PROSPECTIVES OF CERVICAL CANCER PREVENTION IN CROATIA

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Summary
The situation of cervical cancer prevention in Croatia is hardly well established, in spite of the fact that opportunistic screening is on going for some time and that cervical cancer is on the 8th place of female cancer. Each year, approximately 350 women develop cervical cancer and about 100 die from the disease. A matter of concern is the steady state of the mortality rate. Thus, appropriate cervical cancer prevention programmes should be set up without delay in Croatia.

Key words: cervix, cancer, screening, HPV vaccination, prevention, Croatia

INTRODUCTION

This paper has been written as a contribution to a special issue of Central European Journal of Public Health edited at the occasion of the Human papillomavirus (HPV) in Human Pathology Congress, Prague (Czech Republic), 1–3 May, 2008. This congress offers an excellent opportunity to exchange and discuss the actual knowledge and possibilities on cervical cancer prevention. Cervical cancer contributes considerable health burden and loss of lives in Croatia. In the present study, we presented the burden of cervical cancer in Croatia in the last two decades as well as future prospective of disease prevention.

CERVICAL CANCER BURDEN IN CROATIA

Background

Cervical cancer is the second most common female cancer worldwide with about 493,000 incident cases per year. There are about 273,000 cervical cancer deaths in the world yearly, 85% of which take place in developing countries (1). The majority of incident cases occur between ages 30 and 50.

In Europe, there are about 50,000 new cases and about 25,000 deaths yearly (1). Although many European countries have some form of cervical screening, substantial regional variations are observed in Europe where cervical cancer incidence and mortality rates in Northern and Western Europe are almost half those seen in Central, Eastern and Southern Europe, differences that are mainly due to the presence or absence of effective cervical screening. The lowest European age-standardised incidence (4.3/100,000 women-years) and mortality (1.8/100,000 women-years) rates in 2002 were reported in Finland, while the highest incidence rate (27.4/100,000 women-years) was in Serbia and Montenegro and the highest mortality rate (13/100,000 women-years) was in Romania (2). Croatia has lower cervical cancer incidence (13.3/100,000 women-years) and mortality (5/100,000 women-years) age-standardised rates than most Central and Eastern European countries, but it is still much higher than in countries with organised cervical cancer screening programmes. In countries with organised cervical cancer screening programmes, cervical cancer is usually the 10th most common female cancer, while it is on the 8th place of female cancer in Croatia with on average 350 new cases, and about 100 deaths each year (3).

The Current Situation

Opportunistic cervical cancer screening was introduced in Croatia in the 1960s and this was accompanied with decreasing cervical cancer incidence rates until the year 1991 but no further consistent decrease has been observed afterwards (Fig. 1) (3). The cervical cancer mortality rates remained at a low level during the entire period but no decrease was observed over the last decade (Fig. 1) (3).

It is evident that opportunistic cervical cancer screening in Croatia had an impact on cervical cancer control. The number of Pap smears taken yearly is still increasing and reached more

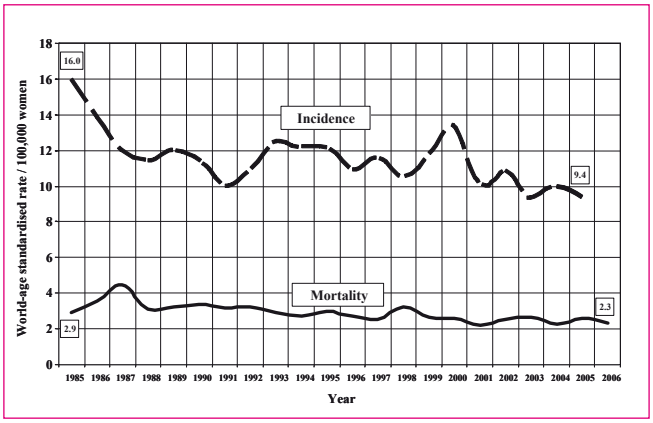

Fig. 1. *World age-standardised incidence and mortality rates (per 100,000 women-years) of cervical cancer in Croatia from 1985 to 2006 (Source: Cancer Registry of Croatia).*

than 500,000 in 2005 in a whole country (4). However, in the absence of an organised population-based programme it is difficult to assess the efficacy of this screening and it is clear that a large proportion of target population still remains un-screened or under-screened. The only way to achieve further reductions in cervical cancer cases is through the introduction of an organised cervical cancer screening programme. Indeed, this is the only way that enables further reduction of cervical cancer rates, while providing equitable, cost-effective protection. Such effective programmes enable a reduction of cervical cancer incidence and mortality by more than 80%, particularly in British Columbia and the Nordic countries (Finland, Denmark, Iceland, Norway and Sweden) (5).

PREVENTIVE STRATEGIES FOR CERVICAL CANCER IN CROATIA

Proposal for the National Cervical Cancer Screening Programme

Following the recommendations for cervical cancer screening in Europe in 2003 (6), a working group of the Croatian Ministry of Health and Welfare has proposed a national cervical cancer screening programme, although this has not yet been introduced (7). The proposed programme comprises screening of women aged 25–64 years every three years by Pap-smear in the first phase. In the second phase of the programme, in addition to Pap-smear, HPV test would be introduced for women aged 30–64, with five-year screening intervals. The Croatian proposal for cervical cancer screening is in line with the European guidelines, which specify that cervical cancer screening programmes should target the age-group 25–64 years (8) and the International Agency for Research on Cancer (IARC), which recommends the introduction of HPV-DNA screening within organised programmes in such a way that the efficacy and effectiveness can be evaluated (5).

The gynecologists were the first to perform microscopic analysis of cervical smears as in most European countries that implemented Papanicolaou test. However, in Croatia Dr. Jasna Ivic, who devoted her work exclusively to gynecological cytology since 1959, established in 1968 the first Laboratory of Cytology in Zagreb, which further, in 1984, became the Institute of Gynecological Cytology (4). Since then continuous development of gynecological cytology in the professional, scientific and educational aspects was ongoing. A uniform classification named Zagreb 2002, a modification of Zagreb 1990 and NCI Bethesda System 2001, has been used in cytological analysis of cervical smears (9). This uniform classification enables both internal and external quality control of the laboratory performance, along with appropriate reproducibility of cervical cytology relative to the terminology adopted in the world. Recently, efforts to introduce high sensitivity methods of sample preparation (Liquid Based Cytology – LBC) are made to further improve the cytology service at the national level.

With a tradition of more than half a century and a network of cytology laboratories with highly competent cytologists and cytotechnologists more than 500,000 Pap tests can be performed each year (4). The Croatian population is 4.4 million according to 2001 census (10), while the target screen population 25–64 years is 1.2 million women. Thus, with the actual capacity of gynecologists (smear takers), cytologists and cytotechnologists, 3 years would be necessary to enrol the whole target screen population. HPV testing was implemented in Croatia from 1995 and is available in several centres throughout the country, although higher capacity will be needed when implemented as a screening test (11). Diagnostic and treatment procedures including colposcopy, repeat cytology, HPV testing and follow-up are well established in Croatia (12, 13). At present, only the political will is needed to implement the national organised screening programme (14).

HPV Vaccination

Two HPV vaccines have been developed and designed to protect against oncogenic HPV types 16 and 18, which are together responsible for about 70% of cervical cancers worldwide and a substantial proportion of abnormal cytological smears (15, 16). Vaccination has been shown to provide the most effective protection if given to young women before they have been exposed to the HPV types contained in the vaccine and they have not been shown to provide effective protection if women are already infected with these types at the time of vaccination. In addition, the current HPV vaccines will not prevent infection with all oncogenic HPV types and therefore cannot replace the traditional cervical cancer cytological screening. However, upon implementation of HPV vaccination, screening methods and intervals may be modified to account for changes in population risk for the development of cervical cancer.

Both vaccines, or at least one, are currently available within many European countries including Croatia. Vaccination against HPV will clearly be an important tool in the battle against cervical cancer, and all European countries now need to be planning comprehensive cervical cancer prevention programmes that effectively integrate cervical screening together with HPV vaccination as it is the combination of these that will offer the most effective long-term protection against this disease.

So far, several recommendations for the use of vaccination were issued by different professional medical associations in Croatia, but still no consensus was reached. Additionally, the cost of vaccination is not covered by the Croatian Health Insurance. In order to ensure reimbursement of vaccination by the Croatian Health Insurance Institute, a request would need to be produced and an expert committee would then decide if the request is to be accepted (17). These procedures will probably be engaged in the near future. Making a decision on the reimbursement of the vaccination requires careful consideration and a comparison of the cost-effectiveness of a mandatory vaccination against other competing public health priorities.

Regardless of the reimbursement policy for recommended vaccination, it is evident that the priority in Croatia is to establish primarily a nation-wide organised cervical cancer screening programme, and immediately after include HPV vaccination within a well designed vaccination programme. This could be achieved by introducing HPV vaccination into the mandatory Childhood Vaccination Programme (17).

CONCLUSION

Opportunistic screening in Croatia did reduce the incidence and the mortality rates of cervical cancer among Croatian women in the last two decades because it was and still is based on a high quality of conventional gynecological cytology but still, rates are very high compared to countries that implemented organised cervical cancer screening. Now, there is a very urgent need to move forward with the introduction of a comprehensive organised cervical cancer prevention programme in Croatia that will include organised cervical screening of adult women and organised HPV vaccination of adolescent girls. Indeed, this is the only way how to further reduce cervical cancer rates, while providing equitable, cost-effective protection to all women in Croatia.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM, editors. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon: IARC Press; 2004.
2. Arbyn M, Primic-Zakelj M, Raifu AO, Grce M, Paraskevaidis E, Diakomanolis E, et al. The burden of cervical cancer in couth-east Europe at the beginning of the 21st century. Coll Antropol. 2007 Apr;31 Suppl 2:7-10.
3. Croatian National Institute of Public Health. Cancer incidence in Croatia. Bulletins Croatian National Institute of Public Health Zagreb. 1983-2006;no.1-29.
4. Pajtler M, Audy-Jurković S, Kardum-Skelin I, Mahovlić V, Mozetič-Vrdoljak D, Ovanin-Rakić A. Organisation of cervical cytology screening in Croatia: past, present and future. Coll Antropol. 2007 Apr;31 Suppl 2:47-54.
5. IARC Working Group on the Evaluation of Cancer Preventive Strategies. Cervix cancer screening. IARC handbooks of cancer prevention, vol.10. Lyon: IARC Press; 2005.
6. The Council of the European Union. Council recommendation of 2 December on cancer screening. Off J Eur Union. 2003;878:34-8.
7. Znaor A, Babić D, Ćorušić A, Grce M, Mahovlić V, Pajtler M, et al. Proposal for cervical cancer early detection programme in Croatia. Lijec Vjesn. 2007;129:158-63. (In Croatian.)
8. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al, editors. European guidelines for quality assurance in cervical cancer screening. 2nd ed. Luxembourg: Office for Official Publications of the European Communities; 2008.
9. Ovanin-Rakić A, Pajtler M, Stankovic T, Audy-Jurković S, Ljubojević N, Grubišić G, et al. Classification of cervical cytological smears „Zagreb 2002“. Modification of the classification „Zagreb 1990“ and „NCI Bethesda 2001“. Gynaecol Perinatol. 2003;12 (4):148-53. (In Croatian.)
10. Republic of Croatia. Central Bureau of Statistics [homepage on the Internet]. Zagreb: Census of population, households and dwellings, 31st March 2001 [cited 2008 Mar 11]. Available from: http://www.dzs.hr.
11. Grce M, Grahovac B, Rukavina T, Vrdoljak Mozetič D, Glavaš-Obrovac L, Kaliterna V, et al. HPV testing for cervical cancer screening in Croatia. Coll Antropol. 2007 Apr;31 Suppl 2:67-71.
12. Ljubojević N, Babić S, Audy-Jurković S, Ovanin-Rakić A, Grubišić G, Jukić S, et al. Diagnostic and therapeutic guideline for premalignat cervical lesions. Gynaecol Perinatol. 2001;10:85-9. (In Croatian.)
13. Grubišić G. Limitations of colposcopy in early invasive cervical cancer detection. Coll Antropol. 2007 Apr;31 Suppl 2:135-8.
14. Znaor A, Strnad M. Cervical cancer in Croatia: state of the art and possibilities for prevention. Coll Antropol. 2007 Apr;31 Suppl 2:37-40.
15. Gissmann L, Müller M. Development of prophylactic HPV vaccines. Coll Antropol. 2007 Apr;31 Suppl 2:113-5.
16. Davies P, Bogdanovic-Guillion A, Grce M, Sancho-Garnier H. The future of cervical cancer prevention in Europe. Coll Antropol. 2007 Apr;31 Suppl 2:11-6.
17. Kaić B, Gjenero-Margan I, Brzović M, Lakoseljac D, Aleraj B, Nemeth-Blazić T, et al. Vaccine regulations in Croatia. Coll Antropol. 2007 Apr;31 Suppl 2:117-20.