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ORIGINAL ARTICLE

Prevention of cervical cancer with screening programme in Branicevo District and cost-effectiveness analysis adjusted to the territory of the Republic of Serbia

S. Perovic

Republic Health Insurance Fund of Serbia, WHO Office, Belgrade, Serbia

Summary

Purpose: *To establish the so-called positive screening instead of the current opportunistic screening for cervical cancer.*

Patients and methods: *The program of positive screening covered all female persons aged 30-49 years living in the Branicevo District. All women were sent an invitation to participate in the screening and those who responded had Papanicolaou smear test done on the results of which further diagnostic procedures would be determined.*

Results: *The invitation to examination was responded by 11,200 (48.70%) out of 23,000 women invited. The costs of organized screening per capita amounted to Republic of Serbia dinar (RSD) 380.00 (EUR 4.75). 954 patients in total underwent colposcopy and conization, resulting in RSD total costs of 11,926,373.70 (149,079.00 EUR). Assuming the same incidence rate among the population that did not respond to the invitation, the number of women that would have such an intervention would be increased by 893.*

Conclusion: *One-year screening programme is more effective than 3-year programme (180 lives saved compared to 113), but more expensive. This is our cost-effectiveness analysis (CEA) relevant opinion, but not for adoption in practice.*

Key words: cervical cancer, cost effectiveness, Papanicolaou smear, screening

Introduction

Invasive cancer of the cervix uteri is the second most common cancer worldwide with almost half a million new cases each year and constitutes 12% of all cancer cases in female population [1]. The majority of cervical cancer cases (75%) [2] have been registered in less developed regions where the average standardized incidence rate is 19.1 per 100,000 [3], which is almost double compared with the developed regions in which it is 10.3 per 100,000. Similarly, 80% of deaths caused by cervical cancer occur in less developed regions [2], where the mortality rates standardized by age are 2.8 times higher (11.2 per 100,000) than in the developed regions (4 per 100,000) [3].

Cervical cancer in Serbia is the 12th most frequent cause of death and constitutes 6% of all deaths in women [4]. Serbia has the highest incidence of cervical cancer (24.3 per 100,000) among all other republics of the former Socialist Federal Republic of Yugoslavia [3]. In 3 regions of eastern Serbia the incidence is higher than 30: Branicevo District 41.6; Zajecar District 32.9; and Moravica District 30. The highest mortality rate has been recorded in Zajecar District [4].

Article 35, paragraph 2 of the Law on Health Insurance stipulates that "the Government will pass the Republic programme of prevention and early diagnosis of diseases with high sociomedical importance" According to the Regulations on the content and scope of the right to health protection and participation for 2008, adopted by the Republic Health Insurance Fund (RHIF) and the above mentioned Republic programme, the right to preventive gynecological examination for early diagnosis of breast and cervical cancer applies to all women (health insurance beneficiaries) aged 25 to 65 years, once every 2 years (so-called opportunistic screening).

Correspondence to: Sasa Perovic, MBA. Republic Health Insurance Fund of Serbia, Dr Aleksandra Kostica 9, 11000 Belgrade, Serbia.
Tel: +381 11 2657820; +381 63 229149, Fax: +381 11 2688420, E-mail: sasha.perovich@rzzo.sr.gov.yu; yannakis@nadlanu.com

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In developing countries, screening women once in their lifetime, at the age of 35 years, with one or two-visit screening strategy involving visual inspection of the cervix uteri with acetic acid or DNA testing for human papillomavirus (HPV) in cervical cell samples, reduced the lifetime risk of cancer by 25 to 36% and cost less than 500 dollars per year of life saved [5].

Over a lifetime, screening can avoid up to 735 invasive cancers per 100,000 women screened compared with no screening. Among women destined to develop cancer in the absence of screening, screening saves up to 2.7 discounted years of life per woman (1.3-10.9 undiscounted years). Cost-effectiveness analyses are an important source of information for the design and evaluation of policies to reduce cervical cancer [5].

Patients and methods

The invitation to examination within the "organized, positive screening" sent to female population in their home address was responded by 11,200 (48.70%) out of 23,000 women invited in Branicevo District. The invitation, among others, contained also basic information on the importance of periodical check-ups, information on cervical cancer risks and how to diagnose the disease in its initial stage when the chances for cure are best.

The screening normally begun 3 years after the commencement of sexual activity and by the age of 20 at the latest. After 3 successive normal annual cytological smears, the next periodical check-up might be done in 2-3 years [6]. For sexually active women under 30 years of age, cytological smears had to be done annually. The women that had been submitted to total hysterectomy were not subjected to screening, nor the ones who had never had sexual activities and the ones with previously diagnosed cervical cancer.

Women had the Papanicolaou smear test done and the following cytological classification was established:

I: Normal findings
II: Existing inflammation, benign reactive and repair changes
IIIa: Atypical cells of undetermined importance (squamous, glandular)- ACS-US, ACS-H, AGUS
IIIb: Mild dyskaryosis, moderate dyskaryosis -L-SIL (CIN 1), H-SIL (CIN 2), ACG
IV: Severe dyskaryosis-H-SIL (CIN 3), AIS
V: Malignant cells - invasive cancer

Women with I-III b and IV H-SIL group findings were subjected to colposcopy, while the ones with IV AIS group, in addition to colposcopy were subjected to endocervical curettage (ECC) as well. Women in group V were subjected to colposcopy and biopsy and/or ECC.

Upon obtaining a histopathological diagnosis, further procedures were conducted according to the protocol [7].

For evaluation of choice of different screening strategies CEA was used, examining 3 strategies of cervical screening in Serbia per saved life.

Results

It is estimated that 1,016,703 women aged 30-49 years live in the Republic of Serbia [8]. We presume that the response to the first organized screening would be 60%, to the second after 3 years 70% and finally to the third after 6 years 80%.

The costs of the organized screening *per capita* amounted to 380.00 RSD, which equals 4.75 EUR. To supplement direct medical costs, including staff, invitation letters and leaflets, supplies, disposables and equipment depreciation using country-specific data, we used alternative techniques to quantify cervical cytology and HPV DNA laboratory sample processing costs.

A total of 954 patients had colposcopy and conization carried out, resulting in a total cost of 11,926,373.70 RSD, or 149,079.00 EUR.

Assuming the same incidence rate among the population that did not respond to the invitation, the number of women that would have had such an intervention would be increased by 893.

Regretfully, 90 women from the above number will most probably reach some FIGO cervical cancer stage should they continue to ignore the invitations in the future.

FIGO disease stage at the time of diagnosis is shown in Table 1.

The FIGO staging procedures required the following actions and cost:

Table 1. FIGO disease stage at diagnosis and treatment

FIGO stage	*Treatment*	*Patients n*	*Patients %*
0/Ia	Surgical therapy	31	32
Ib	Postoperative RT	25	26
IIa	Postoperative RT	2	2
IIb	Inoperable; radical RT	22	23
III	Concomitant chemoRT	15	16
IV	Concomitant chemoRT	1	1

RT: radiation treatment

- Colposcopy 442.42 RSD
- Biopsy 1,868.20 RSD
- Chest x-rays 84.26 RSD
- Biochemical analyses 916.41 RSD
- Scanner 3,570.95 RSD,

amounting to a total cost of 193,194.60 RSD or 2,415 EUR for 30 patients.

Eighteen patients had Wertheim operation plus radiotherapy, amounting to 7,547,147.10 RSD or 94,339.00 EUR.

Twelve patients had only radiotherapy, amounting to 4,231,870.56 RSD or 52,898.00 EUR.

The treatment costs for the patients who responded to the invitation amounted to a total cost of 23,898,586.02 RSD or 298,732 EUR.

Extrapolation of the results of the organized screening carried out in Branicevo District to the Republic of Serbia is shown in Table 2.

Discussion

One-year screening programme is more effective than 3-year programme (180 lives saved compared to 113), but more expensive. This is our CEA relevant opinion, but not for adoption in practice.

There is no doubt that the positive screening covers considerably larger number of target population (39-49 years) than the opportunistic screening which shows the very low level of health education, as well as the knowledge over possible consequences of one's health negligence. CEA shows that financing the positive screening is far more cost-effective than paying for further treatment of cervical cancer and hospitalization, including the reimbursements for the temporary work disability of the employed patients.

In addition, one of the most important project components is the increase of quality-adjusted life-years and general health condition of the project target group.

In comparison with Pap screening every 2 years, only 25% of the HPV-based screening strategies were cost-effective. However, in comparison with Pap screening every 1, 3, or 5 years, 83%, 55%, and 92% of HPV screening strategies respectively were cost-effective. Results for settings with annual Pap screening are based on models assuming 100% screening coverage [8,9].

It has been proven that screening of extended target population has better effects than more often screening of the same group of women [10].

Immaterial losses refer to the employed female patients, as well as to the unemployed ones. Our society and particularly family as its primary cell, is founded on the deep traditional role of woman. Severe forms of cancer upset the family harmony and all family members suffer a certain degree of trauma and immaterial damage.

Following those stated above, a conclusion can be drawn that with more rational disposal of limited resources, the argument is in favor of preventive action in the form of organized cervical cancer screening (3-year organized screening), which has proven its value in practice in many countries, especially considering the ratio between costs and saved lives, survival years and improved quality of life [11].

When several realistic interventions exist for addressing a serious public health problem, CEA can provide one useful type of information for decision makers. When primary cost data are lacking because a specific type of program has yet to be implemented in a given country, it is possible to use other techniques whose simplifying assumptions allow their data requirements to be satisfied with publicly available data. Because of the uncertainty introduced by simplifying assumptions, the techniques can also be used to generate plausible ranges of estimates for sensitivity analyses. In the context of cervical cancer screening and prevention, use of these techniques helped to quantify important component costs that influenced the overall results of cost-effectiveness analysis in developing countries [12].

To improve cervical cancer prevention it is necessary to assure the following data:

a) National incidence data from good-quality cancer registries;

Table 2. Cost-effectiveness (CE) analysis examining 3 strategies of cervical screening in Serbia per saved life*

Strategy	*Cost in EUR*	*Marginal cost*	*Effectiveness*	*Marginal effectiveness*	*CE ratio*
Nothing	0	–	0 lives	–	–
3-year screening (within 6 years)	10,299,645.00	10,299,645.00	113 lives	113	91,147.30
1-year screening (within 7 years)	24,953,508.00	14,653,863.00	180 lives	67	218,714.40

*If we predict mortality reduction by 25% in 3-year screening programme, a 40% in 1-year programme according to the worldwide experience, and according to data showing that in Serbia every year 450 women die of cervical cancer

b) National mortality data, with estimation of incidence using sets of regression models specific for site, sex, and age, derived from local cancer registry data (incidence plus mortality) [13]. The models may be specific to country, region, or developing countries as a whole;

c) Local (regional) incidence data from one or more regional cancer registries within a country;

d) Frequency data, when only data on the relative frequency of different cancers (by age and sex) are available. The frequencies are applied to an estimated "all sites" incidence rate derived from existing cancer registry results in the same region [14].

For example, cervical cancer mortality in England and Wales in women younger than 35 years rose 3-fold from 1967 to 1987. By 1988, incidence in this age-range was among the highest in the world despite substantial opportunistic screening. Since national screening was started in 1988, this rising trend has been reversed [15].

According to health funds, a 3-year programme is closer to reality. CEA shows that financing the positive screening is better option in comparison to treatment of end-stage cervical cancer, including the reimbursement for the temporary work disability. Social loss cannot be estimated, but must not be ignored.

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