

The importance of HPV testing for cervical cancer screening in Israel

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Cervical cancer is a major health burden worldwide. More than 500,000 women are diagnosed with cervical cancer each year and more than 200,000 related deaths are reported, with more than 80% of cases occurring in developing countries [1,2].

In Israel, the age-standardized incidence rate of cervical cancer is persistently low. According to the Israel National Cancer Registry, in 2013 the age-adjusted incidence rate of cervical cancer in Israeli Jewish women was 5.07 per 100,000 and 3.18 per 100,000 in Israeli Arabs, for a total of 200 new invasive cervical cancer cases in that year [3]. Although we have a low prevalence of cervical cancer in Israel as compared to other countries, the mortality rate, which is 2.1 per 100,000, is similar to that reported in the Western world [4]. It is estimated that the similar mortality rates are related to the fact that in Israel due to the low incidence of cervical cancer, its prevention is based on opportunistic screening and not on an organized national Papanicolaou (Pap) screening program [5-7]. Nevertheless, these deaths are preventable. It is well known that the use of Pap smear as a screening tool for the early detection of pre-malignant cervical lesions and their treatment leads to a significant decrease of 70% in the death rate from this disease [8]. Thus, the recommendation

of the Israeli Society of Colposcopy and Cervical Pathology is to perform a routine Pap smear once every 3 years starting at 25 years until the age of 65 [9].

Human papillomavirus (HPV) is the major cause of cervical pre-malignant and malignant lesions. HPV is a common sexually transmitted infection that is untreatable. Usually it clears spontaneously with no severe sequela. However, persistent infection with high-risk HPV types, particularly type 16, is the most important factor for the development of cervical pre-malignant and malignant lesions [10-13]. It was demonstrated that at 10 years of follow-up, the cumulative incidence rates of cervical intraepithelial neoplasia (CIN)-3 in women who tested positive for HPV 16 and HPV 18 at enrollment were 17% and 14%, respectively. In women who were positive for other high-risk HPV types but negative for HPV 16 and HPV 18, the rate was only 3% [10]. Recent results from the HPV Screening Trial (Swedescreen) in Sweden also indicated that women with persistent infection will develop severe dysplasia (CIN 2-3) as compared to when the infection is cleared [13].

Data regarding HPV prevalence in Israel are lacking. Since the Pap test is opportunistic and voluntary there is no information regarding HPV prevalence in the general population. Some studies, however, tried to evaluate HPV incidence in different cervical pathologies. HPV was detected in 80–98% of cervical cancers and CIN 3 lesions obtained from paraffin samples [14-16]. The most frequent HPV type was HPV 16, present in 54–95% of the samples in the different studies. High-risk HPV types were also found in 24.7% of low-grade cytology specimens, such as atypical squamous cells

of undetermined significance (ASCUS) or low grade squamous intra-epithelial lesion (LGSIL) [17].

In the current issue of the Israeli Medical Association Journal, Siegler and colleagues [18] report the results of the largest Israeli study on the prevalence of HPV types in women at risk for cervical neoplasia in northern Israel. They obtained 6654 samples from women with either ASCUS on a Pap test or due to complaints suggestive of cervical neoplasia, including postcoital bleeding, cervical ectropion, or erosion. These samples were evaluated for the presence of 51 HPV types. Of the total, 3085 (46.4%) samples were positive for any HPV type, of which 2528/3085 (81.9%) were positive for high-risk HPV types. As expected, the high-risk types were more frequently observed in patients subsequently diagnosed with CIN 2-3 and cervical cancer (88.4% and 92.4%, respectively). HPV 16 was the most common type with overall prevalence of 10.4%. Its prevalence was particularly high in CIN 2-3 patients (42.9%) and cervical cancer (55.9%) as compared to CIN 1 (13.5%). Other frequent high-risk types found in CIN 2-3 were HPV 31 (9.7%) and 18 (5.3%). However, in the cervical cancer patients, HPV 18 was more prevalent (9%) compared to type 31 which was present in only 2.8% of cases.

The interesting and clinically significant findings of this study are related to the 2210 patients with ASCUS in their samples. In 991 (44.8%) samples, HPV-DNA was found, which was high-risk in 812 of the positive samples (81.9%). Again, HPV 16 was the most common type followed by HPV 31 and HPV 18.

The article by Siegler et al. [18] presents the largest comprehensive data from Israel

on the prevalence of HPV in women with potential risk for cervical neoplasia. Of those diagnosed, 46.4% will test positive for HPV, which will be mostly high risk. Many studies have shown the importance of adding HPV testing to the Pap test to increase the screening sensitivity and to better diagnose cervical premalignant and treatable lesions [19]. The present data highlight the importance of implementing HPV testing also in Israel as part of the routine screening for cervical cancer. Furthermore, women found to have ASCUS on their Pap test should be evaluated for the presence of HPV. If these tests are conducted, 55.2% could be spared unnecessary colposcopy and invasive procedures.

HPV 16 was the most common type found in the HPV-positive samples, particularly in women subsequently diagnosed with CIN 2-3 and cervical cancer. Previous studies have shown that HPV types 16 and 18 are diagnosed in 71% of cervical cancer cases [2]. For this reason a vaccine against these types was developed in the last 2 decades. It was introduced for teenagers in many developed countries, including Israel. The data presented by Siegler and co-authors [18] indicate that this vaccine can prevent more than 60% of the diagnosed cancers that were related to HPV 16 and 18. These data highlight the importance of continuous implementation and completion of the prophylactic vaccine series in adolescence to achieve maximum protection against these types.

Since cervical cancer is rare in Israeli Jewish and Arab women, there is no national consensus regarding screening and vaccination. The data that we have, and that influence Israeli health authority decisions, are driven from studies published on small series from medical centers [14,15,20] or from larger but not equal health maintenance organization populations [6,7,16]. Furthermore, there is no laboratory standardization regarding Pap test and HPV typing. Thus, results of these studies give us different and conflicting numbers about the prevalence of CIN, cervical cancer, and

HPV in Israel and cause confusion regarding national guidelines.

The study by Siegler and colleagues [18] presents the largest data sample of information regarding HPV prevalence in women with potential cervical pathology. Thousands of women were HPV positive, most of them with high-risk HPV types. These data indicate that it is time to consider greater utilization of HPV typing as part of an organized national screening and as a triage for further evaluation and treatment.

CONCLUSIONS

In conclusion, Israel still has non-uniform and confusing guidelines regarding cervical cancer screening and prevention. Results from large national surveys, as the one presented here will contribute to simplify decision making to reduce morbidity and mortality, which for HPV related diseases, are by far preventable.

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