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# Impact of War on Central Nervous System Tumors Incidence – A 15-Year Retrospective Study in Istria County, Croatia

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## ABSTRACT

*The aim of study was to analyze epidemiological features of central nervous system (CNS) tumors diagnosed in Istria County, Croatia, with a particular emphasis on incidence dynamics during the wartime (1991–1995). The data were extracted from the medical records of patients with CNS tumors admitted to the Department of Neurology of Pula General Hospital in the period from the 1<sup>st</sup> January 1986 to the 31<sup>st</sup> December 2000, N=364. For calculation of rates, we used data from the 2001 Croatian census <http://www.dzs.hr/Eng/Census/census2001.htm><sup>1</sup>. Data are presented as counts and incidence rates (IRs) per 100,000 persons-years in the case of annual rates. Annual incidence rates are shown as »raw« incidence rates and smoothed 5-year rolling average rates. The examined patient-related variables were: sex, age, occupation, premorbidity and comorbidity, with a particular emphasis on psychosomatic disorders and negative habits. The analyzed tumor-related variables included clinical manifestation, localization, and applied diagnostic and therapeutic methods. Primary tumors were separated from the metastatic, and the latter were analysed with respect to their site of origin. The lowest incidence of CNS tumors (10 patients) was reported in 1990, and the highest (42 patients) in 1993. The incidence dynamics of CNS tumors showed a rapidly progressive increase over the 1991–1995 period, followed by the return to average values. The access to a better and more readily available diagnostics may only partially explain this phenomenon. Therefore, we analyzed other factors that may have contributed towards the rapid increase in the number of CNS tumors, such as its coincidence with the war or psychotrauma. The results confirm the observational clinical hypothesis of an extreme increase in the number of CNS tumors during the period under consideration.*

**Key words:** CNS tumors, war, epidemiology, incidence, Croatia, psychotrauma

## Introduction

Tumors of central nervous system (CNS) account for 3–5%, and together with childhood tumors up to 10%, of all neoplasms<sup>2,3</sup>. The annual incidence falls in the range of 11–20 per population of 100,000<sup>3–5</sup>. The expected annual incidence in the population that gravitates to Pula General Hospital is 15–22 cases per year.

The war in Croatia (1991–1995) had a direct impact on the mortality and morbidity of directly exposed military and civilian population. The indirect influence of war on a decrease in life quality of the population that was not under a direct exposure was also significant. Contributing factors were the fear of death and destruction, the increased poverty accompanied by inadequate nutrition, the increase in smoking, alcohol abuse and other negative habits, as well as the immune system failure.

## Subjects and Methods

We analyzed clinical histories and medical records of a total of 364 patients diagnosed with CNS tumors who were admitted to the Department of Neurology of Pula General Hospital in the period from the 1<sup>st</sup> January 1986 to the 31<sup>st</sup> December 2000.

The examined patient-related variables were: sex, age, occupation (intellectual or manual work, retired), premorbidity and comorbidity. We paid a particular attention to psychosomatic disorders (hypertension, peptic ulcer, diabetes mellitus, and cardiac disease) and negative habits (smoking, alcohol). We also analyzed the presence of depressive syndrome premorbidly and after the diagnosis of a CNS tumor. The examined tumor-related variables included the clinical picture and tumor localization. Primary CNS tumors were separated from the

metastatic, and the latter were analyzed with respect to their site of origin. We also studied diagnostic and therapeutic methods. The diagnostic methods included computerized tomography (CT), electroencephalography (EEG), nuclear magnetic resonance (NMR), and pathohistological evaluation. The applied therapeutic methods were surgery, chemotherapy, radiation and conservative approaches.

### Data presentation and analysis

Data are presented as counts and incidence rates (IRs) per 100,000 person-years (p-y), i.e., per 100,000 persons in the case of annual rates. Annual incidence rates are shown as »raw« incidence rates and as smoothed 5-year rolling average rates.

Differences between IRs are presented as incidence rate ratios (IRRs) with exact Poisson-based 95% confidence limits (CL) and associated Fisher's exact p-values.

For calculation of rates, we used data from the 2001 Croatian census<sup>1</sup>. In 2001, there were 175,167 residents  $\geq 15$  years of age in the Istria County, 84,041 men and 91,126 women. This data, together with data on annual changes due to migrations (primarily refugees from the regions directly affected by the war) that are also available from the census, were used to approximate the population size for the years 1986–2000.

## Results

A total of 364 patients diagnosed with a CNS tumor were treated over the 15-year period: 210 (57.69%) were male, 154 (42.31%) were female, 62.36% were retired,

27.20% manual and 10.44% intellectual workers. The average age was  $57.52 \pm 3.66$  years.

The number of newly diagnosed patients with CNS tumors (»cases«), and incidence rates (IR per 100,000 person-years) of primary and metastatic CNS tumors in population 15 years of age in Istria County for the period 1986–2000 is shown in Table 1. Data are counts, IRs or rate ratios with 95% confidence limits (CL), median (range) for age at disease onset, and median difference with 95% CL.

The incidence of the CNS tumors per 100,000 inhabitants is shown in Figure 1. Raw incidence rates and »smoothed« (five year rolling average) curves are shown.

Incidence rates (per 100,000 p-y) of primary and metastatic CNS tumors for the period 1986–1991, 1992–1997 and 1998–2000 is shown in Figure 2. Estimated differences (with 95% CI) in incidence rates in Figure 3 are shown as incidence rate ratios (IRR) between the periods 1992–1997 vs. 1986–1991, and 1998–2000 vs. 1992–1997. Higher IRR indicates higher incidence rate (per 100,000 p-y) in the numerator period.

Incidence rates of primary and metastatic CNS tumors by age-group and sex is shown in Figure 4.

With respect to the premorbidity and negative habits, 7.37% of the patients had peptic ulcer, 25.26% hypertension, 25.05% heart disease, 10.75% diabetes mellitus, 18.56% smoked and 13.05% abused alcohol.

In 81.87% of the patients, the tumor was localized supratentorially, in 12.64% occurred below the tentorium and in 5.49% spinally. Primary CNS tumors were found in 207 (56.87%) patients and metastatic neoplasms in 157 (43.13%).

**TABLE 1**  
NUMBER OF NEWLY DIAGNOSED PATIENTS WITH CENTRAL NERVOUS SYSTEM (CNS) TUMORS IN ISTRIA COUNTY, CROATIA (1986–2000)

|                            | Primary tumors   | Metastatic tumors | All tumors       | Primary / metastatic tumors | p     |
|----------------------------|------------------|-------------------|------------------|-----------------------------|-------|
| Number of patients         |                  |                   |                  |                             |       |
| Men                        | 116              | 94                | 210              |                             |       |
| Women                      | 91               | 63                | 154              |                             |       |
| Total                      | 207              | 157               | 364              |                             |       |
| Incidence rates            |                  |                   |                  |                             |       |
| Men median (range)         | 10.1 (8.4–12.2)  | 8.2 (6.6–10.0)    | 18.3 (15.9–21.0) | 1.23 (0.93–1.64)            | 0.147 |
| Women median (range)       | 7.4 (6.0–9.1)    | 5.1 (3.9–6.6)     | 12.6 (10.7–14.7) | 1.44 (1.04–2.02)            | 0.024 |
| Total median (range)       | 8.7 (7.6–10.0)   | 6.6 (5.6–7.8)     | 15.4 (13.8–17.0) | 1.32 (1.07–1.63)            | 0.01  |
| Men / women median (range) | 1.36 (1.03–1.81) | 1.59 (1.47–2.23)  | 1.48 (1.18–1.88) | /                           | /     |
| p                          | 0.027            | 0.004             | <0.001           | /                           | /     |
| Age at diagnosis (years)   |                  |                   |                  |                             |       |
| Men median (range)         | 58.5 (15–88)     | 64 (34–91)        | 62 (15–91)       | –5 (–9 – –2)                | 0.004 |
| Women median (range)       | 59 (23–88)       | 61 (25–84)        | 60 (23–88)       | –3 (–7–1)                   | 0.209 |
| Total median (range)       | 59 (15–88)       | 63 (25–91)        | 61 (15–91)       | –4 (–7 – –2)                | 0.002 |
| Men / women median (range) | –1 (–5–3)        | 2 (–2–5)          | 1 (–2–3)         | /                           | /     |
| p                          | 0.609            | 0.292             | 0.654            | /                           | /     |

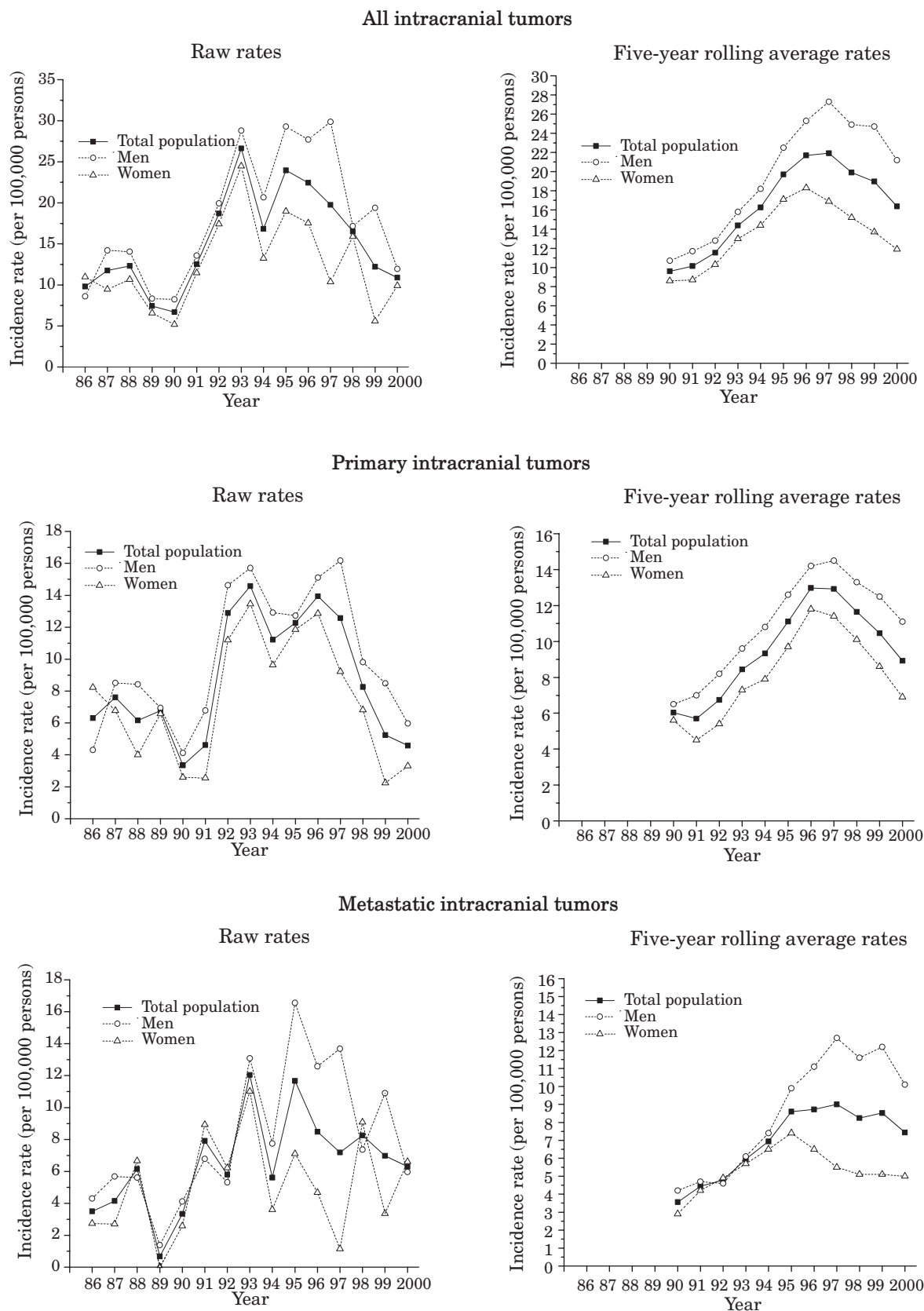


Fig. 1. Annual incidence rates of central nervous system tumors in the adult population of the Istria County, Croatia (1986–2000), overall and by sex.

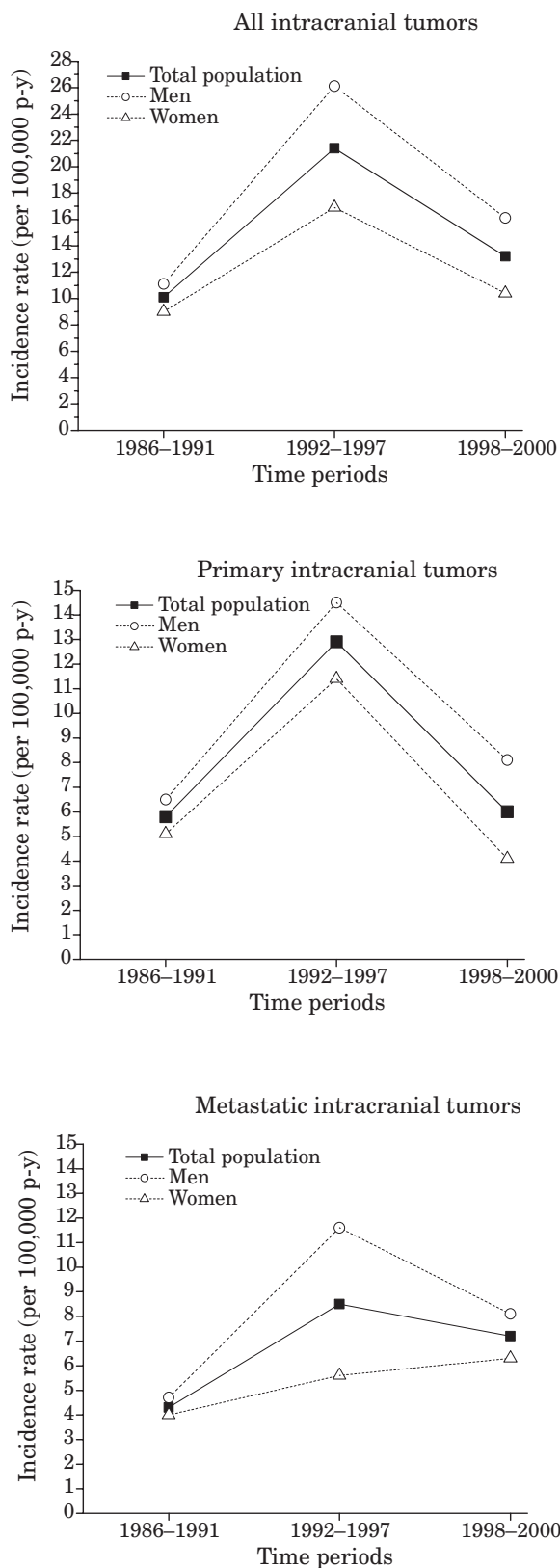


Fig. 2. Incidence rate of central nervous system tumors (primary and metastatic) in the adult population of Istria County, Croatia for the period 1986–1991, 1992–1997 and 1998–2000, overall and by sex.

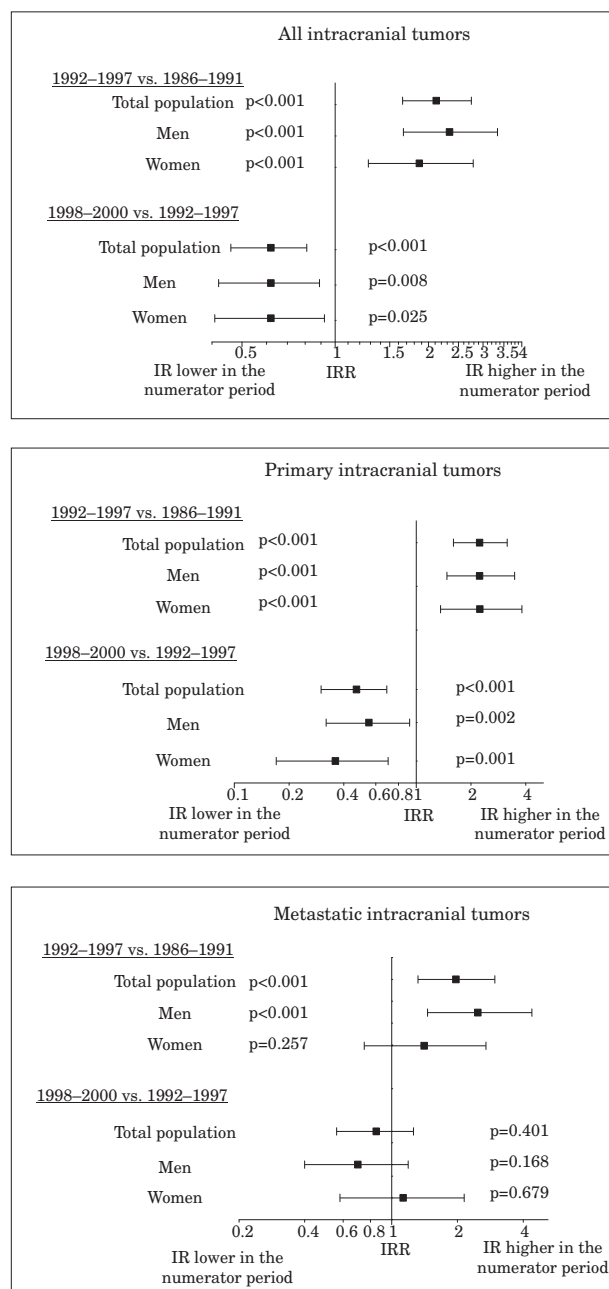


Fig. 3. Estimated differences (with 95% confidence interval) in incidence rates (IR) shown as incidence rate ratios (IRR) between the periods 1992–1997 vs. 1986–1991, and 1998–2000 vs. 1992–1997 for the central nervous system tumors (primary and metastatic) in the adult population of the Istria County, Croatia overall and by sex.

The secondary tumors site of origin was most frequently lungs (41.40%), then a melanoma (17.19%), colon (14.01%), and breast (12.10%). Other organs (kidney, prostate, stomach, ovary, etc) account for the remaining 3.48%. In 11.46% of the patients, the site of tumor origin was unknown. One female patient had two, and one male had three primary tumors: prostate, colon and melanoma.

The incomplete pathohistological findings indicate the following sequence of frequencies with respect to the histological tumor type: glioblastoma, meningioma, astro-

cytoma, pituitary tumors, neurinoma, oligodendroglioma and others.

One hundred and eighty-four patients, or 50.54%, underwent a surgical treatment, while in 20.32% of the patients chemotherapy and radiation therapy were applied. In 338 patients (92.85%) the diagnosis was established by CT. A total of 42 patients (11.53%) underwent NMR examination and 291 (79.94%) EEG.

## Discussion

A comparison of the obtained results with the data reported in literature<sup>2,4</sup> confirmed that our data conformed to the expected sex and age distributions. Most patients were retired, what corresponded to our expectations regarding their age group.

The comparison of our patients according to age groups and gender did not show statistically significant difference. The incidence of all tumors (primary and metastatic) was increased in age group from 50–59 years, same in both gender (Figure 4).

The localizations of tumors also corresponded to the usual sequence of frequencies. Most tumors were situated supratentorially, then infratentorially, and the least number spinally. The recorded clinical manifestations also did not show any peculiarities and they primarily included central nervous deficit-type symptoms such as hemiparesis, then psychoorganic syndrome, and in the least number of cases, peripheral neurological deficit. The metastatic tumors sites of origins corresponded to those reported in the literature<sup>4,6</sup> with the exception that our patients had slightly more primary tumors of colon.

The ratio of primary versus secondary tumors is, however, uncommon. According to the literature, metastatic CNS tumors account for 12–27% of the total number of CNS neoplasms<sup>2,4,6</sup>. We found 43.13% metastatic tumors, what is more than expected. The incomplete pathological evaluation of the histological samples prevented an adequate analysis, but the available data confirmed that the frequencies of specific tumor types corresponded to the frequencies reported in literature: a prevailing number of gliomatous neoplasms of varying malignancy, followed by meningioma<sup>3,4,7</sup>.

Because many patients were treated in other departments (neurosurgery or oncology) and because other methods were applied during the later course of their treatments, to complement the originally administered surgical or conservative treatment, the data on therapeutic methods are imperfect.

In most patients the presence of a tumor was established by CT. A small number of patients underwent NMR. NMR was infrequently applied because in early years of the study period this method had not been in use and in later years the small number of apparatuses and financial reasons resulted in the application of NMR only in cases when the original diagnosis had to be verified. EEG, as a non-invasive and simple method, was used in most patients, particularly those suffering from seizures.

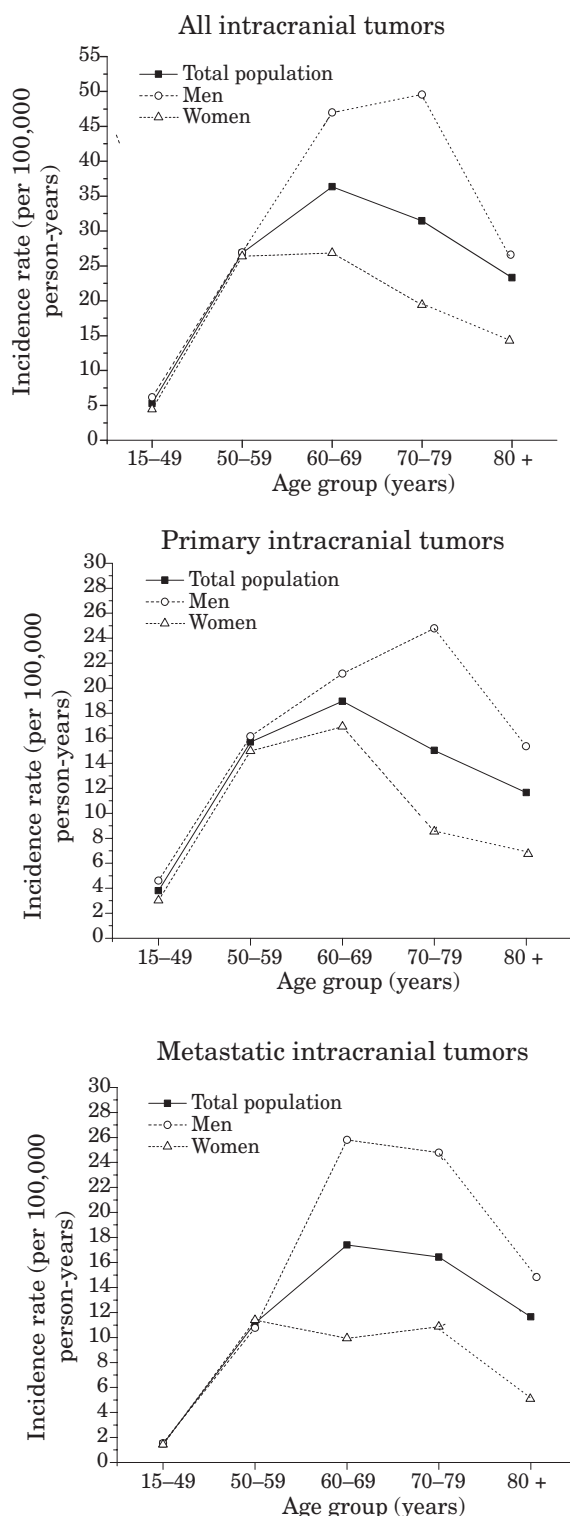


Fig. 4. Age-specific incidence rates of central nervous system tumors (primary and metastatic) in the adult population of the Istria County, Croatia (1986–2000).



The incidence dynamics showed significant variations and deviations from the expected values. From 1986 to 1991 the number of tumors conformed to the expected values, in 1989 and 1990 there was a drop in the diagnosed cases, and from 1991 to 1995 a rapidly progressive increase was recorded (from 1991 to 1993 the number of diagnosed CNS tumors was 42, or three times the expected). After 1995, the incidence gradually returned to the expected values.

Estimated differences (with 95% CI) in incidence rates in three periods (Figure 3) showed the statistically significant increase of incidence rate ratios (IRR) in war period versus the periods before and after war.

The access to a better and more available diagnostics<sup>8</sup> may only partially explain the observed phenomenon. Therefore, we analyzed other factors that may have contributed towards the rapid increase in the number of CNS tumors such as the war, psychotrauma, and stress. With respect to that, we examined premorbidity and comorbidity placing a particular emphasis on psychosomatic disorders, negative habits, and diseases of maladaptation (so called General Maladaptation Syndrome).

Dr. Hans Selye was the pioneer in stress research<sup>11</sup> and the founder of the concept of stress. According to Selye, the response of the organism to stress<sup>9,10</sup> may be divided in three phases:

1. The alarm phase
2. The resistance phase
3. The exhaustion phase

Psychosomatic disorders such as hypertension or gastric ulcer appear in the second phase. The exhaustion phase is characterized by a reduced immune response, a propensity towards banal infections and a more rapid development of metastatic cancer<sup>12</sup>.

This may explain the large portion of metastatic tumor in the total number of CNS neoplasms in our patients who were exposed to both direct and indirect impact of the war. Our hypothesis is in accordance with the results of a group of authors who studied the increase of tumor incidence in a neighboring country<sup>13</sup>. Such drastic increases were not recorded in regions that did not experience the war<sup>14</sup>.

On the basis of earlier results<sup>15</sup>, it has been proven that stress increases the spreading of metastases and it can facilitate the metastatic process via suppression of the immune system.

In the war the alcohol consumption is increased, what influences the tumor progression, corresponding to the results of previous studies<sup>16</sup>.

Psychoneuroimmunological (PN) results point that surgical excision of the primary tumor can promote tumor metastasis<sup>17</sup>.

According to the results of relevant studies<sup>18</sup>, it has been proven that acute stress, by releasing catecholamines from the adrenal glands and activating beta (1)- and beta(2)-adrenoreceptors, suppresses the natural killer cell activity (NKA) and consequently compromises resistance to natural killer (NK)-sensitive metastasis.

In the past it has been thought that schizophrenia might be a protection against cancer, while depression has been thought to increase the likelihood of cancer. However, precise confirmation of this assumption does not exist<sup>19</sup>, as the tumor itself can reactively lead to depression, endogenously or exogenously, so it is not possible to claim that it is the matter of connection of these two entities or of coincidence.

The war is a universal stressor that besides a loss and suffering of the military and civilians causes a number of other difficulties, such as feelings of fear and uncertainty, increased poverty accompanied with inadequate hygiene and nutrition, and mourning over the dead, missing, imprisoned or wounded family members. All these factors affect the incidence of numerous diseases including CNS tumors. The psychological trauma in general population is strongly correlated with the increase in CNS tumors incidence. The results of this study confirmed the observational clinical hypothesis of an extreme increase in the number of CNS tumors during the period under consideration.

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## **UTJECAJ RATA NA INCIDENCIJU TUMORA SREDIŠNJEG ŽIVČANOG SUSTAVA, PETNAESTOGODIŠNJA RETROSPEKTIVNA STUDIJA U ISTARSKOJ ŽUPANIJI**

### **S A Ž E T A K**

Cilj studije je epidemiološka analiza bolesnika sa dijagnosticiranim tumorom središnjeg živčanog sustava (SŽS) u Istarskoj županiji, Hrvatska, s posebnim osvrtom na dinamiku incidencije tijekom ratnih godina (1991–1995). Podaci su prikupljeni analizom medicinske dokumentacije bolesnika liječenih na Odjelu za neurologiju Opće bolnice Pula u razdoblju od 1. siječnja 1986.g. do 31. prosinca 2000.g., N=364. Za demografsku analizu korišteni su podaci Državnog zavoda za statistiku – <http://www.dzs.hr/Eng/Census/census2001.htm><sup>1</sup> te je uz deskriptivnu statistiku odgovarajućim statističkim metodama izračunata godišnja stopa incidencije tumora na 100.000 osoba. Analizirane su osobine bolesnika u odnosu na spol, dob i zanimanje, te premorbiditet i komorbiditet s posebnim osvrtom na psihosomatske bolesti i negativne navike. Prikazane su karakteristike ekspanzivnih procesa u odnosu na kliničku manifestaciju i lokalizaciju te dijagnostičke metode i postupke terapije. Također su izdvojeni primarni tumori od metastatskih kod kojih je analizirano ishodišno sjelo. Najniža incidencija zabilježena je 1990. godine – 10, a najviša 1993.godine – 42 tumora. Istraživanjem dinamike incidencije prikazan je rapidno progresivni porast u godinama od 1991. do 1995., a nakon toga pad prema prosječnim vrijednostima. Respektirajući bolju i dostupniju dijagnostiku koje samo djelomično mogu utjecati na navedeni prikaz, analizirani su i drugi čimbenici naglog povećanja broja tumora SŽS, posebice koincidiranje s neposrednim ratnim godinama i psihotraumom. Rezultati istraživanja također potvrđuju empirijsku kliničku pretpostavku o ekstremnom povećanju ekspanzivnih procesa SŽS u navedenom razdoblju.