendants is significantly higher than in those born in other continents, possibly due to genetic factors. In view of the similarities to other populations the reason for the low incidence in Israel remains obscure, and whether it can be attributed to genetic reasons or to some traditional habits is yet to be confirmed

IMAJ 2011; 13: 700–704

KEY WORDS: Israeli Jewish women, incidence, cervical squamous cell carcinoma, cervical adenocarcinoma, inter-ethnic differences, risk factors, traditional habits

Worldwide, cervical cancer is the second most common cancer in women. About 500,000 new cases and more than 250,000 deaths occur annually. In developing countries, where more than 80% of the cases occur, the incidence may be as high as 80/100,000. The majority are squamous cell carcinoma and adenocarcinoma, while other types are much less common [1].

Cervical cancers are attributed to infection with the human papillomavirus and about 70% of them are caused by types 16 and 18. They are preceded by cervical intraepithelial neoplasia, mainly its immediate precursor CIN3. While HPV is a necessary cause of cervical cancer, other cofactors are necessary for progression from cervical HPV infection to cancer. These cofactors include long-term use of hormonal contraceptives, high parity, tobacco smoking, and co-infection with human immunodeficiency virus. Additional probable cofactors are co-infection with herpes simplex virus type 2 and *Chlamydia trachomatis*, immunosuppression, certain dietary deficiencies, and genetic and immunological host factors [2]. Cervical cytological screening may lead to diagnosis of the precursor lesions, which can be treated very successfully. The decreased incidence of cervical cancer in many western countries is usually attributed to the introduction of cervical cytological mass screening programs.

Although the prevalence of CIN3 is similar to that in other populations, the incidence of invasive cervical cancer remains persistently low in Israeli Jewish women

CIN = cervical intraepithelial neoplasia
HPV = human papillomavirus

Braithwaite [3] first noted in 1901 that cervical cancer "was seldom or never met among numerous Jewesses" attending his clinics. He offered two explanations for his observation: the difference in race and the difference in diet, namely the "absence of bacon and ham in the diet of Jews." The infrequency of cervical cancer in Jewish women has since been repeatedly confirmed and it holds true for Israeli Jewish women as well.

The purpose of the present report is to review investigations dealing with characteristics of Israeli Jewish women with cervical neoplasia in order to summarize the information that has accumulated in this low risk population. A PubMed search of investigations published since the establishment of the State of Israel in 1948 containing the term Israeli Jewish women in combination with cervical cancer, cervical intraepithelial neoplasm, cervical cytology, cervical cancer risk factors (including infections and genetic factors) was performed. Publications dealing particularly with characteristics of Israeli Jewish women were reviewed and abstracted. Excluded were letters to the editor, case reports, series containing fewer than 15 patients, and publications dealing with data not necessarily specific for cervical neoplasms of Israeli Jewish women.

INCIDENCE

On the basis of observations on selected cohorts or in individual institutions it has been predicted for years that the incidence of cervical cancer in Israeli Jewish women will increase [4]. However, population-based studies refute this prediction [5-7]. The age-standardized incidence rate of invasive cervical cancer in Israel (about 5.0/100,000) is persistently lower compared to that in many other countries. During the period 2000–2005 the total incidence of cervical cancer ranged from 4.8 to 5.0/100,000 [6]. Similarly low annual incidence rates were also found during the period 1961–1971 compared to those during 2002–2004

[7]. Regarding SCC, not only has the incidence not increased but during the latter period it has significantly decreased, from 6.0 to 4.4 ($P < 0.01$). In view of the lack of a mass screening program in Israel, this decrease cannot be attributed to cytological screening and its reason is obscure.

A cohort analysis of 1052 cases of cervical cancer in Israeli Jewish women diagnosed between 1961 and 1981 [8] showed that among women born in Europe and America the highest risk was seen in those born in 1891–1895 and 1941–1945 and the lowest in women born between 1926 and 1935. Immigration to Israel at a younger age was correlated with reduced risk for cervical cancer. There was an increased risk for women of all origins born after 1940 and in women who were sexually active during the 1967–1970 epidemic of sexually transmitted diseases. The authors suggested that should the relative risk for cervical cancer in women exposed during that epidemic continue to be high, screening may prove worthwhile.

According to the Israel National Cancer Registry the incidence of CIN3 increased from about 12/100,000 in 1990 to about 15/100,000 in 1999. However, since then the incidence has stabilized [9]. The increase coincides with the mass immigration to Israel from the former Soviet Union. But it may have been also due to more frequent cervical cytological examinations.

The incidence of cervical cancer is higher in North African born women and their Israeli born descendants

INTER-ETHNIC DIFFERENCES

The Israeli population comprises various ethnic subgroups that have emigrated from various countries and continents where they have lived for many centuries. Each of these subgroups is characterized by some unique genetic disease, lifestyle habits, and exposure. In an older study it was proposed that the low incidence of cervical cancer in Israeli Jewish women is not a racial (i.e., genetic) phenomenon since it is similar in women of Ashkenazi* and non-Ashkenazi descent [10]. However, the ethnic origin regarding medical and other statistics is reported by the Israeli Central Bureau of Statistics according to continent of birth or is documented as Israeli born. When analyzed according to continent of birth, population-based studies repeatedly found that great ethnic variations exist and that the incidence in Jewish women born in North Africa, particularly those born in Morocco, was significantly higher than those born in other continents [5-8,11-13]. The mean age-adjusted incidence rate in North African born women in one of these studies [5] was 8.3/100,000 compared to 3.6, 2.8 and 2.5 ($P < 0.01$) in those born in Europe, Asia and Israel respectively.

SCC = squamous cell carcinoma
CIN = cervical intraepithelial neoplasia

*Jews of East European descent

HISTOLOGICAL DISTRIBUTION

As in other populations the most common histological type in Israeli Jewish women is squamous cell carcinoma. Of 434 cases of cervical cancer diagnosed in Israel between 2002 and 2004, 350 (80.6%) had SCC. The percentage of adenocarcinoma, adenosquamous carcinoma, anaplastic carcinoma and unclassified carcinomas was 11.8%, 3.9%, 1.4% and 2.3% respectively [7].

As in other populations, different characteristics were noted for SCC and adenocarcinoma. Of 532 cervical cancer patients diagnosed in Israel during the period 1961–1971, 52 (9.8%) had adenocarcinoma [5]. Contrary to SCC, the incidence of adenocarcinoma continued to rise until age 70+ and only minimal differences between ethnic groups were found during that period. In contrast to other western countries where the rate of SCC decreased and the relative frequency of AC increased, the total incidence rates and frequency rates of adenocarcinoma during 1961–1971 and during 2002–2004 in a population-based study were statistically not different (9.8% vs.11.8% respectively, $P = 0.3$) [7]. Contrary to the first period, the incidence of adenocarcinoma during the latter period was significantly higher in the North African born than in the other ethnic groups. In addition, a significant increase in the proportion of adenosquamous carcinoma was found (from 0.8% to 3.9%, $P < 0.001$) and was attributed to increased specificity in histological diagnosis of subtypes. The reason for the increase in incidence of adenocarcinoma in the North African born is not clear. Since HPV18 is more prevalent in adenocarcinoma, it has been speculated that it may be due to a more frequent exposure to this virus type in Israel than in their native country.

SCREENING AND CYTOLOGICAL FINDINGS

In view of the low incidence of cervical cancer, the need for cytological screening in Israel is controversial. The Israel Society of Obstetrics and Gynecology recommends screening every 3 years from the age of 25. On the other hand, the Israel National Oncology Council states that routine screening is unnecessary in women at regular risk and that it should be restricted to women at high risk, i.e., according to sexual habits, history of infection with high risk HPV types, and history of a previous cervical abnormal cytological smear or biopsy. No organized mass screening program exists in Israel and actually screening is opportunistic. The exact percent of women screened is unknown and nationwide data regarding the frequency of abnormal cytological smears and their trend are unavailable.

Following are the results of non-population based studies. No case of cervical intraepithelial lesions or malignancy was found among 3317 Israeli Jewish women using oral contraceptives who underwent a routine cytological smear [14]. In another study of 2150 women referred to a colposcopy clinic

(reason unspecified), the overall rate of cytological cervical dysplasia was 2.1% [15]. On the basis of observations in a selected population in an individual institution [16], there seemed to be an increase in the frequency of abnormal cytological smears in Israeli Jewish women. However, in the largest published study that analyzed the results of 297,849 cytological smears examined in a single laboratory during 9 years (1991–1999), the prevalence of cytological intraepithelial lesions (0.69% and 0.29% respectively) did not change during the study period [17].

A poor concordance was found between referral and medical center cytology reports of 95 women [18]. There was a tendency for over-diagnosis in both cytology report categories when compared to the final histological report, indicating the need for quality control of cervical cytology smears.

The low incidence in Israel remains obscure and whether it may be attributed to genetic reasons or to some traditional habits has yet to be confirmed

Atypical glandular cells of undetermined significance were identified in 45 (0.38%) of 11,800 Israeli Jewish women who underwent a cytological smear [19]. In 31 of these women atypical squamous cells of unknown significance were observed as well. Biopsy showed one microinvasive adenocarcinoma and two microinvasive SCCs. CIN2/3 was found in 21 patients (47%). The rate of atypical glandular cells of undetermined significance and of significant histological abnormalities was similar to that in other populations.

RISK FACTORS

The presence of well-known risk factors for cervical neoplasia in Israeli Jewish women is similar to that in other populations. A younger age at first sexual intercourse and a larger number of sexual partners was found among 391 Israeli women with various cervical cytological abnormalities [16] and among 222 SCC patients compared with controls [20].

Abnormal cytological and histological findings were found to be significantly more frequent among in utero diethylstilbestrol-exposed women [21] and in women with vulvar condyloma acuminata than in controls [22].

Prior to the discovery of the etiological role of HPV, herpes simplex virus type 2 sexually transmitted infection was implicated in the etiology of SCC. It has been shown that HSV2 infection is a cofactor and may act in conjunction with HPV infection to increase the risk of both SCC and adenocarcinoma. The association of HSV2 infection and cervical carcinoma was assessed in Israeli Jewish women as well. A low seroprevalence of HSV2 infection compared to other western populations has been found [23,24]. In two studies no association was found between the prevalence of HSV2 antibodies and cervical cancer [20] and with HPV16/18 infection [24]. Contrary results were obtained in another study [25]. In this study the sera HSV2 titers of 39 patients were compared to the titers in women with benign gynecological diseases matched by age and country of origin and to the titers of healthy subjects. The HSV2 titers were significantly higher in patients than in the controls and in the range of the rates reported in cervical cancer patients in other populations. However, the HSV2 titers in the healthy women were lower than in other populations, possibly explaining the infrequency of cervical cancer in Israeli Jewish women. Significantly increased levels of HSV2 antibodies as compared with controls were found also in 16 Israeli adenocarinoma patients [26].

Similar to other populations, cervical neoplasia in Israel is also associated with HPV infections. By blot hybridization HPV sequences were detected in 9 of 15 CIN and in 8 of 16 SCC lesions [27]. By the more sensitive DNA polymerase chain reaction amplification method the presence of HPV16/18 DNA in tissue of 10 CIN3 and 32 invasive cervical cancer patients was detected in 80% and 78% of the specimens respectively [28].

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

The most common main complaint of 350 SCC patients diagnosed according to the Israel National Cancer Registry during 2000–2004 [29] was discharge/bleeding (about 46% including post-coital bleeding). Compared to other populations, only a low rate of patients (7.4%) was diagnosed subsequent to an abnormal cervical cytology smear. The rate of patients diagnosed in stage I (about 48%) was similar to that in other populations. The overall 5 year survival and the survival in stage I of the study group patients (70% and 83.8% respectively) was also in the range reported in other western countries. This outcome was obtained although the treatment of cervical cancer in Israel is dispersed over many institutions and the annual case volume in each of them is small, limiting their therapeutic expertise. It should be mentioned, however, that the stage and main complaint in that population-based retrospective study were not recorded in about a third of the patients. Similarly favorable outcome rates were observed in individual institutions after treatment by radical hysterectomy or radiotherapy [30-32].

Recently, population-based studies of selected demographic characteristics of 1108 CIN3 [33] and 350 SCC patients [13] diagnosed and histologically confirmed during 2002–2004 according to the Israel National Cancer Registry were reported. The incidence of the CIN3 patients was 13.9/100,000 and their mean age was 38.4 years. Higher CIN3 rates were observed in 30–49 year old women, divorced women, and Israeli born women. The mean age of the SCC patients was 50.3 years. High SCC incidence rates of single women 40+ years old, of married women 30+ years old, and of divorced and widowed women in the 40–49 age group were found. No excess rate was found

HSV2 = herpes simplex virus-2

for multiparity. Contrary to some studies in other populations, no association with low socioeconomic status was observed in both neoplastic categories. This may possibly be attributed to the universal compulsory government-funded health care for all Israeli citizens irrespective of socioeconomic status.

DISTINCT CHARACTERISTICS

Several characteristics distinguish Jewish women from women in other populations. Jewish newborn males undergo ritual circumcision 8 days after birth. Whether the low incidence of cervical cancer in Israeli Jewish women can be ascribed to circumcision is not clear. In pooled data on 1913 couples in other populations, circumcision was shown to significantly reduce the risk of penile HPV infection in men and of cervical cancer of the female partners of men who practiced high risk sexual behavior. However, only a non-significant reduction in cervical cancer among women with circumcised male partners in the general population was demonstrated [34]. The results of this study have been criticized for several reasons: a) many confounding factors were not accounted for; b) samples for HPV testing were obtained by swabbing of the dry circumcised and the moist uncircumcised penises (swabbing of moist penises increases the likelihood of detecting HPV regardless of the actual rate of infection); and c) in the same participants the HPV genotypes in the men did not match those in their partners. Thus, whether the effect of male circumcision on the occurrence of cervical cancer in their female partners in general and in Israeli Jewish women in particular can be ascribed to circumcision remains controversial.

An additional distinct characteristic is the observance of the Jewish religious law of *Nidah*, i.e., prohibition of sexual intercourse both during menses and 7 days after its complete cessation. Cervical cancer seems indeed to be more common in secular than in Orthodox Jewish women who observe the law. However, the orthodox population also lacks many other risk factors such as early coitarche, multiple partners, and smoking. Although, with time, the great majority of Israeli Jewish women do not observe the law of *Nidah*, the incidence of cervical cancer has not increased.

Regarding the low incidence in Jewish women, Braithwaite [3] commented in 1901 that "there may be something in race," i.e., in genetics. Currently there is some evidence that genetic factors may indeed play a role in the etiology of cervical cancer. Significant familial clustering of cervical cancer has been observed among biologic relatives [35]. It has also been shown that the homozygous arginine polymorphism at codon 72 of p53 is a significant risk factor in the development of HPV-associated cervical cancer [36]. Although this subject is controversial, it seems to hold true for Israeli Jewish women. Homozygous arginine was found in a significantly higher percentage of 23 patients than in 162 controls (34.8% vs. 14.8% respectively, $P = 0.01$) [37]. The prevalence of the arginine homozygous p53 polymorphism paralleled the pattern of cervical cancer in Israel, i.e., it was lower than in other populations and significantly more common among those of North African than among those of other origins (30.3% vs. 10.8%, $P < 0.01$). The role of genetics in the incidence and in the ethnic distribution in Israeli Jewish women is also supported by the finding in a population-based study that the higher risk of cervical cancer persists in the second-generation Israeli born descendants of North African born women compared with those of other origins [6].

Israeli women seem to have a lower risk for progression from dysplasia to invasive carcinoma than other populations. This perception is based on an old finding that the rate of dysplasia (4.4%) among 250 women who underwent hysterectomy for non-malignant reasons and the rate of coexistence of carcinoma in situ with SCC (36%) among 50 cases of SCC were similar to those in other populations [38]. The authors concluded: "it appears that in a majority of Jewish women the histological spectrum leading to cervical cancer inexplicably stops at the dysplastic stage." In this context it should be mentioned that the prevalence of cytological low and high grade squamous intraepithelial lesions seems not to be different to that in other populations [17]. In an attempt to explain the incidence discrepancy between CIN3 and SCC in Israeli women, the proportion of known risk factors (age, place of birth, place of birth of parents, level of education, age at coitarche, number of partners, marital status, age at first pregnancy, number of pregnancies, number of children, type of contraception used, smoking) were compared according to a prestructured questionnaire between 41 CIN3 and 69 SCC patients [39]. No statistically significant difference regarding the variables assessed between the two entities was found.

Among a selective group of 84 Israeli Jewish women referred for colposcopic examination, mostly because of an abnormal cytological smear or biopsy (42%) or previous CIN2/3 (20%), the prevalence of high risk genotypes in the 37 HPV-positive samples was 41% of patients for HPV16, 22% for HPV39, 19% for HPV52, and 14% for HPV18 [40]. According to studies in other populations cited by the authors, infections with high risk genotypes other than HPV16/18 and with mixed infections seem less prone to progress to high grade CIN and invasive cancer. The authors suggested that the presence of a relatively high percentage of HPV types 39 and 52 and the relatively high incidence (59%) of infections with mixtures of genotypes may be one of the reasons for the low rate of conversion from high grade squamous intraepithelial lesions to invasive carcinoma in Israeli women.

Correspondence:
Dr. J. Menczer
Gynecologic Oncology Unit, Wolfson Medical Center, Holon 58100, Israel
Phone: (972-3) 502-8490
Fax: (972-3) 502-8107
email: joseph12@internet-zahav.net

References

1. Parkin DM, Bray F. The burden of HPV-related cancers. *Vaccine* 2006; 24 (Suppl 3): S11-25.
2. Munoz N, Castellsagué X, Berrington de González A, Gissmannet L. HPV in the etiology of human cancer. *Vaccine* 2006; 24 (Suppl 3): S1.
3. Braithwaite J. Excess of salt in the diet: a probable factor in the causation of cancer. *Lancet* 1901; ii: 1578-80.
4. Glezerman M, Piura B, Insler V. Cervical cancer in Jewish women. *Am J Obstet Gynecol* 1989; 161: 1186-90.
5. Menczer J, Modan B, Oelsner G, Sharon Z, Steintiz R, Sampson S. Adenocarcinoma of the uterine cervix in Jewish women: a distinct epidemiological entity. *Cancer* 1978; 41: 2464-7.
6. Menczer J, Barchana M, Chetrit A, Liphshitz I, Sadetzki S. Incidence rates of cervical carcinoma among first- and second-generation women of North African origin in Israel. *Int J Gynecol Cancer* 2009; 19: 1606-9.
7. Menczer J, Kogan L, Liphshiz I, Barchana M. Incidence trends of cervical adenocarcinoma in Israeli Jewish women. A population-based study. *Acta Obstet Gynecol Scand* 2009; 88 (3): 280-5.
8. Heering SL, Beller U, Baras M, Ben-Shlomo I, Steinitz R, Harlap S. A cohort analysis of cervical cancer in Israeli Jewish women. *Gynecol Oncol* 1990; 39: 244-8.
9. Special reports: Trends in incidence of malignant diseases in Israel 1990-2006. www.health.gov.il/pages/default.asp?maincat=22
10. Hochman A, Ratzkowski E, Schreiber H. Incidence of carcinoma of the cervix in Israel. *Br J Cancer* 1955; 9: 358-64.
11. Modan B, Sharon Z, Shani M, Sheba C. A comparison of some epidemiological aspects of cervical and endometrial carcinoma. *Pathol Microbiol (Basel)* 1970; 35 (1): 192-7.
12. Sharon Z, Shani M, Modan B. Clinicoepidemiologic study of uterine cancer. Comparative aspects of the endometrial and cervical sites. *Obstet Gynecol* 1977; 50: 536-40.
13. Menczer J, Kogan L, Schejter E, Liphshitz I, Barchana M. A population based study of selected demographic characteristics of Israeli Jewish women with cervical squamous cell carcinoma. *Arch Obstet Gyneol* 2011; 283 (2): 329-33.
14. Schachter A, Avram E, Gorodeski I. Cytologic findings in oral contraceptive users among Israeli Jewish women. *Acta Cytol* 1983; 27: 142-5.
15. Suprun HZ, Schwartz J, Spira H. Cervical intraepithelial neoplasia and associated condylomatous lesions. A preliminary report on 4,764 women from northern Israel. *Acta Cytol* 1985; 29: 334-40.
16. Bar-Am A, Niv J, Yavetz H, Jaffa AJ, Peyser RM. Are Israeli women in a low risk group for developing squamous cell carcinoma of the uterine cervix? *Acta Obstet Gynecol Scand* 1995; 74: 472-7.
17. Sadan O, Schejter E, Ginath S, et al. Premalignant lesions of the uterine cervix in a large cohort of Israeli Jewish women. *Arch Gynecol Obstet* 2004; 269: 188-91.
18. Korach J, Menczer J, Lusky A. A comparison between referral and hospital cervical cytology laboratory reports. *Isr J Med Sci* 1995; 31: 352-5.
19. Gutman G, Bachar R, Pauzner D, Lessing JB, Schejter E. Clinical evaluation of atypical glandular cells of undetermined significance upon cervical cytologic examination in Israeli Jewish women. *Br J Cancer* 2004; 90: 2194-6.
20. Pridan H, Lilienfeld AM. Carcinoma of the cervix in Jewish women in Israel, 1960-67. An epidemiological study. *Isr J Med Sci* 1971; 7: 1465-70.
21. Ben-Baruch G, Rothenberg O, Modan M, Menczer J. Abnormal cervical cytologic, colposcopic and histologic findings in exposed DES young Israeli Jewish women. *Clin Exp Obstet Gynecol* 1991; 18: 71-4.
22. Sadan O, Bilevsky E, Shejter E, et al. Occurrence of cervical intraepithelial neoplasia in generally healthy women with exophytic vulvar condyloma acuminata. *Infect Dis Obstet Gynecol* 2005; 13: 141-3.
23. Isacsohn M, Bar On E, Yaeger Y, Smetana Z, Weiner D, Slater PE. A seroprevalence study of herpes virus type 2 infection in Israeli women: implications for routine screening. *Isr J Med Sci* 1994; 30 (5-6): 379-83.
24. Isacsohn M, Dolberg L, Sabag SG, et al. The inter-relationship of herpes virus, papilloma 16/18 virus infection and Pap smear pathology in Israeli women. *Isr J Med Sci* 1994; 30: 383-7.
25. Menczer J, Leventon-Kriss S, Modan M, Oelsner G, Gerichter CB. Antibodies to Herpes simplex virus in Jewish women with cervical cancer and in healthy Jewish women of Israel. *J Natl Cancer Inst* 1975; 55: 3-6.
26. Menczer J, Yaron-Schiffer O, Leventon-Kriss S, Modan M, Modan B. Herpesvirus type 2 in adenocarcinoma of the uterine cervix: a possible association. *Cancer* 1981; 48: 1497-9.
27. Mitrani-Rosenbaum S, Gal D, Friedman M, et al. Papillomaviruses in lesions of the lower genital tract in Israeli patients. *Eur J Cancer Clin Oncol* 1988; 24: 725-31.
28. Menczer J, Fintsi Y, Arbel-Alon S, et al. The presence of HPV 16, 18 and p53 immunohistochemical staining in tumor tissue of Israeli Jewish women with cervical and vulvar neoplasia. *Eur J Gynaecol Oncol* 2000; 21: 30-4.
29. Kogan L, Menczer J, Schejter E, Liphshitz J, Barchana M. Selected clinical characteristics of Israeli Jewish women with squamous cell carcinoma of the uterine cervix. *IMAJ Isr Med Assoc J* 2011; 13 (2): 84-6.
30. Piura B, Dgani R, Yanai-Inbar I, Cohen Y, Glezerman M. Adenocarcinoma of the uterine cervix: a study of 37 cases. *J Surg Oncol* 1996; 61: 249-55.
31. Piura B, Rabinovich A, Friger M. Number and distribution of pelvic lymph nodes and effect of surgical pathologic factors on pelvic lymph node status in patients with early-stage cervical carcinoma treated with radical hysterectomy and pelvic lymph node dissection. *Eur J Gynaecol Oncol* 2006; 27: 463-6.
32. Menczer J, Atlas M, Werner A, et al. Survival data of Israeli Jewish patients with squamous cell carcinoma of the cervix treated by irradiation. *Gynecol Obstet Invest* 1983; 15: 141-6.
33. Kogan L, Menczer J, Shejter E, Liphshitz I, Barchana M. Selected demographic characteristics of Israeli Jewish women with high-grade cervical intraepithelial neoplasia (CIN3): a population-based study. *Arch Gynecol Obstet* 2011; 283 (2): 329-33.
34. Castellsagué X, Bosch FX, Muñoz N, et al. International Agency for Research on Cancer Multicenter Cervical Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002; 346: 1105-12.
35. Magnusson PK, Gyllensten UB. Cervical cancer risk: is there a genetic component? *Mol Med Today* 2000; 6: 145-8.
36. Storey A, Thomas M, Kalita A, et al. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature* 1998; 393: 229-34.
37. Arbel-Alon S, Menczer J, Feldman N, Glezerman, Yeremini L, Friedman E. Codon 72 polymorphism of p53 in Israeli Jewish cervical cancer and healthy women. *Int J Gynecol Cancer* 2002; 12: 741-4.
38. Czernobilsky B, Zeituni M, Lancet M, Mazor B, Baram A, Deligdish L. The prevalence of cervicitis, reserve cell hyperplasia, squamous metaplasia, and cervical dysplasia in Jewish women. *Obstet Gynecol* 1977; 49: 587-91.
39. Menczer J, Ben-Shem E, Golan A, Levy T. Risk factor proportions in Israeli patients with cervical intraepithelial neoplasia 3 and invasive squamous cell carcinoma. *J Low Genit Tract Dis* 2008; 12: 220-3.
40. Grisaru D, Avidor B, Niv J, et al. Pilot study of prevalence of high-risk human papillomavirus genotypes in Israeli Jewish women referred for colposcopic examination. *J Clin Microbiol* 2008; 46: 1602-5.

"Knowledge tells us that a tomato is a fruit; wisdom prevents us from putting it into a fruit salad"

Miles Kington (1941-2008), British journalist, musician and broadcaster

"I saw the angel in the marble and carved until I set him free"

Michelangelo (1475-1564), Italian Renaissance painter, sculptor, architect, poet, and engineer who exerted an unparalleled influence on the development of Western art