Incidence and mortality trends of gastric and colorectal cancers in Croatia, 1988-2008

**Aim** To estimate the incidence and mortality trends of gastric and colorectal cancers in Croatia between 1988 and 2008.

**Methods** Incidence data for the period 1988-2008 were obtained from the Croatian National Cancer Registry. The number of deaths from gastric and colorectal cancers were obtained from the World Health Organization mortality database. Joinpoint regression analysis was used to describe changes in trends by sex.

**Results** Gastric cancer incidence rates declined steadily during the study period, with estimated annual percent change (EAPC) of -3.2% for men and -2.8% for women. Mortality rates in men decreased, with EAPC of -5.0% from 1988-1995 and -2.5% from 1995-2008. Mortality rates in women decreased, with EAPC of -3.2% throughout the study period. For colorectal cancer in men, joinpoint analysis revealed increasing trends of both incidence (EAPC 2.9%) and mortality (EAPC 2.1%). In women, the increase in incidence was not significant, but mortality rates in the last 15 years showed a significant increase (EAPC 1.1%).

**Conclusion** The incidence and mortality trends of gastric cancer in Croatia are similar to other European countries, while the still increasing colorectal cancer mortality calls for more efficient prevention and treatment.
The two most important gastrointestinal cancers in Croatia are gastric and colorectal cancer, which together contribute to about one fifth of Croatian cancer incidence and mortality (1).

Gastric cancer

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death worldwide (1,2), with high case fatality rate and five-year survival of less than 20% (3). It displays a substantial geographic variability across the continents, with rates in Asia, some parts of Eastern Europe, and Latin America being several times higher than those in western countries (2).

The etiology of gastric cancer has not been entirely elucidated. The most common risk factors reported in the literature are chronic mucosal infection with Helicobacter pylori (4), consumption of salt and salt-preserved foods (5), low socio-economic status (6), presence of contaminants in drinking water (7,8), smoking (9), and certain occupational exposures (10,11).

During the second half of the 20th century, incidence and mortality rates of gastric cancer have declined steeply throughout Europe (12,13) and around the world (14), mainly as a result of the remarkable improvement in the living conditions (15-18). This improvement may have contributed to a declining prevalence of H. Pylori infection in younger birth cohorts (19) and the use of eradication therapy in older cohorts may have further contributed to the lowering of incidence and mortality rates (20). H. Pylori infection plays an important role in the sequence of events that can lead to gastric cancer and is classified as a type I carcinogen according to the International Agency for Research on Cancer criteria (4).

According to the most recent data from the Croatian National Cancer Registry, the gastric cancer crude incidence rate per 100,000 men in 2008 was 29.0 (617 cases), making it the fifth most common cancer; for women the rate was 17.0 per 100,000 (390 cases), making it the eighth most common cancer (21). Among cancer-related causes of death in 2008, gastric cancer ranked fourth both in men, with a crude mortality rate of 24.2 per 100,000 (514 deaths), and in women, with a crude mortality rate of 15.9 per 100,000 (364 deaths) (22).

Colorectal cancer

Colorectal cancer is a major global public health problem, with approximately 950,000 newly diagnosed cases each year (1). The risk of colorectal cancer increases steeply with age, and in many developed countries colorectal cancer burden is increasing with increasing life expectancy. The incidence is also increasing in many developing countries, as diet and lifestyle become more similar to those in developed countries. Colorectal cancer five-year relative survival in Europe for both sexes combined is 56.2% (23).

Family history of hereditary colorectal cancer is a recognized risk factor, accounting for 15%-20% of cases at the population level (24). Additional 6% excess risk can be attributed to genetic predisposition due to common causal variants in the genome (25-29). Increased colorectal cancer risk is also associated with dietary factors such as high fat and red meat consumption and low vegetable intake, as well as with physical inactivity, excess body weight, and high alcohol consumption (30). On the other hand, it has been inversely associated with the use of exogenous female hormones (31).

Western European countries introduced the secondary cancer prevention in mid-2000s, most often based on fecal occult blood test followed by colonoscopy (32). Croatia initiated the national colorectal cancer screening program in 2007. Apart from active screening, changes in colorectal cancer trends worldwide could be attributed to standardization and availability of evidence-based surgical, chemo-, and radiotherapy (33,34).

The aim of this study was to analyze gastric and colorectal cancer incidence and mortality trends in Croatia from 1988 to 2008 for both sexes, and to evaluate these findings in comparison to other European countries and in the context of changing environmental and social conditions, with possible implications for the health policies.

METHODS

Data sources

Incidence data for the period 1988-2008 were obtained from the Croatian National Cancer Registry. The Registry, founded in 1959, covers the whole Croatian population (approximately 4.4 million persons) and relies on mandatory cancer notifications from primary and secondary health care sources and death certificates from the Croatian Bureau of Statistics. The Registry contributed data to the last three volumes of the Cancer incidence in Five Continents series (35-37). In addition to incidence data, these publications report indices
of data quality (proportion of morphologically verified cases, proportion of cases registered from death certificates only, and mortality to incidence ratio). At the Registry, gastric cancer was defined as ICD-9 (38) code 151 from 1988 to 2000 and ICD-10 (39) code C16 from 2001 to 2008. Colorectal cancer was defined as cancer of the hepatic flexure (153.0), transverse colon (153.1), cecum (153.4), appendix (153.5), ascending colon (153.6), splenic flexure (153.7), descending colon (153.2), sigmoid colon (153.3), recto sigmoid junction (154.0), rectum (154.1), and unspecified (153.8 and 153.9) in ICD-9; and the colon (C18.0-C18.9), recto sigmoid junction (C19.0-C19.9), rectum (C20.0-C20.9), and anus (C21) in ICD-10. The number of deaths from gastric and colorectal cancer as the underlying cause were obtained from the World Health Organization mortality database (40). For calculating age-specific rates, we used the population estimates from the Population Division of the Department of Economic and Social Affairs of the United Nations (41).

Statistical analysis

Age-standardized rates of cancer incidence in Croatia were calculated by the direct standardization method, using the world standard population as a reference (42). To describe incidence and mortality time trends, we carried out joinpoint regression analysis using the software Joinpoint Regression Program, Version 3.5.0. April 2011 (43). The analysis included the logarithmic transformation of the rates, standard error, maximum number of five joinpoints, and minimum of four years between two joinpoints. All other program parameters were set to default values. The aim of the approach is to identify possible joinpoints where a significant change in the trend occurs. The method identifies joinpoints based on regression models with 0-5 joinpoints. The final model selected was the most parsimonious of these, with the estimated annual percent change (EAPC) -3.2%; 95% confidence interval [CI], -3.6 to -2.7, with the best fitting model having no joinpoints, while mortality rates decreased sharply between 1988 and 1995 (EAPC -5.0%; 95% CI, -6.5 to -3.4) and then less sharply between 1995 and 2008 (EAPC -2.5%; 95% CI, -3.1 to -1.8). In women, incidence rates decreased (EAPC -2.8%; 95% CI, -3.5 to -2.2), also with no joinpoints in the final model, and the mortality rates de-

### RESULTS

#### Gastric cancer

During the period 1988-2008, there were 25 183 cases of gastric cancer and 21 313 deaths. The age-standardized incidence rate per 100 000 decreased from 29.5 in the first 5-year period (1988-1992) to 16.9 in the last 5-year period (2004-2008) in men (43%), and from 11.7 to 7.0 in women (40%). The age-standardized mortality rate per 100 000 decreased from 25.2 to 14.8 in men (41% decrease), and from 10.0 to 5.8 in women (42% decrease) (Tables 1 and 2).

In both sexes, gastric cancer incidence and mortality rates declined steadily (Figure 1 and 2). In men, incidence rates decreased over the entire period (EAPC -3.2%; 95% confidence interval [CI], -3.6 to -2.7), with the best fitting model having no joinpoints, while mortality rates decreased sharply between 1988 and 1995 (EAPC -5.0%; 95% CI, -6.5 to -3.4) and then less sharply between 1995 and 2008 (EAPC -2.5%; 95% CI, -3.1 to -1.8). In women, incidence rates decreased (EAPC -2.8%; 95% CI, -3.5 to -2.2), also with no joinpoints in the final model, and the mortality rates de-

#### TABLE 1. Male gastric cancer incidence and mortality in Croatia in the period 1988-2008. Number of cases, crude rate and age standardized rate (ASR) per 100 000 (using world standard population)

| Year | Incidence | Mortality |
|------|-----------|-----------|
|      | N   | crude rate | ASR | N   | crude rate | ASR |
| 1988 | 847 | 39.0 | 30.9 | 736 | 33.9 | 26.8 |
| 1989 | 844 | 38.8 | 29.8 | 752 | 34.5 | 26.9 |
| 1990 | 872 | 39.9 | 31.2 | 726 | 33.2 | 25.9 |
| 1991 | 821 | 37.3 | 28.6 | 719 | 32.7 | 24.8 |
| 1992 | 786 | 35.5 | 26.7 | 621 | 28.0 | 21.4 |
| 1993 | 704 | 31.5 | 23.2 | 678 | 30.4 | 22.3 |
| 1994 | 754 | 33.6 | 24.1 | 634 | 28.2 | 20.1 |
| 1995 | 756 | 33.6 | 23.0 | 635 | 28.2 | 19.4 |
| 1996 | 720 | 32.1 | 21.7 | 606 | 27.0 | 18.4 |
| 1997 | 782 | 35.1 | 23.1 | 627 | 28.1 | 18.6 |
| 1998 | 683 | 30.9 | 20.0 | 610 | 27.6 | 17.6 |
| 1999 | 831 | 38.0 | 24.3 | 634 | 29.0 | 18.4 |
| 2000 | 719 | 33.1 | 20.8 | 610 | 28.1 | 17.7 |
| 2001 | 710 | 32.9 | 20.4 | 573 | 26.5 | 16.2 |
| 2002 | 711 | 33.1 | 20.1 | 580 | 27.0 | 16.3 |
| 2003 | 718 | 33.5 | 19.9 | 617 | 28.8 | 16.7 |
| 2004 | 662 | 30.9 | 18.1 | 610 | 28.5 | 16.4 |
| 2005 | 667 | 31.2 | 17.8 | 556 | 26.0 | 14.9 |
| 2006 | 604 | 28.3 | 16.1 | 539 | 25.3 | 14.1 |
| 2007 | 628 | 29.5 | 16.4 | 578 | 27.1 | 15.3 |
| 2008 | 617 | 29.0 | 16.0 | 514 | 24.2 | 13.1 |
increased over the entire period (EAPC -3.2%; 95% CI, -3.7 to -2.7) (Table 3).

Colorectal cancer

From 1988 to 2008, there were 25,964 cases of colorectal cancer in men (Table 4). The number of male colorectal cancer cases increased more than 2-fold, from 767 in 1988 to 1818 in 2008, while ASR increased from 27.8 to 47.5. In that period, 15,983 male colorectal cancer patients died. The number of colorectal cancer deaths doubled, from 509 in 1988 to 1052 in 2008, while ASR increased from 19.0 to 26.0/100,000. Joinpoint analysis in men did not identify any joinpoints (Table 5 and Figure 3). The inci-

| Year | Incidence | Mortality |
|------|-----------|-----------|
| 1988 | 541       | 482       |
| 1989 | 527       | 458       |
| 1990 | 556       | 469       |
| 1991 | 503       | 432       |
| 1992 | 460       | 372       |
| 1993 | 436       | 398       |
| 1994 | 447       | 388       |
| 1995 | 504       | 394       |
| 1996 | 494       | 408       |
| 1997 | 404       | 393       |
| 1998 | 432       | 389       |
| 1999 | 466       | 349       |
| 2000 | 516       | 359       |
| 2001 | 474       | 374       |
| 2002 | 474       | 395       |
| 2003 | 435       | 378       |
| 2004 | 430       | 357       |
| 2005 | 397       | 350       |
| 2006 | 374       | 317       |
| 2007 | 397       | 332       |
| 2008 | 390       | 364       |

TABLE 4. Male colorectal cancer incidence and mortality in Croatia in the period 1988-2008. Number of cases, crude rate, and age standardized rate (ASR) per 100 000 (using world standard population)

| Year | Incidence | Mortality |
|------|-----------|-----------|
| 1988 | 767       | 509       |
| 1989 | 729       | 535       |
| 1990 | 837       | 523       |
| 1991 | 780       | 522       |
| 1992 | 886       | 582       |
| 1993 | 876       | 601       |
| 1994 | 947       | 601       |
| 1995 | 1096      | 631       |
| 1996 | 1076      | 702       |
| 1997 | 1172      | 718       |
| 1998 | 1198      | 758       |
| 2000 | 1503      | 841       |
| 2001 | 1369      | 770       |
| 2002 | 1544      | 885       |
| 2003 | 1482      | 956       |
| 2004 | 1556      | 898       |
| 2005 | 1609      | 998       |
| 2006 | 1595      | 1028      |
| 2007 | 1626      | 982       |
| 2008 | 1818      | 1052      |

FIGURE 1. Joinpoint analyses of incidence (rhombus) and mortality (triangles) for gastric cancer in Croatia in the period 1988-2008 for men. ASR (W) – age-standardized rate per 100 000 (using world standard population).

that period, 15,983 male colorectal cancer patients died. The number of colorectal cancer deaths doubled, from 509 in 1988 to 1052 in 2008, while ASR increased from 19.0 to 26.0/100,000. Joinpoint analysis in men did not identify any joinpoints (Table 5 and Figure 3). The inci-

| Year | Incidence | Mortality |
|------|-----------|-----------|
| 1988 | 35.3      | 23.4      |
| 1989 | 33.5      | 24.6      |
| 1990 | 38.3      | 23.9      |
| 1991 | 35.5      | 23.7      |
| 1992 | 40.0      | 26.3      |
| 1993 | 39.2      | 26.9      |
| 1994 | 42.2      | 26.8      |
| 1995 | 48.7      | 28.0      |
| 1996 | 48.0      | 31.3      |
| 1997 | 52.6      | 32.2      |
| 1998 | 54.3      | 34.3      |
| 1999 | 68.5      | 36.6      |
| 2000 | 69.3      | 38.8      |
| 2001 | 63.4      | 35.7      |
| 2002 | 71.8      | 41.2      |
| 2003 | 69.1      | 44.6      |
| 2004 | 72.6      | 41.9      |
| 2005 | 75.2      | 46.7      |
| 2006 | 74.7      | 48.2      |
| 2007 | 76.3      | 46.1      |
| 2008 | 85.5      | 49.5      |
The incidence trend significantly increased (EAPC 2.9%; 95% CI, 2.3 to 3.9%), as well as the mortality trend (EAPC 2.1%; 95% CI, 1.7 to 2.4%).

There were 20,752 cases of female colorectal cancer (Table 6). From 1988 to 2008, the number of cases increased almost 2-fold, from 685 to 1,254. The ASR increased from 16.4/100,000 to 23.4/100,000. In the same period, 12,999 female colorectal cancer patients died. The number of colorectal cancer deaths increased from 508 in 1988 to 803 in 2008, while ASR increased from 11.9/100,000 to 13.1/100,000. Joinpoint analysis of female colorectal cancer incidence trends (Table 5 and Figure 4) identified two joinpoints, in 1996 and 1999, resulting in three separate trends: from 1988 to 1996

### Table 6. Female colorectal cancer incidence and mortality in Croatia in the period 1988-2008. Number of cases, crude rate, and age standardized rate (ASR) per 100,000 (using world standard population)

| Year | Incidence N | crude rate / 100,000 | Incidence AsR / 100,000 | Mortality N | crude rate / 100,000 | Mortality AsR / 100,000 |
|------|-------------|----------------------|-------------------------|-------------|----------------------|-------------------------|
| 1988 | 685         | 29.6                 | 16.4                    | 508         | 21.9                 | 11.91                   |
| 1989 | 770         | 33.2                 | 17.9                    | 556         | 24.0                 | 12.66                   |
| 1990 | 811         | 34.8                 | 19.4                    | 525         | 22.5                 | 11.68                   |
| 1991 | 734         | 31.3                 | 17.1                    | 545         | 23.2                 | 12.34                   |
| 1992 | 766         | 32.3                 | 17.4                    | 518         | 21.8                 | 11.27                   |
| 1993 | 755         | 31.5                 | 16.8                    | 518         | 21.6                 | 10.90                   |
| 1994 | 827         | 34.3                 | 17.9                    | 530         | 22.0                 | 10.97                   |
| 1995 | 823         | 34.0                 | 17.1                    | 540         | 22.3                 | 10.88                   |
| 1996 | 824         | 34.2                 | 17.0                    | 553         | 22.9                 | 10.79                   |
| 1997 | 963         | 40.2                 | 20.5                    | 570         | 23.8                 | 11.60                   |
| 1998 | 986         | 41.5                 | 20.2                    | 604         | 25.4                 | 11.67                   |
| 1999 | 1186        | 50.4                 | 25.1                    | 639         | 27.2                 | 12.50                   |
| 2000 | 1197        | 51.3                 | 24.0                    | 668         | 28.6                 | 12.59                   |
| 2001 | 1072        | 46.2                 | 21.7                    | 640         | 27.6                 | 11.62                   |
| 2002 | 1116        | 48.2                 | 22.6                    | 673         | 29.1                 | 12.59                   |
| 2003 | 1213        | 52.5                 | 23.5                    | 666         | 28.8                 | 11.84                   |
| 2004 | 1143        | 49.5                 | 22.0                    | 666         | 28.9                 | 11.59                   |
| 2005 | 1237        | 53.7                 | 23.7                    | 749         | 32.5                 | 12.38                   |
| 2006 | 1175        | 51.1                 | 21.9                    | 772         | 33.6                 | 12.84                   |
| 2007 | 1215        | 52.9                 | 22.9                    | 756         | 32.9                 | 12.51                   |
| 2008 | 1254        | 54.7                 | 23.4                    | 803         | 35.0                 | 13.07                   |
the trend was stable (EAPC -0.2%; 95% CI, -1.9 to 1.6%), from 1996 to 1999 the trend showed a non-significant increase (EAPC 10.6%; 95% CI, -3.7 to 27.1%), and from 1999 to 2008 the trend was again stable (EAPC -0.5; 95% CI, -1.7 to 0.7%). AAPC for the period from 1996 (when the first increase in incidence was noted) to 2008 showed a non-significant increase (AAPC 2.2%; 95% CI, -1.1 to 5.6%). Joinpoint analysis of female colorectal cancer mortality identified one joinpoint in 1994, resulting in two separate trends: the trend from 1988 to 1994 showed non-significant decrease (EAPC -1.9%; 95% CI, -4.1 to 0.3%), while from 1994 to 2008 it showed a significant increase (EAPC 1.1%; 95% CI, 0.5 to 1.7%).

DISCUSSION

This is the first study to systematically analyze the time trends of gastric and colorectal cancer incidence and mortality in Croatia. We chose to use joinpoint regression modeling as the optimal method to detect and depict sharp changes in trends, reflecting changes in cancer prevention and care policies.

Gastric cancer

Our analysis revealed a persistent and steady decrease in gastric cancer incidence and mortality rates in Croatia between 1988 and 2008, with rates at the end of the study period being ~40% lower than at the beginning. The decrease was observed in both men and women, and the trends did not level off in the recent years. Croatia is in the upper half of the list of European countries according to age-standardized gastric cancer incidence and mortality rates for both men and women. According to the GLOBOCAN database, the highest incidence and mortality rates in Europe are observed in Belarus, Albania, and Russian Federation (incidence rates between 25-34/100000 in men and 12-18/100000 in women; and mortality rates between 21-30/100000 in men and 10-15/100000 in women), with much higher rates in Central and Eastern European countries than in more developed Western or Northern European countries (1).

In the EU from 1980 to 1999, a steady and persistent decrease in gastric cancer mortality rates was observed (from 18.6 to 9.8/100 000 in men and from 8.9 to 4.6/100 000 in women, ~50% for each sex) (13,46). Decreases were also reported between 2000 and 2005 (47). The reasons for the decrease are complex, and not completely understood. They include more varied and better nutrition, better food preservation (refrigeration), decreased prevalence of H. pylori infection due to improved living conditions and changes in lifestyle (48-50), and, at least to some extent, decreased smoking prevalence in men (51). The lowering of incidence rates leads to lowering of mortality rates, with a possible contribution of improved medical treatment (52).

During the second half of the twentieth century, Croatian society experienced both industrial and nutritional changes. The availability of various food products, such as fruits and products of animal origin, was facilitated by the introduction of refrigerators (53). Progressive globalization after the war in Croatia (1991-1995) led to a smaller need for homemade food production, which was heavily salted, marinated, and low in antioxidants (54).

The prevalence of H. Pylori infection in Croatia in 1998 in a random sample of individuals aged 20-70 was 60.4%, with higher rates in the southern parts of the country (55). This is considered to be an average value, since the prevalence ranges from 30% in the western countries to 60%-88% in Asian countries (56). Unfortunately, more recent data for Croatia are not available.

The prevalence of smoking in 1995 was 34% among men and 27% among women in 18-65 age group (57), while the prevalence in 2003 was 34% among men and 22% among women in 18+ age group (58). The relatively stable proportion of smokers in Croatia may indicate that the lowering of gastric cancer rates was not influenced by changes in smoking habits.
The use of joinpoint regression model allows a fresh approach to interpretation of trends in cancer mortality over a longer time period. This study, as well as other studies of gastric cancer trends (13,14), shows a decline in mortality, with no signs of leveling off in the recent years. Thus, it is expected that the decrease in incidence and mortality rates will continue (59), especially because such decreases are also observed in the countries that already have relatively low gastric cancer incidence and mortality rates, such as Iceland, Cyprus, and Sweden (incidence rates between 4.7-6.6 /100,000 in men and between 2.5 and 3.1/100,000 in women; and mortality rates between 4.1-4.2/100,000 in men and between 1.8-2.4/100,000 in women) (1).

Colorectal cancer

The incidence trend of colorectal cancer showed a significant increase in men (EAPC 2.9%). In women, there was no significant change in trend, though there was a constant non-significant increase. In 2008, with 1818 new cases colorectal cancer was the third most common cancer in Croatian male population and with 1052 deaths, the second cause of cancer mortality (21). In women, with 1254 new cases it was the second most common cancer, and with 803 deaths the second cause of cancer death. Compared to GLOBOCAN 2008 estimates for Europe, Croatia ranked ninth according to incidence of colorectal cancer (ASR 44.4/100,000) in men and fifteenth (ASR 24.3/100,000) in women, but fourth according to mortality in both men (ASR 25.4/100,000) and women (ASR 13.1/100,000) (1).

Incidence trends vary across Europe, with persistent increases or no change in Eastern European countries and persistent slight decreases in Western Europe (17). The increase in the incidence in Eastern Europe (eg, Slovakia or Czech Republic, as well as Croatia) could be attributed to lifestyle changes, presumably introduced by westernization, resulting in obesity and physical inactivity (60). In fact, in 2003 over 1.3 million people in Croatia were either obese or overweight (61). The observed variations of the incidence rates of colorectal cancer reflect the distributions of risk factors across European countries, as well as disparities in the effective cancer prevention and detection (62). However, such results should be interpreted with caution since all registries from which the data have been obtained do not comply with quality requirements, and a substantial number of Eastern European countries eg, Greece, Bosnia and Herzegovina, FYR Macedonia, and Romania, do not have established national cancer registration (63).

In the European Union, colorectal cancer mortality has been declining since the early 1980s by around 1% per year in women, and since the early 1990s by 0.6% per year in men (64). Decreases were found in Austria, Finland, Ireland, Netherlands, Norway, Sweden, Switzerland, United Kingdom, France, and Italy, and even earlier in Belgium, Germany, and Denmark (65). On the other hand, increases were observed in Bulgaria, Poland, Romania, Greece, Portugal, and Spain. In the Czech Republic, Slovakia, and Hungary, the rates were exceedingly high, but remained constant in the recent years (65).

Incidence and the mortality rates may also be affected by screening and early detection. All but three countries (Greece, Russia, and Turkey) (66-68) participate in some form of colorectal cancer screening. However, only five European countries have an organized population-based screening program (Croatia, Finland, France, Italy, the UK) (69-72) and only five have screening guidelines – Finland, France, Germany, (73) Italy, and the UK. There is still room for improvement since the participation rate in the voluntary screening is 15% and up to 60% in the organized screening programs (74). In the Croatian national screening, the participation rate was 19.9% (69).

Several randomized trials and one Cochrane review provided strong evidence that fecal occult blood test followed by colonoscopy, if offered every 2 years, reduced mortality rates associated with colorectal cancer by 16% (75,76). In the United States, where screening was introduced in the 1970s, long-term screening programs have played a relevant role in reducing colorectal cancer incidence and mortality over the last two decades. One of the explanations for better survival rates in the United States is an increased detection and removal of colorectal polyps, which often precede colorectal cancer development. Screening programs have been implemented in Europe, including Croatia, only recently, so their impact on the incidence and mortality may become more visible in the future (76). Nevertheless, increased patient awareness of signs and symptoms, recognition in the primary care, and access to diagnostic modalities may have already played a role.

In the past ten years, countries across the EU have initiated national policies for improvement in diagnostics, referral, and assurance of quality of care in specialized centers with attending multidisciplinary cancer teams. The main goals were to improve survival and quality of life and to reduce regional differences in treatment options. Following the publication of the Campbell Report, the UK
has implemented specialization of cancer services, which proved to be closely related to a reduction in mortality. Another important step is the shortening of the period between the symptom appearance and the referral to diagnostics (33).

Another important factor that explains the observed patterns of survival and mortality, alongside screening, is the progress in therapy (77). The general improvement in surgical techniques for localized and metastatic tumors substantially prolonged survival (78,79). Only the adoption of surgical training (subspecialization) and pathological evaluation of specimens (quality control) in rectal cancer management resulted in an overall improvement in survival (34,80,81). The wider adoption of new treatment protocols and adjuvant therapies, including progressive increase in sequential adjuvant chemotherapy for advanced non-localized tumors, and preoperative chemo- and radiotherapy for rectal cancers (82), may have favorably influenced colorectal cancer mortality (47,77,83,84). Moreover, in the past fifteen years five new drugs have been introduced (85,86).

We believe that the discrepancy between the incidence (9th in male and 15th in female colorectal cancer) and mortality (4th for both sexes) rank of Croatia in Europe strongly indicates the need for improvement of prevention and treatment.

There are still no standardized protocols for treatment and referral, or requirements for the availability of multidisciplinary teams for colorectal cancer treatment in most Croatian hospitals, with the exception of university hospitals. Due to the high incidence and increasing mortality, Croatian Society of Coloproctology and Croatian Society of Oncology have launched an incentive for quality control and referral improvements for colorectal cancer patients, recognizing the current lack of availability of all treatment modalities at different hospitals (87). Hopefully, establishing accrediting centers for colorectal cancer treatment with trained staff would ensure that every patient receives optimal surgical, neo adjuvant or adjuvant treatment, systemic and local (radiotherapy), and regular follow-up.

Acknowledgment We thank Professor Branko Papa for critical reading of the manuscript and helpful suggestions.

Funding This study was partly supported by the Croatian Ministry of Science, Education and Sport grant No. 005-1080315-0294.

Ethical approval Not required.

Declaration of authorship IK performed the study design, data collection, data analysis, and manuscript editing and review. MS participated in the data collection, interpretation of the results, manuscript preparation, manuscript editing and review of the manuscript. IS participated in data collection, interpretation of the results, manuscript preparation, manuscript editing, and manuscript review. AZ participated in study design and coordination, interpretation of the results, manuscript preparation, manuscript editing, and manuscript review. XK participated in study design, data collection, data analysis, manuscript editing, and manuscript review. AZ participated in study design and coordination, interpretation of the results, manuscript preparation, manuscript editing, and manuscript review. TK participated in study design, data collection, data analysis, manuscript editing, and manuscript review. A2 participated in study design and coordination, interpretation of the results, manuscript preparation, manuscript editing, and manuscript review.

Competing interests All authors have completed the Unified Competing Interest form at www.cmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr. Accessed: March 28, 2012.

2. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12:354-62. Medline:16489633

3. Verdeccchia A, Mariotto A, Gatta G, Bastamante-Teixeira MT, Ajiki W. Comparison of stomach cancer incidence and survival in four continents. Eur J Cancer. 2003;39:1603-9. Medline:12855268 doi:10.1016/S0959-8049(03)00360-5

4. Cancer WIAfRo, editor: IARC monographs on the evaluation of carcinogenic risks to humans: Shistosomes, Liver Flukes and Helicobacter pylori: Lyon (France): IARC; 1994.

5. Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. Int J Epidemiol. 1996;25:494-504. Medline:8671549 doi:10.1093/ije/25.3.494

6. Nagel G, Linseisen J, Boshuizen HC, Pera G, Del Giudice G, Westert GP, et al. Socioeconomic position and the risk of gastric and oesophageal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Int J Epidemiol. 2007;36:66-76. Medline:17227779 doi:10.1093/ije/dyl275

7. Barrett JH, Parslow RC, McKinney PA, Law GR, Forman D. Nitrate in drinking water and the incidence of gastric, esophageal, and brain cancer in Yorkshire, England. Cancer Causes Control. 1998;9:153-9. Medline:9578292 doi:10.1023/A:1008871826535

8. Morales-Suarez-Varela MM, Llopis-Gonzalez A, Tejerizo-Perez ML. Impact of nitrates in drinking water on cancer mortality in Valencia, Spain. Eur J Epidemiol. 1995;11:15-21. Medline:7489769 doi:10.1007/BF01719941

9. Tredaniel J, Boffetta P, Buiaiti E, Saracci R, Hirsch A. Tobacco smoking and gastric cancer: Review and meta-analysis. Int J Cancer. 1997;72:565-73. Medline:9259392 doi:10.1002/(SICI)1097-0215(19970807)72:4<565::AID-IJC3>3.0.CO;2-O

10. Aragones N, Pollan M, Gustavsson P. Stomach cancer and
Gastric and colorectal cancers in Croatia

Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008;19:689-701. Medline:18293090 doi:10.1007/s10552-008-9132-y

Hartgrink HH, Bonenkamp HJ, van de Velde CJ. Influence of surgery on outcomes in gastric cancer. Surg Oncol Clin N Am. 2000;9:97-117. Medline:10601527

La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk. Br J Cancer. 1990;62:136-7. Medline:2390474 doi:10.1038/bjc.1990.245

Kono S, Hirohata T. Nutrition and stomach cancer. Cancer Causes Control. 1996;7:41-55. Medline:8850434 doi:10.1007/BF00115637

Babus V, Presecki V, Katic M, Balija M, Zoric I, Kronja L, et al. Distribution of Helicobacter pylori infection in the adult population of Croatia [in Croatian]. Lijec Vjesn. 1997;119:139-42. Medline:9379819

Prinz C, Schwendy S, Voland P. H pylori and gastric cancer: shifting the global burden. World J Gastroenterol. 2006;12:5458-64. Medline:17006981

Turek S, Rudan I, Smolj-Naranvic S, Szirovita L, Cubrilro-Turek M, Zerjavic-hrabak V, et al. A large cross-sectional study of health attitudes, knowledge, behaviour and risks in the post-war Croatian population (the First Croatian health Project). Coll Antropol. 1996;7:41-55. Medline:8850434 doi:10.1007/bF00115637

Kovacic L, Gazdek D, Samardzic S. Croatian health survey: cigarette smoking [in Croatian]. Acta Med Croatica. 2007;61:281-5. Medline:17629103

Amiri M, Janssen F, Kunst AE. The decline in stomach cancer mortality: exploration of future trends in seven European countries. Eur J Epidemiol. 2011;26:23-8. Medline:21086022 doi:10.1007/s10654-010-9522-9

Zatorski W, Didkowska J. Closing the gap: cancer in Central and Eastern Europe (CEE). Eur J Cancer. 2008;44:1425-37. Medline:18358713 doi:10.1016/j.ejca.2008.02.014

Heim I, Leontic K, Gostovic MJ. Obesity and overweight in Croatia [in Croatian]. Acta Med Croatica. 2007;61:267-73. Medline:17629101

Lopez-Abente G, Ardanaz E, Torrella-Ramos A, Mateos A, Delgado-Sanz C, Chiriqula MD. Changes in colorectal cancer incidence and mortality trends in Spain. Ann Oncol. 2010;21 Suppl 3:i376-82. Medline:20423764 doi:10.1093/annonc/mdp091

Zatorski W, Didkowska J. Closing the gap: cancer in Central and Eastern Europe (CEE). Eur J Cancer. 2008;44:1425-37. Medline:18358713 doi:10.1016/j.ejca.2008.02.014

European Network of Cancer Registries. Available from: http://www.encr.com.fr/. Accessed: April 5, 2012.

La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol. 2010;21:1323-60. Medline:19948741 doi:10.1093/annonc/mdp530

Fernandez E, La Vecchia C, Gonzalez JR, Lucchini F, Negri E, Levi F. Converging patterns of colorectal cancer mortality in Europe. Eur J Cancer. 2005;41:430-7. Medline:15691644 doi:10.1016/j.ejca.2004.11.014
Geitona M, Kanavos P. Colorectal cancer management and prevention policies in Greece. Eur J Health Econ. 2010;10 Suppl 1:59-65. Medline:20012668 doi:10.1007/s10198-009-0197-7

Katičić M, Antoljak N, Strnad Pešikan M, Kujundžić M, Šimac D, Šmaja M, et al. National Colorectal Cancer Screening Program in Croatia 2007-2010. Bosn J Basic Med Sci. 2011;11 Suppl 1:567-72.

Chevreul K. Colorectal cancer in France. Eur J Health Econ. 2010;10 Suppl 1:515-20. Medline:20012142 doi:10.1007/s10198-009-0185-y

Masseria C. Colorectal cancer in Italy: a review of current national and regional practice on screening and treatment. Eur J Health Econ. 2010;10 Suppl 1:541-9. Medline:20012136 doi:10.1007/s10198-009-0191-0

Schurer W, Kanavos P. Colorectal cancer management in the United Kingdom: current practice and challenges. Eur J Health Econ. 2010;10 Suppl 1:585-90. Medline:20012128 doi:10.1007/s10198-009-0202-1

European Commission. Health in the European Union. Special Eurobarometer 272ve/Wave 66.2. 2007. Available from: http://ec.europa.eu/health/ph_publication/eb_health_en.pdf. Accessed: April 4, 2012.

Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ. 1998;317:559-65. Medline:9721111 doi:10.1136/bmj.317.7158.559

Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA Cancer J Clin. 2009;59:366-78. Medline:19897840 doi:10.3322/caac.20038

Cunningham D, Atkin W, Lenz HJ, Minsky B, Nordlinger B, et al. Colorectal cancer. Lancet. 2010;375:1030-47. Medline:20304247 doi:10.1016/s0140-6736(10)60535-4

Primrose J, Treasure T, Fioriello F. Lung metastasectomy in colorectal cancer: is this surgery effective in prolonging life? Respirology. 2010;15:742-6. Medline:20456671 doi:10.1111/j.1440-1843.2010.01759.x

Primrose JN. Surgery for colorectal liver metastases. Br J Cancer. 2010;102:1313-8. Medline:20424612 doi:10.1038/bjc.6605659

Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1:1479-82. Medline:2425199 doi:10.1016/s0140-6736(86)91510-2

Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study that recruited consecutive patients with rectal cancer. Ann Surg. 2011;2011:13. Epub ahead of print. Medline:21239985

Hospers GA, Punt CJ, Tesselaar ME, Cats A, Havenga K, Leer JW, et al. Preoperative chemoradiotherapy with capecitabine and oxaliplatin in locally advanced rectal cancer. A phase I-II multicenter study of the Dutch Colorectal Cancer Group. Ann Surg Oncol. 2007;14:2773-9. Medline:17653805 doi:10.1245/s10434-007-9396-6

Javle M, Hsueng CT. Recent advances in gastrointestinal oncology–updates and insights from the 2009 annual meeting of the American society of clinical oncology. J Hematol Oncol. 2010;3:11. Medline:20331897 doi:10.1186/1756-8722-3-11

de Leon MP, Pezzi A, Benatti P, Mancini A, Rossi G, di Gregorio C, et al. Survival, surgical management and perioperative mortality of colorectal cancer in the 21-year experience of a specialised registry. Int J Colorectal Dis. 2009;24:777-88. Medline:19280201 doi:10.1007/s00384-009-0687-1

Salf MW, Kang SP, Chu E. Treatment of metastatic colorectal cancer: from cytotoxic agents to molecular agents and multitargeted strategies. Oncology. 2006;20 Suppl 10:11-9. Williston Park. Medline:17354513

Lucas AS, O’Neill BH, Goldberg RM. A decade of advances in cytotoxic chemotherapy for metastatic colorectal cancer. Clin Colorectal Cancer. 2011;10:238-44. Medline:21820973 doi:10.1016/j.ccl.2011.06.012

Vrdoljak E, Plestina S, Dintinjana RD, Tomas I, Sobat H, Separovic R, et al. Clinical recommendations for diagnosis, treatment and monitoring of patients with colorectal cancer [in Croatian]. Lijec Vjesn. 2011;133:366-9. Medline:22329291