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### ANALYSIS OF THE ACHIEVEMENT OF THE GLOBAL PURPOSE OF ELIMINATION OF CERVICAL CANCER IN UKRAINE

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Based on the analysis of the epidemiological situation in Ukraine, the study assesses the probability of achieving the purposes of the Global Strategy to accelerate the elimination of cervical cancer. Cervical cancer is a significant cause of death for Ukrainian women. In 2020, 30 % of all deaths were due to malignant neoplasms of the female genital organs, and approximately one in five deaths of women aged 30–45 years as a result of neoplasms was caused by cervical cancer. A comparative analysis with developed countries showed a higher probability of dying prematurely and a more significant contribution of the disease to the formation of the Global Burden of Disease indicator in young and old age. On the other hand, in Ukraine, there is a paradoxical phenomenon of decreasing mortality from cervical cancer with age. The COVID-19 pandemic was reflected in a decrease in the level of detection of new cases of the disease and an increase in the share of those detected in the advanced stage (in 2020 – 30.5 %, in 2021 – 31.1 % of deaths). It is suggested that there may be an increase in mortality due to untimely diagnosis and treatment of cervical cancer, which occurs against the background of a high prevalence of HIV infection, lower coverage of vaccination against human papillomavirus, and the low probability of Ukraine achieving the 90–70–90 goals by 2030.

**Key words:** cervical cancer, neoplasms, age-related mortality, premature mortality.

### Н.О. Рингач, О.Г. Курик, С.П. Григорчук, І.В. Думицька, К.В. Баздирев, С.С. Мирвода, В.В. Баздирев АНАЛІЗ ДОСЯЖНОСТІ ГЛОБАЛЬНОЇ ЦІЛІ ЕЛІМІНАЦІЇ РАКУ ШИЙКИ МАТКИ В УКРАЇНІ

У статті на основі аналізу епідеміологічної ситуації в Україні здійснено оцінку ймовірності досягнення цілей Глобальної стратегії прискорення ліквідації раку шийки матки. Рак шийки матки є вагомою причиною смерті українських жінок. У 2020 р. 30 % всіх смертей через злоякісні новоутворення жіночих статевих органів, і приблизно кожну п'яту смерть жінок у віці 30–45 років в результаті новоутворень зумовлював рак шийки матки. Компаративний аналіз з розвинутими країнами показав вищу ймовірність померти передчасно та вагомий внесок захворювання у формування показника Глобального тягаря хвороб у молодому і зрілому віці. Також в Україні спостерігається парадоксальне явище зниження смертності від раку шийки матки з віком. Пандемія COVID-19 віддзеркалилася у зниженні рівня виявлення нових випадків захворювання, зростанні частки виявлених у занедбаній стадії (у 2020 р. – 30,5 %, у 2021 р. – 31,1 % смертей). Висловлено припущення щодо можливого підвищення смертності через несвочасні діагностику та лікування раку шийки матки, що відбувається на тлі високої поширеності ВІЛ-інфекції, та нижчого охоплення вакцинацією проти вірусу папіломи людини, та малої ймовірності досягнення Україною цілей 90–70–90 до 2030 року.

**Ключові слова:** рак шийки матки, новоутворення, смертність за віком, передчасна смертність.

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Cervical cancer (CC) is an example of a disease resulting from which death can be avoided with timely treatment, detection and adequate treatment. Pathology ranks fourth among common types of cancer worldwide and seventh for women in the WHO European Region. In 2020, more than 604 thousand women worldwide were diagnosed with cervical cancer (6.5 % of all oncological diseases) [12]. According to estimates, almost 342,000 women died from cervical cancer in 2020 [10].

Profound differences in morbidity and mortality rates between high- and low-income countries and wealthy and poor strata of the population within the same country are mainly due to differences in the prevalence of human papillomavirus infection (HPV). High HPV incidence is associated with low access and quality of medical services. The burden of CC is especially significant in the countries of Eastern Europe (including Ukraine), where there is an increase in morbidity and mortality rates [8]. The leading cause of CC is long-term HPV infection, which is sexually transmitted. Proven effective strategies to combat CC at all stages of the aid cycle are recognized as:

- HPV vaccination;
- screening and treatment of precancerous conditions;
- early detection and urgent treatment of invasive cancer in the early stages;
- palliative care.

The Global Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 identifies HPV vaccination, screening and treatment for CC as the “best choice”. The WHO-recommended primary target population for vaccination is girls aged 9–14 (before puberty). Although the Pap test (“pap-smear” or cytological screening) has been used for a long time and is widely used, vaccination against HPV in Ukraine is included in the National calendar of preventive vaccinations only as recommended.

In 2020, during the World Health Assembly, 194 WHO countries undertook for the first time the commitment to eliminate not an infectious disease (as has already happened before!) but an oncological one. WHO has approved a strategy to eliminate CC worldwide within several generations. It aims to reach 90 % of girls under the age of 15 with HPV vaccination by 2030, screening 70 % of women using high-performance tests (at age 35 and again at age 45); providing treatment to 90 % of women with detected CC. If the strategy's goals are achieved over the next century, it can reduce mortality by almost 99 % and prevent more than 62 million deaths from cervical cancer [2, 5].

Advisor to the Director General of the WHO, Dr. P. N. Simelela, considers the fight against CC a fight for women's rights because “the unjustified suffering caused by this disease is a consequence of those manifestations of inequality that affect only women throughout the world” [14]. The global strategy has set a threshold: cervical cancer will no longer be considered a public health problem when all countries reach an annual incidence rate of 4 or fewer cases per 100 thousand women. In 2019, the share of the contribution of CC to the Global Burden of Disease was 0.75 % for women worldwide and 0.66 % in Ukraine.

When developing a strategy for the implementation of the Agenda in the field of sustainable development until 2030, in particular, the performance of the task of reducing premature mortality from non-communicable diseases, Ukraine has set the national indicator of Sustainable Development Goal 3 “Strong health and well-being” as the number of deaths of women from malignant neoplasms of the cervix aged 30–59 years, per 100,000 women of the corresponding age [11].

**The purpose** of the study was to evaluate the situation regarding CC in Ukraine and to show the significance of this pathology in the array of mortality due to all neoplasms, determine the characteristics of female mortality caused by it depending on age and place of residence; to show actual and probable changes caused by the spread of the COVID-19 pandemic, and prospects for achieving both the National Sustainable Development Goal SDG3 and the global goal for CC elimination in Ukraine.

**Materials and methods.** The official data of the State Statistics Service of Ukraine on mortality for 2015–2021 became the information base for the statistical analysis of the situation with mortality from CC. In particular, we used statistical data on the distribution of the number of deaths by cause, age, gender and place of residence for individual nosological forms of Class II. Neoplasms (codes according to ICD-10 C00-D48). Disclaimer: All data for Ukraine after 2013 do not include the temporarily occupied territory of the Autonomous Republic of Crimea, the city of Sevastopol, and part of the temporarily occupied territories in the Donetsk and Luhansk regions. Accordingly, the calculations of the crude and age-standardized mortality rates were considered.

The proportion of deaths of Ukrainian women caused by cervical cancer (code according to ICD-10–C53) in the array of all deaths due to all neoplasms and from malignant neoplasms of the female genital organs (C51–C58)\* Ukraine: excluding the temporarily occupied territory of the Autonomous Republic of Crimea, Sevastopol and parts of the temporarily occupied territories in Donetsk and Luhansk regions was calculated, by separate age groups.

The analysis also used the indicators of morbidity and mortality on cervical cancer in Ukraine for 2019–2020 from the National Cancer Register of Ukraine (NCRU) [8].

A comparison of the contribution of cervical cancer to the Global Burden of Disease indicator for Ukrainian women aged 15–49 years in 2019 with a similar one for Swedish women was made according to calculations by The Institute for Health Metrics and Evaluation (IHME).

For a comparative analysis with European countries (EU until 2004, Poland and Sweden), data on mortality from the international database European Health Information Gateway [9] were used. To avoid the influence of gender and age distribution in selected countries, comparisons were made using an age-standardized indicator (European standard).

**Results of the study and their discussion:** Analysis of data on the mortality of Ukrainian women for certain nosological forms of neoplasms indicates a relatively significant role in cervical cancer. Malignant neoplasms of the cervix (ICD-10 code C53) caused the death of 1896 women in 2020 (or almost 30 % of all deaths due to malignant neoplasms (MN) of the female genital organs and about half (48.8 %) of deaths due to uterine cancer). The following year, despite the population decline, deaths remained virtually unchanged (1,874 cases). The data is presented in Table 1.

Table 1

**Mortality due to neoplasms, number of deaths and index per 100,000 population, Ukraine, women, 2020.**

ICD10 code	Nosological form	Women	
		persons	per 100,000 population
C00-D48	Class II. Neoplasms, incl.	34585	166.4
C15-C26	Gastrointestinal cancer	11596	55.9
C30-C39	Lung cancer	2403	11.6
C50	Breast cancer	6558	31.3
C51-C58	Gynecologic cancer	6425	30.6
C64-C68	Urinary cancer	1160	5.6
C76-C80	Cancer (inaccurately defined, secondary, and unspecified locations)	1019	4.8
C81-C96	Cancer of the Lymphoid, Hematopoietic, and Related Tissue	1939	9.5

The vast majority of women’s deaths are concentrated between the ages of 50 and 69 – both in 2020 and 2021 (fig. 1).

The importance of cervical cancer as a cause of death for women in the array of all deaths due to neoplasms changes with age. Starting from the age group of 20–24 years, the first deaths are registered, and the last are over 100 years old. The most significant contribution of cervical cancer to the mortality of women of childbearing age (from 30 to 45 years) is that it was responsible for approximately one in five deaths due to neoplasms in 2021 (fig. 2).

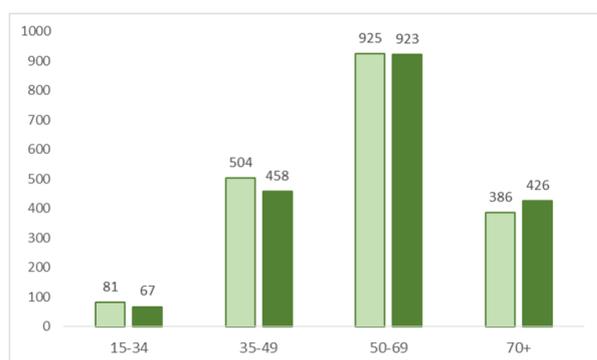


Fig. 1. Distribution of the absolute number of deaths due to cervical cancer by age group, Ukraine, 2020-2021, Source: State Statistics Service of Ukraine

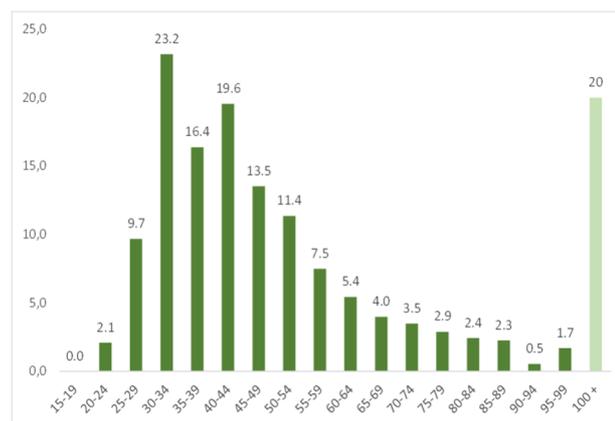


Fig. 2. The share of women's deaths from CC by age group, Ukraine, 2021, %, Source: State Statistics Service of Ukraine

Let's compare similar calculations based on data from 2020. We should note a relatively lower number of registered deaths in the 35–39 age group (recall that when moving from the age group of 30–34 to the group of 35–39 years, the number of deaths of women from cervical cancer in 2020 doubled). The proportion of 20 % for women aged 100 years and older should not be taken into account due to the small numbers – one reported death in only five cases classified as cancer deaths at this age.

In Ukraine, mortality rates from all neoplasms in urban and rural women differ (fig. 3).

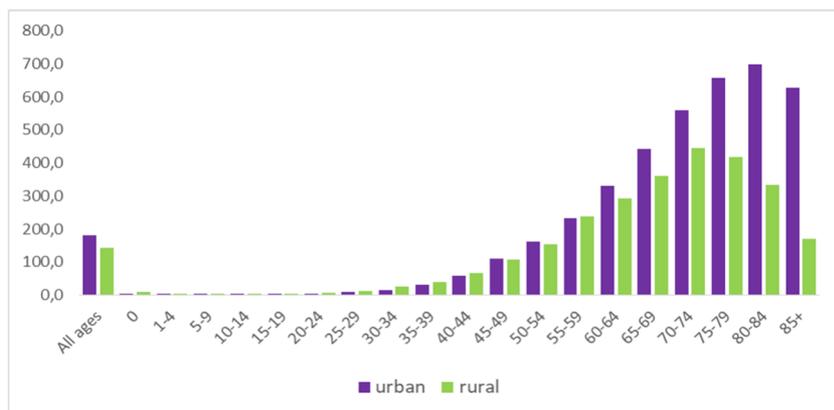


Fig. 3. Mortality of women from neoplasms, by age group and place of residence, rough rate per 100,000 population, Ukraine, 2020, Source: State Statistics Service of Ukraine

It can be assumed that some rural women with a cancer diagnosis are treated in cities; respectively, the fact of death in fatal cases can be registered at the place of death. However, only a tiny part of the relatives of the deceased issue a death certificate in the city. Most Ukrainian families (following both the traditions and wishes of the deceased and the difference in the cost of burial

in the city and the village) still register the death by the place of residence. The gap in the mortality rate with urban peers increases rapidly with age. In our opinion, the main reason for this is that rural women, as a rule, have less access to high-quality qualified diagnosis and treatment (all neoplasms, and CC in particular). The routine practice of giving the usual diagnosis such as “Ischemic heart disease, atherosclerotic cardiosclerosis” in the case of death of women of the oldest age is also pointed out.

If we consider the mortality rates from CC by place of residence, the mortality rate of rural women is higher than in cities (10.4 versus 8.3 per 100,000 population).

In the age group of 45–59 years (in the interval of the last 15 years of the officially declared working age in Ukraine), Ukrainian women die from CC almost five times more often than their Swedish peers. This coincides with the fact that the contribution of CC to the Global Burden of Disease indicator for Ukrainian women aged 15–49 was 1.21 %, for those aged 50–69 – 2.44 %; while for Swedish – only 0.46 % and 0.64 %, respectively.

At the same time, which is quite natural, the risk of developing cancer increases with age, and the ability to recover decreases (including due to the accumulation of aggravating concomitant diseases, decreased immunity, etc.), which is illustrated by the trend line of age-standardized indicators in Sweden (Fig. 4A). Fig. 4B reflects the monitoring of reducing premature mortality according to the national index “The number of deaths of women from malignant neoplasm of the cervix aged 30–59 years, per 100 thousand women of the corresponding age”.

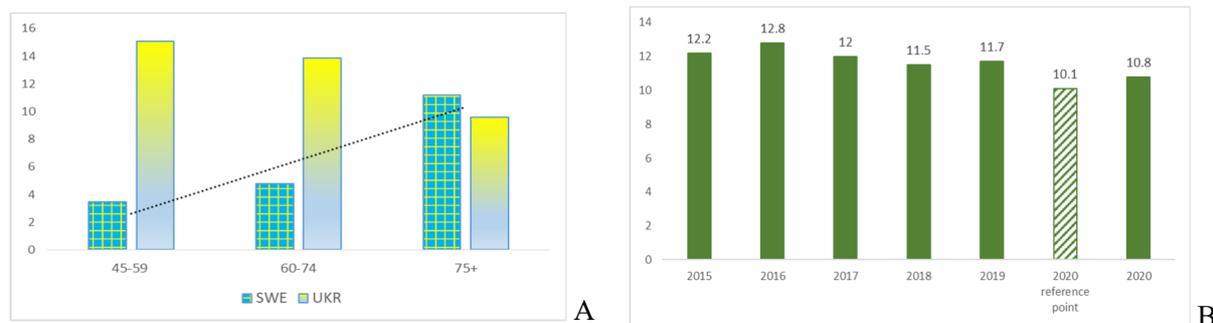


Fig. 4. Mortality of women from cervical cancer. A – Mortality of women from cervical cancer aged 30–59 years, crude rate per 100,000 population, 2015–2020. B – Mortality of women from cervical cancer, by selected age groups, Ukraine and Sweden, standardized (European standard) rate per 100,000 population, 2017. \*Ukraine: excluding the temporarily occupied territory of the Autonomous Republic of Crimea, Sevastopol and parts of the temporarily occupied territories in Donetsk and Luhansk regions.

On the other hand, in Ukraine, there is a paradoxical phenomenon of decreasing mortality from cervical cancer with age.

There is also a difference in the direction of the dynamics of mortality rates from CC compared to 1991: if in neighbouring Poland, EU member states until 2004 and, to the greatest extent, in Sweden, there was a decrease in the mortality rate before reaching the age of 65, then in Ukraine, on the contrary, it increased by 22 % (table 2).

In our opinion, the decrease in the indicator in the group over 65 years of age cannot be regarded as a positive phenomenon due to the assumption mentioned above about incomplete registration of such deaths at an older age.

As evidenced by calculations based on 2020 data, the actual figure exceeded the target set for 2020.

It will be recalled that 90 % of the world's deaths from CC occur in low- and middle-income countries, and after diagnosis, more than 60 % of women die there, while in high-income countries, less than 30 % [5].

Table 2

**Mortality of women from cervical cancer aged 0–64 and 65+, in selected European countries, standardized (European standard) rate per 100,000 population, 1991, 2017.**

	0–64			65+		
	1991	2017	since 1991, %	1991	2017	since 1991, %
Poland	8.1	4.2	-48.1	31.88	20.14	-36.83
Ukraine	5.0	6.1	+22.0	28.36	12.12	-57.26
Sweden	1.9	1.4	-26.3	12.67	7.96	-37.17
EU before May 2004	2.3	1.5	-34.8	11.4	5,57*	-51.14

Note: Data for 2016. Source: European Health Information Gateway

Directing the main forces and resources, especially primary medical care, to fight against COVID-19, together with the extended quarantine due to the spread of the COVID-19 pandemic, harmed the timely diagnosis of neoplasms and their treatment, and has negatively affected the timely diagnosis of neoplasms and their treatment due to restrictions on patient's access to healthcare facilities. Some women were forced to postpone planned examinations (at the family doctor or gynecologist), examinations, or even medical interventions. Medical professionals had to reduce preventive activity and limit or even cancel specific preventive measures. As a result, in 2020 in Ukraine, a malignant neoplasm of the cervix in almost every third woman (30.5 % of all cases) was detected in the advanced stage [4], and in 2021, according to the NCRU – in 31.1 %. It can be argued that with the prolongation of pandemic problems and the lack of an adequate operational response by the public health service to existing risks in the country, an increase in the mortality rate is likely as a result of untimely detection and treatment of cervical cancer and cancer of other localizations. The need to balance delay in cancer diagnosis or treatment with the risk of potential exposure to COVID-19, reduce the chances of service disruptions associated with social distancing behaviors, and allocate limited resources appropriately [6] has been recognized. At the same time, Ukraine belongs to those European countries where the use of the HPV vaccine, which is effective in preventing cervical cancer, remains extremely low [13].

A meta-analysis of 24 studies analyzing the association between HIV infection and cervical cancer (Africa, Asia, Europe, and North America), which included 236,127 women living with HIV, showed that the combined risk of cervical cancer among these women is six times higher compared to women without HIV [9]. They believe that almost 5 % of all cervical cancer cases worldwide are related to HIV infection. However, this share varies significantly by region and is highest in southern and eastern Africa. According to the simulation results, the estimated number of people living with HIV in Ukraine at the end of 2019 reached 250,000 people, and the incidence rate of HIV infection, according to official registration data in 2019, was 42.5 per 100,000 people [7]. The situation in Ukraine, a country with a significant prevalence of HIV, remains unfavorable in terms of minimizing the effect of this additional risk factor for the development of RSM (and, therefore, mortality from it).

According to WHO experts, the quality of mortality registration in Ukraine (for the period 2007–2016) was assessed as average [1]. According to official statistics, out of the total number of deaths in 2021, the cause of death was determined by autopsy in 273 cases (261 in 2020), which was 14.6 %.

Primary prevention should include not only the vaccination of girls but also sexual education of adolescents of both sexes regarding safe sexual behavior (delaying sexual debut, limiting the number of partners, using condoms, etc.). An important aspect is the promotion of tobacco smoking, which increases the risk of developing cervical cancer. Secondary prevention, along with screening with the best available tests for women, starting from the age of 30, should also include as early as a possible effective treatment of precancerous conditions, tertiary – timely application of the necessary complex surgical, radiological interventions and chemotherapy for invasive cancer to all women who need it, at any age.

## Conclusions

1. Analysis of the epidemiological situation in the field of mortality due to cervical cancer in Ukraine showed the importance of this pathology as a cause of death, which caused almost a third of all deaths due to malignant neoplasms of the female genital organs in 2020 nearly a third of all deaths due to

malignant neoplasms of the female genital organs, and approximately one in five deaths of women of childbearing age (from 30 to 45 years) as a result of neoplasms. Comparative analysis of the mortality rate from cervical cancer in developed countries revealed significant differences. In particular, in addition to the higher probability of dying and the more significant contribution of the disease to the formation of the Global Burden of Disease indicator in young and mature age, in Ukraine, there is a paradoxical phenomenon of a decrease in the mortality rate from CC with age.

2. The COVID-19 pandemic caused a worsening of the epidemiological situation regarding all neoplasms in the country (for example, a decrease in the level of detection of new cases of the disease, a reduction in the proportion of neoplasms detected at an early stage, etc.) and about cervical cancer in particular, which indicates detection at an advanced stage (in 2020 – 30.5 %, in 2021 – 31.1 % of its cases). The situation is complicated by the prevalence of HIV infection, a risk factor for the development of CC, which is higher than in developed European countries, and by the lower coverage of HPV vaccination. The combination of these circumstances does not give reason to hope for the rapid elimination of cervical cancer within several generations due to Ukraine's unlikely achievement of the 90–70–90 goals by 2030.

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