

# EPIDEMIOLOGY OF PROSTATE CANCER IN CROATIA – SITUATION AND PERSPECTIVES

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**SUMMARY** – Prostate cancer represents a significant public health burden in Croatia, as well as in other developed countries. The aim of this paper was to present the current epidemiological situation in Croatia in comparison to other similar countries, using basic indicators such as incidence, mortality, prevalence and survival, and to discuss future possibilities in this field. The incidence of prostate cancer in Croatia has been rapidly increasing since the mid-nineties; recent data indicates that the trend is levelling off. Mortality data show constant increase since the 1960s, but mortality trends seem to be stabilizing in the recent period; however, Croatia is still in the top ten countries regarding prostate cancer mortality in Europe. Five-year prevalence in 2012 was estimated at 7,592 cases (426.7/100,000), ranking Croatia in the middle of European countries in the GLOBOCAN 2012 database. According to the CONCORD-2 study, five-year net survival in Croatia in the 2005-2009 period was 75.1%, which is lower than in similar European countries. The epidemiological pattern of prostate cancer in Croatia indicates a relatively low incidence, with significant room for improvement in mortality and survival data. Given the recent discussions regarding prostate cancer screening modalities, a debate is warranted and should be encouraged regarding the role of PSA testing in Croatia.

**Key words:** *Prostate cancer; Croatia; Incidence; Mortality; Survival; PSA testing*

## Introduction

Prostate cancer is the second most common cancer in men worldwide and the fifth cause of cancer death<sup>1</sup>. Epidemiological indicators of the disease have changed immensely in the last couple of decades with the introduction of PSA testing and improvements in treatment. The disease poses a significant health and financial burden, especially in more developed countries, so it is important to explore epidemiological indicators and trends.

Risk factors for prostate cancer include, most importantly, older age, as well as heredity and ethnic ori-

gin<sup>2</sup>. A variety of other possible risk factors has been discussed, including, but not limited to, nutrition, occupational exposure and sexual behaviour. There are no primary prevention programmes for prostate cancer; the role of PSA testing in population-based control of prostate cancer has been a matter of fierce debate over the recent years<sup>3</sup>, with recent studies emphasizing the possibility of a tailored limited screening programme in a narrow age-group and including active surveillance for men with low-risk tumours<sup>4</sup>.

The aim of this paper was to summarize the current epidemiological situation regarding prostate cancer in Croatia using available data and the implications of those data for future actions in prostate cancer control, with a focus on prostate cancer screening. Emphasis was placed on four main indicators of epidemiological situation regarding cancer in a particular country (in-

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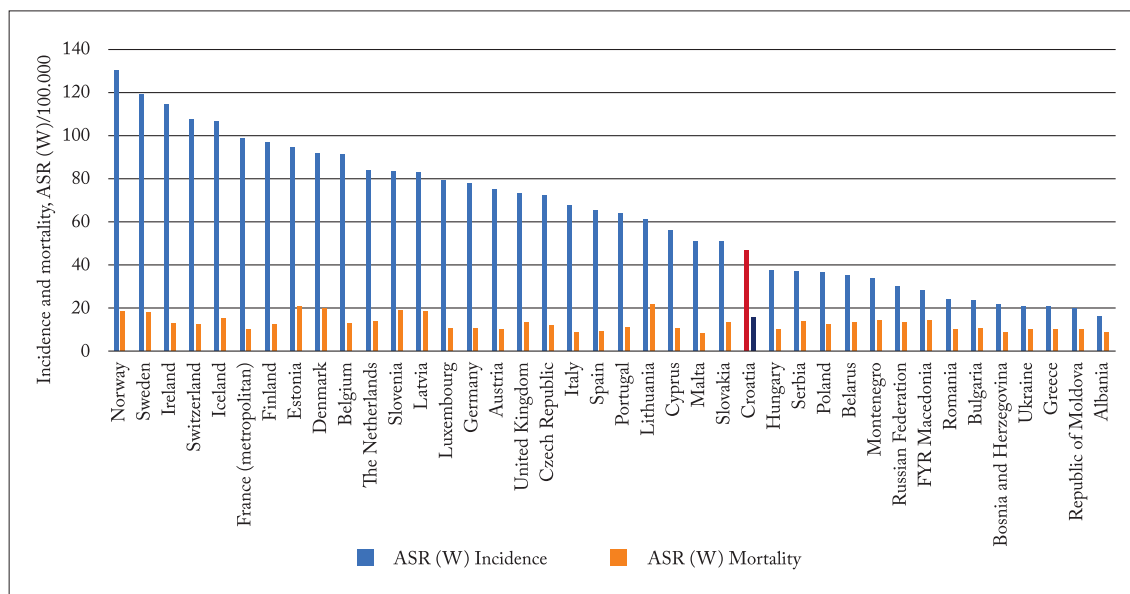


Fig. 1. Estimates of age standardized (ASR-W) rates of incidence and mortality for prostate cancer in 2012, according to GLOBOCAN 2012 (5)

idence, mortality, survival and prevalence) and we aimed to present the latest available data, the relative position of Croatia in comparison to other similar countries and trends over time (before and after the wider introduction of PSA testing in our country).

### Incidence of prostate cancer

According to estimates for 2012, there were more than a million (1,094,916; ASR=30.6/100,000) newly diagnosed cases of prostate cancer worldwide, and 307,481 deaths (ASR=7.8/100,000)<sup>1</sup>. Prostate cancer incidence shows substantial geographic differences, more than 25-fold variations between countries with the highest rates (such as France and Norway) and those with the lowest rates (Uzbekistan, Bangladesh, Nepal, Bhutan). Generally, more developed countries have higher incidence, and the rise in incidence rates coincides with the implementation of PSA testing in these countries. Only 30% of prostate cancer cases worldwide are diagnosed in less developed regions.

Incidence pattern in Europe also corresponds to the level of development – age-standardized incidence rates are higher in Western (ASR=85.8/100 000) and Northern Europe (ASR=85/100 000), and noticeably lower in Southern (ASR=58.6/100 000) and Central and Eastern Europe (ASR=31.3/100 000)<sup>5</sup>.

Compared to GLOBOCAN 2012 estimates for other European countries, Croatia has an intermediate incidence rate of prostate cancer<sup>5</sup>. With age-standardized rate (ASR) of 46.2/100 000, it is ranked 26th of 40 European countries (Fig. 1). The highest ASR of 129.7/100 000 was found in Norway and the lowest of 15.8/100 000 in Albania. With regard to mortality data, Croatia is ranked eighth, with ASR of 15.0/100 000. The highest rate of 21.4/100 000 was found in Lithuania, and the lowest of 7.8/100 000 in Malta (Fig. 1).

Virtually all European and other developed countries have experienced an increase in prostate cancer incidence<sup>6</sup>. The most prominent increase in the US occurred in the early 1990s, reaching its peak in this period as a result of the introduction of a larger-scale PSA testing<sup>7</sup>. Similar increases are described in some European countries; a publication by Center *et al.*<sup>6</sup> displayed that the average annual percent change in the most recent 10-year period was significantly increasing in 80% (32 out of 40) of investigated countries, with changes such as +8.2% in Denmark, +8.1% in Ireland, +4.3% in Norway and +16.4% in Lithuania. In Croatia, prostate cancer incidence in this 10-year period (1998–2007) increased by 8.5%; however, the beginning of this period directly corresponds to a wider introduction of PSA testing in Croatia<sup>8</sup>.

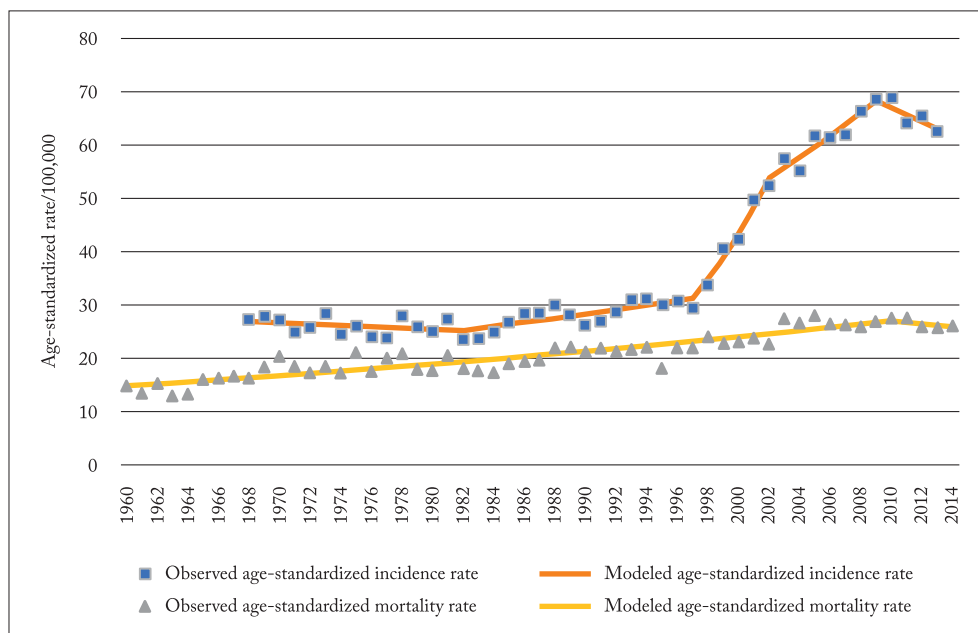


Fig. 2. Prostate cancer incidence (1968–2013) and mortality rate (1960–2014) trends in Croatia; adapted from (9)

When investigating a longer period of time, as was done in a recent publication with incidence trends in Croatia ranging back to 1968<sup>9</sup>, it is clear that until the introduction of PSA testing the trends were increasing modestly (APC of +1.4% in 1982–1997 period, 95%CI 0.7 to 2.1), followed by a steep increase in 1997–2002 (APC +11.5%, 95% CI 7.5 to 15.7), a moderate increase in the 2002–2009 period (APC +3.5%, 95% CI 1.9 to 5.1) and without significant change in trend in the 2009–2013 period (APC -2.0%, 95% CI -4.6 to 0.5) (Fig. 2). This analysis needs to be prolonged with more recent data in order to gauge the magnitude of changes in recent years and to estimate if the incidence of prostate cancer in Croatia has indeed, somewhat unexpectedly, reached its plateau.

The most recent available published data for prostate cancer incidence in Croatia from the Croatian National Cancer Registry<sup>10</sup> show that there were 1708 new cases of prostate cancer in Croatia in 2014; the crude rate was 82.7/100,000, the age-standardized rate (European Standard Population 1976) 64.8/100,000, and the cumulative incidence rate (0–74 years) was 5.5%.

### Prostate cancer mortality

Prostate cancer mortality rates and trends in Europe also differ according to regions, but differences are much

less pronounced than those in incidence. In countries that were EU members before 2004 (which is sometimes used as a proxy measure for more developed countries), the standardized death rate (SDR) decreased from 27.3/100,000 in 1992 to 19.1/100,000 in 2012 (11). In the same 20-year period mortality increased in countries that became EU members after 2004, from SDR=18.04/100,000 to SDR=21.3/100,000. According to the same source, prostate cancer mortality in Croatia increased from 22.8/100,000 in 1992 to 26.6/100,000 in 2012<sup>11</sup>.

Recent analysis of trends in prostate cancer mortality in Croatia<sup>9</sup> indicated that in the period from 1960–2010, prostate cancer mortality was increasing with a statistically significant annual percent change of +1.2% (95%CI 1.0 to 1.4); there was a joinpoint in 2010 and the trend in 2010–2014 period was statistically not significant (APC -1.2%, 95% CI -5.5 to 3.4).

The data for 2014, available at EUROSTAT webpage<sup>12</sup>, also indicate that Croatia is among top ten EU countries in prostate cancer mortality (Fig. 3), with the age-standardized mortality rate of 54.9/100,000 and share of all deaths in men of 3.0 in 2014. The share of all deaths in men that are attributable to prostate cancer ranged from 1.7% in Bulgaria to 5.6% in Sweden.

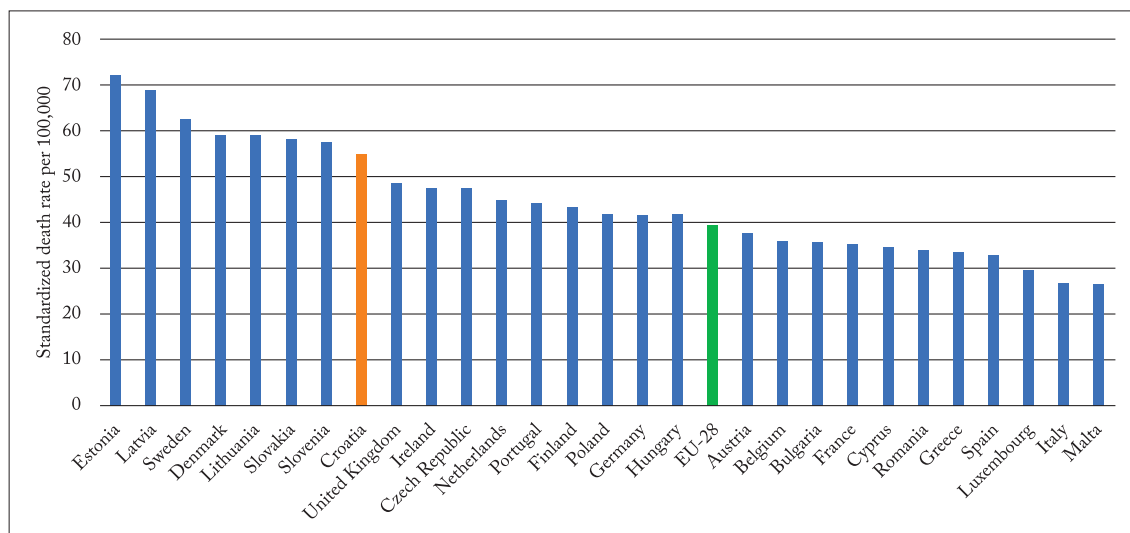


Fig. 3. Standardized mortality rates (ASR-E) for prostate cancer in EU countries, according to EUROSTAT (12)

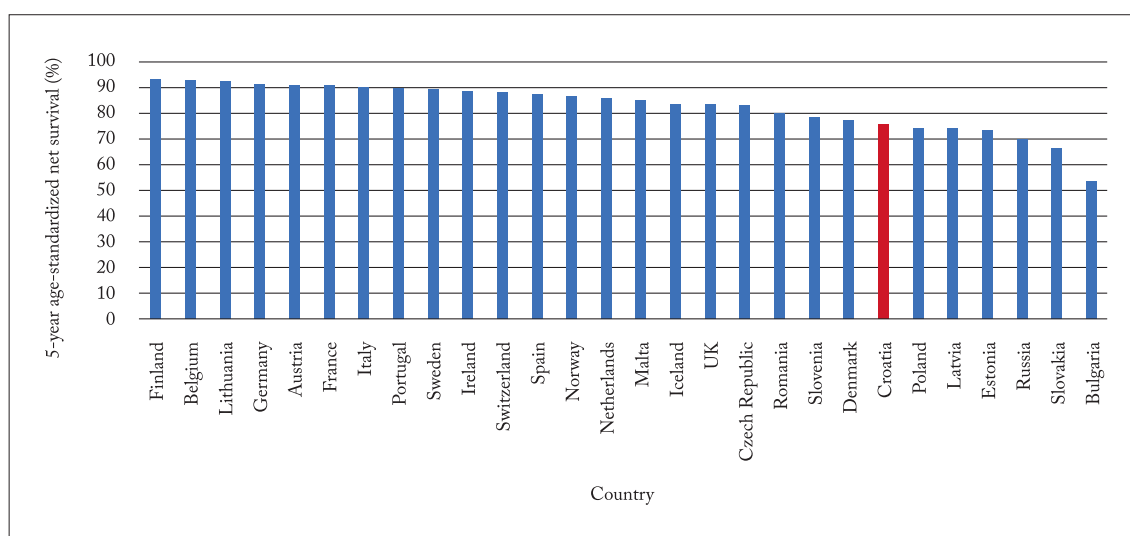


Fig. 4. Five-year age-standardized net survival of prostate cancer in European countries, according to CONCORD-2 study (13)

The latest available mortality data for Croatia show that there were 769 deaths resulting from prostate cancer in 2016, with the crude rate of 38.2/100.000.

### Prostate cancer survival

Prostate cancer survival can also be influenced by early detection of the disease, which can artificially lengthen survival time (lead-time bias). The amount of

PSA testing that is taking place in a country should always be taken into account when interpreting survival and trends in survival.

Recent data on prostate cancer survival from two major international studies show that survival in Croatia is below the European average. For men diagnosed between 2000 and 2007, the EUROCARE-5 study showed a 5-year relative survival of 71.2% in Croatia<sup>13</sup>, and the European average of 83.4%. the

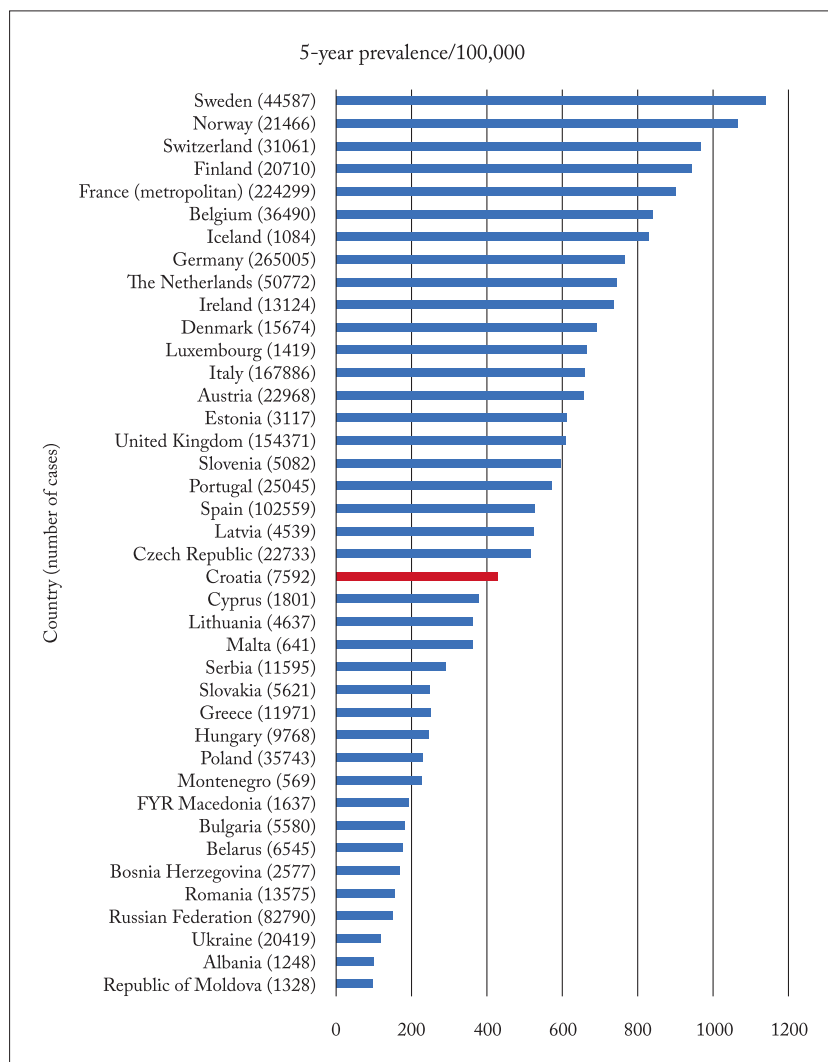


Fig. 5. Estimates of 5-year prevalence of prostate cancer in European countries, according to (5)

CONCORD-2 study<sup>14</sup> showed a 75.1% 5-year net survival for men diagnosed with prostate cancer in the 2005-2009 period, which is an improvement from the data for the periods 2000-2004 (67.7%) and 1995-1999 (61.4%); however, Croatia still has survival that is below the average of European countries (Fig. 4).

### Prostate cancer prevalence

The increasing number of prostate cancers being detected through higher uptake of PSA screening has repercussions not only on survival, but on the preva-

lence of prostate cancer as well. The latest estimates from the International Agency for Research on Cancer (GLOBOCAN 2012)<sup>5</sup> indicate that the highest 5-year prevalence (the number/rate of persons alive that were diagnosed in the last 5 years) in Europe was observed in Sweden, Norway and Switzerland, where around 1/100 of all men were diagnosed with prostate cancer in the past 5 years (Fig. 5). The lowest 5-year prevalence was observed in the Republic of Moldova, Albania and the Ukraine, where around 1 in 1000 men were diagnosed with prostate cancer in the past 5 years. Croatia is ranked in the middle, with the rate of 426.7/100.000 (Figure 5).

## PSA testing in Croatia and screening possibilities

While the highly cited US Preventive Services Task Force (USPSTF) recommendations in 2012 advised against prostate cancer screening due to concerns that a significant proportion of screening-detected cancers may be overdiagnosed and overtreated, the 2017 draft of the recommendations suggested an individualized decision-making about screening for prostate cancer after a discussion with a clinician for men between the ages of 55–69<sup>15</sup>. Future studies and pilot projects in this field are needed, while modelling and microsimulation studies suggest various possible approaches depending on the context in which the screening could be done<sup>3,15,16</sup>.

A recent position paper<sup>3</sup> suggested that starting a pilot programme involving a limited age-group could be the next step in the control of prostate cancer, while future developments in active surveillance, stratified screening strategies along with advances in biomarkers and risk prediction may further improve the cost-effectiveness by improving the benefits and harms ratio. Also, the recent re-analysis of PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) and ERSPC (European Randomized Study of Screening for Prostate Cancer) data via mean lead times indicated that, contrary to previously published data, when differences in the settings and implementation of the trials are controlled for, both of these studies provide evidence in favour of prostate cancer mortality reduction with screening<sup>17</sup>.

Other approaches, such as the so-called “basal PSA testing”, should also be taken into account. According to the works of Vickers and Lilja<sup>18,19</sup>, by adopting the “basal PSA-testing” strategy in the late forties, we could identify the population at the highest risk of prostate cancer development in the following years. Such an approach, coupled with a less frequent use of PSA testing at older age, might be useful in the reduction of PSA overutilization and the introduction of more rational and efficient principles in the field of early diagnosis of high-risk prostate cancer. The dogmatic practice of regular annual PSA testing for every man over 50 that has been in practice in Croatia, regardless of recent and previous PSA values, has not met the expectations regarding improvement in the public health burden of prostate cancer.

In Croatia, PSA testing was widely introduced in the late 1990s and is currently applied as a mode of

opportunistic screening in men aged 50 and over, defined as individual case findings initiated by the patient and/or his physician. A debate involving all relevant stakeholders in Croatia on the benefits and harms of implementing/starting a possible different prostate cancer screening programme should be initiated, with relevant national organisations and professional societies and committees leading the way towards the implementation of the best possible scenario in the Croatian setting.

## Summary

Croatia is a country with an intermediate incidence of prostate cancer (in comparison to other European countries), but high prostate cancer mortality. Increasing trends in incidence are expected, while there are no indications of decreasing trends in mortality which have been observed in other similar countries. The prevalence of prostate cancer in Croatia is average, while survival rates are below those of comparable European countries.

Although there are no reliable data on the uptake of PSA testing in Croatia, this combination of basic epidemiological parameters indicates that there is room for improvement regarding the overall prognosis and risks associated with prostate cancer in Croatian population. The combination of adopting new approaches in finding prostate cancer earlier in patients who would benefit most from it and following European trends in the diagnostics and treatment of detected prostate cancer should be the way to move forward.

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## Sažetak

## EPIDEMIOLOGIJA RAKA PROSTATE U HRVATSKOJ - STANJE I PERSPEKTIVE

*A. Reljić, P. Čukelj, I. Tomašković, B. Ružić i M. Šekerija*

Rak prostate predstavlja značajan javnozdravstveni problem, kako u Hrvatskoj, tako i u drugim razvijenim zemljama. Cilj ovog članka je prikazati trenutnu epidemiološku situaciju povezanu s rakom prostate u Hrvatskoj u usporedbi s drugim sličnim zemljama korištenjem osnovnih epidemioloških indikatora kao što su incidencija, mortalitet, prevalencija i preživljenje, te razmotriti koje su daljnje mogućnosti za poboljšanje istih. Incidencija raka prostate u Hrvatskoj je u značajnom porastu od sredine 90-tih godina; posljednji dostupni podaci ukazuju da je taj trend potencijalno dosegao plato. Podaci o mortalitetu pokazuju stalan rast od 1960-ih, no iako vidimo stabilizaciju tog trenda u posljednjem periodu, Hrvatska je i dalje među prvih deset zemalja u Europi po smrtnosti od raka prostate. Procijenjeno je da je petogodišnja prevalencija u 2012. iznosila 7.592 slučaja (426.7/100.000), što Hrvatsku smješta u sredinu europskih zemalja prema bazi podataka GLOBOCAN 2012. Petogodišnje preživljenje od raka prostate, prema istraživanju CONCORD-2, iznosi 75.1%, što je niže od preživljenja u nama sličnim europskim zemljama. Epidemiološki trendovi raka prostate u Hrvatskoj pokazuju relativno nisku incidenciju, dok prema podacima o mortalitetu i preživljenju vidimo da postoji mnogo mjesta za napredak. U svjetlu nedavnih diskusija o modelu ranog otkrivanja raka prostate, potrebno je održati i poticati raspravu o ulozi PSA testiranja u Hrvatskoj.

Ključne riječi: *Rak prostate; Hrvatska; Incidencija; Mortalitet; Preživljenje; PSA testiranje*