Assessment of the Effectiveness of Cervical Cancer Screening in Tbilisi

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Summary

According to the US Center for Disease Control (CDC 2013), a reliable statistical tendency of decreasing cervical cancer incidence and mortality caused by this disease has been recorded in the United States over the recent 40 years that relates to high rate coverage of a female population by Pap test screening. This tendency is proved by American Cancer Society (ACS, 2012). According to Gold M.A. (2006), 70-80 % decrease of cervical cancer incidence has been achieved by Pap test screening in developed countries. According to the Norwegian Cervical Cancer Screening Program (NCCSP, 2014), screening has contributed to 25 % decrease of cervical cancer incidence and 50 % decrease of mortality caused by this disease in Norway. According to Nanda K. et al. (2000) data, in case of cervical cancer CIN 2/3, Pap test sensitivity and specificity vary within the range 47 % - 62 % and 60% - 85% correspondingly. We have studied the cost-effectiveness of cervical cancer screening program, based on 5 year period data (2010–2014): 66,324 women received gynecological examination and Pap test and 12,147 received colposcopy, targeted biopsy and morphological analysis. In 2013, 13,584 women received cervical cancer screening, among them 7,416 women at the National Screening Center (NCC). The indicators of diagnostic effectiveness of gynecological examination, Pap test, colposcopy and combination of a Pap test and colposcopy have been studied based on NCC data with a purpose of assessment. In 2013, the prevalence of severe cervical dysplasia (CIN3) and intraepithelial carcinoma (CIS) per 1,000 female population eligible for screening constituted 9,8 % and cancer prevalence was 6,1 %. The study has found that making of alterations in a screening guideline and re-adjusting of a target group from 25-59 to 30-64 age group will increase the number of detected cervical cancer cases and decrease needed expenditures: in case of 50 % coverage of a target group by ~93,000 GEL and by ~130,000 GEL in case of 70 % coverage. i.e. making of alterations to the screening guideline and re-adjusting of a target group to 30-64 age group will significantly enhance the cost-effectiveness of cervical cancer screening.

Abbreviations: CIS-Carcinoma in Situ, CIN-Cervical Intra-epithelial Neoplasia
Key words: cervical cancer, screening, cost-effectiveness, Tbilisi.

Problems Statement:

According to the US Center for Disease Control (CDC 2013), a reliable statistical tendency of decreasing cervical cancer and mortality caused by this disease has been recorded in the United States over the recent 40 years that relates to high rate coverage of a female population by Pap test screening.

Decreasing tendency of mortality caused by cervical cancer and its relation to Pap test screening of the female population is also proved by American Cancer Society (ACS, 2012).

According to Willoughby B.J. et al. (2006) data, cervical cancer incidence and mortality caused by this disease in the world developed countries has decreased by 75 % in recent 50 years.

According to the Lofters A.K. et al. (2011) data, in Ontario, the coverage rate of cervical cancer screening of the female population in the target age group 20 -69 is 85 %.

It should be noted, that different guidelines of cervical cancer screening are used in different countries. e.g. 2 guidelines (USPSTF, 2012; Saslow D. et al., 2011), recommended by USPSTF and ACS/ASCCP/ASCP have been used for screening in the United States in 2012.

According to Sasieni P. et al. (2009) data, all women in 25-64 age group receive screening at 3-5 year period. During the last 20 years, cervical cancer incidence has decreased by half. e.g. 1988, when cervical cancer screening program was launched, 4,132 women were diagnosed with cervical cancer, i.e. Relative to Age Standardized Rates (ASR) 16,2 women per 100,000 of female population were affected by this disease that year. To compare, in 2008 only 2,369 cases of this localization cancer was revealed, i.e. 8,3 women per 100,000 of female population were affected by the disease in 2008.

According to Gold M.A. (2006), cervical Pap testing applied in screening program in many countries, makes it possible to identify the patients with pre-cervical cancer diseases, provide treatment and follow-up observation. In world developed countries, Pap test screening has resulted in 70-80 % decrease of cervical cancer incidence.

According to Nanda K. et al. (2000) data, the Pap test sensitivity range within 47%-62 % and specificity within 60%-85 %.

According to the Cancer Registry of Finland (2014), effective functioning of cervical cancer screening program resulted in a 80 % decrease in cervical cancer incidence and mortality caused by this disease.

Dickinson J.A. et al. (2012) has released the data of the Canadian Cancer Registry, stating that mortality caused by cervical cancer per 100,000 female population during the period from 1952 to 2006, has decreased from 13,5 up to 2,2. Due to the screening program, cervical cancer incidence In Canada was reduced by 58% and mortality caused by this disease by 71% during the period of 1972-2006.

Basing on the results of own study, Goldie S.J. et al. (2001) recommends that annual cytological screening for HIV infected patients instead of 3-5 year interval is the cost-effective modification of existing guideline.

According to Andrae B. et al. (2012) data, women that regularly participate in the cervical screening program, has a low risk of mortality caused by this disease due to early detection of a disease.

According to the Norwegian cervical cancer screening program (NCCSP, 2014), screening has contributed to 25 % decrease of cervical cancer incidence and 50 % decrease of mortality caused by this disease.

In 2008, breast and cervical cancer screening program has been launched in Georgia. To date, more than 80,000 women received screening diagnostic examination. At the same time, there is no epidemiological study conducted for the assessment of the cost-effectiveness of a screening program, a diagnostic value of tests used while screening and until now, there is no academic proof for optimization of female health advocacy.

Goals and objectives of the study:

Screening program materials and the data collected as a result of its realization have been used in a scientific study. Designed for epidemiological assessment of a current screening program, it was directed at solving of a below provided objective:

◊ Carry out the epidemiological assessment of a diagnostic value of cervical cancer screening tests and cost-effectiveness of the program in Tbilisi.

Study Target Groups and Methodology:

81,973 women have been examined within the framework of cervical cancer screening program during the period of 2008-2014. Cervical Cancer screening diagnostic guideline implied the following tests: gynecological examination (PV et PR) and Pap test; colposcopy, biopsy and histology were provided if needed.

Screening program cost-effectiveness was studied based on a data of the 5 year period (2010 -2014): gynecological examination and Pap test was provided to 66,324 women and 12,147 women received colposcopy, biopsy and histological analysis. In 2013, cervical cancer screening was provided in total to 13,584 women, among them 7,416 (54,6%) women were examined at the National Screening Center. Thus, the assessment of cervical cancer screening effectiveness based on the data of the National Screening Center was considered quite valid.

To assess the diagnostic value of cervical cancer screening basing on a data of the National Screening Center, following indicators of gynecological examination, Pap tests, colposcopy and combination of Pap test and colposcopy have been studied: sensitivity, specificity, positive and negative predictive values and efficiency of tests.

While assessing the diagnostic value of the test, each examination result was compared with a clinical diagnosis, made on a basis of complex examination in case of each individual patient.

Results of the research:

Statistical indicators collected as a result of a study have been analyzed and presented in tables and charts.

The data of the National Screening Center since 2013 (See Chart # 1) has been analyzed for the assessment of cervical cancer screening test effectiveness in Tbilisi.

Chart 1. Age distribution of women were examined at the National Screening Center in 2013
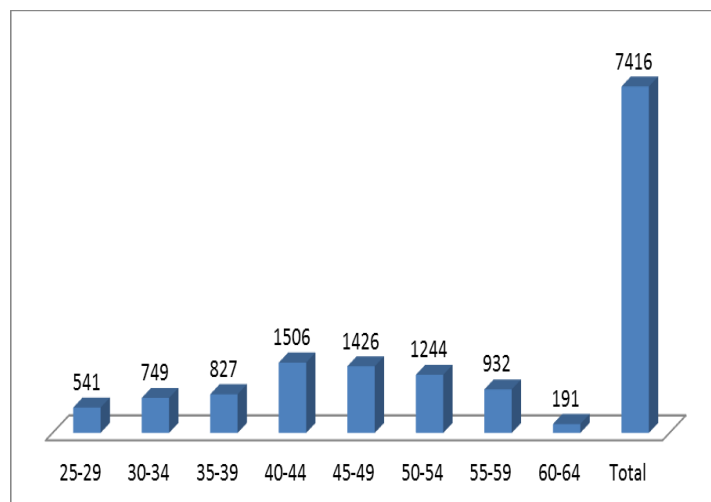
In 2013, cervical cancer screening was provided in total to 13,584 women, among them 7,416 (54,6%) women were examined at the National Screening Center. Thus, the assessment of cervical cancer screening effectiveness based on the data of the National Screening Center was considered quite valid.

Screening-diagnostic results of women examined at the National Screening Center in 2013 according the age groups are provided in a table 1.

Table 1. Screening-diagnostic results of women examined at the National Screening Center in 2013 according the age groups

Age	Absolute quantity	Standard	Clinical Diagnose		
			Atypia, mild and moderate dysplasia (CIN 1, CIN2)	Pre-Cancer diseases (severe dysplasia -CIN3 and CIS)	Cancer
25-29	541	509	27	4	1
30-34	749	686	54	7	2
35-39	827	745	61	13	8
40-44	1506	1383	93	21	9
45-49	1426	1325	75	15	11
50-54	1244	1189	43	8	4
55-59	932	886	34	4	8
60-64	191	181	7	1	2
Total	7,416	6,904	394	73	45

45 cases of cervical cancer and 73 cases of severe cervical dysplasia (CIN3) and intraepithelial carcinoma (CIS) have been detected among 7,416 women, examined at the National Screening Center in 2013.

The prevalence of severe cervical dysplasia (CIN3) and intraepithelial carcinoma (CIS) per 1,000 the women eligible for screening equaled to 9,8%0 in 2013. High level of severe cervical dysplasia and (CIN3) and intraepithelial carcinoma (CIS) was noted in 35-49 age group (See Chart 2).

Chart 2. The prevalence of pre-cancer diseases (CIN3/CIS) per 1,000 (%0) of screening eligible women in Tbilisi, in 2013, according the age groups
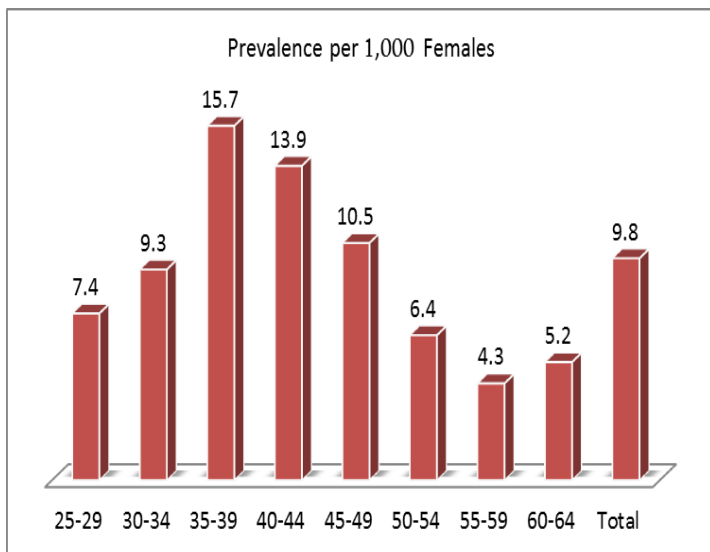
The prevalence of cervical cancer per 1,000 screening eligible women equaled to 6,1%0 in 2013. The peak of Cervical cancer prevalence (10,5%0) was identified in 60-64 age group (See Chart 3).

Chart 3. The prevalence of cervical cancer per 1,000 (%0) of Pap screening eligible women in Tbilisi, in 2013, according the age groups
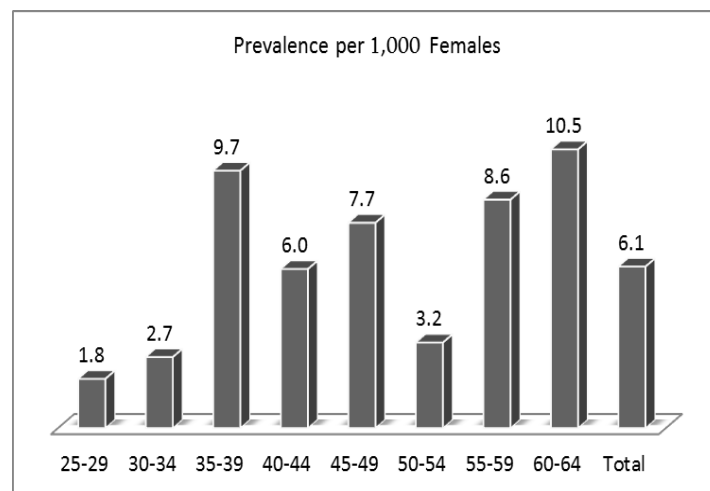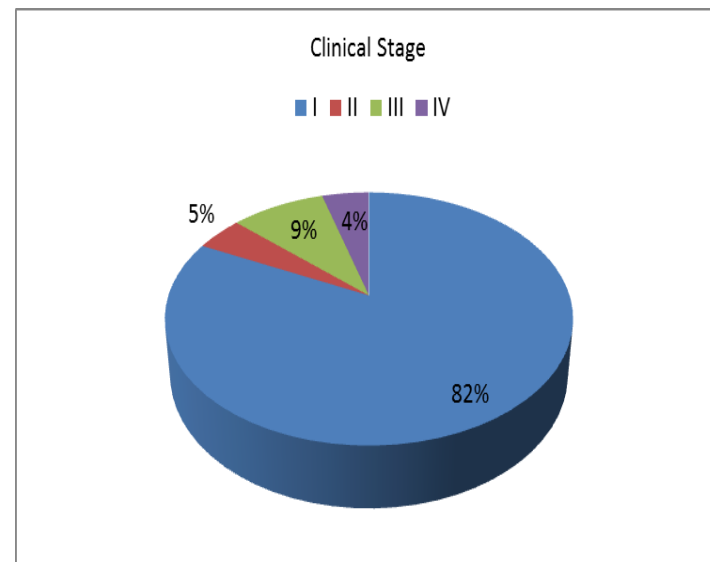

Chart 4. Specific weights of clinical stages of cervical cancer cases detected at the National Screening Center in 2013

The great majority (82%) of 45 cervical cancer cases detected at the National Screening Center in 2013 was diagnosed at I clinical stage (See Chart 4).

Comparison of gynecological examination results with the clinical diagnoses in cervical cancer and CIS cases is provided in a table 2.
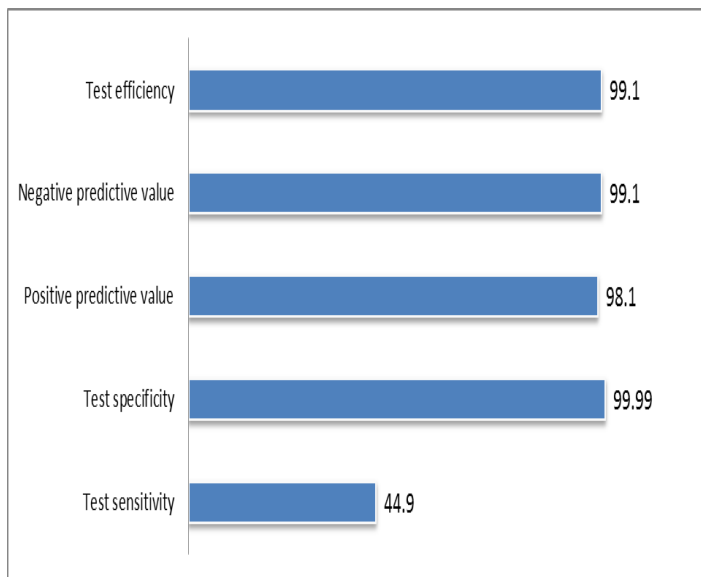
Table 2. Comparison of gynecological examination results with the clinical diagnosis in cervical cancer and CIS cases, detected at the National Screening Center in 2013

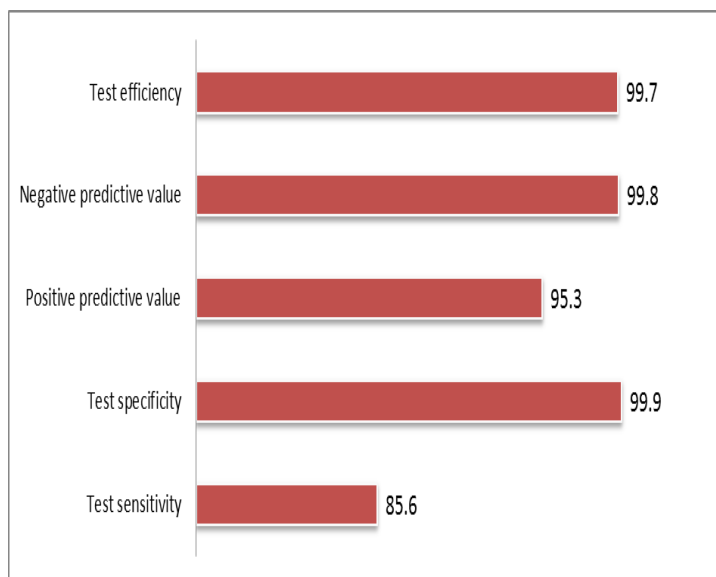| Gynecological examination results	Clinical Diagnose		Total
	Cancer/ CIS	Standard	
Cancer/ CIS	53	1	54
Standard	65	7297	7362
Total	118	7298	7416
χ^2= 3240; p<0,001			

Table 3. Comparison of Pap test results with the clinical diagnosis in cervical cancer and CIS cases, detected at the National Screening Center in 2013

Pap test results	Clinical diagnoses		Total
	Cancer/ CIS	Standard	
Cancer/ CIS	101	5	106
Standard	17	7293	7310
Total	118	7298	7416
χ^2= 6030; p,0,001			

118 patients from 7,416 women examined at the National Screening Center in 2013 were diagnosed with cervical cancer and CIS, among them in 53 cases, the diagnosis was confirmed by gynecological examination as well. No cervical cancer pathology has been established by gynecological examination of 7,362 women, including 65 cases of CIS, i.e. 0,9% cases of hypo diagnostics and 4,7 % cases of hyper diagnostics have occurred during the gynecological examination.

Diagnostic effectiveness rates of gynecological examination are provided in a chart # 5. Gynecological examination sensitivity equaled to 44,9 %, specificity – 99.99%, positive prognosis ratio - 98.1%, negative prognosis ratio - 99.1%, and the value ratio - 99.1%.

Chart 5. Assessment of the effectiveness of gynecological examination in cervical cancer and CIS cases detected at the National Screening center in 2013

118 patients from 7,416 women examined at the National Screening Center in 2013 were diagnosed with cervical cancer and CIS, among them in 101 cases, the diagnosis was confirmed by a Pap test. No cervical cancer pathology has been established by the results of a Pap test in 7,362 women, including 17 cases of CIS, i.e. 0,2 % cases of hypo diagnostics and 4,7 % cases of hyper diagnostics have occurred during the Pap test examination.

Diagnostic effectiveness rates of the Pap test are provided in a chart # 6. Pap test sensitivity equals to 85,6 %, specificity – 99.9%, positive prognosis ratio – 95,3%, negative prognosis ratio – 99,8%, and the value ratio - 99.7%.

Chart 6. Assessment of the effectiveness of the Pap test in cervical cancer and CIS cases detected at the National Screening center in 2013


Test efficiency	99.1
Negative predictive value	99.1
Positive predictive value	98.1
Test specificity	99.99
Test sensitivity	44.9

Test efficiency	99.7
Negative predictive value	99.8
Positive predictive value	95.3
Test specificity	99.9
Test sensitivity	85.6

Comparison of Pap test results with the clinical diagnoses in cervical cancer and CIS cases is provided in a table 3.

Comparison of colposcopy results with the clinical diagnoses in cervical cancer and CIS cases is provided in a table 4.

Table 4. Comparison of coploscopy results with the clinical diagnosis in cervical cancer and CIS cases, detected at the National Screening Center in 2013

Colposcopy results	Clinical diagnoses		Total
	Cancer/ CIS	Standard	
Cancer/ CIS	108	3	111
Standard	10	1254	1264
Total	118	1257	1375
$\chi^2 = 625$; $p < 0,001$			

1,375 women received colposcopy examination at the National Screening Center in 2013. The diagnose of 108 women from 118 cases of cervical cancer and intraepithelial carcinoma was confirmed by colposcopy. No cervical cancer pathology has been established based on colposcopy results in 10 cases. i.e. 0,8 % cases of hypo diagnostics and 3 cases (2,7%) from 111 of hyper diagnostics have occurred.

Chart 7. Assessment of the effectiveness of colposcopy in cervical cancer and CIS cases detected at the National Screening center in 2013
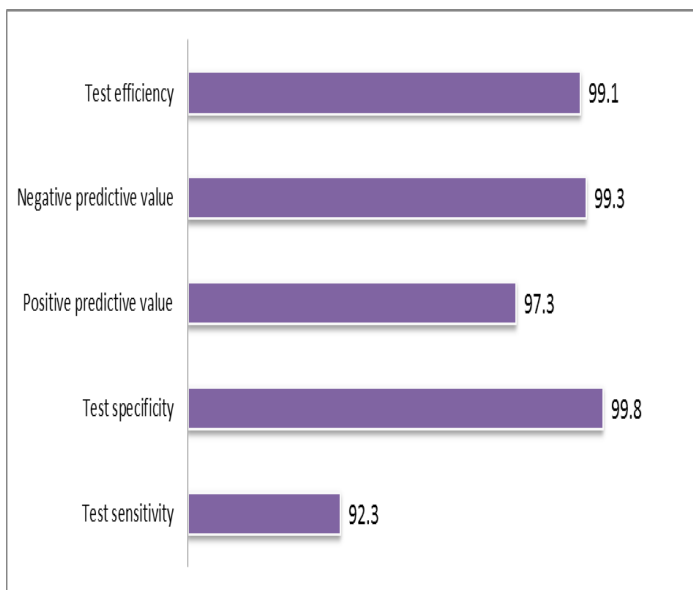
Diagnostic effectiveness rates of colposcopy are provided on a chart # 7. Colposcopy sensitivity equals to 91,5 %, specificity – 99.8%, positive prognosis ratio – 97,3%, negative prognosis ratio – 99,2%, and the value ratio - 99.1%.

Relative analysis of the diagnostic effectiveness of gynecological examination, Pap test and colposcopy has shown, that in diagnostics of cervical cancer and intraepithelial carcinoma (CIS), these tests mainly differ in the sensitivity ratio (See Chart 8).

Chart 8. Comparison of the sensitivity of gynecological examination, Pap test and colposcopy in cervical cancer and CIS cases detected at the National Screening center in 2013
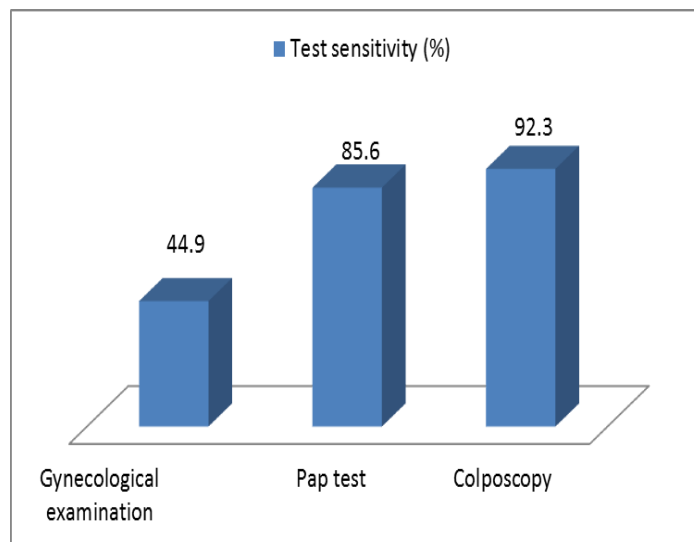

It is known, that test sensitivity reflects the probability, when disease affected individuals are classified as patients. Compared to gynecological examination (44.9%), the high sensitivity rate was noted in Pap test (85,6%) and colposcopy examination (92,3%) cases. In addition to this, special positive feature of the Pap test, as of a main tool of screening, is a low rate of hypodiagnostics (0,2%). Pap test effectiveness significantly increases by the histological test of the material, taken from damaged areas during the colposcopy examination.

In addition, the results of Pap test and colposcopy combination in 162 cases were compared with clinical diagnoses and the effectiveness of this combination was studied (See Table 5 and Chart 9).

Table 5. Comparison of the results of Pap test and colposcopy combination with clinical diagnoses, in cervical cancer and CIS cases detected at the National Screening Center in 2013

Pap test and colposcopy combination	Clinical diagnoses		Total
	Cancer/ CIS	Standard	
Cancer/ CIS	26	2	28
Standard	1	133	134
Total	27	135	162
$\chi^2 = 141$; $p < 0,001$			

Chart 9. Assessment of the effectiveness of Pap test and colposcopy combination in cervical cancer and CIS cases detected at the National Screening Center in 2013
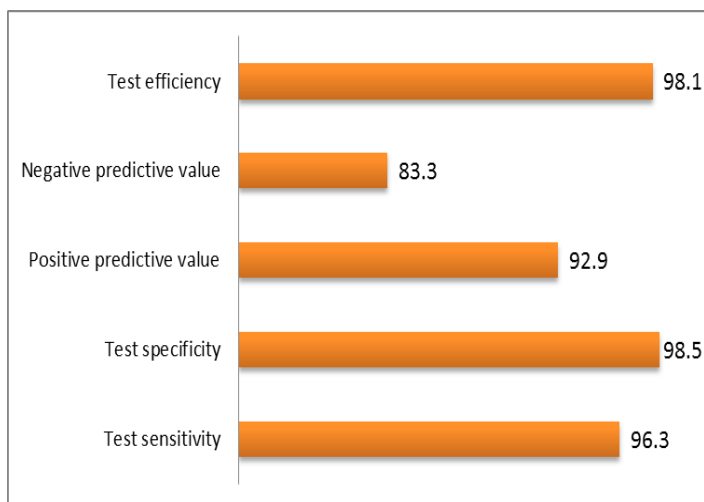
Pap test and colposcopy combination sensitivity equaled to 96,3 %, specificity 98.5%, positive prognosis ratio – 92.9%, negative prognosis ratio – 83.3%, and the value ratio - 98.1%.

The absolute quantities of the tests conducted at the National Screening Center and sub-contracting organizations during the 5 year cycle (2010-2014) have been studied for economic assessment of cervical cancer screening program (See Table 6).

Table 6. The absolute quantity of examinations carried out within the framework of cervical cancer screening program, in Tbilisi, during the period of 2010-2014

Year	Gynecological exam + Pap test	Colposcopy + Biopsy+ Histology
2010	14,552	2,094
2011	12,130	2,224
2012	13,151	2,499
2013	13,584	2,712
2014	12,907	2,618
Total absolute quantity	66,324	12,147
%	100	18

During the period of 2010-2014, within the framework of the cervical screening program, 66,324 women received gynecological examination and Pap test; and colposcopy, marked biopsy and morphological tests were conducted in 12,147 women, i.e. 18 % of screening eligible women.

The cost of cervical cancer screening conducted in Tbilisi during the period of 2010-2014 is provided in a table 7.

Table 7. Cost of cervical cancer screening, conducted in Tbilisi during the period of 2010 -2014

Cervical cancer screening	2010-2014 25-59 age group abso-lute quant.	Cost (GEL) 1 test unit	Total (GEL)
Gynecological exam + Pap test	66,324	21.80	1,445,863
Colposcopy + Biopsy + Histology	12,147	45.70	555,118
Total			2,000,981

Total cost of cervical cancer screening provided to 66,324 women in Tbilisi during the period of 2010-2014, equaled to 2,000,981 GEL.

According to the population census of 2002, the number of female population in Tbilisi in 25-59 age group equaled to 290, 007 and in 30-64 age group to 280,883 women.

According to cervical cancer screening guideline being currently in operation, women in 25-59 age group are eligible for screening program, i.e. During the period of 2010-2014, only 23 % of target population eligible for screening have received the test. At the same time, improvement of screening efficiency requires at least 50% coverage of a target group and as it is known, in case of 70 % coverage, actual reduction of cervical cancer related death rate starts.

The cost of cervical cancer screening in 25-59 and 30-64 age groups in case of 50 % and 70 % coverage of the target groups have been calculated, basing on data of female population census of 2002 (See Tables 8 and 9).

To enhance the effectiveness of cervical cancer screening, stage by stage 2-3 times increase of a number of screening eligible women is necessary. To achieve this goal, it is necessary on the one hand to educate the female population of Georgia and develop a habit of getting periodical screening and on the other hand to increase the financing of the screening program. In case of 50 % coverage of 25-59 age group, the cost of the cervical screening program will equal to 4,353,886 GEL and in case of 70 % coverage it will be 6,095,427 GEL. In case of 50 % coverage of 30-64 age group, the cost of the cervical screening program will be 4,216,908 GEL and in case of 70 % coverage it will be 5,903,652 GEL.

As our epidemiological study have showed, making of alteration in screening guideline and re-adjusting of a target group from 25-59 to 30-64 age group will on the one hand increase the number of detected cervical cancer cases (compared to 25-59 age group, cervical cancer incidence rate is 1,2 times higher in 30-64 age group relative to SRR and in 8,8 % higher relative to Relative Frequency; The peak level (10,5%0) of cervical cancer prevalence in screening eligible women group was noted in 60- 64 age group of female population) and on the other hand it will decrease needed expenditures – in case of 50 % coverage of a target group by ~ 137,000 GEL and by ~ 192,000 GEL in case of 70 % coverage. i.e. Making of alterations to the screening guideline and re-adjusting of a target group to 30 -64 age group will significantly enhance the cost-effectiveness of cervical cancer screening.

Table 8. Cost of cervical cancer screening in 25-59 and 30-64 age groups of female population based on 2002 census data, in case of 50 % and 70 % coverage of a target group of female population

Cervical cancer screening	Target group: 25-59 age group	Target group relative to screening coverage		I test unit	Cost (GEL)	
					Total	
					Target group coverage	
		50%	70%		50%	70%
Gynecological exam + Pap test		145,004	203,005	21.80	3,161,087	4,425,509
Colposcopy + Biopsy + Histology		26,101	36,541	45.70	1,192,799	1,669,918
Total	290,007				4,353,886	6,095,427

Table 9. Cost of cervical cancer screening in 30-64 age group of female population based 2002 census data, in case of 50 % and 70 % coverage of a target group of female population

Cervical cancer screening	Target group: 30-64 age group	Target group relative to screening coverage		I test unit	Cost (GEL)	
					Total	
					Target group coverage	
		50%	70%		50%	70%
Gynecological exam + Pap test		140,442	196,618	21.80	3,061,636	4,286,272
Colposcopy + Biopsy + Histology		25,279	35,391	45.70	1,155,272	1,617,380
Total	280,883				4,216,908	5,903,652

Chart 10. Cost of cervical cancer screening in 25-59 and 30-64 age groups in case of 50 % and 70 % coverage of the target groups
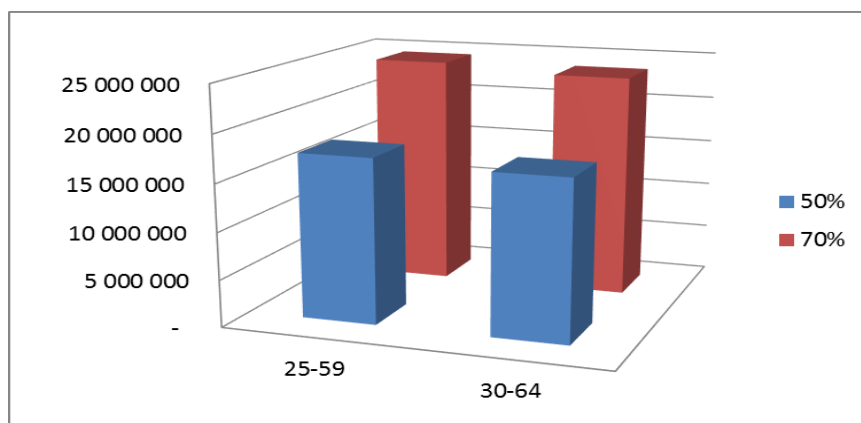
Conclusions:

1. The prevalence of severe cervical dysplasia (CIN3) and intraepithelial carcinoma (CIS) per 1,000 screening eligible women equaled to 9,8% in 2013. High rate of cervical dysplasia (CIN3) and intraepithelial carcinoma (CIS) was noted in 35-49 age group of female population

2. The prevalence of cervical cancer per 1,000 screening eligible women equaled to 6,1%. The peak of cervical cancer prevalence (10,5%0) was noted in 60-64 age group. In a great majority (82%) of cervical cancer cases, the disease was diagnosed at I clinical stage.

3. 0,2 % cases of hypo diagnostics and 4,7 % cases of hyper diagnostics have occurred during the Pap test examination. Pap test sensitivity equaled to 85,6 %, specificity – 99.9%, positive prognosis ratio – 95,3%, negative prognosis ratio – 99,8%, and a value ratio - 99.7%.

4. 0,8 % cases of hypo diagnostics and 2,7% of hyper diagnostics have occurred in colposcopy examinations. Colposcopy sensitivity equaled to 91,5 %, specificity – 99.8%, positive prognosis ratio – 97,3%, negative prognosis ratio – 99,2%, and the value ratio - 99.1%.

5. Pap test and colposcopy combination sensitivity equaled to 96,3 %, specificity 98.5%, positive prognosis ratio – 92.9%, negative prognosis ratio – 83.3%, and the value ratio - 98.1%.

6. Making of alteration in screening guideline and re-adjusting of a target group from 25-59 to 30-64 age group will on the one hand increase the number of detected cervical cancer cases and on the other hand will decrease needed expenditures – in case of 50 % coverage of a target group by ~ 137,000 and by ~ 192,000 GEL in case of 70 % coverage. i.e. Making of alterations in the screening guideline and re-adjusting of a target group to 30-64 age group will significantly enhance the cost-effectiveness of cervical cancer screening.

Recommendations :

1. To enhance the effectiveness of cervical cancer screening, stage by stage 2-3 times increase of a number of screening eligible women is necessary. To achieve this goal, it is necessary on the one hand to educate the female population of Georgia and develop a habit of getting periodical screening and on the other hand to increase the financing of the screening program. In case of 50 % coverage of 25-59 age group, the cost of the cervical screening program will equal to 4,353,886 GEL and in case of 70 % coverage it will be 6,095,427 GEL. In case of 50 % coverage of 30-64 age group, the cost of the cervical screening program will be 4,216,908 GEL and in case of 70 % coverage it will be 5,903,652 GEL.

2. Based on the conducted epidemiological study, it is recommended to make an alteration in a screening guideline and re-adjust a target group from 25-59 to 30 -64 age group that will on the one hand increase the number of detected cervical cancer cases and on the other hand will decrease needed expenditures – in case of 50 % coverage of a target group by ~ 137,000 GEL and by ~ 192,000 GEL in case of 70 % coverage. i.e. Making of alterations to the screening guideline and re-adjusting of a target group of 30-64 age group will significantly enhance the cost-effectiveness of cervical cancer screening.

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