Analysis of cancer incidence and mortality in Bosnia and Herzegovina and comparison with Slovenia, Croatia and Serbia

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Abstract
Bosnia and Herzegovina (BiH) is a country in South-Eastern Europe, bordered by Croatia, Serbia and Montenegro. Bosnia and Herzegovina is divided into Federation of Bosnia and Herzegovina (FBiH), Republic of Srpska (RS) and Brčko District (BD). We carried analysis of data available from Public Health Institute of the Federation of Bosnia and Herzegovina, Public Health Institute of Republic of Srpska and from Agency for statistics of Bosnia and Herzegovina. From this analysis we assessed cancer incidence and mortality in Federation of Bosnia and Herzegovina, Republic of Srpska and Brčko District. After that we compared our data with other countries Croatia, Slovenia and Serbia. We developed multiple linear regression model for prediction of male and female crude death rate from gross value added for health and social work and incidence in FBiH. We have found that there is extremely high number of newly diagnosed patients in HercegovinaNeretva canton comparing to different cantons of FBiH. This result should be further examined. Eight leading causes of cancer death in FBiH (bronchus and lung, colon and rectum, stomach, liver and intrahepatic bile ducts, breast, pancreas, brain, prostate) were analyzed for different periods and for difference between genders.

1. INTRODUCTION
Cancer is one of the major causes of deaths in the world. According to the World Health Organization (WHO) cancer is a leading cause of death in the world. In year 2008 7.6 million people died because of cancer and this number is around 13% of all deaths in the world (WHO, Cancer, Globocan 2008).

Bosnia and Herzegovina (BiH) is a country in the South-East Europe. It is bordered by Croatia, Serbia and Montenegro. This country is divided to three main parts: Federation of Bosnia and Herzegovina (FBiH), Republic of Srpska (RS) and Brčko District (BD).

1.429.668 total, 1.160.651 males and 37,816 females. In a year 2011. 20.9% deaths were because of cancer, 24.3% males and 17.4% females (Institute for public health of FBiH, Health statistics work and incidence in FBiH. We have found that there is extremely high number of newly diagnosed patients in HercegovinaNeretva canton comparing to different cantons of FBiH. This result should be further examined. Eight leading causes of cancer death in FBiH (bronchus and lung, colon and rectum, stomach, liver and intrahepatic bile ducts, breast, pancreas, brain, prostate) were analyzed for different periods and for difference between genders.

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year 2011. 15.6% deaths were because of cancer, 13.6% males and 11.9% females (Bosnia and Herzegovina. Agency for statistics of Bosnia and Herzegovina. Demographics in Brčko District Bosnia and Herzegovina for years 2007-2011). The main factors which influence cancer incidence and mortality are high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use. According to WHO about 30% of cancer deaths are due to those five behavioral and dietary risks (WHO, Cancer, Globocan 2008) which are also evident in BiH. In FBiH 41% of adult citizens is overweight (16.5% men and 25% women), almost 70% of population is physically inactive, 37.6% of population is smoking (49.2 men and 29.7 women), and 29.5% is consuming alcohol (54.1% men and 12.5% women) (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020). Another important risk factor is exposure to depleted uranium originating from depleted uranium containing ammunition used by NATO (North Atlantic Treaty Organization) forces in war 1992-1995 (Obralić 2005). Number of deaths because of cancer is different for countries belonging to different income groups. It is estimated that in year 2008 about 70% of all cancer deaths occurred in countries with low- and middle-income (The World Health Organization (2011): NCD country profiles: Bosnia and Herzegovina). BiH belongs to the upper middle income group (The World Health Organization (2011): NCD country profiles: Bosnia and Herzegovina). Social and economic situation in one country has important impact on health of citizens. BiH is faced with economic and political instability which is slowing already started reforms in healthcare system. It is estimated that in year 2011 about 15% of FBiH citizens has status of poverty and 44.5% of working age population is unemployed (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020). In RS 24.5% of working age population is unemployed and 15.6% of citizens have status of poverty (Republic Institute for Statistics of Republic of Srpska. 2012, This is Republic of Srpska).

Since large number of cancer cases can be prevented, FBiH adopted Strategy for prevention, treatment and control of malignant neoplasms in December 2011. This strategy was written according to principles of WHO Action Plan for the Global Strategy for the Prevention and Control of Non-communicable Diseases, 2008-2013 (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020). Since Bosnia and Herzegovina is divided to three main parts, statistics is also divided to FBiH, RS and Brčko District. Public Health Institute of the Federation of Bosnia and Herzegovina is presenting data about cancer statistics in FBiH, Public Health Institute of Republic of Srpska is presenting data about cancer statistics in RS and Agency for statistics of Bosnia and Herzegovina is presenting data about cancer statistics in BD.

2. METHODS AND MATERIALS

Cancer incidence and mortality for FBiH have been rendered by Public Health Institute of the Federation of Bosnia and Herzegovina, for RS by Public Health Institute of Republic of Srpska, for BD by Agency for statistics of Bosnia and Herzegovina. For analysis of the most frequent cancer forms we selected seven most frequent forms for men and women in year 2011 in FBiH. Age adjusted rates were not calculated since there are no relevant data about current population in Bosnia and Herzegovina. Multiple linear regression was used to create model of influence of incidence and gross value added for health and social work on death rates. After we created model for male and female population the Chow test was used to compare the regression coefficients. With this test we were able to determine whether the same theoretical model could be applied to both males and females. The null hypothesis is that corresponding regression coefficients in the equations for males and females are equal. Statistically significant difference in Chow test means that one or more of the coefficients are not equal.

Type 1 ANOVA was used to compare death rates between different parts of Bosnia and Herzegovina (FBiH, RS, BD) and other countries (Croatia, Serbia and Slovenia). Data for Croatia were collected from Cancer register of Croatian national institute of public health. Data for Serbia were collected from Institute of public health of Serbia „Dr. Milan JovanovićBatut”. Data for Slovenia were collected from Institute of oncology Ljubljana, Epidemiology and cancer registry. To precise the analysis of temporal trends for the leading sites of neoplasms time period have been divided into two parts. For calculation of trend rate we used the least square method. Mean (m) with
95% confidence intervals (CI) was calculated and periods were compared by their means and confidence intervals. Only if confidence intervals of the means of the differences between time periods did not overlap they were considered as statistically significant.

For analyses we used SPSS for Windows v. 16 (SPSS Inc., Chicago, IL, USA), and Excel program with the level of significance P<0.05.

3. RESULTS AND DISCUSSION

3.1. Estimation of influence of incidence, gender and gross value added for health and social work on crude death rates in Federation of Bosnia and Herzegovina

We used multiple linear regression to develop models of influence of incidence and gross value added for health and social work on crude death rates for male and female population in FBiH. We used data for period between 2005 and 2011. Backward stepwise procedure with elimination of those variables that were not significant at the α=0.1 level was used. For male population incidence had to be removed from the model (Sig. 0.695). After removal of incidence we obtained the model which is weak (adjusted R square value is 0.699) with the equation:

Male crude death rate=148.294 + 0.053 gross value added for health and social work

For the female population we had different situation. Value of adjusted R square for female model was 0.875 meaning that 87.5% of variability of crude death rate for female population is explained by the variability of incidence and gross value. This model has very small coefficient of variation 0.037% so we can conclude that it is useful for prediction purposes.

Equation is:

Female crude death rate=55.91 + 0.167*incidence + 0.049 gross value added for health and social work

Model has next characteristics:
- No outliers (histogram for the standardized residuals)
- Linearity – our model is linear
- The errors are identically and independently distributed (Q-Q plot of unstandardized residual)
- Homogeneity of variance (homoscedasticity) – our model has mild heteroscedasticity
- Independence - the errors associated with one observation are not correlated with the errors of any other observation (Durbin Watson value is above upper limit)
- Model specification - the model is properly specified (including all relevant variables, and excluding irrelevant variables- predictors have significant influence contrary to their square values)
- Influence – there are no individual observations that exert undue influence on the coefficients (centered leverage value smaller then critical value)
- Collinearity – no collinearity (tolerance above limit and variance inflation factor below limit).
- Our model doesn't lack important variables (standardized predicted values were significant predictors contrary to their square values which are not significant predictors).

3.2. Analysis of seven leading neoplasms for males and females in FBiH

In figures (1, 2 and 3) we can see seven leading neoplasms as cause of death in FBiH in year 2011 for men, women and eight leading neoplasms in total population.

![Fig. 1. Seven leading malignant neoplasms as cause of death for men in year 2011](image1)

![Fig. 2. Seven leading malignant neoplasms as cause of death for women in year 2011](image2)
Malignant neoplasms of bronchus and lung

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women in the world. It is estimated that 951,000 men and 427,400 women died and 1.6 million new cases occurred in year 2008 (American Cancer Society. Global Cancer Facts & Figures 2nd Edition).

Malignant neoplasms of bronchus and lung were the first cause of cancer deaths for men and second for women in year 2011. Also, they are the fifth cause of overall deaths in year 2011 in FBiH (Nikšić et al, 2005).

Lung cancer is one of the most preventable cancers. Reduction of smoking could prevent most lung cancers. It is estimated that cigarette smoking is cause for about 80% of lung cancer cases in men and 50% in women in the world (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In FBiH 37.6% of population is smoking (49.2 men and 29.7 women) (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020).

There is statistically significant difference in the rate of the malignant neoplasms of bronchus and lung for the periods 1999-2005 (m=36.37, 95% CI=33.98-38.76) and 2006-2011 (m=42.45, 95% CI=40.42-44.47) (figure 4).

Number of deaths is statistically significantly different between males (m=68.31, 95% CI 65.75-70.87) and females (m=16.90, 95% CI 15.65-18.15) with at least 4 times less females dying (figure 5).

Malignant neoplasms of colon and rectum

In the world, in year 2008 about 608,700 deaths and estimated 1.2 million cases of colorectal cancer occurred. Colorectal cancer is the third most common cancer in men and the second in women worldwide (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In FBiH it is second cancer as cause of death in men, and third in women.

In FBiH we have increase in crude death rate due to cancer of colon and rectum and this difference is statistically significant when we compare 2008-2011 (m=15.95, 95% CI 13.78-18.11) with period 2003-2007 (m=12.88, 95% CI 12.18-13.57) (figure 6).
Obesity and physical inactivity are among the factors which lead to increased risk of colorectal cancer (American Cancer Society. Global Cancer Facts & Figures 2nd Edition), and in FBiH almost 70% of population is physically inactive and 21.5% of population are obese (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020). Those factors together with the fact that screening and early detection and prevention are not on the required level are leading to constant increase of deaths because of colorectal cancer.

Men (m=17.23, 95% CI 14.48-19.98) are statistically significantly dying more than women (m=12.04, 95% CI 10.59-13.50) because of colon and rectum cancer (figure 7).

**Malignant neoplasms of stomach**

In year 2008 stomach cancer was the fourth most common malignancy in the world (estimated 989,600 new cases), with the twice more men patients comparing with women (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In year 2008 about 738,000 people in the world died from stomach cancer. In FBiH in year 2011 stomach cancer was the third leading cause of cancer death in men and the fifth leading cause in women, the same as in the world population (American Cancer Society. Global Cancer Facts & Figures 2nd Edition).

Malignant neoplasms of stomach have similar values of crude death rates for period 2005-2011 (m=12.32, CI 11.60-13.05) (figure 8).

We have found significant difference between men (m=15.50, 95% CI 14.57-16.42) and women (m=9.26, 95% CI 8.09-10.43) mortality due to malignant neoplasms of stomach (figure 9).

**Malignant neoplasms of liver and intrahepatic bile ducts**

Fifth most common cancer in men and the seventh in women is liver cancer. During 2008 there were about 748,300 new liver cancer cases in the world. Rates are more than twice higher in men then in
women. Liver cancer is the second leading cause of cancer death in men and the sixth leading cause among women in the world with about 695,500 dead people worldwide in year 2008 (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In FBiH liver and intrahepatic bile ducts cancer is the fifth leading cause of cancer death in men and the third leading cause among women. Malignant neoplasms of liver and intrahepatic bile ducts in FBiH have similar values of crude death rates for period 1999-2011 (m=11,61, CI 11,20-12,01) (figure 10).

Fig. 10. Crude death rate per 100.000 for malignant neoplasms of liver and intrahepatic bile ducts in FBiH for period 1999-2011

Although men (m=12,81, 95% CI 11,97-13,66) are statistically significantly dying more than women (m=10,30, 95% CI 9,17-11,41), in year 2007 we had situation that more women died because of malignant neoplasms of liver and intrahepatic bile ducts (Figure 11).

Fig. 11. Male and female crude death rate per 100.000 for malignant neoplasms of liver and intrahepatic bile ducts in FBiH for period 2005-2011

Malignant neoplasms of breast

Malignant neoplasms of breast are the leading cancer death cause among women in BiH (Institute for public health of FBiH, Health statistics annual Federation of Bosnia and Herzegovina 2011, Nikšić 2006). Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide. It is estimated that in year 2008 there were 1.4 million new cases and 458,400 deaths because of breast cancer. The stage of diagnosis is the main factor for prognosis of survival of patients with breast cancer (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In Bosnia and Herzegovina, due to lack of systematic sending and examination, lack of technical capacities and qualified personnel early detection of breast carcinoma is on low level (Federation of Bosnia and Herzegovina, Federal Ministry of health. Strategy for prevention, treatment and control of malignant neoplasms in Federation of Bosnia and Herzegovina 2012-2020). In year 2008 female breast cancer incidence rates varied internationally by more than 13-fold, ranging from 8.0 cases per 100,000 in Mongolia and Bhutan to 109.4 per 100,000 in Belgium (American Cancer Society. Global Cancer Facts & Figures 2nd Edition). In RS crude incidence for year 2010 rate was 55.9 per 100,000 (Stanić 2010). In this work we have found that in FBiH we have statistically significant decrease in crude death rate due to breast cancer in period 2005-2011 (m=9,63, 95% CI 8,64-10,62) compared with period 1999-2004 (m=13,93, 95% CI 12,78-15,09) (figure 12). It is important to notice that we have three main periods increase (2000-2003) with trend 1,08, decrease (2004-2005) with trend -2,89 and then slow increase (2006-2011) with trend 0,48 in breast cancer crude death rate.

Fig. 12. Crude death rate per 100.000 for malignant neoplasms of breast in FBiH for period 1999-2011

We suppose that programme for early detection and prevention for breast cancer in Bosnia and Herzegovina canton Sarajevo in period 2000-2006 had impact on this picture of number of deaths.
Malignant neoplasms of pancreas
In FBiH pancreas cancer is the sixth leading cause of cancer death in men and seventh in women. Constant rising trend can be seen for the crude death rate of malignant neoplasms of pancreas for period 1999-2011 (figure 13). There is significant difference in crude death rate for period 1999-2006 (m=6.48, 95% CI 5.88-7.07) and 2007-2011 (m=8.92, 95% CI 8.08-9.76).

In this work we have found that there is no significant difference between men (m=9.35, 95% CI 7.95-10.75) and women (m=7.44, 95% CI 6.20-8.69) in crude death rate for malignant neoplasms of pancreas (figure 14).

Malignant neoplasms of the brain
In FBiH brain cancer is the seventh leading cause of cancer death in men and sixth leading cause in women. Constant rising trend can be seen for the crude death rate of malignant neoplasms of brain for period 1999-2011 (figure 15). There is significant difference in crude death rate for period 1999-2004 (m=6.05, 95% CI 5.46-6.64) and 2005-2011 (m=7.76, 95% CI 6.88-8.65).

Alajbegović et al., 2012 found that at the Neurology Clinic Sarajevo during period 1999 to 2005 there were significantly more man patients with brain tumors and in the period 2005 to 2009 this was reversed to more women patients.
In this work we have found that there is no significant difference between men (m=8.70, 95% CI 7.43-9.75) and women (m=6.88, 95% CI 6.08-7.68) in crude death rate for malignant neoplasms of brain (figure 16).

Malignant neoplasms of prostate
Prostate cancer is the second most frequently diagnosed cancer in men and sixth leading cause of cancer death in men worldwide. It is estimated that 903,500 new cases occurred in 2008 in the world (American Cancer Society. Global Cancer Facts &
In year 2011 in FBiH prostate cancer was the fourth cause of cancer death in men. On figure 17 we can see that in period 2009-2011 (m=7.55, 95% CI 7.04-8.06) we have statistically higher crude death rate when we compare with period 2005-2008 (m=5.84, 95% CI 5.36-6.31).

3.3. Comparison of crude death rates between BD, RS, FBiH, Croatia, Slovenia and Serbia

For comparison of crude death rates between genders and between BD, RS, FBiH, Croatia, Serbia and Slovenia we used Type I ANOVA test. On figure 18 we can see plot of gender and location. On the other side, BD is more homogenous and it is located just in one part of Bosnia and Herzegovina. Because of lack of data we were unable to calculate crude death rate for entire Bosnia and Herzegovina. In the figure 19 we can see chart for male population for five locations observed.

Since we didn’t have data for Slovenia for year 2010 and BD for year 2006 we then compared results for six locations using Games-Howell test. The mean difference in crude death rate for Croatia, Serbia and Slovenia was found not significant. The mean difference in crude death rate for FBiH and BD was found not significant. RS was significantly different from all other locations. BD and FBiH were significantly different from RS, Croatia, Serbia and Slovenia. Observed difference between FBiH and BD from RS is probably because RS consists of different parts in the whole territory of Bosnia and Herzegovina, and from analysis of cantons we can see that also in FBiH we have big differences between different cantons. On the other side, BD is more homogenous and it is located just in one part of Bosnia and Herzegovina.
We were unable to calculate age adjusted death rates since we don’t have exact data about population in Bosnia and Herzegovina. The last census was conducted in year 1991, before the war, which had huge influence on population of our country with the estimated number of 104,732 deaths (Zwierzchowski and Tabeau, 2010).

3.5. Comparison of mean difference in crude death rates per 100.000 for different cantons of Federation of Bosnia and Herzegovina

After comparison of mean difference in crude death rates per 100.000 for different cantons of FBiH in year 2011 by ANOVA and Tukey test we have results presented in table 1:

3.6. Comparison of number of patients between different cantons of Federation of Bosnia and Herzegovina
From figures 21 and 22 we can see that cantons with the biggest number of patients are HercegovinaNeretva and Sarajevo. This is mainly due to better diagnostics of cancer and it is not the real situation. However, it is important to point out that in Sarajevo canton we have the best diagnostics resources and despite this fact HercegovinaNeretva canton (m=1650, CI 95% 1432.21-1867.79) has significantly higher number of patients when compared with Sarajevo canton (m=1185, CI 95% 1048.43-1321.57) for period 2008-2011. We suppose that there is some factor in HercegovinaNeretva canton which has influence on number of patients. This should be further investigated.

Fig. 21. Comparison of number of patients (rate per 100.00) between cantons in FBiH for years 2005 to 2011

Fig. 22. Comparison of number of patients (rate per 100.00) between cantons in FBiH for year 2011
4. CONCLUSIONS

Bosnia and Herzegovina has lower cancer mortality when compared to Croatia, Slovenia and Serbia. On the other side there are increasing trends of some of the leading cancer deaths (bronchus and lung, colorectal cancer, brain, pancreas, prostate). There should be more programs for cancer prevention with the aim to reduce number of cancer deaths. Also, it is important to further investigate and try to find explanation about very high cancer incidence in HercegovinaNeretva canton, especially in the last few years (2008-2011).

REFERENCES


