EPIDEMIOLOGY OF CANCER IN CROATIA
– RECENT INSIGHTS AND INTERNATIONAL COMPARISONS

MARIO ŠEKERIJA[1,2], MAŠA ALFIREVIĆ[3], URŠULA FABIJANIĆ[4],
NADA RAJAČIĆ[5] and NATAŠA ANTOLJAK[6]

[1]Croatian National Cancer Registry, Croatian Institute of Public Health, Zagreb, Croatia;
[2]School of Public Health Dr Andrija Štampar, School of Medicine, University of Zagreb, Zagreb, Croatia;
[3]Ministry of Defence of the Republic of Croatia, Zagreb, Croatia;
[4]Health Center Zagreb – Center, Zagreb, Croatia;
[5]Department of Oncology and Hematology Dr Mladen Ćepulić, Children's Hospital Zagreb,
Zagreb, Croatia;
[6]Department of Adult Population Screening, Croatian Institute of Public Health, Zagreb, Croatia

Summary

Cancer is a major public health issue worldwide. It is very important to have high-quality epidemiological data to plan the measures in primary, secondary and tertiary prevention, to benchmark in comparison to other countries and to assess trends for particular cancer sites. This paper presents the basic epidemiology indicators for Croatia, explains the concepts surrounding the data collection and analytical procedures for essential epidemiological parameters and presents the most recent data, estimates and comparisons in the advent of the first Croatian National Cancer Plan.

KEYWORDS: *Croatia, cancer registry, incidence, mortality, survival, GLOBOCAN, ECIS*

EPIDEMIOLOGIJA RAKA U HRVATSKOJ – NEDAVNI UVIDI I MEĐUNARODNE USPOREDBE

Sažetak

Rak je veliki javnozdravstveni problem na cijelom svijetu. Iznimno je važno imati kvalitetne epidemiološke podatke kako bismo mogli planirati mjere primarne, sekundarne i tercijarne prevencije, usporediti se s drugim državama i procijeniti trendove za pojedina sijela raka. Ovaj članak opisuje osnovne epidemiološke indikatore za Hrvatsku, razjašnjava načine prikupljanja podataka i analitičkih procedura za te indikatore te iznosi najnovije podatke, procjene i usporedbe u osvit prvog hrvatskog Nacionalnog plana za borbu protiv raka.

KLJUČNE RIJEČI: *Hrvatska, registar za rak, incidencija, mortalitet, preživljenje, GLOBOCAN, ECIS*

INTRODUCTION

Cancer has become an extremely important public health problem for modern society with its importance at population level increasing due to the improvements in life expectancy. It is often re-ferred to as a single disease, however it is an extremely heterogeneous group of diseases that begin with a malignant change of one cell of an organism that further uncontrollably divides (1). The reasons for this change may be different for different types of cancer (risk factors) and it is im-

portant to understand which ones are associated with which cancer type in order to know which populations are at higher risk (2).

Majority of this information is based on the results of scientific studies and population-based data (e.g. connection between smoking and lung cancer) (3). Over time, with improvement of the health status in developing countries and changes in the prevalence of possible risk factors, it became increasingly important to have a systematic insight in cancer burden on a national or regional level. The first regional cancer registries were established before World War II and became significant in the second half of the 20th century (4).

As a basic dataset, cancer registries collect data on cancer patients, type of cancer (site, type, stage) and vital status of the person (alive/dead) (5) in order to calculate three of the four basic epidemiological parameters to estimate the burden of cancer: incidence, representing a number of new cases in one year; prevalence (number of people currently alive that were diagnosed with cancer) and survival (usually 5-year survival, the percentage of people still alive five years after being diagnosed with cancer). The fourth basic parameter, cancer mortality (number of deaths due to cancer in one year) is based on coroner's assessment of the underlying cause of death, which is then used as an additional source of data. Taking into account the methods of collecting and controlling of data quality, most of the cancer registries publish their annual reports one and a half to two years after the end of calendar year to which the data relate (6).

Regions or countries are usually compared by two basic criteria, incidence (number of new cases per 100 000 population) and mortality (number of deaths per 100 000 population), because it is easier to collect reliable data for those two than for survival and prevalence. These indicators can show us the main priorities in a country, how it fares in comparison to other countries, and are there some favourable or unfavourable trends. The so-called age-standardized rate is used when comparing countries with cancer incidence rates or cancer mortality rates (or disease trends over certain period). This age-standardized rate (can be calculated using different standard populations) controls for differences between populations in their age structure and removes possible confounding by age (7). These differences must always be taken into account when making comparisons or assessing trends, e.g., there are many more newly cancer patients today and the overall (crude) incidence rate of cancer in Croatia now is much higher than 50 years ago (8), but there are also far more elderly people (both in absolute and relative terms) living in Croatia today than in 1969.

WORLDWIDE ESTIMATES

International Agency for Research on Cancer (IARC) is responsible for several key projects like GLOBOCAN (https://gco.iarc.fr/), Cancer Incidence in Five Continents (http://ci5.iarc.fr/Default.aspx), International Incidence of Childhood Cancer (https://iicc.iarc.fr/), and many others. The Global Cancer Observatory is a platform where the latest global estimates for 2018 can be found, along with actual cancer registries' data for up to 2012 and trends over time (9-11). This data can further be analysed and presented using a variety of analytical and visual options, providing us with some answers in the understanding of cancer epidemiology, and indicating possible etiologic causes.

For example, the most common diagnoses of cancer (incidence) by country in women (Figure 1) are influenced by various factors. These can be due to genetic factors, behavioural and environmental risk factors and the availability of diagnostic procedures; we can see that breast cancer is the most commonly diagnosed cancer in women in 85% countries in the world.

The most important causes of cancer mortality in women by country (Figure 2) indicate a different situation, influenced of course by prognosis for each particular cancer type, with breast cancer being the leading cause of death for 56% of the countries worldwide, and a significant number countries having lung or cervical cancer as the main cancer cause of death in women.

EUROPEAN ESTIMATES

Detailed data and estimates across European countries can be found at ECIS (European Cancer Information System; https://ecis.jrc.ec.europa.eu/). This website provides not only incidence and mortality estimates (developed in collaboration with IARC), but also survival rates from a major EUROCARE study on survival of cancer patients

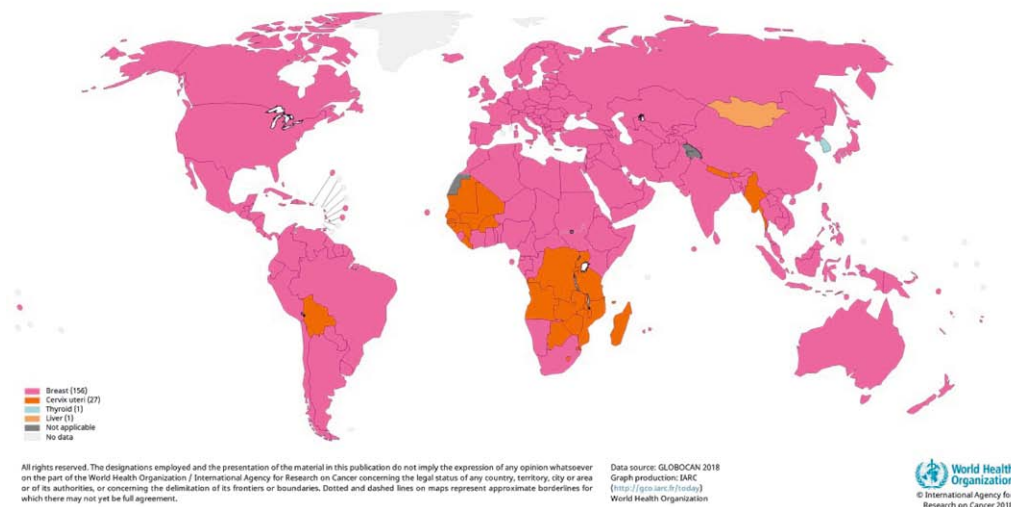Top cancer per country, estimated age-standardized incidence rates (World) in 2018, females, all ages

Breast (156)
Cervix uteri (27)
Thyroid (1)
Liver (1)
Not applicable
No data

Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization
© International Agency for Research on Cancer 2018

Figure 1. The most common cancer by incidence in world, 2018, females (11)

Top cancer per country, estimated age-standardized mortality rates (World) in 2018, females, all ages

Breast (104)
Cervix uteri (64)
Lung (29)
Stomach (4)
Liver (3)
Colorectum (1)
Not applicable
No data

Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization
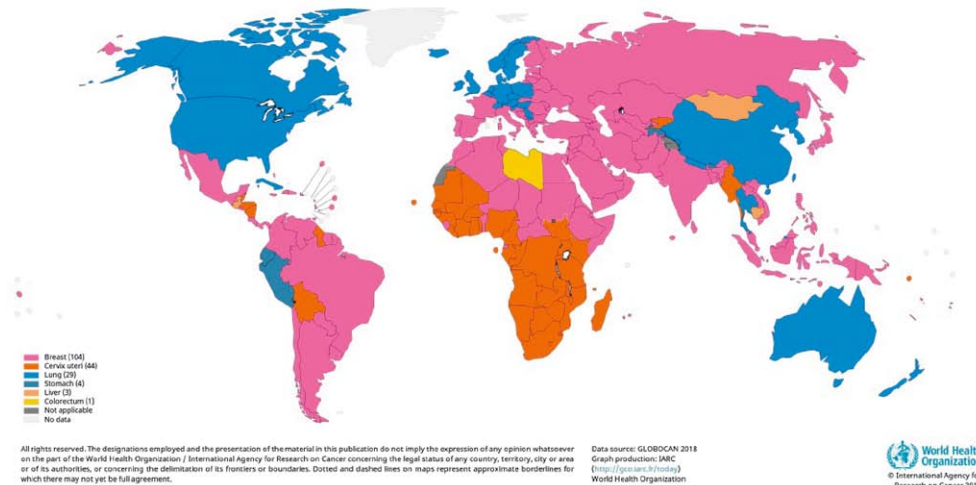© International Agency for Research on Cancer 2018

Figure 2. The most common cancer by mortality rates in world, 2018, females (11)

in Europe (12). Taking into account European estimates of cancer incidence and mortality in 2018, using the new European Standard Population (Figures 3 and 4), Croatia is a country with a medium to high cancer incidence rates and high mortality rates.

CROATIAN NATIONAL CANCER REGISTRY

The Croatian National Cancer Registry has started collecting data in 1959, making it one of the oldest registries in Europe and worldwide. The first report was published in 1968 (14). There are four basic data sources: notifications from primary health care providers (family medicine practitioners) and tertiary care providers (hospitals), copies of histopathological findings confirming cancer diagnosis, and information on causes of death in Croatia. Patient discharge diagnosis is a supplementary data source, which are then used for case finding procedures to complement the database and improve data coverage and quality.
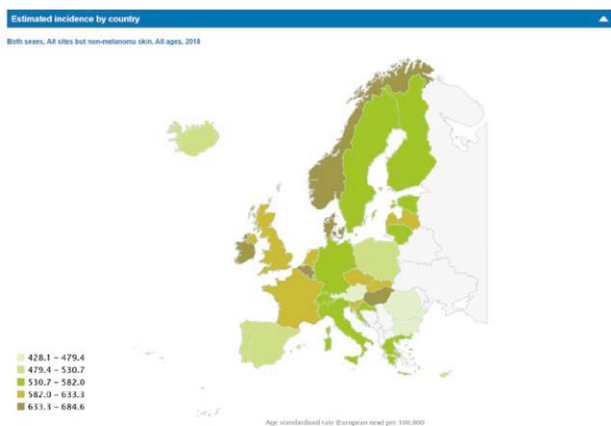
Figure 3. Cancer incidence rates in Europe in 2018, European Cancer Information System (13)
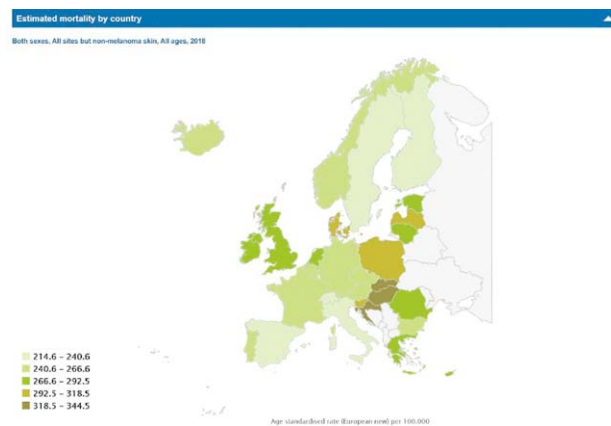

Figure 4. Cancer mortality rates in Europe in 2018, European Cancer Information System (13)

According to the latest official data from the Croatian National Cancer Registry for 2016, 23,650 new cases of malignancies (12,632 in men and 11,018 in women) were confirmed, crude incidence rate was 566,6/100,000 (626,9/100,000 for men and 510,2/100,000 for women) (15). Findings are related to C00-C96 diagnoses, classified by International Classification of Diseases, 10th Edition, excluding non-melanoma skin cancers (C44).

Latest records for Croatia, in 2018, found that the total number of deaths from invasive cancer (without non-melanoma skin cancers) was 13,809 (crude mortality rate 337,8/100,000), of which 8,049 were men (mortality rate 407,5/100,000) and 5,849 women (mortality rate 272,6/100,000) (16).

The most common causes of death in 2018 in Croatian men were lung cancer (2,097 deaths), colorectal cancer (1,321) and prostate cancer (772), while in women the most common ones were colorectal cancer (919), lung cancer (860) and breast cancer (789) (16).

Using cancer registry data, the regional distribution of cancer cases can also be assessed, visualising the current situation, highlighting differences in the regional cancer burden and supporting further research into possible reasons for these differences.

TRENDS

Perhaps the most important information that can be elucidated from the cancer registry data are trends for each cancer type. These trends are ex-

tremely important for measuring the changes in cancer burden that come along with changes in the environmental and behavioural risk factors, as well as changes in the availability of diagnostic and therapeutic modalities, including screening programmes.

For instance, with a time delay, lung cancer trends will follow up changes in the prevalence of smoking in the population, since smoking is considered as cause of about 85% of all lung cancer cases. Although lung cancer is still far more common in men than in women, incidence and mortality trends are completely opposite (Figures 5 and 6); in men, the age-standardized incidence rate per 100,000 population declines with an annual percentage change (APC) of -1.4% (95% CI -1.8 to -1.0) and mortality declines with APC of
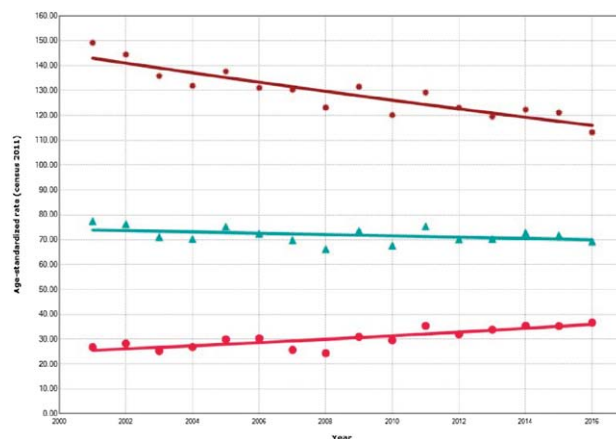

Figure 5. Trends in age-standardised incidence for lung cancer in Croatia, by sex, 2001-2016
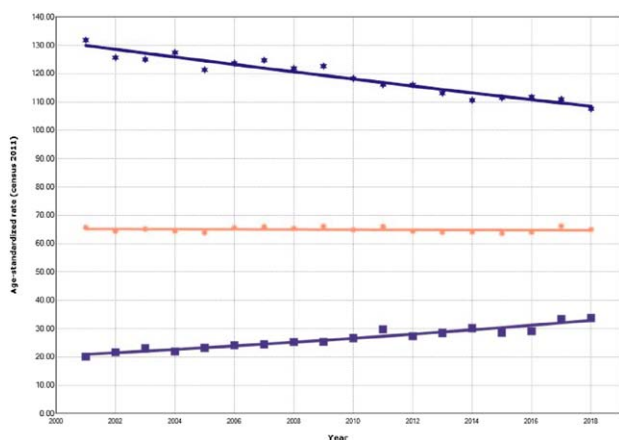
Figure 6. Trends in age-standardised mortality rates for lung cancer in Croatia, by sex, 2001-2018

-1.1% (95% CI -1.2 to -0.9). In women, incidence rates increase with an APC of +2.3% (95% CI 1.4 to 3.2) and mortality rates with an APC of +2.7% (95% CI 2.3 to 3.1); all p values less than 0.001.

CANCER SURVIVAL

Prognosis after a diagnosis of a certain disease is a major factor for anyone included in health care system. Besides cancer incidence and cancer mortality, it is necessary to ascertain survival rates for each type of cancer and compare those results

with other countries, as a benchmarking tool. The CONCORD-3 study, published in 2018 (17), analysed medical data from 322 cancer registries in 71 countries in order to compare 5-year net survival in more than 37.5 million patients (adult and children) diagnosed with one of the 18 most common cancer types, in the period from 2000 to 2014.

The Croatian National Cancer Registry also took part in this study. Data for more than 220,000 patients were included and compared to data collected from countries all over the world. The survival rates from Croatia and other participating European countries are presented here for the last 5-year period (2010-2014).

It is important to emphasize that for almost all types of cancer, cancer survival in Croatia is improving (Figure 7). However, when observing trends and data from earlier years, other comparable countries are often improving faster so there is plenty of room for further progress.

PREVALENCE

Prevalence (number of all people alive at some point and found to be affected by specific disease/condition) has been rarely used basic parameter in cancer epidemiology for many reasons. However, due to improvements in prognosis for many malignancies and longer life expectancy, it is becom-
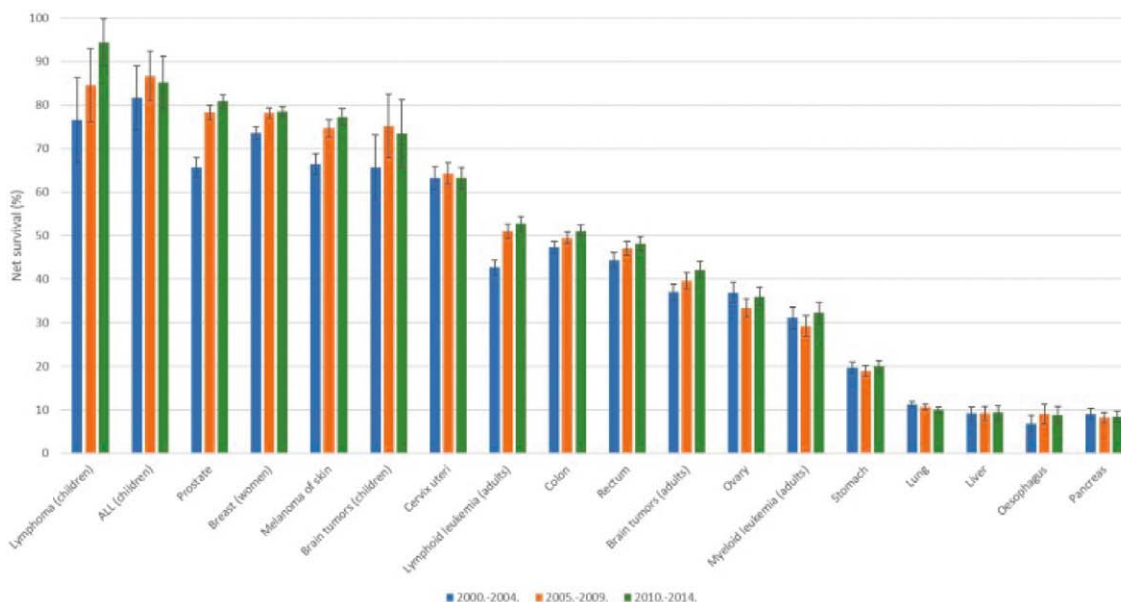

Figure 7. Survival trends in Croatia for selected cancer sites, 2000-2014, according to CONCORD-3 study (17)

ing more important to know what proportion of population has been affected by cancer during their lifetime, even if the diagnosis has been made more than five years ago. Considering human migration in Croatia over the last 30 years, the exact cancer prevalence is difficult to ascertain. Preliminary estimates based on cancer registry data indicate that around 170,000 people living in Croatia have been diagnosed with a malignant disease at some point in their lives, equalling around 4% of the total population (data not yet published). About 65,000 of those cases were diagnosed in the last 5 years, based on the estimates from the GLOBOCAN 2018.

RISK FACTORS AND LEVELS OF PREVENTION

Data on the health-related habits of Croatian population are also worrying; according to the percentage of smokers, the percentage of obese people and those not adhering to recommended nutrition we are far worse than the EU average, which of course has a significant impact on the higher incidence of cancer (18). At the primary level, activities are needed to promote healthy lifestyles and prevention of harmful living habits, with the participation of the Croatian Institute of Public Health and the network of county public health institutes through various programs, coordinated by the Ministry of Health.

Three national cancer screening programs have been launched in Croatia, coordinated by the Croatian Institute of Public Health: breast, colon and cervical cancer, which are, at the population level, considered as the most effective secondary prevention measure (19-21). The program for introduction of lung cancer screening is currently in its preparation phase, expecting the start of the program in 2020 (22).

Tertiary prevention is carried out by ensuring that the required therapeutic modalities are available to those who are needed. Western countries' experiences show that it is of utmost importance to have a clear strategy on how to improve the epidemiological situation. This is achieved through the adoption of a National Cancer Plan, and it is considered that the adoption of the National Cancer Control Plan will bring additional improvements to the comprehensive monitoring, prevention and treatment of cancer with integrated tertiary prevention measures and optimization of health care for oncological patients (23). Work on the first Croatian Cancer Plan has been ongoing, under the coordination of the Ministry of Health and with the involvement of experts in the field and the Cancer Plan is expected to be adopted in 2020.

CONCLUSION

Cancer is a complex problem, both from clinical and public health perspective. The epidemiological data for Croatia are worrying, with high mortality and low survival indicating a major impact on the health of people living in Croatia. The gap behind more developed countries is not being reduced, and it represents a major challenge for Croatian society in the following period. The primary prevention efforts need to be coordinated by a multi-sectoral group of stakeholders, not only those related to health care field. In the treatment of an individual patient, it is often necessary to apply different types of therapy with the collaboration of a multidisciplinary team of specialists. The population-level approach for this major issue from the health care perspective should be the same (24): only by involving professionals of different profiles, from clinicians, basic science, general practitioners, public health and epidemiology, management at the Ministry of Health and the Croatian Health Insurance Institute and of course patients' associations, a positive breakthrough in these cancer statistics and a longer and healthier life for citizens of this country can be achieved.

REFERENCES

1. Maman S, Witz IP. A history of exploring cancer in context. Nature Reviews Cancer. 2018;18(6):359-76.
2. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA: a cancer journal for clinicians. 2018;68(1):31-54.
3. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. British medical journal. 1954;1 (4877):1451.
4. Wagner G. History of cancer registration. Cancer registration: principles and methods IARC Scientific Publications. 1991;95:3-6.
5. Esteban D, Whelan S, Laudico A, Parkin DM, Badger D, Gravestock S, et al. Manual for cancer registry personnel: IARC Lyon; 1995.

6. Zanetti R, Sacchetto L, Calvia M, Bordoni A, Hakulinen T, Znaor A, et al. Economic evaluation of cancer registration in Europe. J Registry Manag. 2014;41(1):31-7.

7. Bray F, Ferlay J. Age-standardization. Cancer incidence in five continents. 2002;8:87-9.

8. Reljic A, Cukelj P, Tomaskovic I, Ruzic B, Sekerija M. Epidemiology of prostate cancer in Croatia - situation and erspectives. Acta Clin Croat. 2018;57(Suppl 1):27-34.

9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

10. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.

11. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018. accessed on [12/11/2019]. Available from: https://gco.iarc.fr/today,

12. Rossi S, Baili P, Capocaccia R, Caldora M, Carrani E, Minicozzi P, et al. The EUROCARE-5 study on cancer survival in Europe 1999-2007: Database, quality checks and statistical analysis methods. Eur J Cancer. 2015;51(15):2104-19.

13. ECIS - European Cancer Information System. European Union. 2019 accessed on 12/11/2019. Avaiable from https://ecis.jrc.ec.europa.eu,

14. Šekerija M. Registar za rak. Epoha zdravlja: glasilo Hrvatske mreže zdravih gradova. 2018;10(1):22-.

15. Hrvatski zavod za javno zdravstvo, Registar za rak Republike Hrvatske. Incidencija raka u Hrvatskoj 2016., Bilten 41, Zagreb, 2019. Available from: https://www.hzjz.hr/wp-content/uploads/2017/01/Bilten-2016_zavrsna.pdf accessed on 12/11/2019

16. Hrvatski zavod za javno zdravstvo. Izvješće o umrlim osobama u Hrvatskoj u 2018. godini, Zagreb, 2019. Available from: https://www.hzjz.hr/wp-content/uploads/2019/09/Bilten__Umrli-_2018-1-1.pdf accessed on 12/11/2019

17. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023-75.

18. OECD/European Observatory on Health Systems and Policies (2019), Croatia: Country Health Profile 2019, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. Available from: https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_hr_english.pdf accessed on 12/11/2019

19. Šekerija M, Marković T. Epidemiologija kolorektalnog raka u Hrvatskoj i svijetu. Rad Hrvatske akademije znanosti i umjetnosti: Medicinske znanosti. 2015(522=41):89-94.

20. Vučić K, Orešić T, Habljak K, Kahlina M, Kirac I, Šekerija M. Regional differences of breast cancer risk factors in newly diagnosed female patients in Croatia. Libri Oncologici. 2018;46(2-3):47-54.

21. Basu P, Ponti A, Anttila A, Ronco G, Senore C, Vale DB, et al. Status of implementation and organization of cancer screening in The European Union Member States—Summary results from the second European screening report. International journal of cancer. 2018;142(1):44-56.

22. Ministarstvo zdravstva. Nacionalni program za probir i rano otkrivanje raka pluća 2019. – 2023. [Nacrt]. Available from: https://zdravlje.gov.hr/UserDocsImages/2018%20Vijesti/NACIONALNI%20PROGRAM%20-%20RAK%20PLU%C4%86A.doc accessed on 12/11/2019

23. Oar A, Moraes FY, Romero Y, Ilbawi A, Yap ML. Core elements of national cancer control plans: a tool to support plan development and review. The Lancet Oncology. 2019;20(11):e645-e52.

24. Vrdoljak E. Cancer in Croatia; where do we stand and how to move forward? Croat Med J. 2012;53(2):91-2.

Corresponding author: Mario Šekerija, Croatian National Cancer Registry, Croatian Institute of Public Health, Rockefellerova 7, 10000 Zagreb, Croatia. e-mail: mario.sekerija@hzjz.hr