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Multiple Sclerosis and Cancers in Croatia – A Possible Protective Role of the »Mediterranean Diet«

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A B S T R A C T

Multiple sclerosis (MS) is an autoimmune disease triggered by a combination of genetic and environmental risk factors which are however individually insufficient to provoke the disease. Previous investigations studied the coexistence of cancer in MS patients, and only a few relations between the geographic distribution of MS and that of cancer. The aim of this research was to find an environmental link between the aetiology of MS and cancers in Croatia. Incidence and prevalence of MS in Croatia were compared with the incidence of the most frequent cancer sites: stomach cancer, cancer of the colon and the rectum, pancreatic cancer, lung cancer, cancer of the kidneys and brain cancer. Data for MS were collected from seven population-based epidemiologic studies which used Poser' s diagnostic criteria and reported the number of cases and the magnitude of the studied population. Data for cancers were drawn from the Croatian National Cancer Registry. The analysis was done for single municipalities, grouped in their belonging regions or counties, and separately for the continental and the coastal area. For each rate a 95% confidence interval was calculated. The differences between rates were tested with the chi-square test as well. In addition, MS incidence or prevalence were correlated with the corresponding cancer incidence data. Pearson's correlation coefficients were used to measure the correlation between both diseases. Calculations were done with the statistical package Statistica V 7.1. and the Smith's Statistical Package freeware In the continental area of Croatia the mean annual incidence (per 100,000 inhabitants) of MS was nearly two folds higher than in the coastal area: 2.1 vs. 1.3 (p=0.0029). The difference was lower when expressed by prevalence: 46.5 vs. 36.7 (p=0.0601). Among the malignant neoplasms, in the continental area significantly higher incidence rates were found for stomach (32.9 vs. 20.8; p=3.14E-14) and lung cancer (55.8 vs. 46.4; p=1.21E-05), whilst colon cancer alone (20.4 vs. 15.7; p=9.44E-05) or colorectal cancer (38.3 vs. 31.6; p=8.18E-05) had a significantly higher incidence in the coastal area. The geographic distribution of MS expressed by incidence was significantly correlated with pancreatic (r=0,62024, df=23, p=0.00094) and lung cancer (r=0,46380, df=23, p=0.01953). This research adds further malignant neoplasms, possibly exposure-related, to the list of diseases with geographic distribution like MS. The similarity of MS distribution with the named malignancies is unlikely to be incidental. MS in Gorski Kotar and Slavonia seems to be associated with a diet rich in meat and fat. A diet rich in fat and meat and poor in vegetables is a risk factor for stomach, colorectum, pancreatic as well as lung cancers. Some authors have documented a possible protective role of the »Mediterranean diet« for the named cancers. Olive oil is the main source of fat in the »Mediterranean diet«. Oleocanthal, a phenolic compound of the extra-virgin olive oil was found to inhibit the cyclooxigenase enzymes which are involved in demyelination and tumorigenesis. We hypothesize that the »Mediterranean diet«, olive oil and particularly oleocanthal, to have a protective role in MS too.

Key words: *multiple sclerosis, cancer, epidemiology, incidence, Mediterranean diet, Croatia*

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Introduction

Multiple sclerosis (MS) is an autoimmune disease triggered by a combination of genetic and environmental risk factors which are however individually insufficient to provoke the disease before adolescence[1–3].

The descriptive epidemiology indicates that Croatia is a zone of moderate to high risk for MS[4,5]. The distribution of the disease in Croatia is not homogeneous. Gorski Kotar, a mountainous region in the west of the country, is probably a spatial cluster of MS with the highest incidence and prevalence rates ever noted in Croatia (6.5 respectively 173.1 per 100,000 inhabitants)[5].The remaining of the country shares lower descriptive epidemiological rates. For incidence they range from 0.5 (Island of Korčula, south Adriatic) to 3.4 per 100,000 inhabitants (Donji Miholjac, eastern Slavonia), and for the prevalence from 10.2 (Island of Korčula, south Adriatic) to 91.4 (Pazin, Istria, north Adriatic)[4,5]. Such a figure might reflect a consistent environmental influence related to the aetiology of MS in Croatia.

The analytical epidemiologic investigation shows that a fat-rich diet, light colored eyes, a history of optic neuritis, allergy or head trauma and longer indoor permanence are variables with possible biological plausibility in the ethiopathogenesis of MS in the studied areas[4,6–10].

The aim of this research was to find an environmental link between the aetiology of MS and cancers in Croatia.

Methods

Data Collection

This research includes seven population-based epidemiologic studies on MS published between 1990 and 2000 in which Poser's diagnostic criteria were used and the number of MS cases were reported[7,11–16].

The survey included the most frequent cancer sites for females and males together: stomach, pancreatic, lung and brain cancer, and cancers of the kidneys colon and rectum. Data of new cancer cases in Croatia for the 1988–1994 period were drawn from the Croatian Cancer Register[17].

For the single municipalities (administrative boundaries up to 1992) the mean annual incidence and prevalence rates of MS as well as the mean annual cancer incidence were recalculated from the source data.

Data Analysis and Statistical Analysis

To asses a geographical difference or resemblance between the distribution of MS (expressed through mean annual incidence or prevalence) and malignant neoplasms (expressed through mean annual incidence), the analysis was done for single municipalities, grouped in their belonging regions or counties, and separately for the continental and the coastal area. The average number of inhabitants per year for the observed period was estimated by using the interpolation method[18,19] from the Republic of Croatia Census for 1971, 1981, 1991, and 2001[20–22].

For each rate a 95% confidence interval was calculated using a binomial approximation of the Poisson distribution where the number of cases was less than 100, or the normal approximation for cases ≥ 100 as suggested by Schoenberg[23]. The differences between rates were tested with the chi-square test as well. In addition, MS incidence or prevalence were correlated with the corresponding cancer incidence data. Pearson's correlation coefficients were used to measure the correlation between both diseases.

Calculations were done with the statistical package Statistica V 7.1. and the Smith's Statistical Package freeware (Version 2.5, August 30, 2001; *http://www.economics.pomona.edu/StatSite/SSP.html*). Level of statistical significance was set at $p<0.05$.

Results

MS incidence and prevalence by the single municipality are presented in Figures 1 and 2.

In the continental area of Croatia the mean annual incidence of MS was nearly two folds higher than in the coastal area: 2.1 (95%CI 1.8–2.3) vs. 1.3 (95%CI 1.0–1.7), X2= 8.8587, df=1, p=0.0029. The difference was lower when expressed by prevalence: 46.5 (95%CI 41.4–52.2) vs. 36.7 (95%CI 29.1–45.6), X2=3.5348, df=1; p=0.0601.

Among the malignant neoplasms, in the continental area significantly higher incidence rates were found for stomach 32.9 (95%CI 31.3–34.6) vs. 20.8 (95%CI 18.6–23.2), X2=57.4650, df=1, p=3.14E-14 (Figure 3) and lung cancer 55.8 (95%CI 53.7–58.0) vs. 46.4 (95%CI 43.1–50.0); X2=19.1430; df=1; p=1.21E-05 (Figure 4),

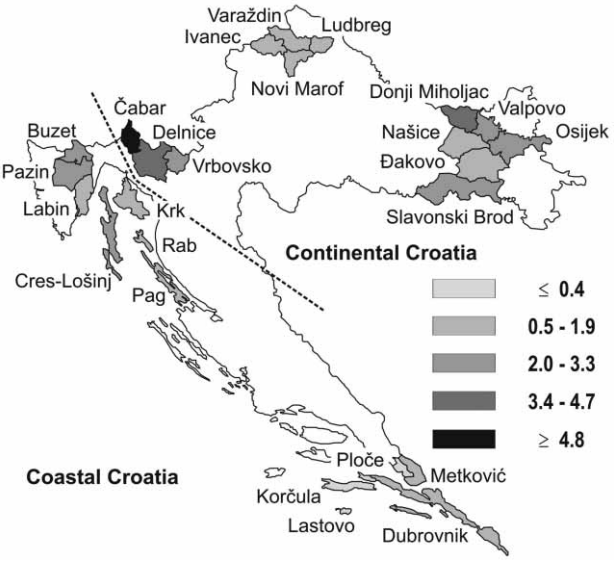

Fig. 1. MS incidences in the surveyed municipalities. Dotted line – boundary between continental and coastal area.

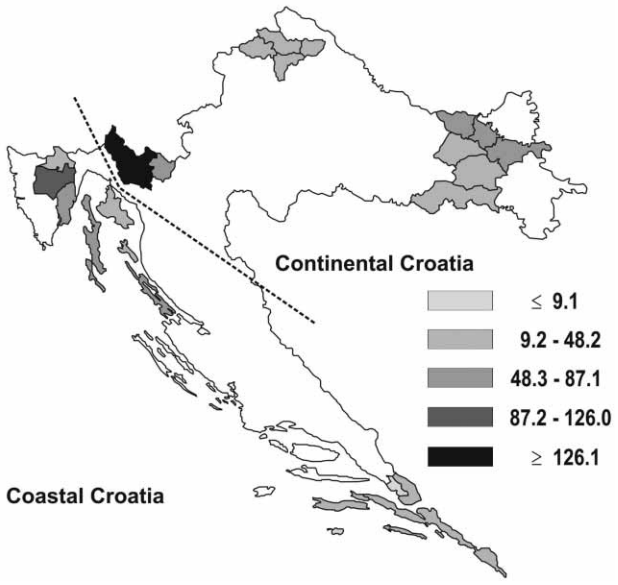

Fig. 2. MS prevalences in the surveyed municipalities. Dotted line – boundary between continental and coastal area.

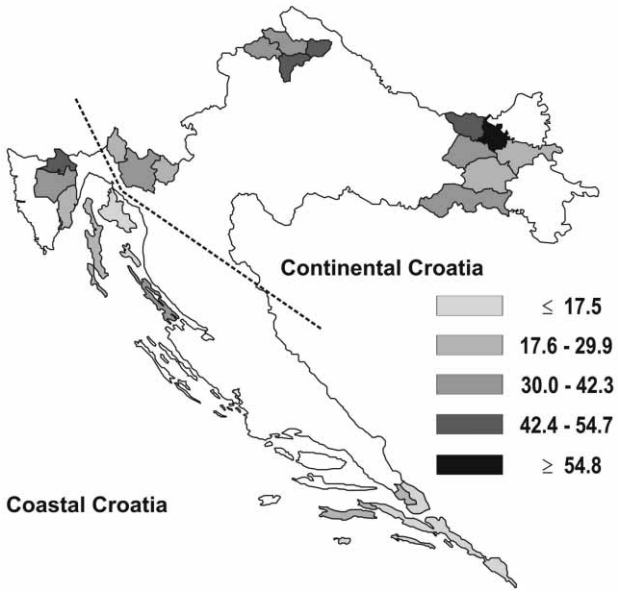

Fig. 3. Incidences of stomach cancer in Croatia 1988–1994. Dotted line – boundary between continental and coastal area.

whilst colorectal cancer had a significantly higher incidence in the coastal area 38.3 (95%CI 35.3–41.5) vs. 31.6 (95%CI 30.0–33.3), X2=15.5168, df=1, p=8.18E-05 (Figure 5). No difference in incidence rates were found for pancreatic cancer: 10.2 (95%CI 8.7–12.0) vs. 9.5 (95%CI 8.7–10.5), X2=0.5399, df=1, p=0.4625 (Figure 6).

The correlations between MS incidence and prevalence and cancers incidences are presented in Table 1.

Considering the whole Croatia the geographic distribution of MS incidence was significantly correlated with the incidence of the malignant neoplasms of the pancreas (r=0.62024, p=0.00094) and the lung (r=0.46380, p=0.01953). Whilst the cancer of the pancreas significantly correlated in both continental and coastal areas (r=0.84024, p=0.00032 and r=0.68901, p=0.01320), the cancer of the lung correlated well only in the coastal area (r=0.63173, p=0.02756). Moreover, in the continental area an increasing correlation was found for the colorectum (r=0.73537, p=0.00418), and/or rectum cancer alone (r=0.78841, p=0.00136).

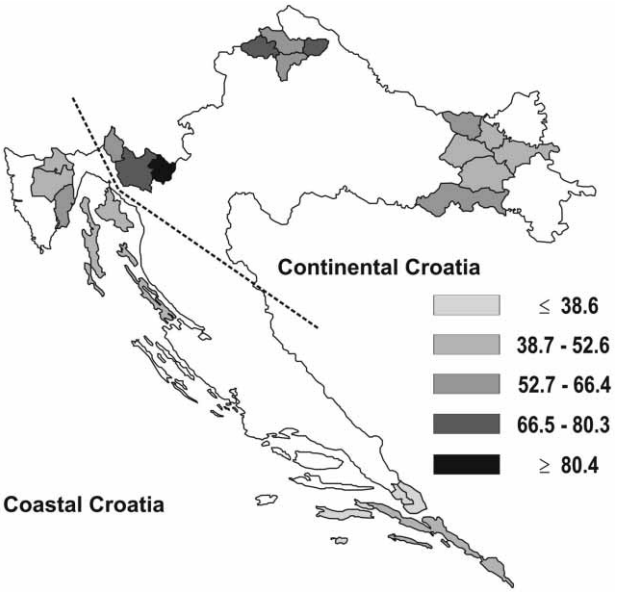

Fig. 4. Incidences of lung cancer in Croatia 1988–1994. Dotted line – boundary between continental and coastal area.

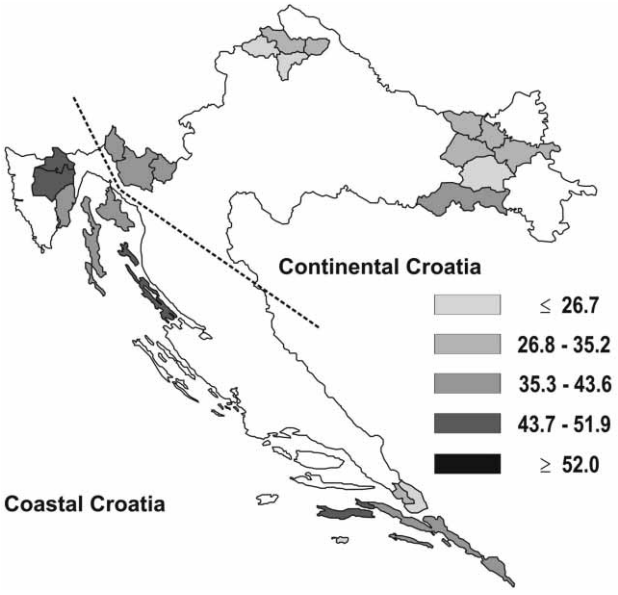

Fig. 5. Incidences of colorectal cancer in Croatia 1988–1994. Dotted line – boundary between continental and coastal area.

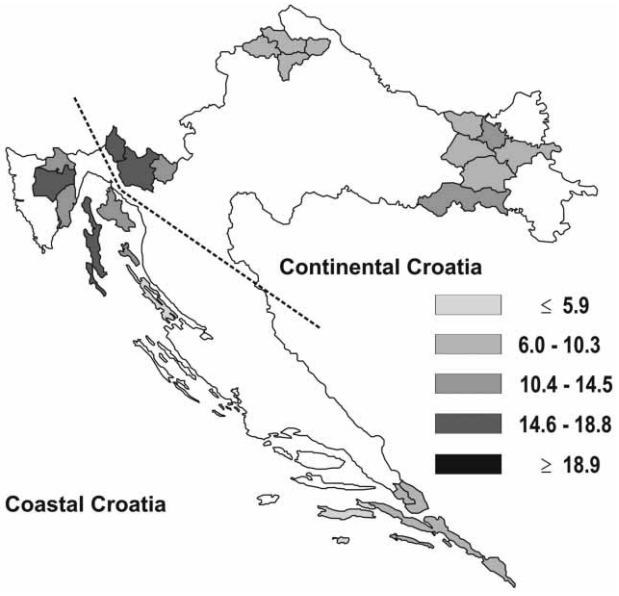

Fig. 6. Incidences of pancreatic cancer in Croatia 1988–1994. Dotted line – boundary between continental and coastal area.

Correlations with MS prevalence implied also the malignant neoplasm of the brain (r=0.41473, p=0.03927).

Discussion

Only few papers analyse the coexistence of cancer in MS patients[24]. Malignant neoplasms, associated with MS were found in 4 (1.8%) out of 219 MS patients in Croatia. Three MS patients were affected by colorectal cancer and one with chronic lymphocytic leukaemia[25]. In comparison, frequencies of cancers as comorbid causes of death ratio among MS deaths in the USA (1990–2001) are higher, 8.5%[26].

Only few studies demonstrated a resemblance between geographic distribution of MS and malignancies (cancer of the colon or prostate)[27,28] or other diseases (dental caries, Parkinson's disease)[29,30].

To test the possible differences in geographical distribution between MS and cancers in this study we used the incidence rates of both nosologic entities and correlations of malignant neoplasms vs. MS incidence and prevalence. Previous studies confronted the mortality rates[27,28].

TABLE 1A
CORRELATIONS BETWEEN MS INCIDENCE AND CANCERS

	Both areas		Continental area		Coastal area	
Site of the malignant neoplasm	Correlation coefficient (Critical r = 0.3961)	p	Correlation coefficient (Critical r = 0.5529)	p	Correlation coefficient (Critical r = 0.5760)	p
All sites	0.44589	0.02548	0.29476	0.32826	0.74372	0.00556
Stomach	0.33038	0.10674	–0.13381	0.66297	0.50668	0.09275
Colon	0.10922	0.60327	0.39658	0.17972	0.38994	0.31133
Rectum	0.34071	0.09559	0.78841	0.00136	0.21018	0.32460
Colorectum	0.30915	0.13265	0.73537	0.00418	0.54023	0.06980
Pancreas	0.62024	0.00094	0.84024	0.00032	0.68901	0.01320
Lung	0.46380	0.01953	0.08429	0.78425	0.63173	0.02756
Kidney	–0.30190	0.14245	–0.03275	0.91541	–0.33811	0.40898
Brain	0.25865	0.21188	0.17839	0.55982	0.28241	0.18680

TABLE 1B
CORRELATIONS BETWEEN MS PREVALENCE AND CANCERS

	Both areas		Continental area		Coastal area	
Site of the malignant neoplasm	Correlation coefficient (Critical r = 0.3961)	p	Correlation coefficient (Critical r = 0.5529)	p	Correlation coefficient (Critical r = 0.5760)	p
All sites	0.62030	0.00094	0.66414	0.01330	0.73764	0.00618
Stomach	0.30596	0.13691	–0.09380	0.76051	0.54923	0.06438
Colon	0.23138	0.26577	0.56277	0.04525	0.40453	0.19211
Rectum	0.39013	0.05386	0.42081	0.15217	0.38627	0.21488
Colorectum	0.43039	0.03175	0.81519	0.00068	0.61031	0.03507
Pancreas	0.65572	0.00037	0.84904	0.00024	0.71985	0.00830
Lung	0.54725	0.00464	0.37719	0.20390	0.64359	0.02394
Kidney	–0.12643	0.54704	0.40188	0.17344	–0.33422	0.28833
Brain	0.41473	0.03927	0.46906	0.10588	0.42909	0.16394

However, the mortality data based on death certificates underestimate the true MS mortality index. MS, besides that, differs from many other diseases in the fact that the majority of patients die in Croatia before the age of 55–60[25]. The use of incidence rate in searching for risk factors of diseases is more proper. Differences of these rates between surveyed areas may reflect a different distribution of genetic and environmental risk factors among the single diseases. The appropriate use of prevalence rate is less indicative, because it is the product of both incidence and disease duration, which depend mainly on success in treatment process.

Considering the environment as the source of potential risk factors for MS, our research is an ecological one. The advantage of our investigation is the homogeneity of the methods used to obtain the rates of MS. The disadvantage is the incompleteness of the geographic distribution, which includes around 20% inhabitants in Croatia (2001). Another defectiveness is the use of crude rates instead of the standardised ones.

However, this research adds further cancers, possibly exposure related, to the list of diseases with geographic distribution like MS. The similarity of MS distribution with the named malignancies is unlikely to be incidental. Although intriguing, it is difficult to interpret the found relationships because of a different association between genetics, lifestyle and diet as well as other environmental risk factors among each disease.

In Europe (and worldwide), MS frequency expressed by incidence and/or prevalence decreases from north toward south[31]. Besides genetic susceptibility, a different interplay between environmental risk and/or protective factors in different geographical areas influence such a distribution. Nevertheless, it is difficult to distinguish their causal from their protective role.

The most plausible imputed environmental risk factors for MS are solar ultraviolet radiation and the role of vitamin D, sex hormones, diet and infections[32–33].

Croatia is relatively a small country (56,594 km2) with a small number of inhabitants (4,437,460 inhabitants according to 2001 census). Nevertheless, significant regional differences in MS frequency exhibiting a north--south gradient were found[5,6]. Like MS (Figure 1–2), significant regional frequency differences manifested defined cancers, particularly of the stomach, colorectum and lung (Figure 3–6, Table 1).

Such regional differences between areas of genetic similarity and geographic closeness may be explained by differences in dietary habit[34] which is typical for Croatia where a variety of its landscape, climate and usage of the soil have conditioned a variety of dietary patterns[35]. A lack of literature or specialized maps about dietary habits, types of food (dairy food; meat products; baked goods, fish and seafood; fruits and vegetables; eggs and poultry), food preservation methods (according to popular tradition or industry processed) and consumption by regions in the Croatian population impose limitations in the analysis of the association of diet in MS as well as in cancers.

MS in Gorski Kotar and Slavonia seems to be associated with a diet rich in meat and fat[8,10]. Such a diet is deficient of essential fatty acids, particularly omega-3 and omega-6 which have protective effect in MS[36,37]. It is supposed that their lack or deficiency may alter the myelin membrane inducing MS[38]. The consumption of processed meat may be explained by the role of nitrophenols in the context of autoimmunity[39].

Recent epidemiological surveys indicate that such a diet may increase the risk of cancers of the lung, stomach, colorectum and pancreas[40–45].

In this study, cancers of the stomach and lung were significantly more frequent in the continental Croatia. A significantly higher incidence rates of all types of malignant neoplasms and particularly of the stomach and the pancreas were found in the continental Croatia also by previous surveys[46,47]. This fact may be explained to derive from a diet rich in meat and fat[48]. Researches on dietary habits in Croatia have found a significantly more frequent use of animal fats, salt added to food, lower consumption of fruits and vegetables and higher consumption of cakes, sweets and cured meat products in the Eastern and Northern regions (continental area) whilst in the Southern and Western regions (coastal area) the dietary pattern was characterized by a significantly more frequent use of vegetable oils, as well as higher consumption of fruit and vegetables, lower consumption of sweets and cakes or salt added to food[48].

According to dietary habits in continental Croatia a higher frequency of colorectal cancers were expected. Our study, as confirmed by other researches[47,50] found the colorectal cancer to be significantly more frequent in the coastal area. It is possible that genetic isolation and inbreeding have a major role in determining the risk for colorectal cancer in island population[51,52].

Some authors have hypothesized a possible protective role of the »Mediterranean diet« against cancers of the stomach, colorectum, pancreas and lung[53–55]. With the exception of the colorectal cancer, a protective role of the »Mediterranean diet« was proved as well as in Croatia[46,47].

The »Mediterranean diet« is characterized by a high consumption of vegetables and fresh fruits, fish, a daily consumption of moderate amounts of alcohol and the use of olive oil as the main source of fat[55].

Recently, oleocanthal, a phenolic compound of the extra-virgin olive oil, was found to inhibit the cyclooxigenase enzymes COX-1 and COX-2[56]. The later enzyme is presumed to contribute to demyelination[57,58] as well as to the tumorigenesis and progression of stomach, colorectal, pancreatic, lung and other types of cancers (hepatocellular, oesophageal, head and neck, breast, bladder, cervical, endometrial, skin)[59,60].

In this regard, the »Mediterranean diet«, olive oil and particularly oleocanthal might have a protective role for MS too. This fact, together with other yet unknown envi-

ronmental influences, may partially explain the decreasing gradient of MS incidence from north Europe to the Mediterranean basin.

Future research should better investigate the genetic and environmental factors which may influence the coexistence or association of MS with malignant neoplasms.

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MULTIPLA SKLEROZA I RAK U HRVATSKOJ – MOGUĆA ZAŠTITNA ULOGA »MEDITERANSKE DIJETE«

SAŽETAK

Multipla skleroza (MS) je autoimuna bolest potaknuta kombinacijom genetskih i okolišnih čimbenika rizika koji, međutim, pojedinačno nisu dovoljni da provociraju bolest. Ranija su istraživanja proučavala koomorbidnost raka u bolesnika sa MS, a malobrojna istraživanja povezanost između zemljopisne rasprostranjenosti MS i raka. Cilj ovog

istraživanja bio je pronaći povezanost MS i raka sa okolinom u Hrvatskoj. Incidencija i prevalencija MS u Hrvatskoj su uspoređene sa incidencijom najučestalijih sijela raka: želudca, kolona i rektuma, gušteraće, pluća, bubrega i mozga. Podaci o MS prikupljeni su iz sedam populacijskih epidemioloških istraživanja koji su primijenili Poserove dijagnostičke kriterij, a izvještavali broj oboljelih i veličinu stanovništva. Podaci za rak preuzeti su iz Registra za rak Hrvatske. Analiza je učinjena za pojedine općine grupirane prema pripadajućim regijama ili županijama, posebno za kontinentalno i priobalno područje. Za svaku pojedinačnu stopu izračunat je 95% interval pouzdanosti. Razlike između stopa testirane su hi-kvadrat testom. Pored toga, incidencija i prevalencija MS su korelirane sa odgovarajućim incidencijama raka primjenom Pearsonov koeficijent korelacije. Izračuni su obavljeni statističkim programima Statistica V 7.1 i Smith's Statistical Package. U kontinentalnom području Hrvatske prosječna godišnja incidencija MS (na 100.000 stanovnika) bila je gotovo dvostruko veća nego u priobalnom području: 2,1 odnosno 1,3 (p=0,0029). Razlika u prevalenciji bila je manja: 46,5 odnosno 36,7 (p=0,0601). Među zloćudnim bolestima u kontinentalnom području značajno veću incidenciju pokazivali su rak želudca (32,9 odnosno 20,8, p=3,14E-14) i pluća (55,8 odnosno 46,4, p=1,.21E-05), dočim je incidencija raka kolona (20,4 prema 15,7, p=9,44E-05) ili kolorektuma (38,3 prema 31,6,; p=8,18E-05) bila značajno veća u priobalnom području. Ovo istraživanje pridodaje još neke zloćudne bolesti popisu bolestima s zemljopisnom rasprostranjenost sličnoj MS a moguće povezane izlaganjem okolini. Sličnost između rasprostranjenosti MS i navedenih zloćudnih bolesti zasigurno nije slučajna. U Gorskome kotaru i Slavoniji MS je povezana s prehranom bogatom u mesu i mastima. Prehrana bogata mastima i mesom je čimbenik rizika za rak želudca, kolorektuma, gušteraće i pluća. Za navedene zloćudne bolesti neki su Autori dokumentirali moguću zaštitnu ulogu »Mediteranske dijete«. U »Mediteranskoj dijeti« maslinovo je ulje glavni izvor masnoća. Oleokantal, polifenolski sastojak ekstra djevičanskog maslinovog ulja inhibira enzime ciklooksigenaze, koji su upleteni u demijelinizacijski proces i tumorigenezi. Predpostavljamo da »Mediteranska dijeta«, maslinovo ulje i napose oleokantal imaju zaštitnu ulogu i za MS.