Statistical analysis of trends and factors in cancer incidence of Ukrainian women in reproductive age

Natalya V. Kovtun[1], Zinaida O. Palian[2], Igor M. Motyzuk[3]

Abstract

The dynamics of reproductive organ cancer of women in Ukraine and their survival in the context of radiation effect of Chronobyl nuclear power station was analyzed in this paper. The attempt was made to evaluate the volume of indirect demographic losses due to cancer incidence of women of reproductive age.

Statistical data of All-Ukrainian cancer institute, National cancer-registry of Ukraine for the period of 1981-2015 and State statistics service of Ukraine was used in the research.

Keywords: *survival analysis, t-test, Levene's criterion*

JEL Classification: C120, C 430, I190

1 Introduction

Formulation of the problem. Each historical epoch is characterized by a set of factors which regulates the number and structure of the population. Life expectancy of current mankind depends to a great extent on endogenous factors, diseases of non-infectious nature, namely cancer ones are among them. In Ukraine, as well as in most industrialized countries, the main cause of women's mortality from cancer diseases is cancer of reproductive system organs. Besides direct losses of women, including fertility cohort, indirect losses occur – non-born children because of permanent or temporary loss of reproductive function as a result of the disease of this location. In view of this, it is important to study the trend of cancer incidence of reproductive organs of women in Ukraine and their survival, in particular of the consequences of the disaster of Chornobyl nuclear power station (ChNPS), and to determine the volume of indirect demographic losses due to cancer incidence of women of reproductive age.

Analysis of recent research and publications. As world scientific researches prove, in recent years there has been an increase in the frequency of multiple primary malignant

[1] Corresponding author: Taras Shevchenko National University of Kyiv, Statistics and Demography Department, Vasylkivska Street, #90. 03022 Kyiv, Ukraine, e-mail: kovtun_natali@ukr.net

[2] Taras Shevchenko National University of Kyiv, Statistics and Demography Department, Vasylkivska Street, #90. 03022 Kyiv, Ukraine, e-mail: zipalyan@ukr.net.

[3] Bogomolets National Medical University, Oncology Department, Lomonosova Street, #33/43. 03022 Kyiv, Ukraine, e-mail: 180978igor@gmail.com

growths, when two or more separate primary malignant growths, which originate from different organs, appear in the organism at the same time or one after another (Merimsky et al., 2001). Multiple primary malignant growths belong to the development of malignant affect de novo, their characteristics totally differ from primary tumor (Xu & Gu, 2014). Breast cancer (BC) constitutes 30-50% of all other primary malignant growths of women who had primary breast cancer (PBC). The risk is 2-6 times more that they will have new primary cancer in contra-lateral breast during their life time (Levi et al., 2003; Jobsen, et al., 2003; Heron, et al., 2000), which constitutes 0.3-1% annually (Jobsen, et al., 2003; Lee, et al., 1999). In the literature, there is uncertainty as to the prediction and survival of the sick with metachronous cancer processes compared with primary one-side breast cancer. In view of this, regularities of the occurrence of metachronous processes of the patients with breast tumors are studied in this paper, their consequences are estimated and predictions are suggested.

The development of multiple processes can be connected with radiation contamination as a result of the disaster at ChNPS. Extra radiation-induced cases of PBC were recorded among irradiated woman after atomic bombing of Hiroshima and Nagasaki (Xu & Gu, 2014).

The development of the cancer location depended on the age of this population group at the moment of irradiation. Higher tumor incidence was observed among the individuals irradiated at the age of 10-19. PBC incidence was lower among the irradiated people at the age of 20. Average latent period, followed by BC, did not depend on the dose and was about 18 years. World literature confirms that BS among women irradiated at the age 19-20 was higher than among those older than 30 years old (Levi et al., 2003).

The purpose of the article is to study the dynamics of cancer incidence of reproductive organs of Ukrainian women and their survival in the context of the disaster at Chronobyl nuclear power station, and to estimate the volume of indirect demographic losses due to cancer diseases of women of reproductive age.

Methodology. Methodological basis of the research includes methods of descriptive statistics and specific methods of statistical analysis which helped make statistic conclusion (Bongers et al., 2016; Palian, 2014). To get general characteristic of the patients' survival, that constituted the basis of the sample, 2032 female-patients were included; they received specific treatment (the second surgery) in the department of breast tumor and its reconstructive surgery of the National cancer institute from the year of 2008 till December, 2015 within the randomized controlled open research aimed at studying the criteria of objective choice in surgery scope of the patients with BC. A separate group consisted of 195

(9.6%) female-patients with multiple malignant growths. The patients were divided into 4 groups: 1) with synchronous breast cancer (SBC); 2) with synchronous breast cancer and other location (SBCO); 3) with metachronous breast cancer (MBC); 4) with metachronous breast cancer and other location (MBCO).

Out of sample (195 women) by 107 patients (54.9%) experienced synchronous processes. The distribution of synchronous processes as to localization was as follows: 56% – breast cancer and 44% – combination of breast cancer with other localizations. 45% of the patients had metachronous processes, 46.6% had localization in breast, and the rest – was the combination of nosologies.

The analytical foundation of statistic conclusion contained special method of in-depth statistical analysis. Thus, a survival function, which characterizes the probability that an individual will live through the time longer than "t", has been built to analyze survival using incomplete (censored) data. In addition, the time tables of life expectancy were developed, the line-up adjustment of the distribution of survival with simultaneous estimation of the parameters of a survival function (Kaplan-Meyer procedure) was made to compare survival in two and more groups.

To statistical test the hypothesis about the variation among average formation periods of metachronous cancer processes before and after the year of 2008, Student's t-criterion was used; to check the hypothesis about the variation of their dispersions, Leven's criterion and Brown-Forsyth criterion were used, they were more stable in case of the availability of possible deviations from standard distribution.

A standard data model was made in EXEL, and an analytical data model – in STATISTICA.

2 Statistical analysis of the dynamics of women's cancer incidence in Ukraine

In current structure of cancer diseases of women in Ukraine, breast cancer takes the first place (19.5%) which causes 20% mortality of all malignant growths. Reproductive organ cancer (corpus uteri and cervix) is among six mostly widely-spread nosological forms of women's cancer. However, the intensity of these diseases among Ukrainian women is almost the same as that in the post-soviet European countries, and the level of breast cancer (41.7 per 100.00 women, 2014 in Ukraine) is even lower than in some industrialized European countries, such us United Kingdom (95 per 100.00 women, 2012), Germany (91.6 per 100.00 women, 2012), France (89.7 per 100.00 women, 2012) (*Cancer Today...*). The latter can be connected with

the fact that more women are covered with preventive examination and better quality medical diagnostics in these countries.

For a short period of time (2003-2015) the level of cancer incidence of women of reproductive age was constantly growing in Ukraine. The frequency of preliminary breast cancer increased more than by 9% (0.8% annually), reproductive organs depending on localization by 7.5% (ovary cancer) and by 21.3% (corpus uteri), respectively. However, the largest number of malignant growths identified for the first time included breast cancer. The coefficient of disease incidence in this localization exceeded three times similar indicators of the three main localizations of a reproductive system (cervix cancer, corpus uteri, ovary). As one can see from Fig. 1, the coefficients of malignant growths of reproductive organs, standardized by world age structure, show enhanced increase, beginning from the year of 2009.

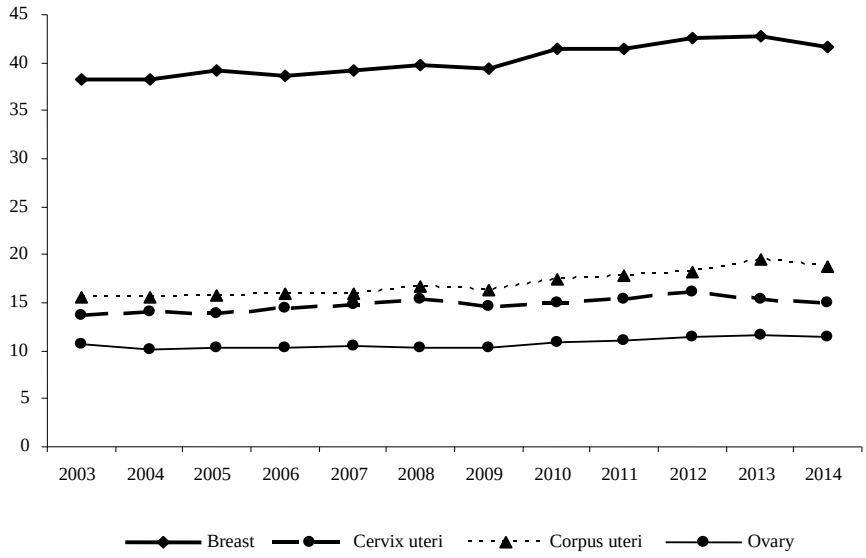

Fig. 1. Age-standardized (world standard) cancer incidence rates of female's reproductive system by sites in Ukraine (per 100,00), 2003-2014 (source: data From the Bulletin of National Cancer Registry of Ukraine).

Mostly this concerns breast and corpus uteri cancer. In 2014 the number of new incidents (per 100.00 women) decreased slightly in every localization due to the fact that the registration of women in annexed and temporarily occupied areas, traditionally with high incidence indicators of the mentioned nosological cancer forms, stopped (the Republic of Crimea, Sevastopol, Donetsk and Luhansk regions).

The indicators of disease incidence signal not only about potential mortal losses of women as a result of malignant growths. As the main nosological cancer forms of women are those of

reproductive system and breast, the issue of indirect demographic losses arises – the number of unborn children because of permanent and continuous disorder of reproductive functions. According to the data of the National cancer-registry of Ukraine, during the last 10 years the highest intensity of breast cancer and that of corpus uteri and cervix was observed among women of older than reproductive age (60-69 years old). At the same time in 2004-2014 age structure of malignant growths among reproductive female-population got worse slightly. For instance, in the structure of breast cancer incidence, the proportion of young and average-age groups (25-39 years old) increased by 4 p.p.; they have shown high birth activity in recent years. Women of an early age (15-19) and those of an early reproductive age (25-29) contributed to ovary cancer incidence, its indicator increasing by 3.7 p.p. However, malignant growths of the mentioned organs do not result in permanent loss of reproductive function, which can be restored provided proper treatment is given. On the contrary, other two localizations (corpus uteri and cervix cancer) lead to permanent loss of the childbearing ability. In Ukraine, 52.8% of the sick with cervix cancer are women of average and older reproductive age (35-39 and 40-44 years old) and fertility of this age-groups increased by 2.3 and 2.5 times in 2004-2014, respectively. Totally, in 2004-2014 the annual number of new incidents of reproductive organ cancer increased by 3.5%, and within the compared territory of Ukraine (including annexed and temporarily occupied regions) this indicator increased by 4% in 2003-2013, i.e., 0.39% annually. The question arises: how big indirect demographic losses can be – the number of unborn children because of new cases of malignant growths among women of a reproductive age. To find the answer, a multiple index model of hypothetic number of unborn children was built, taking into consideration cancer incidence of women at a reproductive age, their age-specific fertility rates and age structure for the years of 2004-2014.

Table 1 shows a relative change of hypothetic number of unborn children taking into account new cases of malignant growths of all nosological forms, concerning a reproductive system, including breast cancer, and also excluding it, i.e. only reproductive organs.

In 2004-2014 total hypothetic losses of child birth due to unrealized reproductive functions by cancer-sick women increased by 89.2. If to exclude women diagnosed with breast cancer whose reproductive ability can be restored after long-term sever therapy, the scope of hypothetic losses would be increased by 80.6%. However, such high growth rates are mostly associated with general tendency of age fertility increase, typical for all Ukrainian women (+62.9%); it is during the last 11 years that reproductive activity of women at the age of 30-40 has increased by two times. The change in the age structure of a women's

reproductive cohort caused the increase of potential child-birth and also hypothetic losses (+2%). Primary cancer incidence of women at a reproductive age led to the increase of hypothetic losses by 11.8% in general, and with permanent loss of reproductive functions because of cancer of a reproductive system the number of unborn children increased by 8.7%. However, a mentioned index model enables to make rough estimation of hypothetic losses of child birth based on the statistics of the annual number of identified new cases of disease. Unfortunately, the lack of the information about age structure of all registered cancer-sick women of a reproductive age does not allow estimating a true number of unborn children. While estimating the losses of child birth, it is advisable to consider age survival probability of the women with malignant growths of reproductive organs. Hence, the next step is to identify the survival parameters of cancer-sick women of a reproductive age.

Changes of hypothetic number of unborn children	**With all nosological forms of reproductive system cancer**	**Without breast cancer**
Total	189.2	180.6
by factors:		
age cancer incidence rates	111.8	108.7
age –specific fertility rates	165.8	162.9
female's age structure	102.1	102.0

Table 1. Dynamics of hypothetical number of unborn children resulted from cancer incidence of women of a reproductive age in Ukraine in 2004-2014, % (source: author's own calculations based on data From the National Cancer Registry of Ukraine).

3 The estimation of women's survival in Ukraine among the sick with malignant growths of reproductive organs

Modeling the survival character of cancer-sick women requires preliminary estimation of their survival, taking into account the fact that patients have synchronous (SMPMNs) and metachronous (MMPMNs) processes of cancer development.

According to the data of sample studies, the probability to live another 125 months for patients on SMPMNs was 0.73, whereas for patients on MMPMNs it was 0.92 ($p = 0.00162$). Thus, disease development of the patients with synchronous cancer is more aggressive and diagnostically unfavorable.

When analyzing time interval between the occurrence of the first and the second disease, it was found out that median of the patients with the first diagnosis of BC before 2009 was 605 weeks, and after 2009 it was decreased to 104 weeks (p = 0.000001). The interval decrease between the occurrences of the second disease after 2009 is explained by the fact that the average age of BC patients was 30.5 before 2009 at the time of the disaster at Chornobyl nuclear power station, after the year of 2009 – 25.5 (p=0.000798). The presented data can confirm more aggressive disease development of BC patients who received radiation at the age of 30 when the disaster happened at ChNPS.

It has been statistically proved that recent years show the decrease of the period between the first and the second disease occurrence (Table 2). Thus, the period between diagnoses when identifying the first incidence before 2008 was 605 weeks (more than 11 years), and beginning from 2008 it decreased by six times and was 94 weeks (1 year and 9 months). Such drastic changes are the grounds for unfavorable prognoses for potential enhancement of the mentioned processes in Ukraine in the near 10-15 years.

Characteristics	**Mean, weeks**		**A Number of patients**		**Standard deviation, weeks**	
	group 1*	**group 2***	**group 1***	**group 2***	**group 1***	**group 2***
Period between diagnoses	605.0**	93.9**	74	16	349.6	105.7

*) group 1 – till 2008, group 2 – 2008 and later;

**) p=0.000000 for Student's criterion, p=0.000008 for Fisher's criterion, p=0.000616 for Leven's criterion, p=0.000221 for Brown-Forsyth's criterion.

Table 2. Duration between diagnoses of patients depending on the moment of the first diagnosis (before 2008 not including it – group 1 and after 2008 including – group 2; source: own calculations based on statistics Ukrainian Institute of Cancer).

The described situation definitely influenced the patients' survival (Fig. 2). It was statistically proved (Table 3), that the probability to live through another 39 months after 101 months for the group of patients whose first diagnosis was made before 2008 was 0.959, and for those whose first diagnosis was made beginning from 2008 – 0.552.

Period when the first diagnosis was made	Metachronous processes	
	Number	Observation time 101 month
Before 2008 (group 1)	74	0.959*
2008 and later (group 2)	16	0.552*

*p=0.03232**.**

Table 3. Survival of patients depending on the time when the first diagnosis was made (before 2008 not including it – group 1 and after 2008 including – group 2; source: own calculations based on statistics Ukrainian Institute of Cancer).

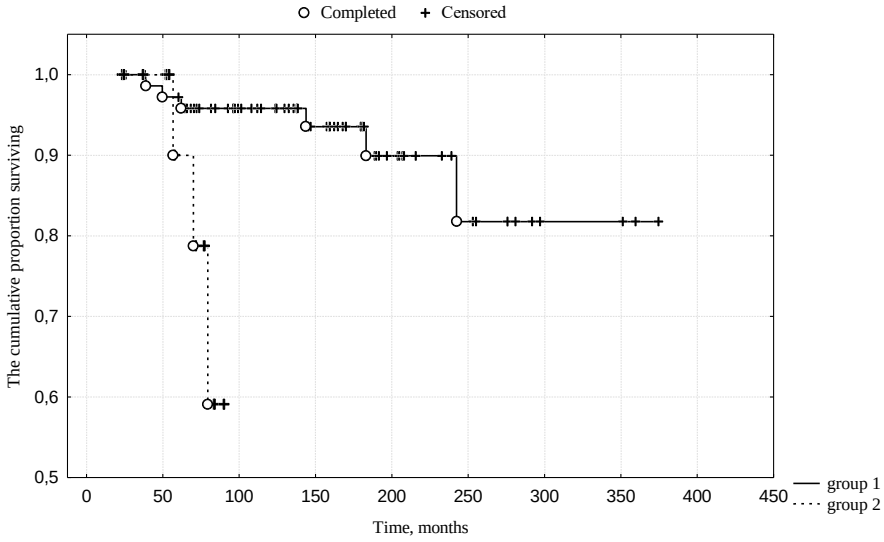

Fig. 2. Cumulative share of survived patients depending on the moment when the first diagnosis was made according to Kaplan-Meyer (before 2008 not including it – group 1 and after 2008 including – group2).

Apparently, the prediction that the situation with cancer incidence in the near 20-25 years will worsen appears to be true. However, the cause of the aggravated situation is to be searched in a complex effect of the factors: not only the consequences of the disaster at Chornobyl nuclear power station, but also worsening of the characteristics of life quality which can be seen in decreasing living standards, environmental pollution and poor health care system. All this taken together leads to the situation when a person is in permanent continuous stress which results in cancer incidence, in particular if someone is inclined to it (the availability of the first cancer diagnosis).

Besides, a more detailed disperse analysis between the periods of cancer incidence in two groups of the sick confirms that these two groups of the sick is a sample of two different

general complexes which are characterized by variations. The exceeding of the variation coefficient by 100% in the group of the sick whose diagnosis was made in 2008 and later proves the availability of latent factors of subjective order which will further classify disease occurrence of Ukraine's population into primary and secondary cancer incidence.

Conclusions

Malignant neoplasms of the female reproductive system not only leading to death of women in fertility age, but also deprive them the childbearing opportunity. To assess the extent of the hypothetical loss of births, we should have proper information on the number of patients who are registered, their age distribution and the probability of surviving to next age-group in the context of each malignancies nosology.

For the last 25 years the frequency of recurrences increased and the interval between the first and the second diagnoses of reproductive organ cancer decreased by six times. For instance, in 1981-2008 the period between the first and the second disease lasted longer than 11 years, then after 2008 and till now it reduced to 2 years on the average. With the help of a survival function, it was established that the probability to live through another 3 years after 8.5 years from the moment the diagnosis of the first cancer disease was made before 2008 was 0.959, and after 2008 – only 0.562. More aggressive development of breast cancer was recorded among women who were 30 years old and were irradiated at the times of the disaster at ChNPS. With probability p=0.000798 it was proved that the formation factors of patients' survival before and after 30 differed greatly, which requires separate studying. We can not state for sure that the patients'age at the time of the disaster at ChNPS impacts their survival, as it is described in scientific literature mentioned before. The age is a formation criterion of two clusters of women as to survival, and statistic significance confirms the hypothesis that cause-effect factors of survival differentiation of these two groups of women have absolutely different nature.

References

Bongers, ML., de Ruysscher, D., Oberije, Cary, C., & Lambin, P. (2016). Multistate statistical modeling: a tool to build a lung cancer microsimulation model that includes parameter uncertainty and patient heterogeneity. *Medical decision making*, *36*(1), 86-100.

CANCER IN UKRAINE, 2014-2015. (n.d.). Retrieved March 23, 2017, from http://www.ncru.inf.ua/publications/BULL_17/index_e.htm

Cancer today. (n.d.). Retrieved March 23, 2017, from http://gco.iarc.fr/today/fact-sheets-cancers

Heron, D. E., Komarnicky, L. T., Hyslop, T., Schwartz, G. F., & Mansfield, C. M. (2000). Bilateral breast carcinoma. *Cancer, 88*(12), 2739-2750.

Jobsen, J., Palen, J. D., Ong, F., & Meerwaldt, J. (2003). Synchronous, bilateral breast cancer: prognostic value and incidence. *The Breast, 12*(2), 83-88.

Lee, M. M., Heimann, R., Powers, C., Weichselbaum, R. R., & Chen, L. M. (1999). Efficacy of Breast Conservation Therapy in Early Stage Bilateral Breast Cancer. *The Breast Journal, 5*(1), 36-41. doi:10.1046/j.1524-4741.1999.005001036.x

Levi, F., Randimbison, L., Te, V., & Vecchia, C. L. (2003). Prognosis of bilateral synchronous breast cancer in Vaud, Switzerland. *The Breast, 12*(2), 89-91.

Merimsky, O., Kollender, Y., Issakov, J., Bickels, J., Flusser, G., Gutman, M., Meller, I. (2001). Multiple primary malignancies in association with soft tissue sarcomas. *Cancer, 91*(7), 1363-1371.

Palian, Z. (2014). Statistical analysis and simulation of the parameters of survival. *Proceedings of the 8th professor Aleksander Zelias international conference on modelling and forecasting of socio-economic phenomena,* 125-134.

Xu, L., & Gu, K. (2014). Clinical retrospective analysis of cases with multiple primary malignant neoplasms. *Genetics and Molecular Research, 13*(4), 9271-9284.