Estimation of Cancer Burden in Brežice Municipality, a Community Neighboring Krško Nuclear Power Plant in Slovenia

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Aim To evaluate cancer risk in Brežice municipality in the period 1984-2003 and compare it with the period 1970-1983, before Krško nuclear power plant started operating in the vicinity.

Methods A descriptive geographical epidemiological study was performed to compare the cancer relative risks (RR) on the national, regional, and local level. We estimated RR for all cancers combined, the five most common cancer sites, and thyroid cancer and leukemias. Standardized incidence ratio (SIR) was used as RR indicator. If the number of cancer cases was small, raw SIRs were smoothed by Bayesian hierarchical model.

Results The number of new cancer cases, as well as the estimated RR for all and individual cancer sites, increased in the period 1984-2003 in Brežice municipality and all over Slovenia. In the period 1984-2003, SIR for all cancers combined in Brežice was below the national and regional average, but RR for colorectal and cervical cancer was above this average. There were no evident clusters of districts with higher/lower RR within Brežice municipality in the period 1984-2003. RR of thyroid cancer and leukemias in Brežice was comparable with Slovenian average both in this period and before it.

Conclusion The obvious increase in cancer burden in Brežice municipality cannot be associated with Krško nuclear power plant, but most likely with unhealthy lifestyle.

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The project of site selection for low and intermediate level radioactive waste repository has been carried out in Slovenia. After the sites offered by local communities were compared from the technical, ecological, and social acceptability point of view (1,2), three locations have been selected in the final stage, community of Brežice, in the southeastern part of the country, being one of them. A detailed potential health hazard analysis has been requested by Brežice's local authorities and residents before making the final decision. The local public is particularly

concerned about probable increased cancer risk, as Krško nuclear power plant is situated in the vicinity (Figure 1). They fear that a new potential radiation source would dramatically increase the cancer risk.

We aimed to asses the current cancer risk in Brežice municipality and to compare it with the risk before the Krško nuclear power plant started to operate. In addition to calculating the risk for all cancers combined and the most common cancer sites, our focus was on leukemias and thyroid cancer, which are typically related to the ionizing radiation exposure (3). After all, our intention was to provide a risk assessment, which can be used in future cancer risk studies if the low and intermediate level radioactive waste repository is built in Brežice municipality.

Material and methods

We conducted a descriptive geographical epidemiological study. Figure 1 presents the geographical units used in the cancer risk assessment. Slovenia is officially divided into 12 statistical regions, 58 administrative units, and 192 municipalities (4). The risk in Spodnjeposavska statistical region, where Brežice municipality and Krško nuclear power plant are situated, was compared with the risk in 11 other Slovenian statistical regions. Further on, the risk in Brežice municipality was compared with the risk in the 15 neighboring municipalities. In the second part of analysis, Brežice municipality was divided into 14 districts and the cancer risk was compared among them (the last division is not mapped).

Data on cancer incidence was obtained from the population-based Cancer Registry of Slovenia, existing since 1950. The main sources of Cancer Registry of Slovenia data are notifications of cancer, which are compulsory and prescribed by the law. Cancer notifications are gathered from all hospitals and diagnostic centers in Slovenia. This information is complemented by death certificates and autopsy protocols stating cancer diagnosis. When needed, requests are sent to notifiers to confirm the information. Coding of the information is performed by trained registrars, supervised by a physician. The coding rules and standards are in compliance with the World Health Organization recommendations. Due to systematic data collection and standardized procedures, the Cancer Registry of Slovenia content was selected for publishing in all eight volumes of the Cancer Incidence in Five Continents and was included in all key international cancer

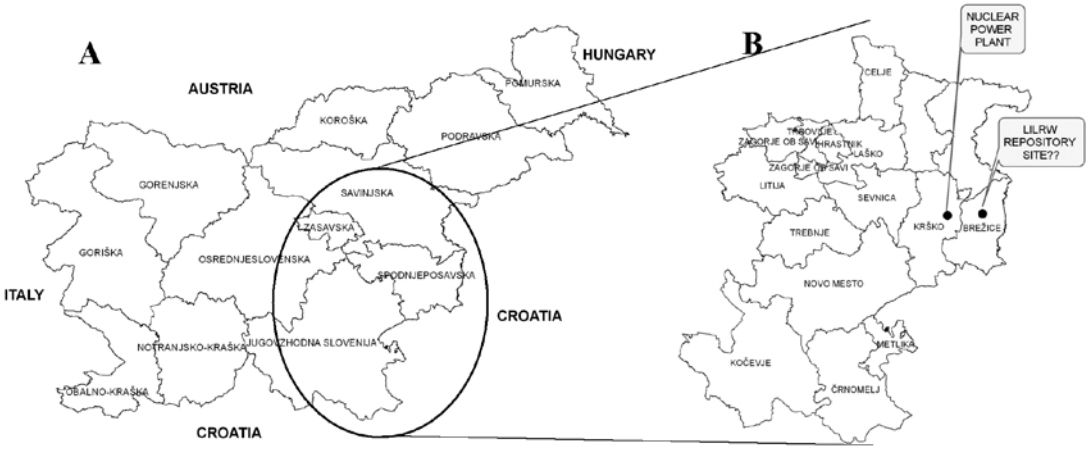

Figure 1. The study area. (**A**) Republic of Slovenia is divided into 12 statistical regions. (**B**) On the regional level, the study area was divided into 16 municipalities. Brežice municipality, with the possible low and intermediate level radioactive waste (LILRW) repository in Brežice municipality, and the nuclear power plant in the neighboring Krško municipality are situated in the Spodnjeposavska statistical region.

databases (ie, GLOBOCAN, ACCIS, EUROCIM) (5,6).

Cancer incidence data including cancer site, sex, age at diagnosis, and place of residence (exact address) at the time of diagnosis were collected for two time periods – 1970-1983 and 1984-2003. Before 1970 there were no reliable data on cancer histology type. Krško nuclear power plant started operating in 1984, and 2003 was the final year for which the data were provided by the Cancer Registry of Slovenia. Individual cancer cases records were divided according to the cancer site, sex, and the period of observation. Each group was analyzed separately. All cases of chronic lymphocytic leukemia (CLL) were excluded as CLL is thought to be less inducible by ionizing radiation than other types of leukemia (7).

Standardized incidence ratio (SIR), defined as the quotient of observed and expected cases in the procedure of indirect age standardization was used as a relative risk indicator (8). The crude incidence rate for the entire observed area and period was chosen as a standard in the calculation of the expected number of cases. SIRs were calculated for each of 12 Slovenian statistical regions and for each of the 16 selected municipalities for both time periods. The information on the resident populations was derived from Statistical Office of the Republic of Slovenia.

The number of cancer cases in a particular area is based on the Poisson distribution, with a variance proportional to the reciprocal value of the expected number of cases. Thus, there is a high sample variability in the areas with small population and this is why SIRs are usually inaccurate in these areas (9). In the second part of the study, when relative risks within Brežice municipality were estimated, the cancer cases data on the district level were scarce and the monitoring of the observed SIR pattern proved to be inefficient. To overcome this problem, raw data were smoothed by York-Mollie-Besag Bayesian hierarchical model, according to the following formula (10):

$$\log O_i = \log E_i + \sum_{j=1}^{J} \beta_j x_{ij} + H_i + S_i \,.$$

In this model, O_i and E_i represent the observed and the expected number of cases in the i-th area; x_j are the set of J explanatory variables or the so called fixed effects; and β_j is the regression coefficient for the j-th explanatory variable. H_i and S_i are two types of random effects, which handle the variation that cannot be explained by fixed effects. H_i are unstructured random effects that are geographically independent and S_i are autocorrelated random effects, which reflect local spatial structure by incorporating the influence of neighboring geographical units.

Prior distributions are assigned to random effects and hyperprior distributions are assigned to the parameters of the prior distributions, thus creating a multilevel hierarchical Bayesian model. In our study, conditional autoregressive prior distributions were assigned to the spatial components S_i (11). In conditional autoregressive distribution, the estimation of the risk in any area depends on the risk of its neighboring areas and the variability τ_s, by which the extent of spatial smoothing is controlled. The heterogeneity components H_i are given as independent normal distributions with mean zero and variance τ_h. As suggested by Bernardinelli et al (12), gamma distribution (0.5, 0.0005) is assigned to τ_s and τ_h. The results are not affected by the hyperprior choice.

The posterior distribution is the target outcome of the described models. It characterizes the estimate of SIR_i, taking into account the initial SIR at region i, the explanatory variables, and the SIRs of the nearby areas. The procedure is called statistical smoothing as the extreme SIRs are smoothed toward the average

SIR of the nearby regions. The posterior distribution was approximated using the Gibbs sampler, part of WinBUGS software (13). Two independent Markov chains were run for 20000 iterations and the first 10000 iterations were discarded as "burn-in" samples. Convergence was confirmed by observing Brooks-Gelman-Rubin statistic (14).

Observed SIRs and Bayesianly estimated SIRs were mapped using geographical information systems. All maps were produced by ArcGIS software (ESRI, Redlands, CA, USA). Due to spatial limitations, not all maps were shown here. Other maps are available in the extended report of our research (15). Eventual clusters of areas with increased cancer risk were estimated by Moran-I statistics (16) for reviewing the observed SIR maps and by the τ_s/τ_h ratio for smoothed SIR maps. The Moran-I statistics calculation was performed using GeoDA software (17). Moran-I close to 1 and τ_s much smaller than τ_h indicated the possibility of cluster. Significance of Moran-I statistics was examined by normal Z-test.

Results

After 1970, the number of cancer cases increased in Brežice municipality, as well as in the entire Slovenia. In Brežice from 1970-1983, there were on average 21.7 new cancer cases annually (87.6/100000 inhabitants), but this number grew to 39.8 (161.2/100000 inhabitants) in the period 1984-2003. Results for all cancers combined were very similar for both sexes. SIRs by sex are summarized in Table 1 and plotted in Figures 2-4. Figures 2A and 2B show SIRs for all cancers combined in 12 Slovenian statistical regions for men for the first and the second period respectively. Figures 2C and 2D present the same information for women. SIRs were higher in the second period in all regions. Further on, all relative risks in Spodnjeposavska region were lower than the Slovenian averages. All cancers combined relative risk for men in Spodnjeposavska region grew from 0.75 (95% confidence interval (CI), 0.71-0.79) in the period 1970-1983 to 0.95 (95% CI, 0.91-0.98) in 1984-2003. Relative risk in women for the first period was 0.75 (95% CI, 0.71-0.79) and grew to 0.99 (95% CI, 0.95-1.03) in the second period (Figure 2). Moran-I statistics for the Figure 2 maps were: 2A: -0.21, 2B: -0.15, 2C: 0.04, and 2D: 0.18.

Figure 3 shows SIRs for all cancers combined in 16 municipalities of the eastern Slovenia in the two analyzed periods for both sexes.

Table 1. Relative risk estimates (standardized incidence ratios) with 95% confidence intervals for different cancer sites in Spodnjeposavska region and Brežice municipality in two consecutive time periods by sex*

	Spodnjeposavska region		Brežice municipality	
Cancer site	1970-1983	1984-2003	1970-1983	1984-2003
Men:				
all cancers combined	0.75 (0.71-0.79)	0.95 (0.91-0.99)	0.73 (0.67-0.80)	0.91 (0.85-0.97)
lung	0.88 (0.79-0.98)	0.90 (0.79-1.01)	1.02 (0.86-1.20)	0.91 (0.79-1.05)
colon and rectum	0.61 (0.51-0.73)	1.15† (1.03-1.28)	0.48 (0.34-0.66)	0.92 (0.76-1.11)
prostate	0.59 (0.48-0.71)	1.04 (0.92-1.17)	0.53 (0.37-0.74)	0.92 (0.74-1.14)
stomach	1.25 (1.10-1.42)	0.90 (0.79-1.02)	1.01 (0.8-1.26)	0.83 (0.67-1.02)
head and neck	0.98 (0.81-1.17)	1.11 (0.96-1.27)	0.67 (0.46-0.94)	0.86 (0.66-1.10)
Women:				
all cancers combined	0.75 (0.71-0.79)	0.99 (0.95-1.03)	0.78 (0.71-0.86)	1.09 (1.02-1.16)
breast	0.70 (0.61-0.79)	0.98 (0.90-1.07)	0.70 (0.56-0.87)	1.10 (0.95-1.27)
colorectal	0.77 (0.65-0.91)	1.08† (1.01-1.16)	0.67 (0.49-0.90)	1.02 (0.84-1.23)
uterine cervix	1.11† (0.91-1.35)	1.20† (1.03-1.39)	1.31† (0.96-1.75)	1.48† (1.17-1.84)
stomach	1.25 (1.06-1.47)	0.90 (0.77-1.05)	1.15 (0.86-1.50)	0.79 (0.6-1.02)
lung	0.62 (0.46-0.82)	0.80 (0.65-0.98)	0.84 (0.52-1.28)	1.05 (0.75-1.42)
thyroid	0.70 (0.43-1.08)	0.94 (0.67-1.28)	0.55 (0.20-1.20)	0.85 (0.46-1.43)
leukemias (CLL‡ excluded)	0.96 (0.71-1.27)	0.92 (0.71-1.17)	0.94 (0.54-1.53)	1.09 (0.72-1.59)

*The reference relative risk for Spodnjeposavska statistical region is the risk in entire Slovenia in the period 1970-2003. The reference relative risk for Brežice municipality is the risk in 16 eastern-Slovenian municipalities in the period 1970-2003.
†High relative risks that satisfied all three clustering criteria (visual cluster at target region; Moran-I close to 1 or -1; $P<0.05$ in Moran-I Z-test).
‡CLL – chronic lymphocytic leukemia.

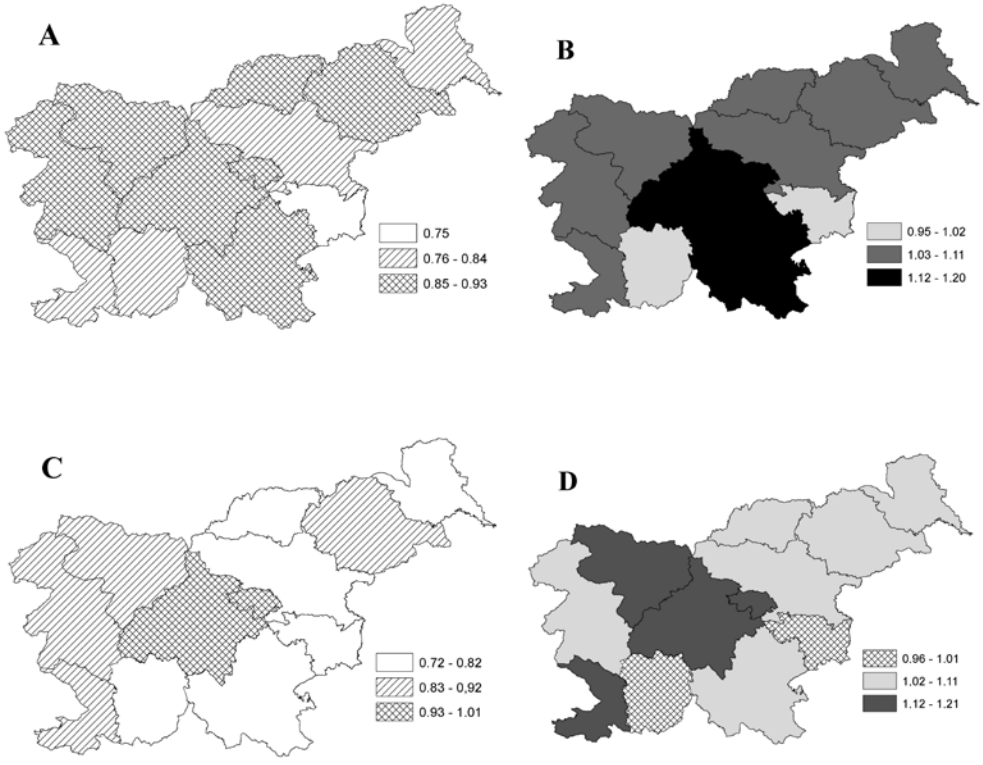

Figure 2. Standardized incidence ratios of all cancers combined by 12 Slovenian statistical regions: (**A**) men 1970-1983, (**B**) men 1984-2003, (**C**) women 1970-1983, (**D**) women 1984-2003.

Similarly as before, there was a higher relative risk in all areas in the later period. In men, relative risk for Brežice municipality grew from 0.73 (95% CI, 0.67-0.80) in the first period to 0.91 (95% CI, 0.85-0.97) in the second period, and was in both periods lower than the average relative risk in the eastern Slovenian municipalities (Figure 3A and 3B). Moran-I statistics were 0.22 and 0.34 for the map A and B, respectively. In women, all cancer combined relative risk grew from 0.78 (95% CI, 0.71-0.86) in the period 1970-1983 to 1.09 (95% CI, 1.02-1.16) in 1984-2003 (Figure 3C and 3D). Moran-I statistics was low for both maps: 0.28 for map 3C and 0.17 for map 3D.

Figure 4 presents the Bayesian smoothed SIRs by 14 districts within Brežice municipality in the two time periods for both sexes. The relative risk was higher in the second period. There were evident clusters of districts with higher/lower relative risk in the later period neither in men nor in women (Figure 4B and 4D). The variability of spatial component is much higher in comparison with the fixed effect variability. $\tau s/\tau h$ ratio for the map 4B is 4.50 (95% CI, 4.12-4.91) and $\tau s/\tau h$ ratio for the map 4D is 14.50 (95% CI, 13.4-15.7). In the first period, in men the total cancer relative risk was significantly lower in the southern part of the municipality (Figure 4A). $\tau s/\tau h$ ratio for 4A map is 0.76 (95% CI, 0.69-0.83). No evident clusters can be observed in the female map for the period 1970-1983 (Figure 4C). $\tau s/\tau h$ ratio for 4C map is 2.06 (95% CI, 1.89-2.23).

Among men in Brežice municipality, the lung, colon and rectum, prostate, stomach, head, and neck were the most common cancer sites in the later period (Table 1). The five most common cancer sites in women between

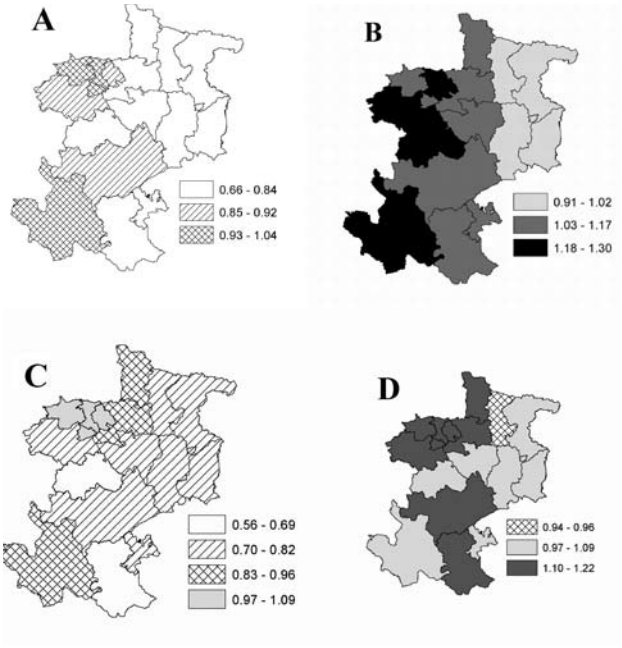

Figure 3. Standardized incidence ratios of all cancers combined by 16 eastern Slovenian municipalities: (**A**) men 1970-1983, (**B**) men 1984-2003, (**C**) women 1970-1983, (**D**) women 1984-2003.

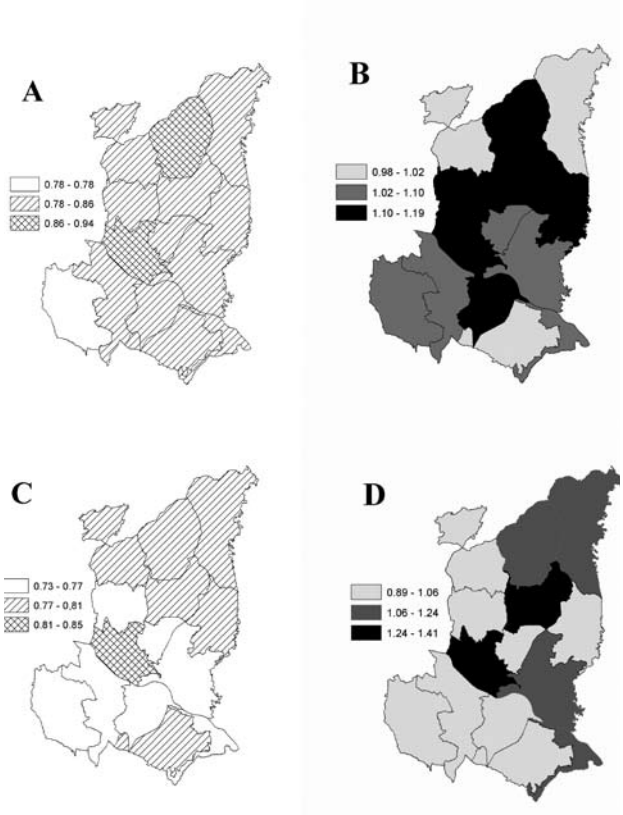

Figure 4. Bayesian estimates of standardized incidence ratios of all cancers combined by 14 districts in Brežice municipality: (**A**) men 1970-1983, (**B**) men 1984-2003, (**C**) women 1970-1983, (**D**) women 1984-2003.

years 1994-2003 were the breast, colon and rectum, uterine cervix, stomach, and lung (Table 1). SIRs for the five most common sites were comparable with the Slovenian averages, with the exception of cervical and stomach cancer in women, which had an unusually high incidence in Brežice municipality compared with the national average. There were 7.6% of cervical cancers among all female cancers in Brežice, but this percentage was only 3.8 on the national level. Cancer of the uterine cervix was the fourth most frequent cancer site in Brežice, whereas it ranks sixth in the entire Slovenia. Similarly, the female stomach cancers represented 5.3% of all cancers in Brežice, occupying the sixth place, whereas on the national level they represent 3.8% of all cancers, occupying the eighth place. The risk assessment for the five most common cancer sites by sex was performed in the same manner as for all cancers combined (Table 1). Our results indicate that the relative risk for the most common cancer sites in Spodnjeposavska region did not differ significantly from the national average inn the period 1984-2003. Nevertheless, there was a higher relative risk in Spodnjeposavska region of colorectal cancer in both sexes and of cervical cancer in women. There was a higher risk of cervical cancer in Brežice municipality than in 16 eastern Slovenian municipalities. In the first period, certain districts in Brežice municipality had greater risk of stomach and lung cancer, and all cancers combined in men. These differences disappeared in the later period. In women, there was greater risk of lung cancer in southern part of the municipality in the later period. The differences within Brežice municipality in both periods were minimal and most probably random.

In addition to the most common cancer sites, a special focus was placed on the relative risk assessment for thyroid cancers and leukemias, as they are related to the ionizing radia-

tion exposure (Table 1). There was an increasing incidence trend for both thyroid cancers and leukemias in Brežice municipality, as well as in the whole Slovenia. The relative risk of thyroid cancers and leukemias in Spodnjeposavska statistical region was roughly equal to the national average before and after the Krško Nuclear Power Plant started to operate. Similarly, there was an average relative risk for these two cancer types in Brežice municipality, when compared with 16 municipalities in the eastern Slovenia. Further on, there was no district within Brežice municipality with a considerably increased number of leukemia or thyroid cancer cases.

Discussion

Cancer burden in Brežice municipality was evaluated before and after the Krško Nuclear Power Plant started operating in the vicinity. A descriptive geographical epidemiological study was used to compare cancer risks on the national, regional, and local level. The results of our study showed that there was no increased cancer burden in Brežice municipality that could be ascribed to ionizing radiation of Krško Nuclear Power Plant.

Data on cancer cases were obtained from the cancer registry, which is a routine data-collection system. As the data in routine data sets are not collected with any specific study in mind, the number of potential confounders was very limited. The only routinely available confounders were personal attributes like age, sex, place of residence, and time of diagnosis. Data on more biological relevant exposures such as reproductive factors, diet, and other life-style characteristic would improve the strength of presented results, but collecting these additional data was beyond the scope of our research. However, these data are of high quality, since the registration procedures and the registry staff have practically not changed in the last twenty-five years. The majority of cases are reported to the Cancer Registry of Slovenia up to two years after the incidence date, with a small and stable proportion (about 4%) of cases registered coincidentally (5). There is no particular completeness study for the Cancer Registry of Slovenia data, but the periodical comparisons with the national mortality database showed that the Cancer Registry of Slovenia database was rather complete (18). The reliability of Cancer Registry of Slovenia information is continuously monitored by assessing the percentage of cancer cases registered on the basis of death certificates and the percentage of microscopically confirmed cases (5,19). As the diagnostic information on death certificates is neither accurate nor precise enough, a high proportion of death certificate cases implies a lack of validity of the data. It usually also implies a lack of completeness. Moreover, for most cases, the accuracy of the stated diagnosis is likely to be higher if it is based on histological examination by a pathologist (6). The percentage of death certificate and microscopically confirmed cases in cancer registries worldwide has been evaluated by the CIV project (20). The exact values of death certificate and microscopically confirmed percentages for different periods for Cancer Registry of Slovenia are available online (21) and in Cancer Registry of Slovenia Annual Reports (5).

Before interpreting the findings of any epidemiological study, it is essential to consider how much they were affected by errors in the design, conduct, and analysis. Our study focused on the geographical distribution of cancer risks at the spatial level. The analysis of maps showing disease incidence data are a basic tool for the assessment of regional public health (22). However, ecological studies are often recognized as unreliable method among epidemiologists. The underlying problem of ecological studies is that each region is

not entirely homogeneous with respect to the exposure. More often, the exposure is heterogeneous within a region, with different levels of exposure and some individuals not being exposed at all (8). This is why the ecological studies are inadequate for the assessment of individual characteristics – just because disease rate is higher in certain region, it does not mean that all individuals living there are at greater risk. Nevertheless, when analyzing the effects of general environment or living conditions, the ecological study can provide more coherent description of the etiology of a disease than individual level studies (23).

The number of new cancer patients in Brežice municipality was increasing from 1970. The incidence has doubled in the period 1984-2003. This time trend in Brežice is comparable with the trends in the neighboring areas and the trend in the entire Slovenia. Aging of population is the main reason for such an increased cancer risk (5). According to the Slovenian population censuses for 1971 (24) and 2002 (25), the number of inhabitants in Brežice municipality older than 65 years increased almost for one third in 2002, but the number of inhabitants older than 75 years doubled in 2002. Nevertheless, our results indicate that, in addition to crude incidence rates, there was also an increase in SIRs in the last period. Eventually, the effect of environmental cancer risk factors in Brežice municipality should not be neglected.

Among all possible environmental cancer risk factors, our main concern was ionizing radiation exposure. There is enough evidence that X-radiation and γ-radiation are carcinogenic to humans (3). The sensitivity of tissues to the carcinogenic effects of ionizing radiation differs widely. Cancers that appear to be readily inducible by ionizing radiation include leukemias (except CLL), cancer of the thyroid gland, breast cancer in women exposed before the menopause, and some gastrointestinal tumors. However, ionizing radiation in high doses can cause any cancer (3). Atomic-bomb survivors who had received a mean dose of 29 mSv showed a significant rise in cancer incidence (26). If there was any exposure to radiation in Brežice municipality, the doses were not high and acute but rather low and prolonged. The most likely source of γ-radiation in their opinion is Krško Nuclear Power Plant. Because of methodological limitations of epidemiological studies, it is impossible to quantify cancer risks in human populations at doses much lower than 10 mSv (27). However, arguments suggest that a linear extrapolation of risks to very low doses is appropriate (27). The effect of low dose chronic exposure to ionizing radiation was investigated by Cardis et al (28) in a multinational retrospective cohort study of cancer mortality among workers in nuclear industry. Their results suggest that there is a small risk of cancer even at low doses and that 1%-2% of cancer deaths among the workers studied may have been caused by radiation exposure.

The radiation emission of Krško Nuclear Power Plant is monitored extremely carefully by regular internal and external experts. According to the monitoring reports, an annual contribution of Krško Nuclear Power Plant to cumulative radiation dose is less than 0.001 mSv (29). Thus, it is very unlikely that the increased risk of total cancer, as well as leukemias and thyroid cancer is due to Krško Nuclear Power Plant radiation emissions. As these cancer risks have increased evenly throughout the whole country, it is more plausible that the increased risks are attributable to some societal low-dose radiation exposures, such as medical x-ray diagnostics. The diagnostic x-ray exposure data for Slovenia are not known. However, the use of this diagnostic method has increased in most of the developed countries. The United Nations monitoring has noticed the 20% increase in the average annual x-ray

frequency between the period of 1980-84 (30) and 1991-96 (7). Berrington et al (31) estimated that in the early 1990s the cancer risk that could be attributed to diagnostic x-rays in 13 investigated developed countries ranged from 0.6%-1.8%. This is about one half of the risk attributed to diagnostic x-rays estimated by Doll and Peto for the USA in 1981 (32).

We also found increased risk of cancers that are closely associated with life-style risk factors. There was an increased risk for colorectal cancers in the eastern part of Slovenia for both sexes. Furthermore, the risk for uterine cervix cancer was significantly above the national and regional average in Brežice municipality. Previous analyses did not find any specific geographical distribution of colon cancer incidence in Slovenia (5,33,34), while the increased risk of rectal cancers was demonstrated in the southeastern part of the country in all of these reports. The so called "western life-style," with fat-rich and fiber-poor diet, misuse of alcohol, smoking, and lack of exercise, is the main risk factor for colon and rectal cancer (35-38). The geographical distribution of dietary habits in Slovenia in the past is unknown, but a recent national cross-sectional study (39) showed that unhealthy eating habits are particularly prevalent in the southeastern Slovenia.

Infection with oncogenic Human papillomaviruses (HPV) is crucial in the uterine cervix cancer etiology (40). We have no information about differences in the HPV infection among Slovenian municipalities nor can we find any convincing argument for the suggestion that the HPV infection is most prevalent only in Brežice municipality. A more likely explanation of high uterine cervix cancer risk in Brežice is the (un)functionality of the screening program, as it can decrease the cancer incidence significantly (41). A nation-wide uterine cervix cancer screening program has been implemented in 2002 in Slovenia. The screening quality indicators of Brežice municipality are similar to the national ones in 2003 and 2004 (42). If high incidence rates of uterine cervix cancer in Brežice municipality in the 1990s indeed reflect a poor screening program, a relative decrease should be expected in a few years, when the benefits of better organized screening program will manifest.

Taken together, the results of geographical analysis of cancer risk in Brežice municipality do not indicate a measurable increase in cancer burden related to Krško Nuclear Power Plant. However, our study suggests that the burden of cancers which are closely associated to unhealthy life-style, especially poor diet and non-attendance in screening programs, is high in Brežice municipality. A well planned health promotion program, respecting the latest European Code Against Cancer (43), should be introduced.

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