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Influence of Cytology Development on Frequency of Pre-Cancerous Lesions and Cervical Cancer in East Croatia, 1978–2001

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ABSTRACT

We analyzed the influence of cytology development to frequency of precancerosa (Cervical intraepithelial neoplasia grade 3 – CIN 3) and cervical cancer. The number of examined Pap smears increased significantly in the analyzed period. The calculated linear trend shows an average four-year increase of 17,283.35 smears. The number of detected CIN 3 increased accordingly. The calculated linear trend shows an average four-year increase by 45.03 and decrease of the rate of 0.07. A slight increase in cervical cancer was also noticed. The calculated linear trend shows an average four-year increase in cancer by 1.6 and decrease in the rate of 0.51. Analyses of cervical cancer by stages showed an increase in number of stage I and decrease of other stages. The calculated linear trend shows an average four-year increase of stage I by 4.94 or decrease in other stages of cervical cancer of 3.29 respectively. The rate of cervical cancer stage I decreased by 0.11 and of other stages by 0.39. Further analyses of the stage I showed that the linear trend of I^A stage had an average four-year increase by 5.40 and decrease in stage I^B of 0.48. The rate of the cervical cancer stage I^A increased by 0.02, whereas the rate of I^B decreased by 0.13. Cytology development in our country has resulted in detection of higher number of CIN 3 and the earliest stage (I^A) of cervical cancer whereas the number of other stages (I^B, II, III, IV) has decreased. However, a total number of cervical cancers haven't changed over the whole period. Thus, it is obvious that opportunistic program of detection, which has been using in Croatia, could not decrease frequency of cervical cancer. In order to achieve it, well-organized national program of detection is needed.

Key words: cytology, cervix, carcinoma cervices, pre-cancerous, incidence, Croatia

Introduction

Cytological smear is a method of choice in detection of precancerosa and early stages of cervical cancer because those lesions are easy to localize, they develop rather slowly and have very well defined phases of development^{1–5}.

Pap smear cannot detect only very rare, rapidly progressive cervical cancers, which do not have the above phases of development but directly grow into stroma, in their early stage^{6,7}. The bad thing is that those cancers are more frequent in women younger than 40. Fortunately, there are only 10.0% of those cancers^{8,9}.

Screening for cancer of the cervix with cervicovaginal smear had been introduced in the United States and developed West European countries more than 30 years ago^{5,10,11}. Just with implementation of the organized national program of detection, which included all women in risk age (older than 30 years), those countries succeeded to reduce total number of cancer and number of late stages of cancer. It has been confirmed in many reports of cervical cancer incidence and mortality rate^{12–15}.

Most number of developing countries use opportunistic program of detection of cervical cancer, which includes only women who visit their gynecologist no matter what reason is^{16,17}. As this program of detection does not include huge amount of risk population, it couldn't significantly decrease cervical cancer incidence and mortality rate^{18,19}.

The aim of this study is to estimate the influence of cytology development and opportunistic detection program in observing period on CIN 3 frequency, cervical cancer frequency, their relationships and also relation between early and late stages of cancer.

Material and Methods

The number of examined Pap smears over four-year periods in the University Hospital »Osijek« (1978–2001) was analyzed. Trends in the number of detected precancerosa and cancers of the uterine cervix were analyzed as well and their relationship and relation between early and advanced stages.

Pap smear as method of secondary prevention of cancer of the uterine cervix was introduced in the University Hospital »Osijek« in 1965. Providing that a woman comes for gynecologic check-up once a year she has her smear examined, and in case of any abnormality Pap smear is examined even more frequent -as recommended by the cytologist. Pap smear is taken from the back fornix of the vagina, from the cervix surface and from the cervical canal – and is placed on a slide.

University Hospital »Osijek« takes care of almost all patients from Osječko-baranjska and Vukovarsko-srijemska counties. On this area live, according to the last census from 2001, 278,127 women. In these two counties there are still three smaller hospitals, but almost all women with cervical cancer have been treated in University Hospital Osijek.

In relation to the rate using Pap smears in detection of precancerosa and cervical cancer, the analyzed period can be divided into three sub periods. In the first sub period 1965–1974, there was only one gynecologist who had completed a course in cytodiagnostics and, besides his regular job at the Department of Gynecology and Obstetrics, he engaged in cytology as well. There was also one cytoscreener and one technician working in the cytological laboratory of the Gynecologic Department. In that sub period Pap smear had been taken sporadically (3,406 smears per year on the average). In the second sub period 1975–1983, the laboratory employed doctors who were specializing medical cytol-

ogy as their primary and only occupation. They also taught young colleagues – cytoscreeners and established Department of Cytology as a part of the Department of Gynecology. Over this sub period Pap smear was taken more frequently but still not every patient who had come for gynecologic check-up was taken Pap smear (7,508 smears per year on the average) In the last sub period 1984–2001, altogether 5 specialists in cytology were employed as well as 5 cytoscreeners and 3 technicians. They all worked at the independent Department of Clinical Cytology. All women coming for gynecologic check-up had Pap smear (25,691 smears per year on the average). It included women who had some gynecological disorders, pregnant women and healthy women who were coming once a year on regular gynecological check-up.

According to the above data it is noticeable that as a consequence of cytology development and doctors' and patients' awareness of the importance of cytology as method of secondary prevention of cervical cancer, the number of Pap smears increased in the analyzed period by 7.5x. But, in spite of cytology development, opportunistic program of cervical cancer detection further is continuing, because organized national program of detection does not exist.

In our analyses we used medical documentation of the Department of Gynecology and Obstetrics and the Department of Clinical Cytology of the University Hospital »Osijek«.

For statistical analyses we used: linear trend equation, linear regression equa-

tion, Pearson's correlation coefficient, Spearman's rank coefficient. The rate for all kinds of lesions in relation to the number of cytological smears over analyzed periods was also calculated.

Results

Over the period 1978–2001 (24 years), 412,825 cytological smears were examined and 1,772 CIN 3 and 760 cervical cancers detected.

Table 1 shows that CIN 3 is the most frequent in women aged from 30 to 50 years, and very rare in age over 50 years. Opposite, cervical cancer is most frequent in women over 50 years, and very rare in women age under 30 years. Cervical cancer was detected in 28 (3.7%) women who submitted cytology detection regularly once a year. Other women have not been submitted to cytology detection.

Figure 1 shows, according to their distribution over the years, that the curve of CIN 3 follows the curve of the examined smears. It also shows that the curve of the number of smears has no influence on the curve of cervical cancers.

In order to get more accurate data we analyzed the number of examined smears, CIN 3 and cervical cancers over four-year periods.

According to the calculated linear trend equation, there is an average four-year increase in the number of examined smears by 17283.35 ($y_c = 41910.8095 + 17283.3492x$) (Figure 2).

TABLE 1
DISTRIBUTION OF PRECANCEROSA AND CERVICAL CANCER ACCORDING TO AGE

Type of the lesion	<30		30–50		>50		Total	
	N	%	N	%	N	%	N	%
CIN 3	475	32.7	875	60.2	103	7.1	1,453	100.0
Cervical cancer	11	2.2	194	39.0	293	58.8	760	100.0

The calculated linear trend equation shows that there is an average four-year increase in the number of cervical cancers by 45.0 as well ($y_c = 174.4286 + 45.0286x$). At the same time, an average four-year trend in the rate decrease of 0.07 ($y_c = 3.3459 - 0.0749x$) was noted. The difference is statistically significant ($\chi^2 = 129.12, \chi^2_{0.05} = 11.07$) (Figure 2).

The calculated linear trend equation shows that there is also an average four-year increase in the number of cervical cancers by 1.66. ($y_c = 122.5238 + 1.6571x$). At the same time, an average four-year

trend in the rate decrease of 0.51 ($y_c = 3.1237 - 0.5085x$) was noted. The difference is statistically significant. ($\chi^2 = 186.52, \chi^2_{0.05} = 11.07$) (Figure 2).

The calculated linear regression equation shows that increase in the number of women with CIN 3 by one will result in an average increase in the number of women with cervical cancer by 0.05 women ($y = 112.7718 + 0.0484x$). With 95% confidence intervals it could be said that the regression coefficient (b) is higher than -0.132 , and lower than 0.229 . Pearson's correlation coefficient shows a weak

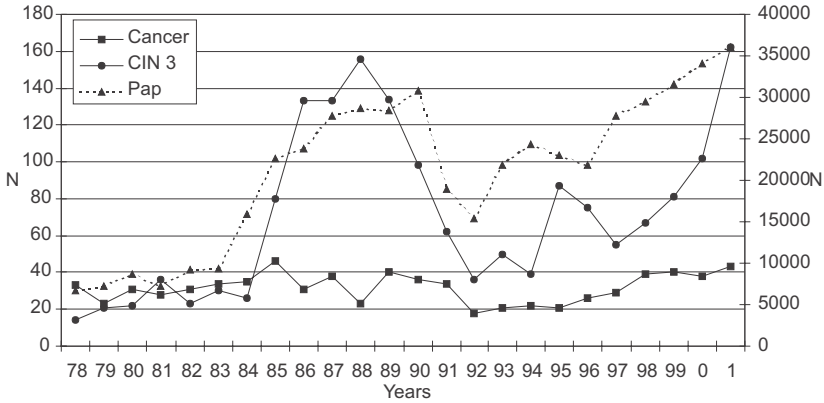


Fig. 1. Distribution of cytological smers, cervical cancers and CIN 3 in the analyzed period.

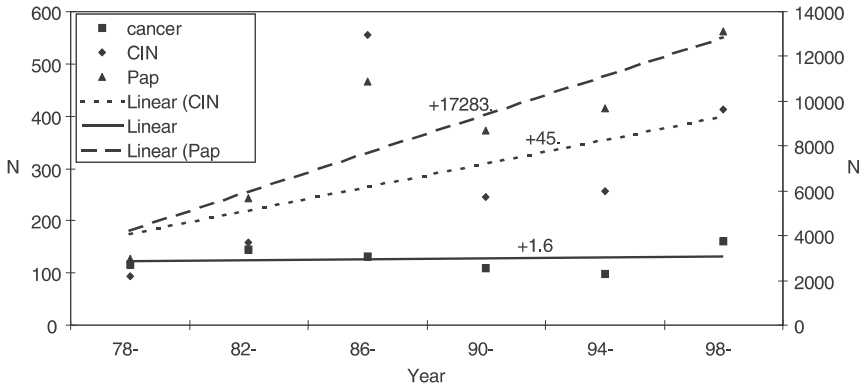


Fig. 2. Linear trend of the average number of patients with CIN 3 and cervical cancers in 4-years period.

TABLE 2
DISTRIBUTION OF NUMBER AND RATE OF CERVICAL CANCER STAGE I AND OTHER STAGES OVER FOUR-YEAR PERIODS

Period	Pap smear	CIN 3		Cervical cancer	
	Number	Number	Rate	Number	Rate
1978–1981	29825	93	3.118	115	3.856
1982–1985	56979	159	2.791	146	2.562
1986–1989	108768	556	5.112	132	1.214
1990–1993	86962	246	2.829	109	1.253
1994–1997	97060	256	2.638	98	1.010
1998–2001	131121	412	3.142	160	1.220

TABLE 3
DISTRIBUTION OF NUMBER AND RATE OF CERVICAL CANCER STAGES IA AND IB OVER FOUR-YEAR PERIODS

Periods	Pap smear	Cervical cancer stage IA		Cervical cancer stage IB	
	Number	Number	Rate	Number	Rate
1978–1981	29,825	4	0.134	28	0.939
1982–1985	56,979	16	0.281	36	0.632
1986–1989	108,768	24	0.221	34	0.313
1990–1993	86,962	18	0.207	19	0.218
1994–1997	97,060	21	0.216	24	0.247
1998–2001	131,121	40	0.305	35	0.267

positive correlation between the number of women with CIN3 and those with cervical cancer ($r=0.349$) but it is not statistically significant. ($t=0.7449$, $t_{0.05}(4)=2.7765$, $p=0.4977$). Spearman's rank coefficient also shows that there is a weak positive correlation ($r_s=0.2$) between the number of women with CIN 3 and those with cervical cancer. It isn't statistically significant as well ($r_s=0.2$, $r_{s0.05}=0.8286$). Distribution of the number of women with early (I) stage and advanced (II, III, IV) stages of cervical cancer over four-year periods was analyzed separately. The calculated linear trend equation shows an average four-year increase in the number of cancers in early stage by 4.49 or decrease in advanced stages of 3.29 respectively ($y_c = 37.4762 + 4.9429x$,

$y_c = 85.0476 - 3.2857x$). At the same time, an average four-year trend in rate decrease of early stage by 0.11 was noted. ($y_c = 0.9462 - 0.1141x$) whereas the rate of advanced stages decreased by 0.39 ($y_c = 2.1777 - 0.3954x$). The difference is statistically significant. ($\chi^2=29.33$ or $\chi^2=181.61$, $\chi^2_{0.05}=11.07$ respectively) (Table 2).

Moreover, we had divided stage I into IA and IB and analyzed separately their distribution over four-year periods. According to the calculated linear trend equation there is an average four-year increase in the number of cancers stage IA by 5.40 and decrease in IB of 0.48 ($y_c = 7.0000 + 5.3999x$, or $y_c = 30.4762 - 0.4571x$ respectively). At the same time we noted an increase in the rate of IA by 0.02 and decrease in IB of 0.13 ($y_c = 0.1821 +$

0.0185x or $y_c = 0.7653 - 0.1317x$). The difference for I^A is not statistically significant but it is significant for I^B. ($\chi^2=4.87$ or $\chi^2=53.50$, $\chi^2_{0.05}=11.07$ respectively) (Table 3).

Discussion

Owing to cytology development and successfully organized screening programs the advanced industrialized countries have lower incidence and mortality of cervical cancer^{20–22}.

Cytology development as an almost ideal method of screening for cervical cancer has been moving up in our country as well. Former cytological laboratory with only one gynecologist, who completed a course in cytology and spent only part of his working hours in the laboratory, has developed into a Department of Clinical Cytology, which employs five cytologists, two of whom practice gynecologic cytology and the others according to circumstances. Besides, there are five cytoscreeners in the laboratory as well.

The above development resulted in growing number of examined Pap smears in the observed period i.e. more women were involved in the screening program.

The increased number of examined Pap smears resulted in higher number of detected CIN 3^{23,24}. At the same time however, statistically significant decrease in CIN 3 rate was noted in relation to the number of cytological examinations. The curves of the Figure showing distribution of the number of examined smears and the number of CIN 3 over the observed period are almost identical. Transitory considerable decrease in the number of examined smears and detected CIN 3 as well as a slight decrease in cervical cancer in the period 1990–1997 is more likely a consequence of political changes and war in the region that influenced migration, especially of female population. On the other hand, women who hadn't left the war-affected region didn't think of

prevention as being the priority at that time.

Positive influence of cytology development to increase in the number of detected precancerosa doesn't influence a gradual decrease in occurrence of invasive cervical cancer – what is to be expected. Moreover, in the observed period we even noted a slight increase in the number of women with cervical cancer. On the other hand, the rate of cervical cancer in relation to the number of examined smears was significantly lower.

According to reference literature it's the same in the whole country. There are no data on decrease in incidence of cervical cancer and mortality²⁵.

As we already mentioned, there were migrations in the region due to war in the period 1990–1997. Because of that all data from that period are not to be taken for granted. The number of examined smears decreased slightly in those four-year periods (1990–1993 and 1994–1997) in relation to the previous one (1986–1989). However, the number of CIN 3 in those four-year periods was halved in relation to the previous one but still it was significantly larger than in the first two analyzed four-year periods (1978–1981 and 1982–1985) when cytology hadn't been developed well enough. The number of women with cervical cancer decreased in those periods as well. After most of the women who had left the region returned (1998–2001) the number of examined smears and cervical cancers increased but the number of detected CIN 3 was almost the same as before the war? In spite of very bad working conditions for secondary prevention of cervical cancer during the war, there was no significant increase in advanced stages of cancer afterwards. It is very likely a consequence of detection of precancerosa and early stages of cancer before the war. An intensive work on secondary prevention in the

last period resulted again in detection of the earliest stages.

In conclusion, it could be said that cytology development in our country resulted in detection of large numbers of women with CIN 3 and the earliest stage of cervical cancer I^A whereas the number of women with other stages (I^B, II, III, IV) declined. On the other hand, a total number of women with cervical cancer remained steady over the whole period. It means that opportunistic program of detection, which has been using in Croatia, could not decrease the incidence of cervical cancer. It just maintains the present state. It is obvious that using this program of detection we did not succeed to

enough reduce the number of women out of detection program.

That part of population that has not been included in screening program yet could be lessening by an intensive campaign in secondary schools and through media (better primary prevention). However, it is proved that significant decrease in incidence and mortality rate of cervical cancer could be achieved by well-organized national program of detection.

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UTJECAJ RAZVOJA CITOLOGIJE NA UČESTALOST PREKANCEROZA I RAKA CERVIKSA U KLINIČKOJ BOLNICI OSIJEK, U RAZDOBLJU OD 1978 DO 2001 GODINE

S A Ž E T A K

Analizirali smo utjecaj razvoja citologije na učestalost prekanceroza (cervikalna intraepitelna neoplazija 3. stupnja – CIN 3) i raka cerviksa. Broj pregleda citološkog obriska cerviksa uterusa značajno je porastao u analiziranom razdoblju. Izračunati linearni trend pokazuje prosječni četverogodišnji rast od 17283.35 citološka obriska. Sukladno tomu porastao je i broj otkrivenih CIN 3. Izračunati linearni trend pokazuje prosječni četverogodišnji porast CIN 3 za 45,03 i pad stope za 0,07. Također je primijećen i blagi porast raka cerviksa. Izračunati linearni trend pokazuje prosječni četverogodišnji porast raka za 1.6 i pad stope za 0,51. Analizom raka cerviksa po stadijima utvrđen je porast broja raka I stadija i pad broja ostalih stadija. Izračunati linearni trend pokazuje prosječni četverogodišnji porast raka I stadija za 4,94 odnosno pad ostalih stadija raka cerviksa za 3,29. Stopa raka cerviksa I stadija pala je za 0,11 a ostalih stadija za 0,39. Daljom analizom I stadija izračunati linearni trend za I^A stadij pokazuje prosječni četverogodišnji porast za 5,40 i pad stadija I^B za 0,48. Stopa raka cerviksa I^A stadija porasla je za 0,02 a stopa I^B je pala za 0,13. Zaključak. Razvoj citologije u nas je imao za posljedicu otkrivanje većeg broja CIN 3 i najranijeg stadija (I^A) raka cerviksa dok se broj ostalih stadija (I^B, II, III, IV) raka smanjio. Ukupan broj karcinoma cerviksa ostao je, međutim, isti kroz čitavo razdoblje. Tako, oportunistički program probira koji se u nas primjenjuje, ne može smanjiti učestalost raka vrata maternice. Da bi se to postiglo potrebno je stvoriti dobar organizirani nacionalni program probira.