

EUROCHIP-II
FINAL SCIENTIFIC REPORT
ANNEX 15c

**REPORT OF
EUROCHIP-2 ACTION IN
SLOVAKIA**

Cervical carcinoma screening program in Slovakia

December 2007

Dr. Ladislav Masak
Head of Gynecologic Oncology Department
Cancer Institute of St. Elisabeth
Bratislava, Slovakia

Dr. Ivan Plesko,
Head Department of Cancer Epidemiology
Cancer Research Institute of Slovak Academy of Sciences
Bratislava, Slovakia
email: ivan.plesko@savba.sk

Uterine cervix cancer in Slovakia - incidence and mortality time trends and screening

Introduction

The highly reliable mortality data on malignant neoplasms in developed countries of world including Slovakia are available generally in or from postwar period, beginning mainly in the period around the year 1948 (1, 2). The development of mortality from uterine cervix cancer in Slovakia indicated high level of rates in early postwar period but a continuous decline till mid 1950s, stabilization until 1968 followed by their increase in following years (1, 3, 4). Official incidence rates (5) from this period showed peaking in 1970 and decrease in the next years and did not correspond with the evolution of mortality rates. There were evident discrepancies between incidence and mortality rates available from official mortality and incidence statistics. The screening of uterine cervix cancer has been introduced relatively early in the late 1960s. The number of women covered with screening using cytology of Pap smears as well as the number of women detected during screening with cancer in stage in.situ was surprisingly high and surely overestimated (6).

Only the data on uterine cervix cancer incidence available from 1968 from the National Cancer Registry of Slovakia are of great validity (3, 4, 5). They correspond with data of mortality available for the period 1968-1985 from mortality statistics computed in registry (5) and later from improved official mortality statistics compiled in Central Statistical Office.

Material and methods

The incidence rates including the numbers and proportion of in situ and invasive uterine cervix cancer for the period 1968- 2003 were derived from the main file of National Cancer Registry. The mortality rates were derived partially from the registry (1968-1985) and for the following years till 2003 from official mortality statistics produced by Central Statistical Office and by National Center of Health Statistics. The incidence and mortality rates were age-adjusted using world standard population. Similar sources were used for computation of age-specific incidence and mortality rates in the year 2003.

The data on screening of this cancer site were obtained from Slovak Society of Gynecology and Obstetrics. In the frame of this Society there are two sections oriented to the problems of oncology: Section of Gynecological Oncology and Section of Colposcopy and Cervical Pathology. These two sections prepared the proposal and project of systematic performance of cytological screening of uterine cervix cancer in Slovakia. The acceptance of the main role of human papiloma virus (HPV) in the etiology of the given cancer led to some modification of secondary prevention, e.g. screening of uterine cervix cancer (7, 8, 9). The consequences of this knowledge for improvement of screening in Slovakia will be mentioned later.

Evolution of incidence and mortality rates of uterine cervix cancer in Slovakia

Age-adjusted mortality and incidence rates of invasive and in situ uterine cervix cancers are demonstrated in Figure No.1. There was a steady decrease of incidence rates in the period studied, from the late 1960s with the lowest rates in the mid 1970 . Gradual increase of incidence rates in following years continued till the early 1990s and was followed by stabilization in the last decade of the studied period. The development of incidence of in situ uterine cervix cancer showed steady increase from only less than 10 cases in one year in the early 1970s to a little more than 100 in the mid 1980s and 350 cases in the last available year –2003, with 542 invasive cases. In this year there were 1,5 cases of invasive to 1 case of in situ cancers.. Despite this favorable evolution the mortality rates showed parallel evolution with the rates of invasive cancers which means that the screening or increase of in situ cancers did not influenced the evolution of mortality rates till the recent years of the time period studied. Experiences from abroad indicate that the opposite relation- two in situ to one invasive cancer of uterine cervix led to diminishing of mortality from this cancer site. It is evident from this figure, that the screening was mainly oriented to the younger age-groups. Trends of mortality of this cancer site in Slovakia remind those ones observed in Spain in the years 1955- 1995 (10).

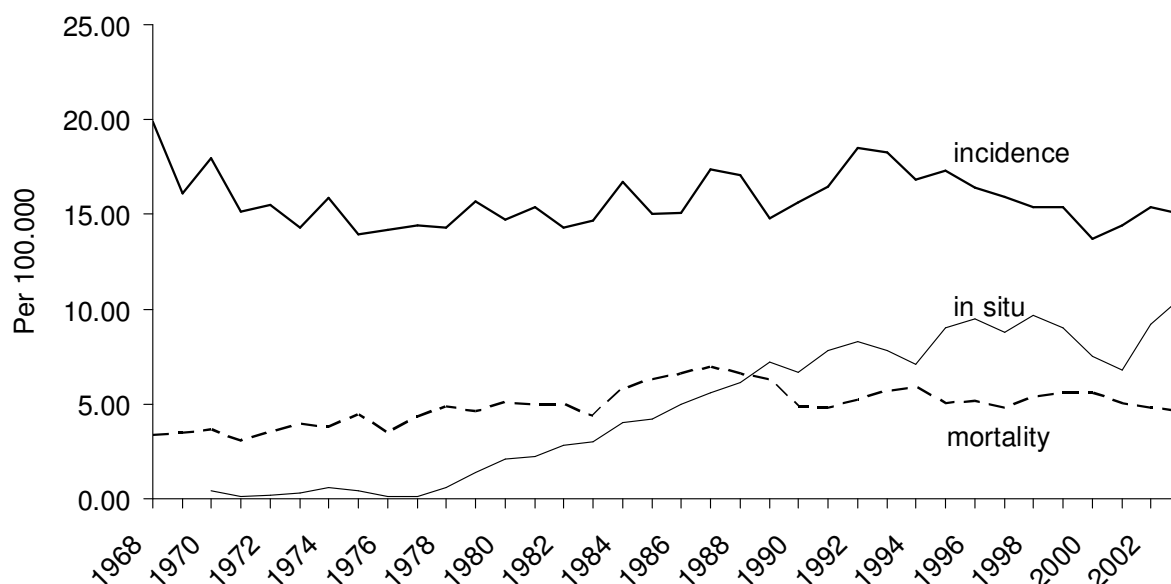


Fig. 1: Development of age-adjusted incidence of invasive and in situ and of mortality of uterine cervix cancer, Slovakia 1968-2003

Age-specific incidence and mortality rates of invasive as well as of in situ uterine cervix cancer are shown in the Figure 2. This figure indicates the strong and sharp increase of incidence of invasive cancers beginning in the age- group 20-24 years and peaking in the age -group 40-49 years, thereafter continuous and gradual decrease in higher age with the lowest rates in the highest age- group 85 and more years. The similar evolution display the age-specific rates of in situ cases, but with increase only till the age -group 30-34 years, plateau till the age-group 40-44 years and gradual decrease in following, higher age-groups.

EUROCHIP-2 Final Report – Annex 15c – EUROCHIP-2 in Slovakia (cervical screening)

The orientation of screening or better compliance of prevention is obviously confined to the younger age-groups of women. Moreover the yielding of in situ cases in older age groups is generally low (10). Different shape display mortality rates which show continuous and gradual increase from lowest till highest age groups. The given age-specific mortality rates suggest also failure of screening to prevent much disease (3, 10).

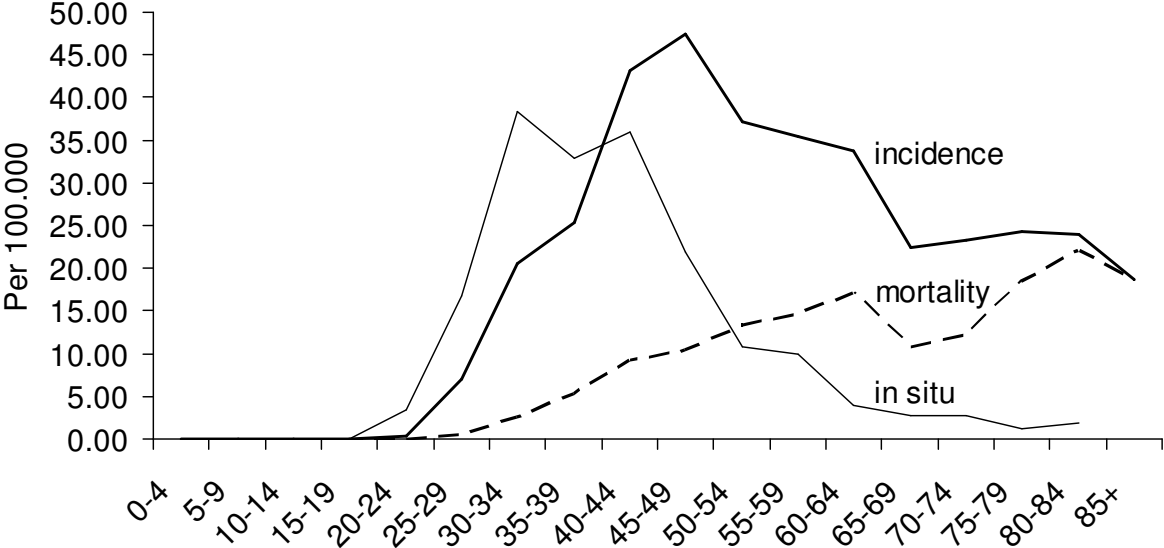


Fig. 2: Age-specific incidence of invasive and in situ and of mortality rates of uterine cervix cancer in Slovakia in 2003

Screening of uterine cervix cancers

Uterine cervix cancer has the great potential for prevention and simultaneously for early detection and adequate follow-up therapy (7, 9, 10). Experiences obtained mainly in Nordic countries with the method of cytological examination of smears from cervix indicated that this method may reveal the presence cytological abnormalities indicating the presence of dysplasias of various grade, of cervical intraepithelial neoplasias (CIN), or low- or high grade cytological abnormalities, as well as in situ (CIN-3) (8, 9, 10). All these early lesions are considered as precancerous lesions which can progress to invasive cancer (8, 9, 10, 11). Their treatment (together with early invasive cancer which could be revealed with this method) is highly effective and when this test and following treatment is systematically applied major reduction in both incidence and mortality as well as survival rates could be achieved (11). These favorable results led WHO experts to advice that countries with limited resources should aim to screen every women once in her lifetime between 35 and 40 years of age. In countries with more resources - the case of Slovakia – the frequency of screening should be increased to every 10 and then every 5-years for women aged 35 to 55 years. Only when this result is achieved it is possible to extend screening to younger age, and rarely below 25 years of age. According to the advices of the experts of WHO in the national cancer control programs wherever the laboratories to examine the smears and facilities for treatment of these abnormalities are available, the initial aim should be to screen every woman aged 35 – 40 years at least once. When 80% of women aged 35-40 years have been screened once, screening frequency should increase to 10-yearly and then to 5-yearly for women aged 30-60 years, if resources permit it this step. WHO experts stress the gradual efforts to increase the quality of laboratory tests and the compliance of the target population (8, 10, 12). It is stressed that extending the screening to younger ages does not compensate for deficiencies in laboratory quality and compliance (8, 10,12). It seems that the introduction of vaccine against HPV infection does not change the necessity of performing the screening (7, 12). Of great importance remain also the role of registries for the evaluation and monitoring of screening programmes (9, 10, 12).

In recent years the attitude to the screening of this cancer site was strongly influenced by the largely accepted knowledge that more than 95% of uterine cervix cancers is caused by persistent infection with high risk types of human papiloma viruses (HPV). This central role of HPV infection in causation of uterine cervix cancers (as well as of the cancers of neighboring genital organs – vulva, vagina, ano-genital region etc.) led to the preparing, use and evaluation of prophylactic vaccination in preventing infection and cervical intraepithelial neoplasia (CIN), and in situ and invasive cancer of uterine cervix (7, 8, 12), On the other hand there were efforts oriented to the detection and typing of HPV viruses responsible for infection. There is also increasing interest to use HPV DNA testing for screening and the international evaluation of this test is under way (7, 8, 9, 10, 12). The performance of screening using smears from uterine cervix and their cytological examination remained the most useful and a viable option for the medium –resourced countries. The method of screening is closely related to the financial resources of the given country. For developing countries with limited resources the more cheap tests are advised and evaluated – visual inspection with acetic acid (VIA) and with Lugol's iodine (VILI) (8, 12).

Screening of uterine cervix cancer in Slovakia

Because of relatively high incidence and mortality from uterine cervix cancer in Slovakia there were efforts to introduce cytological screening during the 1970s. These efforts were stimulated mainly by stabilization of incidence and mortality rates in the early 1970s after their gradual decrease in postwar period mainly during 1960s, followed by increase of both indicators in the late 1970s. The increase of overall incidence and mortality rates was mainly influenced (similarly as in other developed countries of Europe) by dramatic increase of these rates in women aged 30-49 years and born after the calendar year 1930 (4). Simultaneously the given rates in highest age groups remained unchanged or even decreased.

First data on the number of cytological screenings using PAP smears are available beginning with the year 1970 and were regularly notified to Annual Report on the Results of Treatment in Gynecological Cancer, and published by FIGO (International Federation of Gynecology and Obstetrics). In the time period 1973-1976 the number of preventive examinations varied between roughly 500 to 600 thousands yearly and led to the increasing numbers of the tumors revealed by preventive examination of smears from 65 in 1973 to 179 cases in 1976 together with down staging of these malignancies (6). The presented number of cytological screenings was obviously overestimated because the development of mortality rates remained unchanged, and even showed gradual increase and similar tendency as the incidence rates (3, 4). On the other hand there were discrepancies in evaluation of the grade of CIN as well as acceptance of CIN-3 as a cancer in stage in situ (6). Moreover the thorough evaluation of declared data revealed that some women were examined four or even more times in one year and some no once during their whole life.

The concise National Cancer Control Program introduced in 1976 led to some improvement in the given field (13). The main imperfection of this program was its orientation to the very large spectrum –nearly all cancer sites (plus precancerous lesions), without respecting different occurrence and consequently the importance of particular cancer sites. The screening of uterine cervix cancer was also but only marginally mentioned - as the necessity of performance of screening of uterine cervix and breast cancer in women aged 30 years and more (13). In the same year the age of women screened for uterine cervix cancer was decreased to 18 years if they had sexual intercourse. It is evident that this programme did not improved the occurrence of cervical cancer. The number of in situ as well as of invasive cancers increased but simultaneously the increase of mortality rates was remarked. It is evident now that the declared number of Pap smears was overestimated or “improved”. It is also possible that some women were screened several times and some never as mentioned above. Unfortunately the situation in this field showed no improvement also after political changes in this country in 1989 as well as after declaration of independence of Slovakia in 1993. In the present time the cytological screening is limited to the examination of Pap smears in women attending gynecologists for gynecologic diseases or pregnancy (opportunistic screening). There are actually six health insurance companies and they declare to pay every preventive examination to every women, including cytological examination of Pap smears. On the other hand the health insurance companies are well aware on the disinterest of women concerning preventive examinations and moreover they present no activity in the invitation and information of women on importance to participate on preventive examinations. According to the data obtained from biggest health insurance company only about 20% of women in Slovakia participated on preventive examinations –of uterine cervix cancer screening - from 0 to 50 % in different districts.

EUROCHIP-2 Final Report – Annex 15c – EUROCHIP-2 in Slovakia (cervical screening)

The above mentioned sections of Slovak Gynecological and Obstetrics Society oriented to oncology –Section of Gynecological Oncology and Section of Colposcopy and Cervical Pathology prepared recently proposal oriented to the realization of systematic cytological screening of uterine cervix cancer and precancerous lesions in the whole territory of Slovakia. According to this proposal the cytological screening should start 4 years after the beginning of sexual life, lately at the age of 23 years. Cytological smears should be realized using special brush – cytobrush – during the first two years after beginning of screening in one year intervals. If the first two smears are negative the next examination should be performed in three years intervals with the end of screening at the age of 64 years if the three previously performed tests were negative. The smears should be evaluated in accredited cytological laboratories which are able to apply and respect the principles accepted by European Union. The results should be evaluated and formulated according to the Bethesda classification.

The detection of HPV is not in present time a part of screening with regard to the high price of this test. Health insurance companies are but obliged to pay the detection of HPV for women with cytological confirmation of ASCUS (Atypical Squamous Cell of Undetermined Significance) and 6 months after conisation of uterine cervix because of presence of dysplasia (CIN of various degree) using the method HC2 (detection of the presence of HPV without indication of particular type). Colposcopic examination is no more accepted as part of the screening but expert colposcopy is introduced for differential diagnostics of positive cytological findings. Reference center designed for written invitation of women to cytological investigation and for control of the acceptance of invitation and participation on the given examination should be created. The main task of this center should be the control, monitoring and evaluation of the screening in the whole country.

There is actually the discussion in parliament on the change of the law No. 577/2004 dealing with health protection. One part of this law deals with the problem of organization and performance of cytological screening. It seems that that the screening for uterine cervix cancer and premalignant lesions covering the whole female population of Slovakia may start during this very year.

Of great importance in the introduction of problems of systematic screening is the health education of female population oriented to the information on the importance and advantages of screening on its performance and positive consequences. This education campaign is supported by the Glaxo-Smith Kline Company which produces the vaccine Cervarix against infection with HPV. Together with the information for women – mothers on the reasons of vaccination of their daughters against HPV infection they will receive also written invitation for performance of smears for cytological examination which should be performed by local gynecologist. The educational campaign of population is highly supported by League Against Cancer of Slovakia.

Slovakia as a member of EU is obliged to accept the requirement of EMEA (European Medicines Agency) in the introduction of the new medicaments in praxis. As well as I other member countries of EU in Slovakia the vaccines Silgard (quadrivalent vaccine containing proteins of the types 6, 11, 16 and 18 of HPV) and Cervarix (bivalent vaccine containing proteins of the types 16 and 18 of HPV) is accepted and available. Both vaccines could be used for girls from the age 9-10 years and for women under 25-26 years of age. The vaccination of girls is performed by pediatrician, of older girls and women by gynecologist. Vaccination is not covered by health insurance companies, the price of one dose of vaccine is 4 300 SK (about 130 Euro), of the whole vaccination - 3 doses 12 900 SK (about 390 Euros).

EUROCHIP-2 Final Report – Annex 15c – EUROCHIP-2 in Slovakia (cervical screening)

The minimal month salary was at the end of previous year (2007) 8 100 SK (about 242 Euros). Health insurance companies reimburse 10% of the price of vaccine but only to girls aged 12 years. For the major part of population the price of vaccination is too high. Fortunately at the Ministry of Health the Commission for Vaccination is established which propose all-country vaccination programmes. This commission proposed to use the money for public health for the vaccination of the whole cohort of girls aged 12 years in the year 2009. We do hope that in coming years the dramatic improvement in the prevention of uterine cervix cancer expressed by the fall of mortality could be obtained in this country. In conclusion it is necessary to stress the important role of National Cancer Registry in the monitoring and evaluation of this preventive action.

This document was prepared by Dr. Ladislav Masak, Head, of Gynecologic Oncology Department in Cancer Institute of St. Elisabeth in Bratislava, Slovakia and Dr. Ivan Plesko, Head, Department of Cancer Epidemiology, Cancer Research Institute of Slovak Academy of Sciences in Bratislava, Slovakia

References

1. Dolejsi V.: Evolution of the mortality from malignant neoplasms in CSR in the years 1948-1972. *Demografie* 1977; 19:308-314 (in Czech).
2. Hansluwka H.: Cancer mortality in Europe, 1970-1974. *Wrlld. Hlth. Stat.Quarterly* 1978; 31: 159-194.
3. Vlasák V, Pleško I., Dimitrova E, Hudáková G, Recent trends in uterine cervix cancer in Slovakia, 1968-1987. *Neoplasma* 1991; 38: 533-539.
4. Pleško I, Obšitníková A, Occurrence of uterine cervix cancer in Slovakia (1968-1994). *Prakt. Gynecológia* 1998; 5: 161-166 (in Slovak).
5. Plesko I, Dimitrova E, Kramarova E, Vlasak V, Obsitnikova A Development of registration and cancer incidence rates and trends in Slovakia. *Eur. J. Cancer* 27; 1991: 1049-1052.
6. Pleško I, Manka I, Dimitrova E, Epidemiology of cervical and breast cancer. In: *Cytology in Gynaecology and Obstetrics*. County Seminar 9.12.1977, Banská Bystrica, 1978: 10-24.(In Slovak).
7. Sankaranarayanan R, Ferlay J, Worldwide burden of gynecological cancers: The size of the problem. *Best Practice & Research Clin. Obstetrics and Gynaecology* 2006; 20:207-225.
8. Segnan N, Armaroli P, Sancho-Garnier H, Le depistage. In: *Prevention des cancers: Stratégies d'actions à l'usage des ONG européennes*. Geneva, UICC 2005:182-195.
9. Anttilla A, Ronco G, Clifford G, Bray F, Hakama M, Arbyn M, Weiderpass E, Cervical cancer screening programmes and policies in 18 European countries. *Br J Cancer* 2004; 91: 935-941.
10. Sankila E. Démaret E, Hakama M, Lynge E, Shouten LJ, Parkin DM, (eds.): *Evaluation and Monitoring of Screening Programmes*. Brussels – Luxembourg 2000, European Comission, Europe Against Cancer Programme, 267 p.
11. Bielska-Lasota M, Inghelmann R, Van de Poll-Franse L, Capocaccia R, and the EURO CARE Working Group, Trends in cervical cancer survival in Europe, 1983-1994: A population based study. *Gynecol. Oncology* 2007; 107: 609-619.
12. WHO: *National Cancer Control Programmes. Policies and Managerial Guidelines*, 2nd Edition. Geneva, 2002, WHO, 180 p.
13. Ministry of Health: *National Cancer Control Programme in Slovakia*. Bratislava, 1976, Ministry of Health of Slovak Republic, 24 p. (in Slovak).