Theses of the Ph.D. Dissertation

AGE-ADJUSTED MORTALITY RATES RELATED TO MALIGNANT NEOPLASMS AND CARDIOVASCULAR DISEASES BETWEEN 2000-2010 ON FIVE AREAS OF HUNGARY DIFFERENT IN TERMS OF VINE-CULTURE

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1. BACKGROUND AND THE OBJECTIVE OF THE RESEARCH

1.1. Background

Cardiovascular diseases (CVD) and malignant neoplasms (MN) represent the two main causes of death in the developed world for several decades (WHO, 2019). Environment, lifestyle, nutrition, drinking habits play essential roles in both diseases.

Red meat consumption and quality of drinking water have attracted special attention in studies related to nutrition (Jeyakumar et al., 2017). The first, because of tumor-triggering effect associated with it, the latter, because of potential preventiv role in cardiovascular diseases. In the last decades, several evidences suggest beneficial role of „hard" drinking water with high magnesium and calcium content (Rapant et al., 2019). These statements, however, need further verification on larger population according to several studies.

Many publications deal with, that „Mediterranean diet" rich in vegetables, fruits, fish and dairy products usually served with red wines (Farinetti et al., 2017). The beneficial role of red wine is highlighted by earlier publications showing not only improved blood circulation but also prevention of malignant neoplasms. That is why recent years are considered as „golden age of red wine" in nutrition science.

In the light of facts mentioned above, we turned our attention to studying the importance of different types of wine in Hungary. Since scientific results contain many inconsistencies and open questions, we began our common invetigations with professor Dr. Zsolt Horváth on the bases of the proposal by Prof. Dr. Sándor Sipka. Our primary intention was to compare the mortality data for cardiovascular diseases and malignant neoplasms between the areas where population produce and consumpt dominantly red wine or dominantly white wine.

1.2. Setting of objective

Our investigations can be devided into three parts on the bases of chronology, subject and elaboration: 1.) Introductory, baseline study, 2.) Analysis of mortality data for cardiovascular diseases, 3.) Analysis of mortality data for malignant neoplasms. Receiving several new important details during the work, we elaborated each phases step by step manner after evaluating the results and obtaining conclusions from the previous phases. In ecological studies – using data from population level instead of individual data – we compared the hypothetical effects of consumption of red or white wine on the basis of large number of persons died in these two diseases. We chose the 11 year timeperiod between 2000 and 2010, when it was tipical that wine-producing people of a given region comsumed primarily their own wine according to a traditional lifestyle. Therefore, we selected four internationaly famous wine-growing areas with long time tradition – *red wine*: Eger and Szekszárd/Villány region; *white wine*: Tokaj and Balaton region – and a fifth, Hódmezővásárhely served as a *control area*, where viniculture and winemaking are not tipical agricultural work. These five areas cover a population larger than 200,000 in total. Our main question was to answer, if the differences in mortality show any association with wine-production and wine consumption tipical on a given area.

We made an effort to take into account, or to filter out the level of socio-economic development/deprivation as far as possible (Ford–Highfield, 2016). Therefore, to reduce the deviation of data we selected small towns and settlements with urban characters and measured their deprivation. Rural population was omitted from our examinations.

In addition to wine production-consumption in each region, mineral contents of drinking water and soil – especially the water hardness – were also included in the evaluation as potential influential factors. Furthermore, our goal was to compare the quantities of red meat consumption per capita in the regions and the quantities exceeded the „dangerous" level determined by international studies.

1.2.1. The objective of the baseline study/ study 1

a. Comparison of the standardized mortality data of the five selected areas related to cardiovascular diseases and gastrointestinal tumors.

In this first study, we restricted our analysis from all the neoplasms to gastrointestinal tumors (GI) because it was natural to suppose that the effects of nutrition or drinking habits manifest primary on these tumors.

b. Calculation of the order of mortality rates and relative mortality risks by pairs of areas.

c. Cross-checks on data of the areas, related to mortality, deprivation, meat consumption and mineral content (in drinking water and soil).

d. *Drawing conclusions to verify the potential role of the dominant type of wine.*

1.2.2. The objective of study 2

a. Drawing correlation between cardiovascular mortality, hardness of drinking water and indexes of deprivation by settlements.

b. Summation and interpretation of results in context of the five examined areas.

1.2.3. The objective of study 3

a. Comparison of the mortality data including the eight groups of malignant neoplasms, in two regions producing dominantly white wine, with the fifth tipically not winemaking area and the nationwide average.

b. Cross-checks on data of deprivation, red meat consumption and hardness of drinking water.

In this study we restricted our comparison of mortality data to Tokaj and Balaton regions, because in the light of previous data showing favourable effect of Tokaj, a chemically similar and dominantly white wine producing area was chosen.

2. DATA AND METHODS

2.1. The studied areas and their dominant types of wine

From well-known historical winery areas in Hungary we examined the mortality data of the following ones, listing their settlements and dominant type of wine:

- Tokaj (white in 99,8%): Tokaj, Sárospatak, Sátoraljaújhely, dominantly white wine from special shriveled grapes fermented by *Botrytis cinerea*;
- Eger (red in 65%): Eger, Noszvaj, dominantly red wine;
- Balaton (white in 72%): Badacsonytomaj, Badacsonytördemic, Balatonboglár, Balatonfüred, Balatonlelle, Csopak, Dörgicse, dominantly white wine; these settlements were chosen from three wine regions: Balatonfüred – Csopak region, Balatonboglár region and Badacsony region;
- Szekszárd/Villány (red in 83%): dominantly red wine;
- Hódmezővásárhely (HMV): not tipically wine-producing area served as control. (Data of viticulture reflect the actual state on July 31, 2019 cited from the source of National Council of the Wine Communities, Hungary.)

For selection of these settlements, the important aspects were their special, traditional wine culture, the approximately identical index of deprivation (ID) that demonstrates a socio-economic status (SES) exceeding the national average, furthermore the similarity in their annual consumption of swine-bovine carcase meat. It was also essential that data of more than 30,000 persons should be available to investigate on each area for 11 years. We have to note that the control Hódmezővásárhely officialy belongs to the Csongrád wine region producing good quality of wine, however, only in small quantity compared to the production of famous traditional wine regions. Hódmezővásárhely traditionally and primarily is a grain-growing region like majority of the settlements on the Southern great plain. Therefore, it seemed acceptable to use as a „control" area in our studies.

2.2. Age-Adjusted Death Rates

The mortality data in Hungary during the studied 11 year period of 2000–2010 were provided by the Central Office for Administrative and Electronic Public Services and the Hungarian Central Statistical Office (HCSO). Data were grouped according to settlements, gender, age and diagnosis. The CVD and MN diagnoses were classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD) as follows: - cardiovascular diseases: I01, I20–I99 (except of hypertonia and chronic rheumatic heart diseases); the most frequent groups of malignant neoplasms: - digestive organs: C15-C26; respiratory and intrathoracic organs: C30-C39; lip, oral cavity and pharynx: C00-C14; female genital organs: C51-C58; breast: C50; lymphoid, haematopoietic and related tissue: C81-C96; urinary tract: C64-C68; male genital organs: C60-C63. We calculated the age-adjusted death rates (AADR values) for 100,000 subjects in each region focusing on the whole time period, and not on the annual changes or differences. (Direct standardization was applied with the European standard population.)

2.3. Index of Socio-Economic Deprivation (ID)

Characterization and comparison of the socio-economic statuses (SES) of five regions was carried out by the calculation of the deprivation index (ID) using the data of Hungarian Central Statistical Office (HCSO). Deprivation means retardation, the level of underdevelopment in comparation to national average. The negative sign refers to better social state. The values of ID were calculated from the following indicators with principal component amalysis as normalized values:

(1) annual income/ person in the region;

(2) ratio of persons in the population under 15 years not finishing the elementary school;

(3) ratio of unemployments in the population of 15–74 years;

(4) ratio of families with one parent;

(5) proportion of families with three or more children;

(6) number of persons/rooms;

(7) number of cars/100 persons.

Therefore, their 95% fell between -2 and 2 with the average of 0. The index of areas were assigned as population-weighted average from the indexes of their settlements

2.4. Data of meat consumption

The data of red meat consumption (kg/person/year) derived from the National Board for Flesh of Beef and Pork in 2006-2007. These results did not contain the data of smoke-cured meats (sausage, salami, ham, etc.) and meat from poultries.

2.5. Mineral content of soil and drinking water

The source of data related to mineral content of soil was the National Food Chain Safety Office (NFCSO). Data related to mineral content of drinking water were obtained from the Water Department of the National Institute of Health (Budapest). Results in tables are showing the averages which were calculated from the hundreds of controlled and approved measurements carried out officially and regularly between 2005-2010 from at least 30-50 points of the settlements of the 5 different regions.

2.6. Statistical analysis

The AADR values calculated annually during the 11 years were summarized then adjusted to the population sizes of the five different regions. To compare the mortality rates, Pearson's $\chi 2$ tests were applied, first together for all areas then by pairs of areas. Pearson's correlations were calculated between (a) AADR of CVD and hardness of drinking water; (b) AADR of CVD and indices of socio-economic deprivation (ID). $p < 0.05$ values were considered to statistically significant level. The STATA ver. 10.1 (StataCorp LLC, Texas, USA) and the IBM SPSS ver. 24 program (IBM Corp, Armonk, NY, USA) were used for calculations.

3. RESULTS

3.1. Results of the baseline study/ study 1

3.1.1. Age-adjusted death rates (AADR) of gastrointestinal (GI) tumours and cardiovascular diseases (CVD) between 2000 and 2010

The age-adjusted death rate was the lowest (664) in the Tokaj region and the highest in Eger (934) and in Szekszárd/Villány (831) regions. In the regions of Balaton (824) and Hódmezővásárhely (821) these values were between the two extremities, while the nationwide value was 887. In the CVD data, the extreme values occured in reverse order. The smallest mortality was in Szekszárd/Villány (3907) region while the maximal in Tokaj (5955). The relatively smaller values of Balaton (4034) and Eger (4191) fell between the extremities, as well as the relatively higher value of Hódmezővásárhely (5178). The values of Szekszárd/Villány (3907) and Tokaj (5955) showed significant difference in the opposite direction from the nationwide average (4800). These data are shown in Table 1. It is important to note that these tendencies took place in similar manner each year in the studied regions.

Table 1: Summary table: population, age-adjusted death rate, index of deprivation (ID) and red meat consumption in the five studied areas of Hungary between 2000 and 2010

Parameters	Tokaj	Eger	Balaton	Szekszárd/ Villány	Hódmező-vásárhely	Nationwide average
Population (2010, total: 206,159)	33917	56981	30833	37268	47160	
Cardiovascular diseases (AADR)	5955	4191	4034	3907	5178	4800
Gastrointestinal tumors (AADR)	664	934	824	831	821	887
Index of deprivation (ID)	-0,36	-1,1	-1,22	-1,17	-0,43	0,00
Red meat consumption (kg/capita - 2007)	16,15	16,15	18,65	16,95	24,35	

3.1.2. Relative mortality risks of GI tumors and CVD in the studied regions

In the case of GI tumors Tokaj region showed significantly lower risk (-20-30%) compared to all other regions especially Szekszárd/Villány (-20%) and Eger (-29%) regions (Table 2).

Table 2: Relative mortality risks of gastriontestinal (GI) tumors in the five studied areas of Hungary in 2000-2010

	Tokaj	Hódmező-vásárhely	Balaton	Szekszárd/ Villány	Eger
Tokaj	1	1,24* (0,0107)	1,24* (0,0174)	1,25** (0,0094)	1,41**** (0,0000)
Eger	0,71**** (0,0000)	0,88 (0,0522)	0,88 (0,0990)	0,89 (0,1043)	1
Balaton	0,81* (0,0174)	1,0(0,9616)	1	1,01 (0,9085)	1,13 (0,0990)
Szekszárd/ Villány	0,80** (0,0094)	0,99 (0,8582)	0,99 (0,9085)	1	1,12 (0,1043)
Hódmező-vásárhely	0,81* (0,0107)	1	1,0(0,9616)	1,01 (0,8582)	1,14 (0,0522)

Statistical p-value in parenthesis, columns in increasing order of mortality. *: p<0,05; **: p<0,01; ***: p<0,001; ****: p<0,00005.

Table 3: Relative mortality risks of cardiovascular diseases (CVD) in the five studied areas of Hungary in 2000-2010

	Szekszárd-Villány	Balaton	Eger	Hódmező-vásárhely	Tokaj
Tokaj	0,66**** (0,0000)	0,68**** (0,0000)	0,70**** (0,0000)	0,87* (0,0000)	1
Eger	0,93* (0,0311)	0,96 (0,2671)	1	1,24**** (0,0000)	1,42* (0,0000)
Balaton	0,97 (0,3949)	1	1,04 (0,2671)	1,28**** (0,0000)	1,48**** (0,0000)
Szekszárd/ Villány	1	1,03 (0,3949)	1,07* (0,0311)	1,33**** (0,0000)	1,52**** (0,0000)
Hódmező-vásárhely	0,75**** (0,0000)	0,78**** (0,0000)	0,81**** (0,0000)	1	1,15* (0,0000)

Statistical p-value in parenthesis, columns in increasing order of mortality. *: p<0,05; **: p<0,01; ***: p<0,001; ****: p<0,00005.

On the other hand, CVD mortality risk was the lowest in the Szekszárd/ Villány region, while the highest in Tokaj (+52%). Data of Balaton and Hódmezővásárhely fall between the two extremities (Table 3).

3.1.3. Mineral content of soil

Considering mineral elements characteristic in soil of the studied areas and have significant biological effect, the biggest differences were found in P, Ca, K, Mg, Na and Fe concentrations (Table 4). These differences however, do not reflect the tendencies of mortality data.

Table 4: Mineral content of soil in the five studied areas of Hungary

Element (mg/kg)	Tokaj	Eger	Balaton	Szekszárd-Villány	Hódmező-vásárhely
Ca	5600,0	4715,0	45610,0	27808,7	12100,0
Fe	23366,0	22500,0	14135,0	19584,2	24500,0
Mg	4830,0	4212,0	7237,0	10274,9	8557,0
K	2833,0	2170,0	3845,0	1206,0	3228,0
Na	233,0	89,0	144,0	173,0	875,0
P	367,0	314,0	372,0	645,9	672,0
S	197,0	135,0	198,0	149,2	296,0
Zn	58,0	50,0	66,0	47,0	66,0
Mo	1,4	1,0	1,2	0,1	0,9
Se	1,0	1,0	1,0	0,4	1,0

3.1.4. Mineral content of drinking water in the studied areas

Analysing mineral elements characteristic in drinking water of the studied areas and which have significant biological effects, twice as high selenium concentration (considered as an important protective factor against GI tumors) was found in Tokaj region than the other four areas. Recent studies, however, do not support these protective effects of selenium against malignant neoplasms. Additional elements including chromium, manganese, arsenium, chloride, sulphate, orthophosphate were also measured in soil samples, and their concentration was calculated and water hardness was determined as shown in Table 5.

Table 5: Mineral content of drinking water in the five studied areas of Hungary

Element/ compound	Unit	Tokaj	Eger	Balaton	Szekszárd-Villány	Hódmező-vásárhely
Natrium	mg/l	25,50	13,40	13,50	107,10	88,50
Potassium	mg/l	93,00	3,00	6,40	6,50	1,00
Magnesium	mg/l	24,50	26,80	46,20	39,70	14,50
Calcium	mg/l	2,40	86,20	115,40	8,20	27,60
Total hardness	***CaO mg/l***	***138,60***	***194,90***	***249,20***	***294,20***	***81,90***
Phosphate	mg/l	0,10	3,10	n.a.	17,30	n.a.
Orthophosphate	mg/l	0,24	n.a.	n.a.	2,13	n.a.
Chloride	mg/l	29,50	15,90	14,20	95,50	9,30
Sulphate	mg/l	66,50	60,40	59,00	99,10	12,70
Manganese	µg/l	27,30	7,90	14,50	24,90	35,20
Selenium	µg/l	1,40	0,70	0,70	0,80	0,70
Iron	µg/l	33,70	12,80	38,00	41,40	178,00
Arsenium	µg/l	6,00	1,60	0,30	1,10	19,50
Chromium	µg/l	0,00	0,00	0,00	2,50	0,00

3.1.5. Interpretation of the results from the baseline study/ study 1

Comparing studied areas according to CVD and GI mortality data, we found not a simple opposite order. While the minimum (3907) and maximum (5955) of CVD data were significantly different from the nationwide average (4800), the GI mortality data – except Tokaj (664) – were practically close to it. (887).

ID values characterizing living standard were higher than the national average (with negative sign) in all studied areas. In towns of Tokaj region and in Hódmezővásárhely these were approximately equal to each other and somewhat lower than in the three other areas demonstrating lower socio-economic level. It might suggest that CVD mortality could be influenced by deprivation. Regarding GI mortality the role of ID values is not so obvious, since similar ID in Tokaj region and Hódmezővásárhely was associated with significantly different GI mortality rate.

Based on the results the role of red carcase type pork and beef (without smoke-cured meats) consumption is definitely less significant. On the one hand, the wine regions showed almost the same values, on the other hand, the consumed quantities are less than the half of the quantities that can be dangerous according to previous studies.

It was supposed, that consumption of ethyl alcohol – calculated on net alcohol per capita – was not significantly different in the four big wine producing areas. Namely in these regions the rate of alcoholic liver disease looked the same and was close to the

average, while in Hódmezővásárhely, not a tipically wine region, was significantly lower compared to the previous areas (Elekes–Paksi, 1994).

Since the mineral content in soil shows significant variation across the country the calcium reach areas (Balaton, Szekszárd/ Villány) were easily separated from areas with lower calcium content (Tokaj, Eger). It shoud be noted, that the soil mineral content in Tokaj and Eger is very similar, while the mortality rate is quite different. So the „soil-factor" exerts no direct effect on mortality.

There were also significant differences in the territorial distribution of mineral content in drinking water. Looking in detail, only the water hardness showed association with mortality data, which require further examination of the connection between water hardness and CVD mortality at the level of settlements. Additional analyses of oncology data were also carried out, since the group of the malignant neoplasms contains many types of diseases with significantly different malignant potential.

3.2. Results of study 2

3.2.1. Negative correlation between the CVD mortality and the total permanent hardness of drinking

Significant negative correlation was found between the death rate (AADR) from CVD and the hardness of drinking water: $r = -0.731$, $p < 0.007$. The results were obtained from 12 settlements of the five regions, where total population was graeter than 200,000 (Figure 1).

3.2.2. Positive correlation between CVD mortality and the indexes of socio-economic deprivation (ID)

Significant positive correlation was found between the death rate (AADR) from CVD and the indexes of socio-economic deprivation (ID): $r = 0.690$, $p < 0.013$. The results were obtained from 12 settlements of the five regions, where total population was graeter than 200,000. It is important to emphasize that strong correlation was found in these analyses in spite of the relatively small differences between ID values (Figure 2).

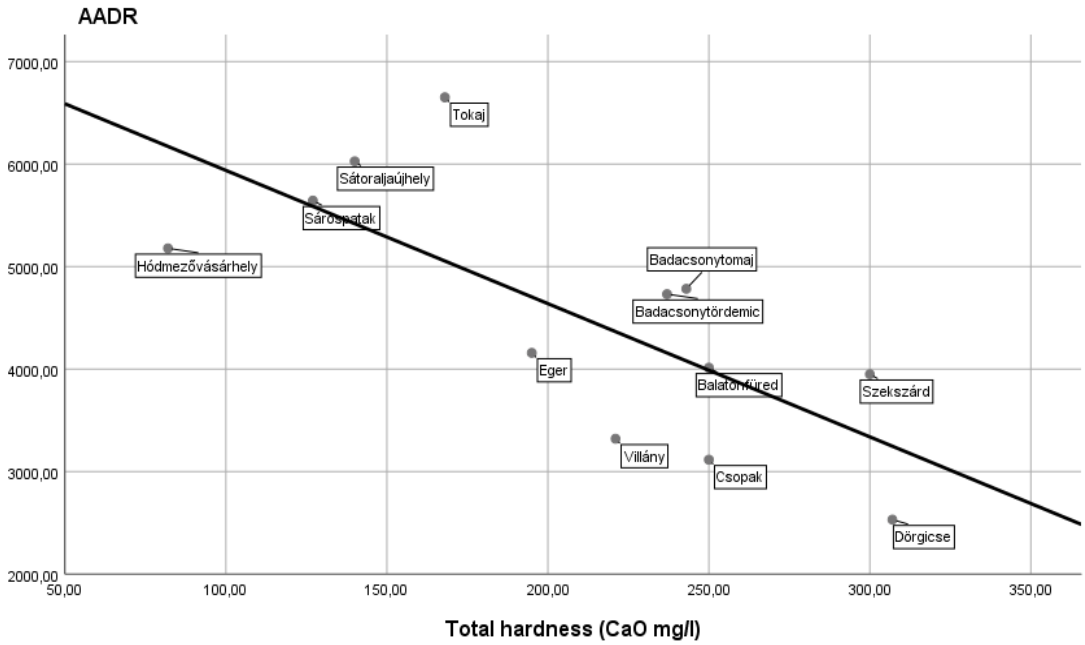

Figure 1: Significant negative correlation (r = - 0.731, p = 0.007) between the mortality rate (AADR) from CVD and the total hardness of drinking water in 12 settlements of Hungary between 2000-2010

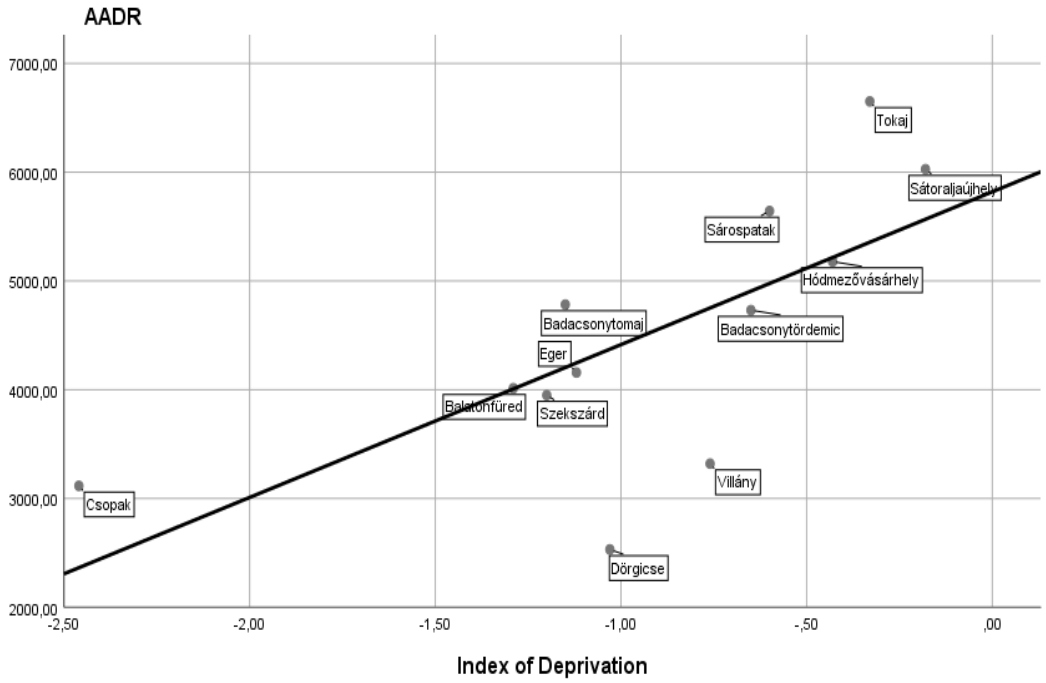

Figure 2: Significant positive correlation (r = 0.690, p = 0.013) between the mortality rate (AADR) from CVD and the index of deprivation (ID) in 12 settlements of Hungary between 2000-2010.

3.2.3. Interpretation of the results of study 2

Main results of this study are as follows:

(a) Significant negative correlation was shown between the hardness of drinking water and the indicators of CVD mortality (AADR) on a large (> 200,000) population in the five studied regions.

(b) Significant positive correlation was found between the indexes of socio-economic deprivation (ID) and the CVD mortality (AADR) on a large population in the five studied regions.

(c) The hardness of drinking water and the socio-economic deprivation seem to have more impact on CVD mortality than the production and the supposed consumption of red" or „white" wines of the studied regions.

(d) The possible greater impact of hard water can be supported by a modest evidence that the numeric value of its correlation co-efficient was 0.731 versus 0.690.

(e) It can be seen that the significant differences in CVD cannot be explained by the dominating "red" or" white" types of local wines, since the values of Szekszárd/Villány (3907) and Eger (4191) designated "red" wine areas are similar to Balaton region (4034) designated „white" wine area.

3.3. Results of study 3

3.3.1. Decreased tumor mortality rates in Tokaj region compared to Balaton region and the nationwide average

In this study we carried out detailed analyses of following data previously presented in our baseline study (shown in Table 1): Population (all regions are remarkable, above 30,000): Tokaj: 33917, Balaton: 30833, HMV: 47160. Deprivation: Tokaj: -0.36, Balaton: -1,22, HMV: -0,43, that means a higher socio-economic state than the nationwide average. Red meat consumption: Tokaj: 16.15, Balaton: 18.65, HMV: 24.35 (kg/capita/year). Hardness of drinking water: Tokaj: 138.60, Balaton: 249.20, HMV: 81.90 (Table 5). The hardness of drinking water and the indicators of GI tumor mortality do not correlate, since Balaton region with its much harder drinking water (249.20 CaO

mg/l) show almost the same mortality as HMV (824 és 821). Deprivation and tumor mortality also show no correlatation, as deprivation of Tokaj and HMV is almost the same, while in tumor mortality there are significant differencies. Likewise, differences between the regions in the contents of mineral elements in soil do not correlate with cancer mortaly rate.

New results are presented in Table 6. The age-adjusted death rates (AADR) from all malignancies and the eight most characteristic groups of tumors in the three studied areas are shown here. Considering all cancers, the indicator in Tokaj (2120, $p < 0.0005$) and in Balaton (2425, $p = 0.003$) region is significantly lower than in HMV (2771). Furthermore, it is significantly lower in Tokaj than in Balaton region ($p = 0.013$). The main groups of malignant neoplasms show the following tendencies:

In six from the eight types of malignancies, the mortality rate in Tokaj region was the lowest, with two exceptions:

(a) The tumors of lip, oral cavity and pharynx occured in graeter number in Tokaj (167) than in Balaton (146) and HMV (105) region or nationwide (155, $p=0.005$).
(b) Mortality from the tumors of respiratory and intrathoracic organs was extremely high in HMV (831) compared to Tokaj (577, $p < 0.0005$) and Balaton (488, $p < 0.0005$) regions.

We performed additional two studies on malignancies associated with lymphoid, hematopoietic and related tissues develop at any ages in human. First, the mortality of all ages was calculated showing the lowest value in Tokaj (102) in contrary to the Balaton (169) region and HMV (183) as well as the nationwide agerage (155, $p=0.015$). Analysis of mortality rate under 25 year of age, however, revealed disappearance of the differences showing the natonwide average. This age related difference might explain the anti-tumor effect of Tokaj wine, since wine consumption usually starts at older ages.

Table 6: The age-adjusted death rate (AADR) values of various types of cancers/malignancies in the three regions and the nationwide data between 2000 and 2010 (rank[1]/ AADR[2])

Cancers/ Malignancies	Tokaj	Balaton	Hódmező-vásárhely	Nationwide	Significance[3]
Gastrointestinal *(C15-C26[4])*	1./664	3./824	2./821	887	1/2(0.009); 1/3(0.018)
Respiratory (C30-C39[4])	2./577	1./488	3./831	772	1/3(<0.0005); 2/3(<0.0005)
Lip, oral, pharyngeal (C00-C14[4])	3./167	2./146	1./105	155	1/nationwide (0.005)
Female genital (C51-C58[4])	1./133	180	2./139	141	-
Female breast (C50[4])	1./128	2./140	3./178	185	1/ nationwide (0.013)
Lymphoid and haematological (C81-C96[4])	1./102	2./148	3./183.	155	1/ nationwide (0.015)
Lymphoid and haemat. <25 years (C81-C96[4])	*6.0*	*7.9*	*18.5*	*6.1*	-
Urinary [5] (C64-C68[4])	1./72	2./106	3./145	123	-
Male genital organs[5] (C60-C63[4])	1./71	3./99	2./95	91	-
All cancers	1./2120	2./2417	3./2771	2773	1/2(0.013); 1/3(<0.0005); 2/3(0.003);

[1]: rank, denotes the lowest, 3 denotes the highest mortality; [2]: AADR = Age-adjusted Death Rate; [3]: significancy, m/n = ranks of compared territories, p-value in parenthesis;
[4]: ICD-10, International Classification of Diseases, Version 10, 2016;
[5]: extrapolated from the period 2005-2010

3.3.2. Interpretation of results of study 3

A significant difference between the Tokaj and Balaton regions was observed in tumour mortality. In order to explain this phenomenon, we suggest essential chemical differences between various white wine, since different environmental factors were excluded in our earlier studies, and both regions produce dominantly white wine.

Based on the above findings it can be supposed that this surprising difference is caused by the group of mainly oxidative molecules (oxidases, H2O2, etc.) derived from "noble yeast" Botrytis cinerea in consequence of the special natural features and oxidative manufacturing technology (Gil-ad et al., 2000). The highly elevated pro-oxidant capability of Tokaj wines (mainly „Aszú") was first observed and described by Sipka and coworkers, whose work served as a basis for a methodology patent with title „Method for the Measurement of Botrytis cinerea Specific Quality of ASZU Wines in Tokaj" (Sipka et al., 2019). Furthermore, high spermidine content also can contribute to the anticancer effect of Tokaj wines (Madeo et al., 2018).

We suppose, that a series of other molecules or chemical agents might play a role in the special biological effects of these wines and need further investigation in the future.

3.4. Summary of all the results of our studies

The most relevant results of our three sudies are summarized in Table 7 and 8 below.

Table 7: Population, age-adjusted death rate (AADR), hardness of drinking water, index of deprivation (ID) and red meat consumption in the five studied areas of Hungary between 2000 and 2010

Parameters	Tokaj	Eger	Balaton	Szekszárd/ Villány	Hódmező-vásárhely	Nationwide average
Population (2010, total: 206,159)	33917	56981	30833	37268	47160	
Cardiovascular mortality (AADR)	5955	4191	4034	3907	5178	4800
Cancer mortality (AADR)	2120	2678	2417	2425	2771	2773
Gastrointestinal tumours (AADR)	664	934	824	831	821	887
Hardness of drinking water (CaO mg/l)	138.6	194.9	249.2	294.2	81.9	
Index of deprivation (ID)	-0.36	-1.1	-1.22	-1.17	-0.43	0.00
Red meat consumption (kg/capita - 2007)	16.15	16.15	18.65	16.95	24.35	

Table 8: Mortality rate for the eight main groups of cancers and cardiovascular diseases (rank[1]/ AADR[2])

Malignant diseases	**Tokaj**	**Eger**	**Balaton**	**Szekszárd/ Villány**	**Hódmező-vásárhely**	**Nationwide average**	**Significance[3]**
Gastrointestinal *(C15-C26[4])*	*1./664*	*5./934*	*3./824*	*4./831*	*2./821*	*887*	*1/2(0.011); 1/3(0.017); 1/4(0.009);1/5(<0.00005)*
Respiratory (C30-C39[4])	3./577	4./673	1./488	2./571	5./831	772	1/5(<0.0005); 1/4(0.001); 2/5(<0.0005); 3/5(<0.0005); 4/5(0.003)
Lip, oral, pharyngeal (C00-C14[4])	5./167	3./130	4./146	1./89	2./105	155	1/5(0.003); 1/4(0.028);2/5(0.017)
Female genital organs (C51-C58[4])	1./133	2./134	5./180	4./141	3./139	141	-
Female breast (C50[4])	1./128	5./212	2./140	4./180	3./178	185	1/5(0.003); 2/5(0.017)
Lymphoid and haematological (C81-C96[4])	1./102	4./169	2./148	3./161	5./183	155	-
Lymphoid and haemat. under 25 years (C81-C96[4])	6.0	7.4	7.9	6.1	18.5	6.1	-
Urinary[5] (C64-C68[4])	1./72	3./114	2./106	4./121	5./145	123	-
Male genital organs[5] (C60-C63[4])	2./71	5./117	4./99	1./64	3./95	91	-
All cancers	1./2120	4./2678	2./2417	3./2425	5./2771	2773	1/2(0.011); 1/3(0.006); 1/4(0.000); 1/5(0.000); 2/4(0.020); 2/5(0.002); 3/4(0.017); 3/5(0.002);
Cardiovascular diseases	5./5955	3./4191	2./4034	1./3907	4./5178	4800	1/3(0.031); 1/4(0.00); 1/5(0.000); 2/4(0.000); 2/5(0.000); 3/4(0.000); 3/5(0.000); 4/5(0.000)

[1]: rank, denotes the lowest, 5 denotes the highest mortality; [2]: AADR = Age-adjusted Death Rate;[3]: significancy, m/n = ranks of compared terriories, p-value in parenthesis; [4]: ICD-10, International Classification of Diseases, Version 10, 2016; [5]: extrapolated from the period 2005-2010

4. NEW SCIENTIFIC RESULTS

a. On the basis of our statistical analysis of mortality data from the period of 2000-2010, performed in a large population (> 200,000 persons) of five studied area of Hungary – 4 of which assigned from several famous traditional wine regions, while the fifth is not a tipical wine-producing area – we found significant differences ($p < 0.031$) in the territorial distribution of cardiovascular and some malignant diseases.

b. Mortality rate for gastrointestinal tumours was more favourable and showed substantially lower values in Tokaj region than in the other studied regions, while there were no significant differences between Hódmezővásárhely, Eger Szekszárd/Villány, Balaton regions and the nationwide average.

c. Considering the significantly lower tumour mortality in Tokaj, we propose a potential explanation, that this phenomenon may be related to the specific pro-oxidant characteristics of Tokaj wines in association probably with *Botrytis cinerea*. It could be assumed that this favorable antitumor effect develops in inhabitants by consumption of these wines over their life course.

d. Cardiovascular mortality showed negative correlation with the hardness of drinking water ($r = -0.731$) and the socio-economic level ($r = 0.690$) of the region. Tokaj region and HMV – with soft drinking water and lower socio-economic background – however, could be characterized by graeter mortality.

e. Hardness of drinking water and socio-economic developement have graeter impact on cardiovascular mortality (AADR) than consumption of different types (red or white) of wine.

f. Our results are based on a large population of over 200,000. This fact contributes to the novelty and strength of our investigations.

5. PRACTICAL USABILITY OF OUR RESULTS

a. Our results can be used partly directly, and partly indirectly creating new questions and research topics to be answered. One of the directly usable results is recognizing and confirming the positive role of water hardness in prevention of cardiovascular mortality. Since the incidence of CVD is on rise the possibility is given to increase distribution and promotion of bottled mineral waters with high calcium and magnesium content in areas where piped drinking water is too soft. The importance of this in public health is currently immeasurable.

b. Our results on water hardness indirectly contribute to the elimination of positive or negative prejudices relating to the red or white nature of wines.

c. As far as cancer mortality is concerned, results of the comparison of white wine regions draws the attention to the likelihood of the potential antineoplastic effect of special Tokaj wines, exposed to the "noble yeast" Botrytis cinerea.

This is the first scientific study in a large population analyzing the probably positive physiological effects of Tokaj wines on major groups of malignant neoplasms. In the case of Tokaj „aszú" wine, the positive pharmacological effect was detected empirically earlier, since this wine was listed among drugs in the fourth edition of the book „Hungarian Pharmacopoeia" (Vámossy et al., 1933) and was in pharmacies in the 1940s. However, our studies do not tarnish the reputation of any wine-growing area. Each tastefully and professionaly prepared wine type has a unique gastronomic value. Moderate wine consumption has been part of the universal human culture for thousands of years and we believe that this will continue in the future.

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List of publications related to the dissertation

Hungarian scientific articles in Hungarian journals (1)

1. **Nagy, J.**, Sipka, S., Kocsis, J., Horváth, Z.: A gastrointestinalis daganatok és szív-ér rendszeri betegségek standardizált halálozási arányszámai Magyarország négy borvidékén és egy nem borvidéken 2000-2010 között.
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