

Epidemiological characteristics of malignant ovarian tumors in Vojvodina

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Summary

Purpose: Ovarian cancer ranks 6th in relation to new cases of malignant diseases among females and 2nd concerning gynecological cancers. The purpose of this study was to determine the epidemiological situation of ovarian cancer in Vojvodina, Serbia.

Methods: In our study, we used a descriptive epidemiological method for the analysis of incidence and mortality of ovarian cancer in Vojvodina, based on the data of the Cancer Registry of Vojvodina.

Results: In the period 1987-2006, the average incidence rate of ovarian cancer was 15.28%/100,000 with an average annual increase of 1.15%; the average mortality

rate for the same period was 9.24/100,000 with an average annual increase of 0.95%. The values of crude incidence rate (15.28/100,000) and standardized incidence rate (range 7.47 - 12.55/100,000) in Vojvodina correspond to the values in eastern and southern Europe.

Conclusion: In the observed period of 20 years, the incidence and mortality rate indicate a tendency for increase, which can be characterized as an unfavorable epidemiological situation. New markers are being studied in order to find a solution for ovarian cancer screening.

Key words: epidemiology, incidence, mortality, ovarian cancer, trend

Introduction

According to the number of newly diagnosed malignant tumors among females ovarian cancer ranks sixth in the world, while it ranks second among gynecological cancers with more than 205,000 newly identified cases per year. Each year 125,000 women die of this disease worldwide [1].

Ovarian cancer is mostly seen in highly developed societies with high living standards; the age-standardized incidence rate (ASR) in the developed part of the world is 10.2/100,000, while it is 5.0/100,000 in the underdeveloped countries.

In Vojvodina, 160 new cases of ovarian cancer are documented each year and 97 of these patients die. In 2006 the incidence rate was 16.9/100,000 and the mortality rate 10.3/100,000 [2].

The "silent killer", as ovarian cancer is referred

to in the English language literature, primarily affects postmenopausal females over the age of 50; over 75% of patients are diagnosed with disease in advanced stages (FIGO III and IV), and the 5-year survival of the patients is about 25% [3,4].

Relevant studies indicate that the symptoms of ovarian cancer are present in 90% of the patients in the early stages of disease. However, the symptoms are usually not taken seriously so 37% of patients visit their doctors at least 6 months after the first symptoms occur [5].

It is considered that about 10% of all cases of ovarian cancer are related to genetic predisposition.

A positive medical history of breast and ovarian cancer occurring in the earlier period of life among family members can point to the presence of "breast-ovarian cancer syndrome" - BRCA1 (chromosome 17q21) and BRCA2 (chromosome 13q12) germline/genetic mutations [6].

The protective effect of oral contraceptives, when speaking of ovarian cancer, is defined and quantified in the numerous epidemiological studies [7-9].

Women who have early menarche, late menopause, are nulliparous, or give birth after the age of 35, have increased risk to get ovarian cancer [4]. All women should do regular gynecological examinations because there are no reliable methods for screening of ovarian cancer.

Methods

The aim of this study was to determine the epidemiological characteristics of malignant ovarian tumors in Vojvodina for the period 1987-2006. The data were taken from the Cancer Registry of Vojvodina, Oncology Institute of Vojvodina, Sremska Kamenica. For data analysis the descriptive epidemiological method was used. The information on the number of inhabitants was based on the 1991 and 2002 censuses. Data processing was done by absolute numbers, relative indexes, and incidence and mortality rates per 100,000 of inhabitants; age-standardized rates were studied in relation to the standard world population and linear trend was used for presenting the trends of incidence and mortality rates. The database of tumors in the Cancer Registry of Vojvodina is classified according to the International Classification of Diseases (10th revision) and the International Classification of Diseases in Oncology (3rd edition). The statistical analysis program *Statistica* was used for data processing.

Results

In the region of Vojvodina, 3,197 new cases of malignant ovarian tumors were registered during in the period 1987 - 2006. The average number of new cases per year was 160. In 2006, this malignancy ranked sixth among women in Vojvodina and third among gynecological cancers. The average incidence rate of ovarian cancer during the studied period was 15.28/100 000; the lowest incidence (12.30/100,000; 127 cases) was in 1991 and the highest (18.34/100 000; 192 cases) in 2000. The incidence rates in the studied time period showed an increasing trend (Figure 1). The average annual increase of incidence was 1.15%; the linear correlation coefficient r was 0.5256, and the increase of incidence rates was statistically significant ($p=0.0173$).

Age-standardized incidence rates in the observed period ranged from 7.47/100 000 in 1993 to 12.55/100,000 in 2000. In 1993, the cumulative risk of

newly diagnosed ovarian cancer in patients up to the age of 74 years was 0.89 and in 2000 it was 1.39, which represented the range between the lowest and the highest value.

The highest rate of 35.70/100,000 was observed among patients aged 60-64 years. For the same age group, the highest value expressed in absolute number (464) was also noticed. The percent of patients diagnosed with ovarian cancer before the age of 40 was 9.38 and before the age of 44 it was 15.40 (Figure 2).

In the last year of the observed period 176 new cases of this disease were documented; the incidence rate was 16.81/100,000, the age-standardized incidence rate was 10.78, and the cumulative risk to develop this malignancy from 0 to 74 years of age was 1.17.

Diagnosis was pathologically confirmed in almost two thirds of ovarian cancer cases for the observed period (Table 1). Epithelial-stromal tumors were confirmed in over 90% of diagnosed ovarian cancer cases; the most common was endometrioid type of ovarian cancer (11.64%) compared to all reported malignant ovarian tumors, or to pathologically verified cancers (18.35%). Most frequent ovarian sex cord-stromal tumor was granulosa cell tumor (1.09%) compared to all reported malignant ovarian tumors or 1.75% per year on average. The most frequent germ cell tumor was dysgerminoma

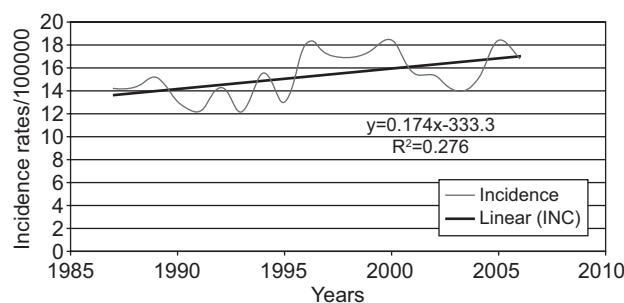


Figure 1. The incidence rates and their trends in newly diagnosed patients with malignant ovarian tumors in Vojvodina, 1987-2006.

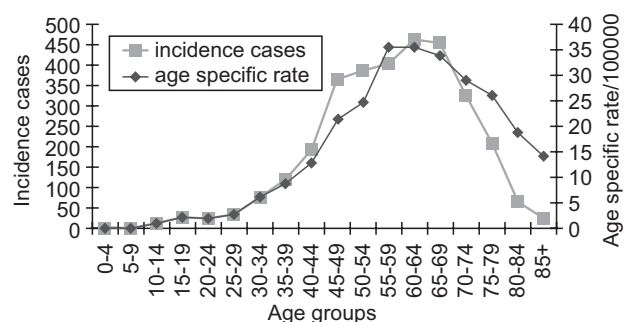


Figure 2. Number of newly diagnosed patients with malignant ovarian tumors according to age and age-specific rate in Vojvodina, 1987-2006.

Table 1. Number of malignant ovarian tumors and the percentage structure of the pathologically confirmed cases in Vojvodina in the period 1987-2006

Pathological diagnosis	Number of patients	%
Endometrioid adenocarcinoma	372	11.64
Adenocarcinoma NOS	299	9.35
Cystadenocarcinoma NOS	282	8.82
Papillary serous cystadenocarcinoma	170	5.32
Serous cystadenocarcinoma	126	3.94
Papillary adenocarcinoma NOS	109	3.41
Mucinous cystadenocarcinoma	104	3.25
Papillary cystadenocarcinoma	99	3.10
Carcinoma NOS	66	2.06
Mucinous adenocarcinoma	55	1.72
Papillary carcinoma	54	1.69
Anaplastic carcinoma	36	1.13
Granulosa cell tumor	35	1.09
Dysgerminoma	30	0.94
Papillary mucinous cystadenocarcinoma	20	0.63
Other pathological diagnoses	170	5.31
Undetermined pathological diagnoses	1170	36.60

NOS: not otherwise specified

(0.94%) or 1.5 per year on average. Ovarian cancers for which pathological diagnosis was not confirmed were 36.60% or 1,170 cases in the observed period.

In the region of Vojvodina, 1,934 women died of malignant ovarian tumors from 1987 to 2006 (97/year on average). Among gynecological cancers, ovarian cancer was the second cause of death. The mortality rate in the mentioned period was 9.24/100,000 on average; the lowest value was documented in 1987 and was 7.65/100,000 or 79 deaths, and the highest value was in 2005 and was 11.08/100,000 or 116 deaths. The mortality rate in the studied period showed a trend of increase (Figure 3). The average annual increase of mortality rate was 0.95%. The linear correlation coefficient r was 0.5530, and the increase of mortality was statistically significant ($p=0.0114$).

The standardized mortality rates in the observed

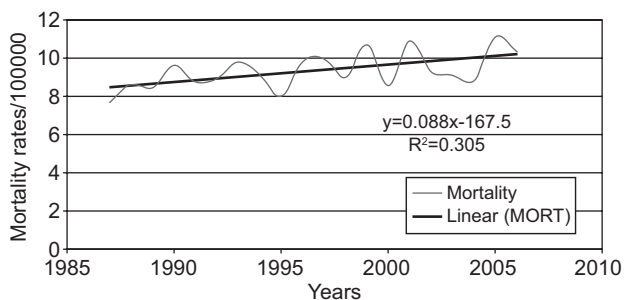


Figure 3. Mortality rate and trend of mortality rate in women who died of malignant ovarian tumors in Vojvodina, 1987-2006.

period started from 4.45/100,000 in 1987 and were up to 6.62/100,000 in 1999. The cumulative risk of death from this disease until the age of 74 years was in the range from 0.52 in 1987 to 0.77 in 2005.

According to the age groups, the highest mortality rates were documented in the age group of 60-64 years (23.49/100,000). For the same age group the highest value in absolute numbers was 307; 4.61% of patients aged up to 40 years died of ovarian cancer (Figure 4).

In 2006, 108 deaths from ovarian cancer were documented; the mortality rate was 10.32/100,000; the age-standardized incidence rate was 5.99 and the cumulative risk of death was 0.72 for the age group of 0-74 years.

Discussion

Our results show that the crude incidence rate and standardized incidence rate in Vojvodina correspond to the values that can be found in the eastern and southern Europe while the values in the western and northern Europe are generally higher [1]. From the countries in the region, Slovenia, Croatia and Hungary have higher values and Romania and FYROMacedonia have lower values [1,10]. The values of incidence rates in Vojvodina during the observed period indicate a tendency for increase. A slight decrease was documented at the beginning of the 1990's and 1999, which could be a consequence of war in the region and poorer registration of patients. In the USA, the incidence rates between 1975 and 1985 had a minor increase, but between 1985 and 2001 they decreased 0.7% per year, and 2.6% per year in the period 2001-2006 [11].

Decreasing or stagnation trend of incidence rates of malignant ovarian tumors is documented also in other developed countries e.g. the United Kingdom [12]. According to the 2009 evaluation in the USA, ovarian cancer was in the second place among patients newly diag-

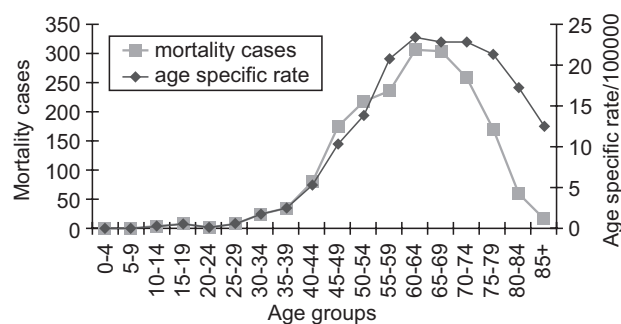


Figure 4. Number of the patients who died of malignant ovarian tumors according to age and to the age-specific rates in Vojvodina, 1987-2006.

nosed with this disease and in the first place in women who died of it, focusing on gynecological malignant diseases only [13]. In Vojvodina, ovarian cancer ranks third in incidence or second in mortality among gynecological malignant diseases. This difference in the incidence rates between the USA and Vojvodina is influenced by the extremely high incidence rates of cervical malignant tumors in our region.

The distribution of women with newly diagnosed ovarian cancer and younger than 44 years (15.4%) is closer to the values in eastern Europe (16.5%) than in northern Europe (10.0%) [1]. In Vojvodina, epithelial-stromal tumors are present in more than 90% of the cases of all pathologically confirmed diagnoses, a figure that corresponds to data found in developed countries [14]. The most common ovarian sex cord-stromal tumor is granulosa cell tumor and the most frequent germ cell tumor is dysgerminoma, which correlates well with the data from developed countries [14].

Crude mortality rates in Vojvodina correspond to relevant rates from eastern and southern Europe [1]. The mortality rates in Vojvodina during the observed period show an increasing trend. In the USA, mortality rates were in decrease (-1.2% per year) during 1975-1982; a slight increase of mortality rates was recorded in the following decade. In 1992-1998, an annual decrease (-1.2%) was documented again, which was followed by a minor increase in the next 5 years; finally in 2002-2006 the mortality rates were decreasing (1.4% per year) [11]. A similar decreasing trend of mortality was documented in many developed countries such as Denmark from 1978 to 2002 [15].

A disturbing fact is that 9.1% of deaths from ovarian cancer happen in women less than 44 years of age, which is considerably higher compared with any other European region, and especially higher than in western Europe (3.2%) [1].

There are 3 major strategies for screening of ovarian cancer. The first of them is transvaginal ultrasound, the second uses the serum tumor marker CA 125 as a primary test and transvaginal ultrasound as secondary test, and the third uses both methods simultaneously. It has been shown that the first strategy offers the higher sensitivity, while the second one has superior specificity and positive predictive value in the early stages of ovarian cancer [16]. CA 125 was expressed in 90% of patients with serous ovarian cancer and only in 25% of patients with mucinous ovarian cancer [17]. Serum CA 125 values were found increased in ovarian carcinoma, but in benign tumors, too [18]. Recommendation for women who have BRCA1 and BRCA2 germline mutations is to carry out an annual clinical pelvic examination, annual serum CA 125 and transvaginal ultrasound

every 6 months, until the age of 35, when it is necessary to consider prophylactic oophorectomy which decreases the risk of ovarian cancer by almost 98% [19-21].

The new ROMA algorithm (Risk of Ovarian Malignancy Algorithm) divides women into those with high risk and low risk to develop epithelial ovarian cancer according to their menopausal status, serum level of human epididymal protein 4 (HE4), and CA 125. Research results so far indicate that the ROMA algorithm has sensitivity of 94.3% and specificity of 75% when benign gynecological diseases are compared with all stages of epithelial ovarian cancer [22]. Six markers known as OvaSure are being already tested, and research indicates that their combination detects ovarian cancer with 95% sensitivity and 99% specificity [23].

Conclusion

Our results showed that the incidence and mortality rates of malignant ovarian tumors in Vojvodina were of medium high values when compared to other regions in Europe. In the observed period of 20 years, the incidence and mortality rates indicated a tendency for increase, which could be characterized as an unfavorable epidemiological situation. The percent of deaths of patients under the age of 44 years was higher when compared to 4 European regions. The main target is to decrease mortality by detection/diagnosis of the disease in its early stages.

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