

EPIDEMIOLOGY OF OVARIAN CANCER IN CROATIA

MARIO ŠEKERIJA and PETRA ČUKELJ

Croatian National Cancer Registry, Croatian Institute of Public Health, Zagreb, Croatia

Summary

Ovarian cancer is one of the most lethal malignant cancers in women, mainly because of the late stage at diagnosis. It is the seventh most common cancer in women in the world in incidence (239,000, 3.6%) and eighth in mortality (152,000, 4.3%). More developed regions have higher incidence and mortality rates than developing countries.

In Croatia, ovarian cancer ranks as the sixth most common cancer in women (430 new cases in 2013) and the sixth malignant cause of death (328 deaths in 2013). Research based on the Croatian National Cancer Registry data also shows that trends of standardized incidence and mortality rates for ovarian cancer in Croatia are relatively stable for the period from 1988 to 2008, while recent studies on cancer survival (EUROCORE-5, CONCORD-2) rank Croatia close to the European mean when it comes to ovarian cancer survival.

Ovarian cancer is a significant public health burden in Croatia. Efforts should be put in education about symptoms, and some modifiable risk factors such as tobacco use, obesity and hormone replacement therapy.

KEY WORDS: *Ovarian neoplasms, Croatia, registries*

EPIDEMIOLOGIJA RAKA JAJNIKA U HRVATSKOJ

Sažetak

Rak jajnika jedna je od najsmrtonosnijih malignih bolesti u žena, uglavnom zbog kasnog dijagnosticiranja. To je sedmi najčešći rak po pojavnosti u žena u svijetu (239.000, 3,6%), a osmi po smrtnosti (152.000, 4,3%). Razvijenije regije imaju više stope učestalosti i smrtnosti od zemalja u razvoju.

U Hrvatskoj, rak jajnika je 2013. godine bio šesti najčešći rak u žena (430 novih slučajeva), te šesti maligni uzrok smrti (328 smrtnih slučajeva u 2013. godini). Istraživanje temeljeno na podacima Registra za rak Republike Hrvatske također pokazuje da trendovi standardiziranih stopa incidencije i mortaliteta za rak jajnika u Hrvatskoj su relativno stabilni u razdoblju od 1988. do 2008. godine, a nedavna istraživanja koja su pratila preživljenje od raka (EUROCORE-5, CONCORD-2) rangiraju Hrvatska blizu europskog prosjeka po pitanju preživljenja od raka jajnika.

Rak jajnika predstavlja značajan javnozdravstveni teret u Hrvatskoj. Napore treba usmjeriti u edukaciju o simptomima i nekim promjenjivim čimbenicima rizika, kao što su uporaba duhana, pretilost i hormonska nadomjesna terapija.

KLJUČNE RIJEČI: *rak jajnika, Hrvatska, registri*

Ovarian cancer is one of the most lethal malignant cancers in women today. Most common malignant type of ovarian cancer is epithelial carcinoma, which can, based on the histology, be further divided in five different types: high-grade

serous, clear cell, endometrioid, mucinous and low-grade serous carcinoma. These types are in fact distinct diseases, as they differ in risk factors, patterns of spread, response to treatment and prognosis. The most prevalent type is the high-

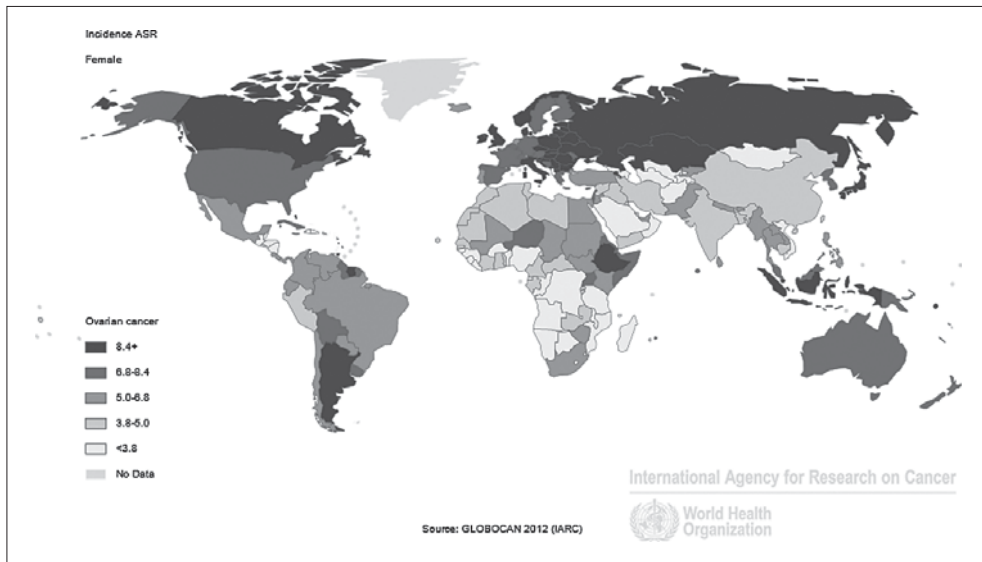


Figure 1 Estimates of age-standardised (World Standard Population - W) incidence rates of ovarian cancer in 2012 (4)

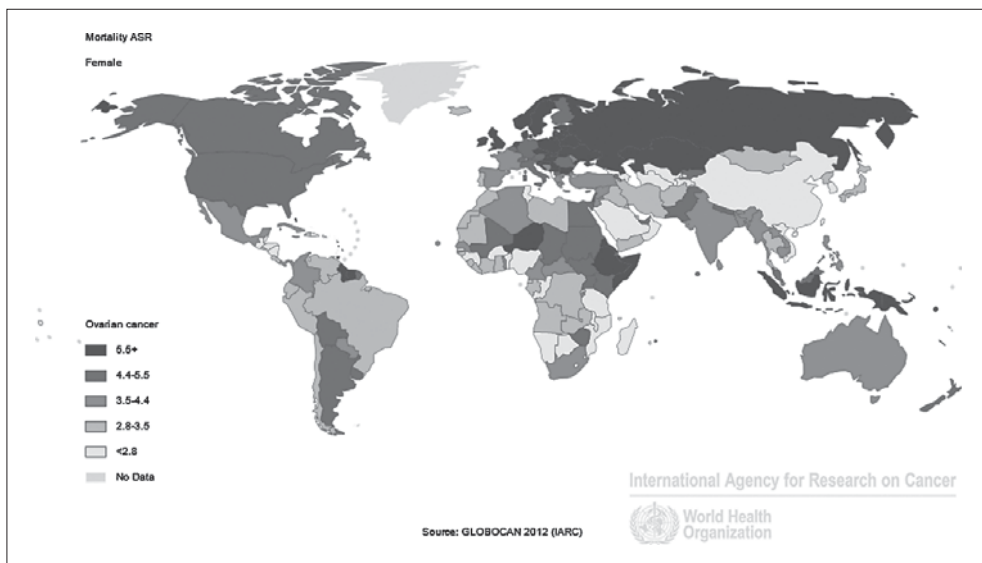


Figure 2 Estimates of age-standardised (W) mortality rates of ovarian cancer in 2012 (4)

grade serous type, which also has the worst prognosis (1).

Women with germline mutations in *BRCA1* or *BRCA2* genes have a higher risk of developing breast and ovarian cancer; the estimated cumulative risk for the latter is 36%-63% in *BRCA1* mutation carriers, and 10%-27% in *BRCA2* mutation carriers, compared with less than 2% in the general population(2).

Early stages of cancer are asymptomatic, and in later stages symptoms can be mistaken for other common maladies as they include bloated stomach, discomfort in the pelvis area, change in bowel habits, and frequent need to urinate. Because of these non-specific symptoms ovarian cancer is usually diagnosed at later stages, when prognosis is poor. Also, very little is known about the aetiology of the disease.

Table 1

RISK FACTORS AND PROTECTIVE FACTORS FOR OVARIAN CANCER, ACCORDING TO (3)

Risk factors	Protective factors
Age	Oral contraceptive use
Family history	Oophorectomy
Nulliparity	Hysterectomy
Increased numbers of lifetime ovulatory cycles	Tubal Ligation
Hormone replacement therapy	Lactation
Dietary Fat	High vegetable intake
Obesity	
Infertility	
Sedentary lifestyle	
Cigarette smoking	
Alcohol consumption	

Ovarian cancer occurs most often in nulliparous women and other risk factors include early age at menarche, late menopause, and no use of oral contraceptives. It can be concluded that suppressed ovulation is a protective factor, and hypotheses about the aetiology of the disease correspond to this observation(1). Incessant ovulation theory considers that constant epithelial repair which happens after every ovulation cycle increases the risk for spontaneous mutations of ovarian epithelial cells. Gonadotropin hypothesis posits that gonadotropin hormones, such as LH and FSH, stimulate the ovarian epithelium and therefore promote proliferation, thereby increasing the risk of neoplastic changes in the epithelium (3).

According to GLOBOCAN 2012 (4), around 239,000 new cases of ovarian cancer occur in the world every year, and a third of that number affects women under the age of 50. It is the seventh most common cancer diagnosed in women (3.6%), and the eighth most common cancer cause of death (152,000, 4.3%) in women. Almost half of all cases occur in Asia (112,000, 47.6%), and almost a third in Europe (66,000, 27.5%), where the highest incidence and mortality rates are found in Central and Eastern Europe. Migration from countries with low disease burden to those having high rates of ovarian cancer results in greater ovarian cancer risk (5), highlighting the importance of non-genetic factors.

In Europe, countries with highest age-standardised incidence rates include Latvia, Bulgaria and Poland while the highest estimated mortality rates in 2012 have been found in Latvia, Lithuania and Poland (4). While Croatia ranks 20th (out of 40 countries included) by incidence rates, it is ranked 6th in mortality, indicating possibilities for improvement of care for women with ovarian cancer.

The most recent official data for Croatia (6) show that ovarian cancer is the sixth most common cancer in women (430 new cases; crude incidence rate 19.5/100,000), and also the sixth most common cancer cause of death (328 deaths, crude mortality rate 14.9/100,000). Distribution of stages at diagnosis from the Croatian National Cancer Registry bulletin for 2013(6) showed that 18% of ovarian cancer cases were diagnosed at a localised stage, 18% with regional spreading or regional metastases, 29% with distant metastases, and the

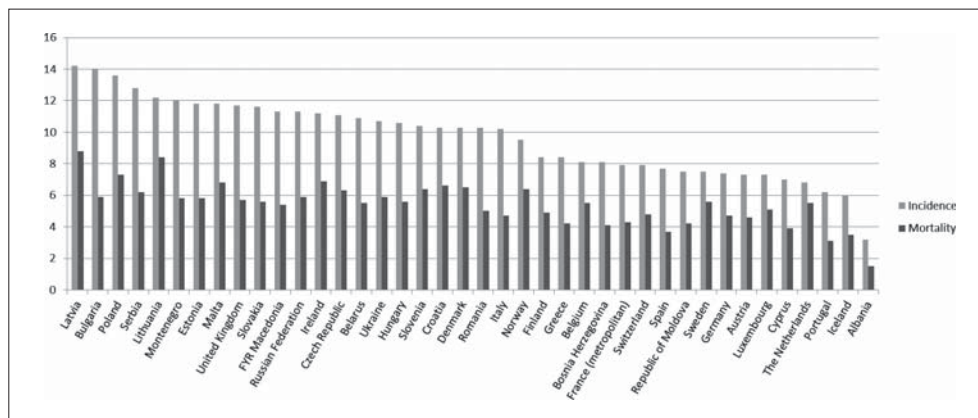


Figure 3 Estimates of age-standardised (W) ovarian cancer incidence and mortality rates in European countries in 2012 (4)

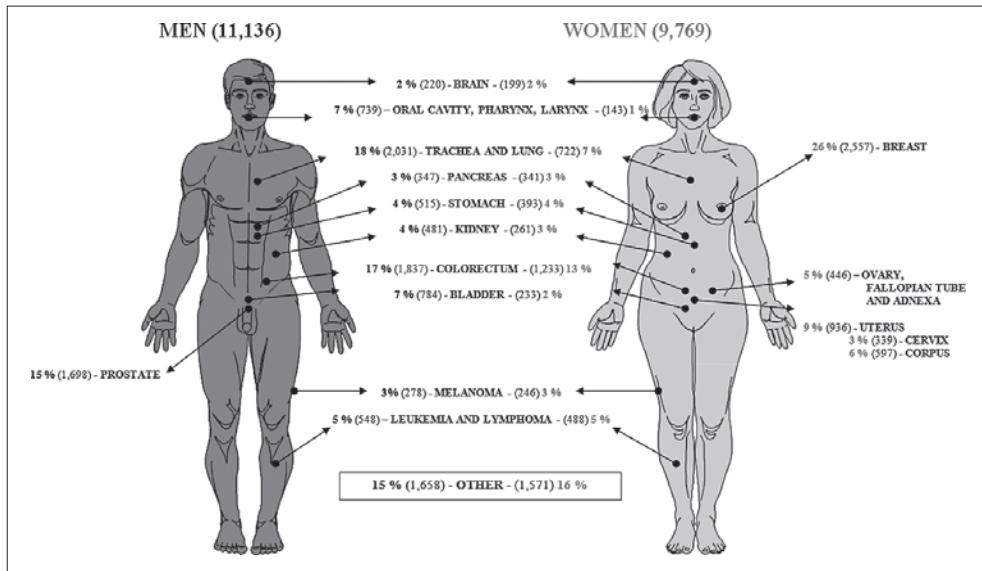


Figure 4 Distribution of new cancer cases in Croatia, 2013(6)

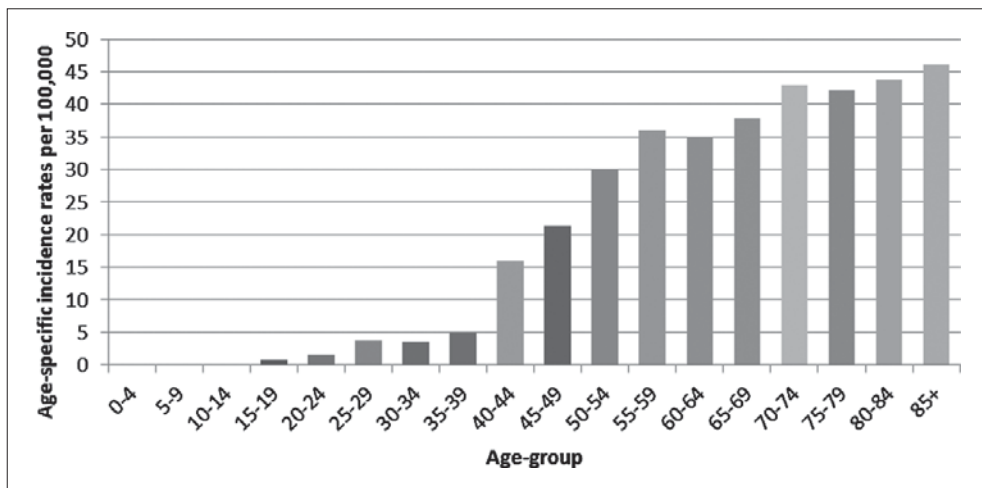


Figure 5 Age-specific incidence rates of ovarian cancer in Croatia, 2013 (6)

stage of the disease was unknown for 35% of the cases at the time of diagnosis.

When analysing age-specific incidence rates in Croatia, we can see that the highest rates are found in the oldest age-groups, with 83% of all ovarian cancers diagnosed in women aged 50 and more.

Croatian data for 2013 show some regional differences in standardised incidence and mortality rates, incidence rate for ovarian cancer being higher in northern and central parts of the country (ranges from 28.5/100,000 to 11.7/100,000) and low-

er in the coastal area (lowest in the Lika-Senj County with 9.4/100,000), with the exception of high incidence (23.8/100,000) in Dubrovnik-Neretva County and Zadar County (20.9/100,000).

Mortality data do not show such clear differences, with standardised mortality rates ranging from 25.6/100,000 to 8.1/100,000, and the highest rates observed in the Bjelovar-Bilogora, Brod-Posavina and Dubrovnik-Neretva Counties.

Epidemiological research of ovarian cancer incidence and mortality trends in Croatia shows three distinct trends in the period from 1988 to

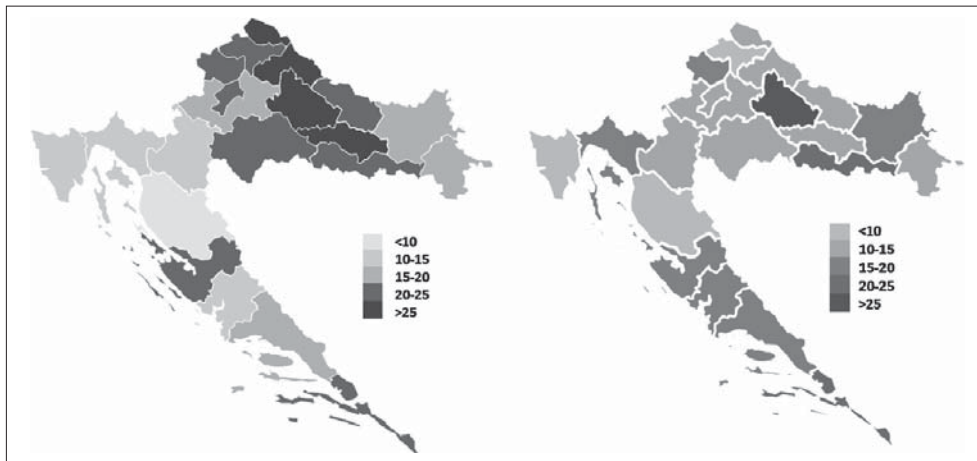


Figure 6 Age-standardised (estimates of Croatian population in 2013) ovarian cancer incidence and mortality rates in Croatian counties in 2013, according to data from (6)

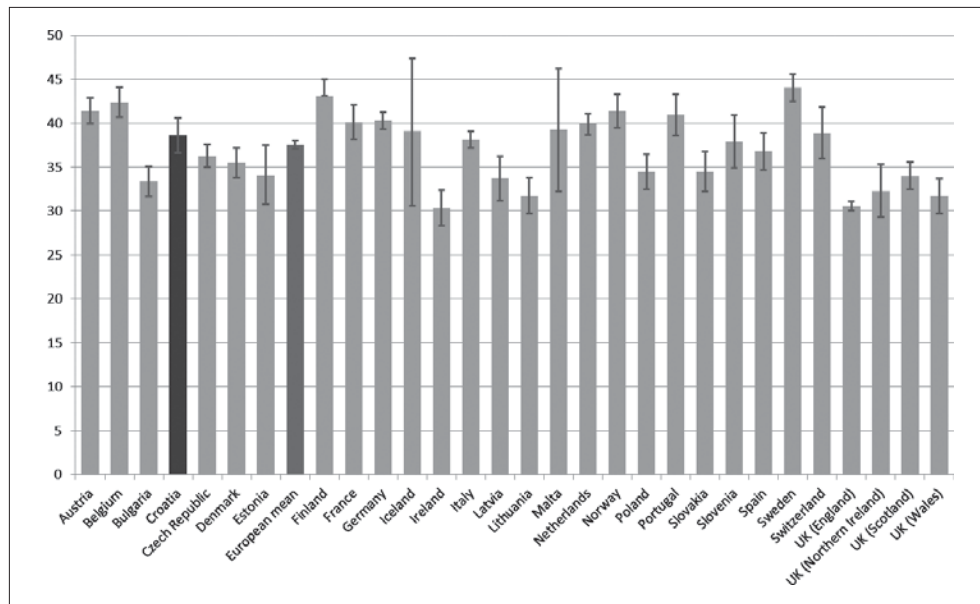


Figure 7 Ovarian cancer 5-year relative survivals in countries participating in EUROCORE-5, adapted from (9)

2008(7). In the period from 1988 to 1997, the trend was stable (Estimated Annual Percent Change (EAPC) 0.4 (95% CI -1.2 to 1.9)), between 1997 and 2000 there was a non-significant increase in incidence (EAPC 8.1 (95% CI -7.4 to 26.2)), and from 2000 to 2008 there was a significant decrease (EAPC -3.1 (95% CI -4.8 to -1.4)). However, when observing the whole period, the trend was stable (Average Annual Percent Change (AAPC) 0.1% (95% CI -2.2 to 2.4)).

The ovarian cancer mortality trends described in the same publication (7) indicate that, in the 1988-1992 period a statistically non-significant decrease in mortality was observed (AAPC -4.1 (95% CI -10.2 to 2.3)), whereas in the 1992-2008 period a statistically significant increase in ovarian cancer mortality was observed in Croatia (AAPC 1.2 (95% CI 0.4 to 1.9)).

Recently, two major studies on cancer survival have been published; EUROCORE-5 (8, 9)

and CONCORD-2 (10). The EUROCORE-5 study on cancer survival in Europe has included, for the first time in its history, data from Croatia. It showed that 5-year relative survival from ovarian cancer (for women diagnosed between 2000 and 2007 and followed-up until the end of 2008) was 38.6%, placing Croatia somewhere in the middle of 25 European countries included in the study.

Another study that focused on cancer survival is the CONCORD-2 study (10) which evaluated cancer survival at the global level. It included information from 67 countries, and a total of over 25 million cancer patients were available for analysis. The most recent data for ovarian cancer in Croatia (5,885 eligible patients) showed that 5-year survival for patients diagnosed in the 2005-2009 period was 36.8%.

In summary, Croatia is a country with an intermediate ovarian cancer incidence (compared to other European countries), but a relatively high, and worrisome, increasing mortality. Data from recent international survival studies have shown that the 5-year survival in Croatia was comparable to that in similar European countries.

While many risk factors for ovarian cancer have been identified (3), they do not account for all of the variability in incidence, nor do they explain large increases in the risk of disease – consequently, a number of possible causes of ovarian cancer are yet to be identified. Efforts should be made to educate about early symptoms, and raise awareness of some modifiable risk factors like tobacco use, sedentary lifestyle, obesity and hormone replacement therapy.

REFERENCES

1. Stewart BW, Wild CP, editors (2014). World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer.
2. Domchek SM, Jhaveri K, Patil S, Stopfer JE, Hudis C, Powers J, et al. Risk of metachronous breast cancer after BRCA mutation-associated ovarian cancer. *Cancer*. 2013;119(7):1344-8.
3. Permuth-Wey J, Besharat A, Sellers TA. Epidemiology of ovarian cancer: an update. *Advances in Diagnosis and Management of Ovarian Cancer*: Springer; 2014. p. 1-21.
4. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. [cited 2016 01/22].
5. Kliewer EV, Smith KR. Ovarian cancer mortality among immigrants in Australia and Canada. *Cancer Epidemiol Biomarkers Prev*. 1995;4(5):453-8.
6. Incidencija raka u Hrvatskoj 2013. Bilten broj 38. Zagreb: Hrvatski zavod za javno zdravstvo; 2015.
7. Kelava I, Tomicic K, Kokic M, Corusic A, Planinic P, Kirac I, et al. Breast and gynecological cancers in Croatia, 1988-2008. *Croatian medical journal*. 2012;53(2): 100-8.
8. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCORE-5-a population-based study. *The Lancet Oncology*. 2014;15(1):23-34.
9. Sant M, Chirlaque Lopez MD, Agresti R, Sanchez Perez MJ, Holleccek B, Bielska-Lasota M, et al. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCORE-5 study. *European journal of cancer*. 2015;51(15):2191-2205.
10. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*. 2015; 385(9972):977-1010.

Author's address: Mario Šekerija, Croatian National Cancer Registry, Croatian Institute of Public Health, 7 Rockefeller str., 10000 Zagreb, Croatia. e-mail: mario.sekerija@hzjz.hr