

Resource utilisation and cost of cervical cancer and dysplasia in Croatia

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Summary

Purpose of investigation: To analyse resource utilisation and costs due to cervical cancer and dysplasia in Croatia. **Materials and Methods:** Patients diagnosed with cervical cancer were identified from the Croatian National Cancer Registry. Resource utilisation and costs of cervical cancer treatment for the period of five years after the date of diagnosis were retrieved from the Croatian Health Insurance Fund Claims Database. Patients diagnosed with cervical dysplasia were identified and their resource utilisation and treatment costs during one year following diagnosis were obtained from the Croatian Health Insurance Fund Claims Database. Results were calculated for different healthcare services and disease stages. **Results:** There were 346 patients diagnosed with cervical cancer in 2008. Total costs of treatment in the five-year period were 2,177,071 Euros, while average cost of treatment per patient was 6,403 Euros. The largest shares of total costs were costs for hospitalisations (73%), followed by outpatient healthcare (17%), and personal sick leave (7%). There were also 14,913 patients with cervical dysplasia diagnosed in 2012. Total costs of their treatment during one year after the diagnosis were 1,609,073 Euros, with average costs per patient of 108 Euros. Outpatient care (48%), followed by hospitalisations (45%), and prescribed medicines (6%) had the greatest share of total costs. **Conclusion:** Treatment of cervical cancer and dysplasia in Croatia is associated with significant costs and healthcare resource utilisation.

Key words: Cervical cancer; Cervical dysplasia; Resource utilisation; Cost of illness.

Introduction

Cervical cancer is the fourth most common cancer in women in the world, with an estimated 528,000 new cases in 2012 [1], mostly occurring in the less developed regions, such as Eastern Asia and Middle Africa. Around half as many women (266,000) die each year due to cervical cancer, with 87% of cervical cancer deaths occurring in the less developed regions.

In Europe, the highest incidence and mortality of cervical cancer is observed in Eastern Europe, with Romania having the highest age-standardized (world population) incidence rate (28.6/100,000) and mortality rate (10.8/100,000), while these rates for Croatia are 10.0/100,000 and 3.2/100,000, respectively [2]. Cervical cancer incidence trends in Croatia show a statistically significant decrease [3], with an estimated annual percent change of -1.0% (95 CI -1.6 to -0.4). It is the ninth most common cancer in women in Croatia, both in terms of incidence and mortality [4]. According to the EURO CARE-5 study, the five-year relative survival for participating countries (women diagnosed between 2000 and 2007) was 62.4% (95% CI 61.8 to 62.9), with the highest survival observed in Norway - 71.0% (95% CI 68.6 to 73.5) and the lowest in Bulgaria - 51.0% (95% CI 49.6 to 52.4). In Croatia, the

five-year relative survival was 65.1% (95% CI 62.9 to 67.4) [5].

Significant proportion of cervical cancer incidence can be prevented through the use of screening tools, which include Pap smear and human papilloma virus (HPV) test. Coverage and quality of cervical cancer screening have significant effect on its incidence. According to Organisation for Economic Co-operation and Development (OECD), coverage of the targeted population in the European Union by cervical cancer screening was estimated around 60% in 2012 [6]. Although many countries of Central and Eastern Europe have offered opportunistic cervical cancer screening for decades, women have lacked awareness about the importance of regular gynaecological examinations [7].

Opportunistic screening using Pap test has been conducted in Croatia since the 1960s, which led to a decrease in cervical cancer incidence and the number of deaths, especially until 1991. The largest drop in the incidence of cervical carcinoma (1985-2004) was recorded for the age group from 25 to 39 years, while no such drop was observed in the age group from 40 to 49 years [8]. During the past ten years, the incidence trend has continued to decrease, albeit insufficiently, which can be attributed to sub-optimal measures of disease prevention and control

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according to Kelava *et al.* [3]. A certain part of female population can be assumed not to receive regular gynaecological care [4, 8]. Two-thirds of newly-diagnosed women are younger than 60 years of age [4], which is especially important in view of the fact that this is the age when women reach their full family and social potential. As these data led to a conclusion that opportunistic screening was no longer an adequate prevention method, health authorities of the Republic of Croatia opted for the organisation and implementation of organised screening. In July 2010, Croatian Government adopted a National Cervical Cancer Screening Programme, whose implementation began in the end of 2012 [9]. The basic screening method used in the Programme is the conventional Pap-smear test. The Programme is conducted by the Croatian Institute of Public Health and the Ministry of Health and executed in collaboration with the Croatian Health Insurance Fund and county public health institutes [9]. As the first cycle of the programme targeting women from the 25-64 year age group has ended recently, the screening coverage data are not available as yet.

Considering the European guidelines for quality assurance in cervical cancer screening propose conducting cost-effectiveness analyses prior to making decisions on the implementation or change of the programme for early detection of cancer [10], this study will contribute to further improvement of its organisation and implementation through the analysis of healthcare resources utilisation and costs connected to cervical neoplasms using data from the period between 2008 and 2013 and data on dysplasia treatment from 2012, prior to the introduction of the National Cervical Cancer Screening Programme.

The aim of this study was to identify resource utilisation and direct medical and personal sick leave costs caused by invasive cervical cancer and cervical dysplasia in Croatia according to the stage of disease.

Materials and Methods

All Croatian citizens and residents have the right to healthcare through mandatory health insurance and a great majority of population in Croatia is covered by the social health insurance scheme operated by the Croatian Health Insurance Fund (CHIF), the sole provider of mandatory health insurance in Croatia, covering around 99% of Croatian citizens [11]. The provided benefits package is quite comprehensive - it includes inpatient and outpatient services, dental care, prescription drugs, therapeutic appliances, other medical supplies, sick leave, maternal leave, travel costs (under certain conditions), and preventive care [11]. Healthcare providers are mostly owned by state and counties and financed by CHIF in accordance with the legal acts and signed contract for providing services under mandatory health insurance. Payment methods vary according to the level of healthcare. Primary healthcare teams had mostly been reimbursed by capitation until 2013, when a combined model of payment was introduced (capitation, fee for service, bonuses regarding key performance and quality indicators, group practices, and counselling) in addition to fee-for-service payment of diagnostic and therapeutic procedures

from a defined list. Hospitals are financed by fee-for-service for outpatient specialist care, per case (according to Diagnosis Related Groups - DRG introduced in 2009) for acute hospital care and by day of hospital treatment for chronic care and rehabilitation.

Patients have a free choice of healthcare providers. Access to specialist care is enabled by referral from primary healthcare physicians (family medicine specialists and general practitioners, primary health care paediatricians and dentists), except in the case of emergency. Gynaecologists that work on primary care level are specialists from whom patients can seek direct care without referral. Patients are required to make co-payments for majority of healthcare services, except for children and pregnancy care, childbirth, cancer treatment, haemodialysis, mandatory immunisations, and several other services. Many co-payments can be avoided by complementary voluntary health insurance provided by the Croatian Health Insurance Fund or private health insurers in Croatia.

The data for this study were obtained from two main sources: Croatian National Cancer Registry and Croatian Health Insurance Fund Claims Database. Croatian National Cancer Registry has been collecting detailed data on patients diagnosed with cancer since 1959. The Registry covers the entire population of Croatia, and each record contains information about the date when a patient was diagnosed with cancer, topography (coded using ICD-10) and morphology (coded using ICD-O-2), disease stage in the moment of diagnosis, as well as basic demographic data on the patient [4]. Registry's primary data sources are notifications from hospitals and outpatient care institutions and offices, pathology reports and mortality databases, whereas supplementary data source are hospital discharge records.

Croatian Health Insurance Fund Claims Database contains comprehensive mandatory insurance information on healthcare utilisation and costs, including inpatient care, outpatient care (except primary health care), prescription drugs, therapeutic appliances, and personal sick leave. It captures the majority of treatment episodes for invasive cervical cancer (ICC) and cervical intraepithelial neoplasia (CIN) and associated costs, but it does not include patients who pay for diagnostics and treatment themselves or through private health insurance. However, the number of these patients is expected to be very small, if any, due to high prices and complexity of cancer treatment, and the fact that a vast majority of population has social health insurance and only a small number has supplementary private health insurance.

Data on 346 patients diagnosed with invasive cervical cancer during 2008 were obtained from the Croatian National Cancer Registry. The data about each patient included her age and stage of the disease at the moment of diagnosis. In order to calculate utilisation and costs associated with ICC treatment, these data were linked with the Croatian Health Insurance Fund Claims Database. Claims associated with ICC were defined as those where either a principal diagnosis or additional diagnosis contained codes for cervical carcinoma (ICD-10: C53, D06) or certain less specific codes used due to imprecision in coding, but labelled as pertaining to ICC for these specific patients (ICD-10: C55, C57, C76.3, C80). The costs for each patient were retrieved for the period of five years from the date of each patient's ICC diagnosis, separately for each year from the first year until the fifth year after the diagnosis date in the period 2008-2013. A five-year follow-up of ICC treatment episodes and related costs was chosen in accordance with other ICC cost studies [12] as a period during which almost all treatment is completed. As Stages 3 and 4 were merged for analysis due to an extremely low number of patients in Stage 4 at the time of diagnosis (two patients), all analyses were done on a combined Stage 3 and 4 groups.

As no data on CIN patients were available from the Croatian

National Cancer Registry, Croatian Health Insurance Fund Claims Database was used to identify these patients, as well as episodes and costs of their treatment. All patients with claims containing CIN codes (ICD-10: N87, D06), either as a principal or additional diagnosis in 2012, were retrieved from the database. Those with C53 diagnosis found in any claim from 2012 until 2013 were excluded to eliminate patients who actually had ICC. All patients who had any claim with CIN or ICC diagnoses in the period 2009-2011 were also excluded as that implied they were not newly diagnosed in 2012. Thus only newly diagnosed cases of CIN in 2012 remained. The treatment episodes and costs for each patient were retrieved for a one-year period following the date of the first CIN diagnosis, based on the presumption that almost all actually treated CIN patients would complete treatment within that period.

Ethics Committee of the Croatian Institute of Public Health granted approval prior to the start of any activities from this study.

Statistical analysis included calculation of mean and standard deviation (SD) for continuous variables which measured utilisation and costs according to the year from diagnosis (for ICC), healthcare mode and stage of disease. Only data for respondents who actually used certain healthcare services in a given time period were included in the calculation.

All costs were calculated in HRK and then converted to Euros according to the middle exchange rates of the Croatian National Bank for years 2008-2012 [13]. The consumer price index (CPI) was applied in order to adjust for inflation (CPIs for 2008-2012 were 91.4%, 93.6%, 94.6%, 96.7%, 100% respectively) [14].

Statistical analysis was performed using SPSS Statistics 23.0 (license: Croatian Institute of Public Health).

Results

A total of 346 cases of ICC were eligible for analysis. The mean age at the time of diagnosis was 55.0 years (SD: 15.4). The youngest patient diagnosed with ICC was 25-years-old and the oldest was 90-years-old. According to the stage of the disease, the mean age was 50.7 years (SD: 14.6) for Stage 1, 60.2 years (SD: 16.0) for Stage 2, and 57.6 years (SD: 10.6) for Stages 3/4.

A total of 14,913 cases of cervical dysplasia were eligible for analysis. The mean age at the time of diagnosis was 38.5 years (SD: 13.7). According to the CIN stage, the mean age was 36.7 years (SD: 12.7) for CIN 1, 34.5 years (SD: 12.2) for CIN 2, and 39.7 years (SD: 13.6) for CIN 3.

Table 1 shows utilisation and costs for ICC patients during five years from the diagnosis according to the healthcare services provided: hospitalisations, outpatient healthcare (primary health care not included), prescribed medicines, prescribed medical non-durable goods, and therapeutic appliances and personal sick leave.

Utilisation of all healthcare services was the most intensive during the first year of treatment and decreased in the following years. Hospitalisations were the most frequently used healthcare services for patients with ICC; however, the share of hospitalised patients decreased sharply from 90% during the first year to only 4% during the fifth year of treatment. Such decrease was less pronounced for outpatient healthcare, prescribed medicine, and personal sick leave. The average numbers of hospital days and outpatient

healthcare episodes were higher in the first year of treatment (among the patients who used these services), while no clear trend was recorded for average numbers of hospitalisations and packages of prescribed medicines.

Total five-year ICC treatment costs for patients diagnosed with ICC in 2008 were 2,177,071 Euros, out of which 73% were the costs for hospitalisations, 17% for outpatient healthcare, 7% for personal sick leave, 3% for prescribed medicines, and 1% for prescribed medical non-durable goods and therapeutic appliances. The share of costs for hospitalisations was the highest in the first year of treatment and decreased in the following years. The opposite was recorded for outpatient healthcare – the share was 13% of the total costs in the first year of treatment, and increased to 28% in the fifth year of treatment.

The costs in the first year of treatment were 71% of total treatment costs, and each of the following year they had a decreasing share in the total costs: 11% for the second year, 9% for the third year, 5% for the fourth year, and 4% for the fifth year.

Average treatment cost per ICC patient for all five years was 6,403 Euros (six ICC patients who did not have any costs recorded were excluded from the calculation). Table 2 shows costs for ICC patients during five years from the diagnosis according to the stage of disease at the moment of diagnosis.

For patients in all stages, costs were the highest in the first year, most pronouncedly in Stage 3/4 patients with 86% of all costs occurring during the first year of treatment. With an increase from Stage 1 to 2, average costs of treatment increased, but then decreased again in Stages 3/4 to almost the same level as Stage 1. Out of the total costs for cervical cancer treatment, the highest share was that for treatment of patients in Stage 2, followed by unknown stage and Stage 1, whereas only 5% was recorded for treatment of patients in Stages 3/4.

As expected, the intensity of resource utilisation among patients with cervical dysplasia was significantly lower compared to ICC patients, with only 9% of CIN patients hospitalised in comparison to 92% of ICC patients. The share of CIN patients who used outpatient specialist care was almost identical to that of ICC patients, but the average number of episodes for those who actually used outpatient specialist care, was almost eight-fold higher among ICC patients.

The costs for treatment of cervical dysplasia according to the healthcare service are shown in Table 3. Total treatment costs for cervical dysplasia in a one-year period were 1,609,073 Euros, out of which outpatient care had the highest share (48%), followed by hospitalisations (45%), and prescribed medicines (6%), while personal sick leave and prescribed medical non-durable goods had the lowest share (< 1%). Average cost of treatment per CIN patient during the year following the diagnosis was 108 Euros.

With respect to CIN grade, share of costs for patients

Table 1 Invasive cervical cancer (ICC) patients - usage of health care services and costs in 5 years after diagnosis

	No. of patients who used the service	% of patients who used the service	Out of those who used the service			Average no. of days of service use (only for hospitalisations and personal sick leave)	SD	Min.	Max.	Total no. of days of service	No. of patients with recorded costs by CHF for the service	Out of those with recorded costs by CHF for the service			Total cost (in EUR)			
			Average no. of episodes/packages	SD	Min.							Max.	Average costs (in EUR)	SD		Min.	Max.	
Hospitalisations																		
First year	310	90%	2,53	1,94	1	12	784	30,78	24,41	1	109	9,543	3,866,87	3,194,72	118,28	24,295,05	1,198,729,07	
Second year	41	12%	2,49	2,04	1	8	102	18,51	21,04	0	90	759	3,590,04	3,271,13	345,33	11,603,09	147,191,61	
Third year	30	9%	2,93	2,56	1	11	88	20,5	20,22	1	109	615	3,918,51	3,357,47	352,97	12,066,27	117,555,22	
Fourth year	20	6%	2,50	2,33	1	10	50	22,15	23,63	1	94	443	3,140,78	2,608,97	451,73	9,298,07	62,815,61	
Fifth year	13	4%	3,85	2,97	1	8	50	20	18,13	4	74	260	4,260,16	3,604,20	392,55	12,021,94	55,382,09	
Total 1st-5th year	317	92%	3,39	3,41	1	20	1,074	36,66	31,24	1	176	11,620	4,989,51	4,781,61	118,28	34,533,76	1,581,673,58	
Usage of outpatient health care (primary health care not included)																		
First year	277	80%	6,99	6,27	1	38	1,936				277	718,38	1,802,77	2,38	16,800,72	198,992,23		
Second year	186	54%	5,17	4,23	1	25	961				186	319,96	699,85	3,56	5,790,65	59,513,32		
Third year	153	44%	5,11	5,07	1	37	782				153	326,84	700,12	6,24	4,884,53	50,006,47		
Fourth year	124	36%	5,29	4,47	1	31	656				124	230,56	460,52	5,98	3,456,40	28,588,91		
Fifth year	104	30%	5,18	5,77	1	33	539				104	257,71	553,02	5,69	3,683,99	26,802,34		
Total 1st-5th year	287	83%	16,98	16,23	1	121	4,874				287	1,267,96	2,375,80	2,38	16,861,18	363,903,27		
Usage of prescribed medicines																		
First year	140	40%	26,58	76,95	1	611	3,721				140	202,28	490,13	4,59	4,084,51	28,319,69		
Second year	69	20%	25,59	50,09	1	270	1,766				69	200,43	345,87	4,69	2,282,55	13,829,68		
Third year	46	13%	27,09	57,24	1	322	1,246				46	209,17	381,69	3,88	1,668,30	9,621,97		
Fourth year	39	11%	33,97	73,85	1	361	1,325				39	167,86	291,83	4,48	1,245,40	6,546,43		
Fifth year	26	8%	27	67,26	1	292	702				26	130,16	309,50	4,47	1,169,25	3,384,05		
Total 1st-5th year	179	52%	48,94	130,24	1	1,224	8,760				179	344,70	733,14	4,47	5,314,45	61,701,84		
Usage of prescribed medical non-durable goods and therapeutic appliances																		
First year	32	9%	156,09	167,19	1	550	4,995				32	116,37	101,46	8,50	483,43	3,723,84		
Second year	17	5%	299,53	415,79	1	1476	5,092				17	207,55	335,78	8,17	1,414,31	3,528,36		
Third year	11	3%	418,55	328,02	1	1,005	4,604				11	182,91	141,70	19,27	474,90	2,012,06		
Fourth year	8	2%	774,88	802,84	1	2,459	6,199				8	589,43	830,78	94,92	2,511,79	4,715,48		
Fifth year	7	2%	1,271,86	1,986,88	1	5,661	8,903				7	1,006,77	2,096,99	72,97	5,754,22	7,047,41		
Total 1st-5th year	55	16%	541,69	1,184,11	1	8,120	29,793				55	382,31	1,122,08	14,75	8,266,01	21,027,15		
Usage of personal sick leave																		
First year	59	17%	1,07	0,31	1	3	63	131,69	81,86	5	287	7,770	1,971,8	1,290,6	190,4	108,447,2	5,337,0	
Second year	9	3%	1,11	0,33	1	2	10	102,78	100,5	14	312	925	1,513,0	1,177,6	124,4	10,591,1	2,804,9	
Third year	7	2%	1	0	1	1	7	177,86	115,4	52	313	1,245	2,467,9	1,809,0	166,9	17,274,9	5,490,6	
Fourth year	7	2%	1	0	1	1	7	94,43	82,61	7	200	661	2,058,9	1,712,0	360,7	10,294,3	3,884,4	
Fifth year	5	1%	1	0	1	1	5	117,2	137,3	1	312	586	719,2	551,8	157,9	2,157,6	1,260,9	
Total 1st-5th year	59	18%	1,46	0,76	1	4	92	177,57	170,2	5	1,112	11,187	2,521,4	2,180,7	124,4	148,765,1	11,641,3	

No: number; CHF: Croatian Health Insurance Fund; EUR: euros.

Table 3 Cervical dysplasia cases - usage of health care services and costs in the first year after diagnosis

	No. of patients who used the service	% of patients who used the service	Out of those who used the service			Average no. of days of service use (only for hospitalisations and personal sick leave)	SD	Min.	Max.	Total no. of days of service use	No. of patients with recorded costs by CHF for the service	Out of those with recorded costs by CHF for the service			Total cost (in EUR)		
			Average no. of episodes/packages	SD	Min.							Max.	Average costs (in EUR)	SD		Min.	Max.
Hospitalisations																	
Usage of outpatient health care (primary health care not included)	1.340	9%	1,22	0,47	1	5	1,638	3,79	3,35	1	34	5,075	545,81	353,30	83,96	3,544,87	731,386,54
Usage of prescribed medicines	12.485	84%	2,23	2,22	1	23	27,878				12.485	61,77	73,1	2,19	1,085,64	771,167,94	
Usage of prescribed medical non-durable goods and therapeutic appliances	6.207	42%	2,6	2,05	1	25	16,115				6.207	15,62	14,2	1,43	182,74	96,948,70	
Usage of personal sick leave	2	0,01%	146	196,6	7	285	292				2	49,79	62,48	5,61	93,98	99,59	
	359	2%	1,25	0,59	1	5	448	18,4	16,95	1	111	6,594	255,96	262,2	15,25	981,46	9,470,49

No: number; CHF: Croatian Health Insurance Fund; EUR: euros.

with CIN 3 was the highest share (41%), followed by unknown CIN (26%), CIN 1 (20%), and CIN 2 (14%) (Table 4).

Discussion

This is the first study assessing resource utilisation and costs of treatment of cervical cancer and dysplasia in Croatia, based on combined data from the Croatian National Cancer Registry and the Croatian Health Insurance Fund Claims Database. Data on treatment costs are essential inputs for economic evaluation of different technologies which, besides Pap smear screening within the National Programme for Early Detection of Cervical Cancer, are becoming increasingly available for the prevention of cervical cancer, such as HPV vaccine that is being introduced in the Croatian immunisation programme and HPV tests. Therefore, data on treatment costs are an important part of any analysis undertaken to enable making decision about

introducing or modifying individual technology for prevention of cervical cancer in Croatia.

Despite a high prevention rate and advances in treatment options, cervical cancer represents significant economic and quality-of-life burden to health budgets and patients. In the United States, cervical cancer was the fourth most costly cancer per death in 2010 [15] as it affects working-age women and brings significant productivity costs for the society. Several studies from both European as well as other countries have reported significant healthcare costs associated with cervical cancer and dysplasia providing stage-specific costs of CIN patients [16-19] or cost of the treatment of cervical cancer patients [20-22]. Studies on this topic from Central and Eastern Europe region are relatively scarce. Significant costs due to uterine cervical lesions were recorded in Poland [23]. A study from Bulgaria has provided stage-specific costs of CIN and cervical cancer patients [24], but the costs have been estimated on the basis of EU data. In a Croatia, vaccination of adolescents

Table 2 Invasive cervical cancer (ICC) cases - total costs in 5 years since diagnosis, by ICC stage

	No. of patients who used health care services	% of patients who used health care	Average costs (in EUR)	SD	Min.	Max.	Total cost (in EUR)	% of total cost for that stage
Stage 1								
First year	97	96%	3.899,15	3.608,96	3,61	16.664,34	378.217,39	67%
Second year	60	59%	903,89	2.396,31	3,56	16.064,49	54.232,53	10%
Third year	52	51%	1.455,09	3.181,35	11,49	12.642,34	75.664,62	13%
Fourth year	42	42%	716,90	1.911,48	5,98	9.315,12	30.109,61	5%
Fifth year	32	32%	848,68	2.004,82	5,72	7.548,78	27.157,70	5%
Total 1st-5th year	98	97%	5.769,20	6.525,95	3,61	34.031,08	565.381,85	
Stage 2								
First year	98	99%	5.244,34	4.360,38	123,94	24.721,04	513.945,47	67%
Second year	65	66%	1.298,72	2.348,67	6,77	10.201,58	84.416,99	11%
Third year	51	52%	1.568,01	2.657,48	11,35	11.956,06	79.968,35	10%
Fourth year	44	44%	1.275,41	3.022,19	6,48	14.204,86	56.117,98	7%
Fifth year	33	33%	898,11	2.543,99	5,72	12.079,63	29.637,69	4%
Total 1st-5th year	98	99%	7.796,80	7.571,61	130,97	43.816,29	764.086,48	
Stage 3/4								
First year	20	100%	5.058,73	5.184,52	154,81	22.536,24	101.174,51	86%
Second year	7	35%	1.418,97	2.876,69	3,81	7.792,74	9.932,81	8%
Third year	5	25%	432,74	353,12	35,48	908,06	2.163,68	2%
Fourth year	4	20%	154,32	146,16	12,96	341,43	617,27	1%
Fifth year	4	20%	966,94	1.154,27	38,65	2.558,69	3.867,76	3%
Total 1st-5th year	20	100%	5.887,80	5.793,54	154,81	24.259,44	117.756,03	
Unknown stage								
First year	124	98%	4.394,15	3.845,50	6,09	19.560,76	544.874,68	75%
Second year	68	54%	1.265,76	3.013,60	12,23	15.291,64	86.071,70	12%
Third year	53	42%	729,70	1.713,30	6,75	8.128,31	38.673,99	5%
Fourth year	46	37%	567,74	1.477,69	4,88	8.369,52	26.115,83	5%
Fifth year	39	31%	874,63	2.276,65	6,19	9.659,26	34.110,38	5%
Total 1st-5th year	124	98%	5.885,86	5.871,85	6,09	39.741,73	729.846,59	

No: number; EUR: euros.

Table 4 Cervical dysplasia cases - total costs in the first year after diagnosis, by CIN grade

	No. of cases	% of total patients	Average total costs (in EUR)	SD	Min.	Max.	Total cost (in EUR)
CIN 1	4.010	27%	79,22	135,63	2,48	1.916,31	317.666,41
CIN 2	1.024	7%	215,51	263,92	2,41	1.768,36	220.679,89
CIN 3	1.834	12%	357,70	432,64	2,98	3.544,87	656.024,99

No: number; EUR: euros.

has been analysed and total costs of cervical cancer treatment estimated at around 45 million HRK annually [25]. However, this cost estimation was not based on actual costs data for Croatia, but on other countries' published costs. This emphasized the need to obtain actual costs data for Croatia.

This study provided data on significant financial burden incurred by treatment of cervical cancer and dysplasia on modest total healthcare expenditures in Croatia (745 Euros/inhabitant in 2013, placing Croatia among countries with the lowest expenditures on healthcare in the EU when measured in Euros/inhabitant) [26]. Consequently, all expenditures must be evaluated and efforts made to reduce costs through effective preventive measures (which, in case of cervical cancer, are plentiful). Traditionally, burden of certain disease in Croatia was primarily assessed through epidemiological indicators (number of deaths and mortality rate, incidence and prevalence) [27]; however, economic evaluations are becoming increasingly important, and especially in the context of the savings policy [28].

The results of this study showed that both resource utilisation (measured in hospital days and episodes of outpatient care) and costs of treatment of ICC patients were the highest during the first year of treatment, which is in agreement with published reports on costs of treatment of cervical and other cancers which showed that initial care period was one of two leading periods of resource utilisation and costs (the other being that of terminal care one year prior to patient's death, which in this study was not identified separately) [29, 30]. When analysed according to the stage of disease, results did not show the pattern seen in other studies which is a continuous increase in five-year treatment costs from Stage 1 to Stage 4 [12, 20, 31, 32]. However, increase in costs from Stage 1 to 3 followed by a decrease in Stage 4 has also been recorded [21], which corresponds to the present findings that an increase in costs occurred from Stage 1 to 2, although not two-fold as observed in other studies, whereas costs from Stage 2 to 3/4 decreased. The exact reasons for this decrease require more in-depth analysis of cervical cancer treatment practices in Croatia, especially concerning patients in Stages 3 and 4. A possible reason could also be a small number of patients in Stages 3 and 4 at the time of diagnosis (only 20, out of which only seven used any healthcare services after the first year of

treatment, only five after the second year of treatment, and only four after the third year of treatment), which made results for patients in Stages 3 and 4 much less reliable in comparison with the results of patients in Stages 1 and 2.

As expected, there was a lower likelihood of healthcare services utilisation among CIN patients compared to ICC patients for all healthcare services (hospitalisations, prescribed medicines, etc.), except for outpatient specialist services, which were used by almost equal share of ICC (83%) and CIN (84%) patients. An almost three-fold increase in treatment costs was recorded from CIN 1 to CIN 2 and a further 1.6-fold increase from CIN 2 to CIN 3, which is in line with the sharpest increase in costs according to CIN grade among published studies [33-35]. This increase is a reflection of very different treatment procedures applied in CIN patients, ranging from Pap smear follow-ups in CIN 1, cryosurgery, laser ablation and conisation, to hysterectomy in some CIN 3 patients.

Certain limitations of this study should be taken into account in further interpretation of its results. A relatively high share of patients with unknown ICC stage (36%) and an even higher share of patients with unknown CIN grade (54%) point to insufficient completeness of the data provided by healthcare professionals. In this study data according to ICC stage / CIN grade were analysed based on patients with known ICC stage and CIN grade, under the presumption that actual distribution of patients with unknown stage/grade was the same.

Previous studies of cervical cancer followed ICC treatment up to the fifth year after the diagnosis [12] with the rationale that in that period almost all costs related to ICC treatment appear, as mortality rate of the patients five years after diagnosis, equals that of the general female population [36]. Therefore, five years after diagnosis should be sufficient to capture almost all costs of ICC treatment. The same holds true for a one-year period after CIN diagnosis, which should be sufficient for capturing almost all CIN treatment costs.

This study included direct and indirect ICC and CIN costs for which data were available; however, some elements of the costs were not included as they were impossible or too difficult to obtain. Concerning direct costs, although those pertaining to primary care gynaecologists in the period 2008-2013 were unavailable, it may be pre-

sumed based on ICC and CIN treatment guidelines that these costs made only a minor part of the total treatment costs, especially when it concerned ICC patients. Among indirect costs, this study included only personal sick leave costs paid by CHIF and a part of transportation costs, whereas transportation costs paid by patient, personal sick leave costs paid by employers, as well as costs of family members' sick leaves and productivity losses of both patients and their family members were not included in this study.

These limitations indicate that costs of ICC/CIN treatment calculated in this study should be interpreted as the lower bound of the overall ICC/CIN costs, and this should be taken into account when using these results.

Healthcare administration in Croatia currently faces the challenge of changing the manner of screening from an opportunistic to an organised one in which context evaluation and analysis of expenditures related to treatment of cervical cancer and dysplasia play an important role.

This economic burden analysis might be of use to healthcare policy makers and managers, as it should enable them to allocate and distribute the available resources and align the strategic documents and research in the given area more easily. The analysis might also serve as an input for economic evaluation of different technologies for prevention and treatment of cervical cancer and dysplasia.

Conclusion

Treatment of cervical cancer and dysplasia in Croatia results in significant costs and health care resource utilisation. The results of this study could be useful in future economic evaluations of different technologies for the prevention and treatment of cervical carcinoma and dysplasia in Croatia.

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