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Thyroid cancer has increased in the adult populations of countries moderately affected by Chernobyl fallout

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Background:

The incidence of thyroid carcinoma increased among children affected by Chernobyl fallout. Less evidence exists for a corresponding effect in adolescents and adults. The Cancer Registry of the Czech Republic provides an opportunity to study various determinants of the occurrence of thyroid cancer.

Material/Methods:

Anonymous population-based incidence data on thyroid carcinoma of the Czech Republic from 1976 to 1999 were obtained from the Czech Statistical Office (CSO) and the Institute of Health Information and Statistics (IHIS). This study covers 247 million person-years. Linear logistic regression models allowing for possible changes in slope (change-points) are suggested for the trends of incidence proportions.

Results:

From 1976 to 1999 a uniform annual increase of 2.0% per year was found in the directly age-standardized thyroid cancer incidence proportion (95%-CI: 1.3–2.7, $p < 0.0001$). From 1990 on, we observed an additional significant increase in the thyroid cancer incidence of 2.6% per year (95%-CI: 1.2–4.1, $p = 0.0003$). This effect (change-point) is essentially independent of age but dependent on gender: females 2.9% per year (95%-CI: 1.3–4.7, $p = 0.0006$), males 1.8% per year (95%-CI: –1.0–4.7, $p = 0.2127$). The estimated minimum latency period for the population as a whole is 4 years.

Conclusions:

Although the Czech Republic received only a relatively moderate amount of radioactive fallout, an unexpected uniformly accelerated increase of thyroid cancer in all age categories is seen from 1990 onwards. Therefore one should look carefully at collective dose and at the group of persons low in individual organ dose but high in number.

key words:

change-point • Chernobyl accident • incidence proportion • logistic regression • trend analysis • thyroid cancer

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BACKGROUND

The explosion of the nuclear reactor in Chernobyl, Ukraine, on 26 April 1986, led to the release of a large quantity of radioactive material in a range of several hundred Mega-Curies over a 10-day period. This radioactive contamination has had serious health consequences for the general population of affected countries. In Belarus, Ukraine, and the Czech Republic (CR), for example, significantly increasing incidences of malignant neoplasms (thyroid, lung, stomach, urinary system, acute leukemia) have been reported [1–4]. Given the many proven and suspected health effects of ionizing radiation, the development of thyroid carcinoma is of special interest for several reasons:

1. Shortly after a nuclear reactor accident, the main exposure would be due to radioactive iodine I-131, which has a relatively short half-life period of 8 days. Radio-iodine is incorporated quickly and completely through inhalation and ingestion. Approximately 90% of the iodine in the human body is to be found in the thyroid gland, and radioactive iodine has strong tumorigenic effects.
2. Increased risks of thyroid cancer were seen in survivors of the atomic bombs in Japan and in Marshall Island residents exposed to fallout from hydrogen bomb testing.
3. Multiple increases (10-fold to 30-fold) in the incidence of thyroid cancers in children after the Chernobyl accident have been reported from Belarus and Ukraine [5–8]. Following prognoses by the WHO and other authorities, one third of the children from the most highly contaminated district of Belarus (Oblast Gomel), who were less than 4 years old at the time of the accident, will develop thyroid cancer in the course of their life [9,10]. Many specialists hold the opinion that only the thyroid glands of children were affected by the Chernobyl fallout [11]. More recently, however, increases in the incidence of thyroid cancer in adolescents and adults have been reported from the Czech Republic, Belarus, Ukraine, Poland, and even from the North of England [3,12–15].

The main objective of this study was to investigate whether an increase in the incidence of thyroid cancer occurred in less contaminated areas also, and whether both sexes and all age categories have possibly been affected. We therefore investigated thyroid cancer incidence as recorded by the Cancer Registry of the Czech Republic. The amount of fallout of radioactive fission products in the Czech Republic is comparable to the fallout in the neighboring areas of the former German Democratic Republic (GDR) and Bavaria, Germany. The Cs-137 deposition in the Czech Republic ranges from the detection limit to 185 kBq/m² [16]. The 1988 UNSCEAR report [17] documents a lower mean contamination (2.3–2.8 kBq/m²) of the western and eastern portions of the former Czechoslovakia compared to the central portion (5.3 kBq/m²). It seems reasonable, therefore, to assume less fallout in West Bohemia than in the remainder of the Czech Republic.

MATERIAL AND METHODS

Registration of malignant neoplasms in the Czech Republic began as early as the late 1950s. In 1976 a population-based

Cancer Registry was established. The basic source of information kept on file by the Czech Cancer Registry is the mandatory form "Report on Neoplasm" filled in by physicians diagnosing the disease. The notification is returned to the district branch of the Registry within 3 months. After check-up and complementation it is included in the data base. The data are supplemented in following years and compared with data on deaths from the Czech Statistical Office (CSO). Since 1994, the publication "Malignant Neoplasms" has used the codes of the 10th Revision of the International Classification of Oncology, 2nd edition. Since January 1, 1995, the TNM Classification of Malignant Neoplasms (4th edition, 2nd revision) has been valid. The Cancer Registry of the Czech Republic is composed of 8 sub-registries, which in turn compile information from the basic registry units in the Czech districts (Figure 1).

A population-based cancer registration is judged to be complete if it contains at least 90% of all newly occurring cases in any year. In general, the completeness of registration depends on the type of cancer considered. The average percentage of morphological verification in the Czech Republic in 1995 was 77% notified cases [18]. It was lowest in Prague (67%), whereas in West Bohemia and North Moravia histological verification was above 80%. Cancer cases not registered are noted on the basis of 'Death-Certificates-Only' (DCO). A satisfactory situation in a given territory is considered to be a DCO proportion of no more than 5%. The highest proportion of DCO cases occurred in Prague (20%). In many other regions DCO frequency was less than 5%; in Central Bohemia it was 6.5%, and in North Moravia it was almost zero. We performed a sample assessment of the quality of the Czech Cancer Registry on the basis of the 10 district sub-registries of the West Bohemian registry. Quality criteria were DCO proportion and proportion of histological verification. It can be concluded that the Cancer Registry of the Czech Republic is comprehensive and complete [3].

Population-based annual age-specific incidence data on thyroid carcinoma, as well as the annual (mid-year) age-specific distribution of the population of the Czech Republic from 1976 to 1999, were obtained from the Czech Statistical Office (CSO) and the Institute of Health Information and Statistics (IHIS). These data, which when obtained were stratified by 5-year age-categories, were reduced to 25-year age-categories to minimize random variation in the statistical analyses and for ease of presentation. A fully age-adjusted and gender-specific analysis is in progress.

The basic statistical measure that we used in this study was the annual (cumulative) incidence [19], defined as the proportion of the total population or the proportion of a certain part of the population (gender, age-group), which, in every year from 1976 to 1999, was newly diagnosed as having developed thyroid cancer. To account for the aging of the population, we directly standardized [19] the thyroid cancer incidence proportions for the mean pre-Chernobyl (1976–1985) age distribution. It seems meaningful, theoretically as well as practically, to model annual absolute incidence (events) as a binomially distributed random variable, with the annual population size as the number of trials. According to Cox [20], linear logistic regression is the most appealing method for binomial variables. Consequently, we performed gender-specific trend analyses of the standardi-



Figure 1. Districts of the Czech Republic (CR). West Bohemian districts (light) used for sample validation of the Czech Cancer Registry, and also as a less exposed region of the Czech Republic (2.3–2.8 kBq/m² Cs-137) compared to the remainder (dark) of the Czech Republic (5.3 kBq/m² Cs-137) [17].

zed overall incidence proportions based on linear logistic regression. Analogously, for the age-specific incidence proportions, synoptic linear logistic models using dummy coding of age-categories and corresponding time*age-category interactions were developed. Possible change-points [21] (jumps or broken sticks) in the time trends of the incidences were estimated. The change-point methodology based on logistic regression has been applied previously to German and European stillbirth and congenital malformation data [22]. An interesting method for clustering longitudinal data sets has been suggested by Bansal and Sharma [23]. The Czech population data and the thyroid cancer incidence data were processed with Microsoft Excel 2000. For statistical analyses we used SAS 8.2 [24].

RESULTS

Overall thyroid cancer incidence in the Czech Republic was 15.0 per million in males (1804 cases) and 44.3 per million in females (5640 cases). Because of this rather large difference, a gender-specific analysis is called for. Besides gender, age is another well-known confounder in analyses of associations of risk factors with cancer (in general, cancer incidence is higher in older categories of a population). Therefore, in a long-term trend analysis of disease frequency it may well happen that a certain increase in the incidence of cancer must be attributed to the aging of the population alone. The mean age of the population of the Czech Republic has increased by approximately 3 years from 1976 to 1999. Because the aging of the population is nil or rather weak from 1976 to 1985, we took the mean total, female, and male age-distributions from this earlier time period to directly standardize the annual incidences from 1976 to 1999.

Figure 2 displays the annual crude incidences, as well as the directly age-standardized incidences for females, males and both genders combined from 1976 to 1999. The observed total number of female thyroid cancer cases was 5640. The directly age-standardized number is 5459. Hence there were 181 female cases, mainly between 1989 and 1999, which could be attributed to the aging of the population alone. For the males, 1804 observed cases were reduced to 1745 directly age-standardized cases, resulting theoretically in 59 excess male cases mainly attributable to the aging of the population after 1989.

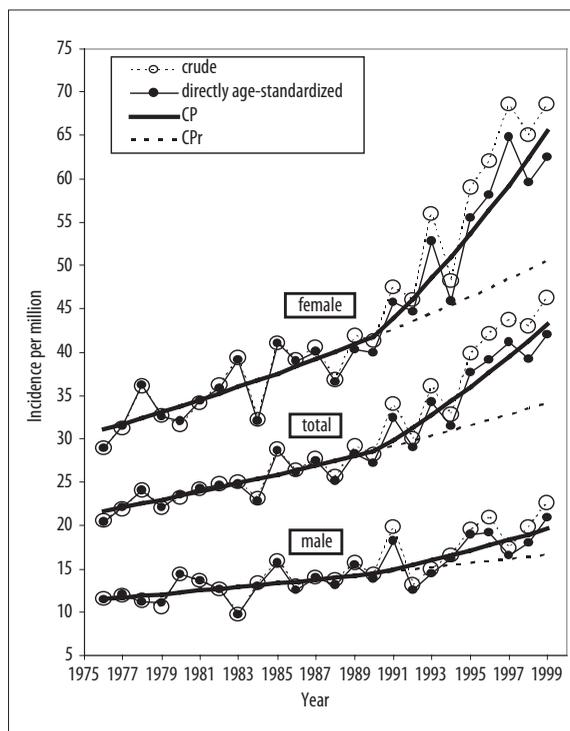


Figure 2. Crude and directly age-standardized incidence of thyroid carcinoma in females, males and both genders combined in the Czech Republic, change-point (CP) and reduced change-point (CPr) linear logistic regression models (see Table 1).

A change-point estimation of the trends of the age-standardized incidences in Figure 2 reveals a significant change-point in 1990 for both genders combined ($p=0.0003$). For males, there is a non-significant change-point in 1992 ($p=0.1416$). For females, the trend changes its slope significantly already in 1989 ($p=0.0005$). The result for both genders combined, therefore, is driven by the strong and highly significant effect for females. For ease of presentation we ignore this slight difference in genders that may partly be due to the large difference in statistical power, and so for the present purposes we assume a change-point in 1990. The non-significant result for males is consistent with the result for females. Model information for the age-standardized analyses is summarized in Table 1. Figure 2 includes the corresponding linear logistic regression lines with the 1990 change-points (CP, solid lines) for all three trend functions. The reduced change-point models (CPr, dashed lines) also included result from setting to zero the interaction effect (t^*d_{90-99}) for the additional increases of the incidences after 1990 in the respective model equations (see Table 1). A comparison of the observed standardized data with the reduced change-point models yields a theoretical excess number of cancer cases of 363 (95%-CI: 148–603) and 69 (95%-CI: –36–194) for females and males, respectively. The excess for males and females combined is consistent with the sum of the gender-specific excesses, and the total excess is somewhat more precisely estimated: 426 total excess cases (95%-CI: 187–688).

The trend of the total incidence in Figure 2 reveals a change-point in 1990, i.e., the minimum deviance is met in 1990.

Table 1. Model information for linear logistic change-point models for directly age-standardized thyroid cancer incidence in the Czech Republic, 1976–1999 (Figure 2).

Category (df, dev)	Variable	Estimate	Std. error	p-value	Odds ratio
Total (21, 21.6)	Time (t)	0.020	0.003	<0.0001	1.020
	Interaction ($t*d_{90-99}$)	0.026	0.007	0.0003	1.026
Female (21, 22.5)	Time (t)	0.021	0.004	<0.0001	1.021
	Interaction ($t*d_{90-99}$)	0.029	0.008	0.0006	1.029
Male (21, 20.9)	Time (t)	0.016	0.006	0.0125	1.016
	Interaction ($t*d_{90-99}$)	0.018	0.014	0.2127	1.018

Change-point for all models: 1990; $d_{90-99}=1$ for 1990–1999 and $d_{90-99}=0$ else; time t transformed to move the year 1990 to the origin: $t=year-1990$ (year=1976,...,1999, $t=-14,...,9$); df – degrees of freedom; dev – deviance; $t*d_{90-99}$ – interaction of time t with time interval d_{90-99}

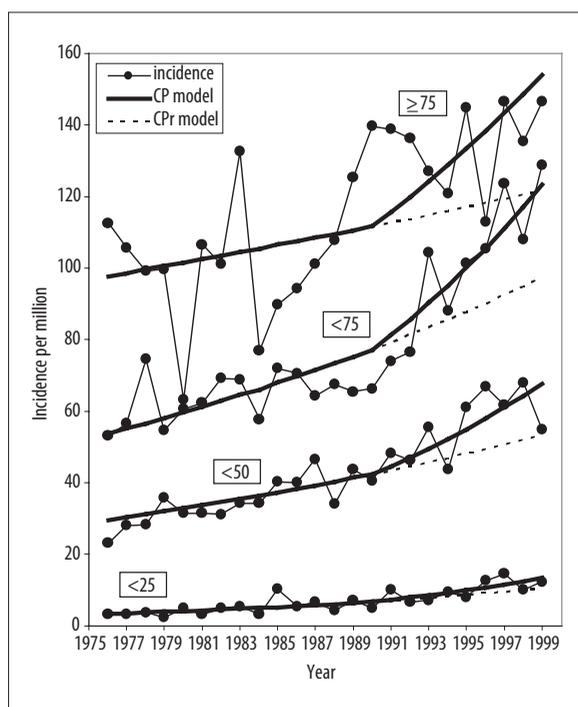


Figure 3. Age-specific incidence for females in the Czech Republic, including synoptic change point (CP, 1990) and reduced change-point (CPr) logistic regression models (cf. Table 2).

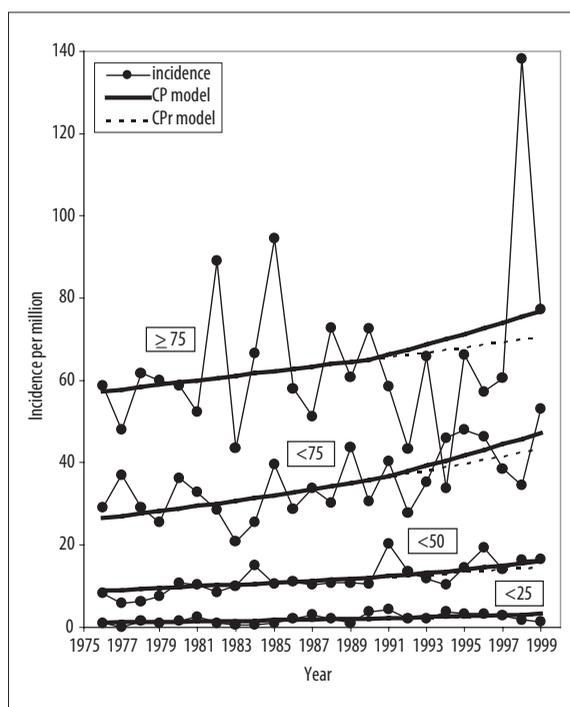


Figure 4. Age specific incidence for males in the Czech Republic, including synoptic change point (CP, 1990) and reduced change point (CPr) logistic regression models (cf. Table 3).

Consequently, we consider the middle of the year 1990 as that point in time when the trend of the thyroid cancer incidence changes its slope significantly. From this position, the minimum of the latency period for the development of additional thyroid cancers after Chernobyl may be approximately 4 years. This agrees quite nicely with a recent finding by Parshkov et al. [13], who reported an overall latency period of 5 years based on a smaller population, resulting in less statistical power. One may speculate that in an “infinite” population the latency period would in fact tend towards zero.

The development of thyroid cancer occurrence within the different age-categories cannot be revealed by analyzing the age-standardized incidences. Therefore, we investigated the trends of thyroid cancer incidence in the four 25-year age-categories, using synoptic linear logistic change-po-

int models to assess the age-specific trends simultaneously. The question arises whether the observed general increase of the thyroid cancer incidence in all years is uniform or different in the respective age categories, and, especially, whether the additional increase after 1990, which could possibly be attributed to the Chernobyl accident, is dependent on age.

Figures 3 and 4 display the incidence proportions for females and males, together with the respective partial change-point and reduced partial change-point models for the four age-categories 0 to 24, 25 to 49, 50 to 74, and 75 years of age and over. The corresponding model information is contained in Tables 2 and 3. An interesting observation here is that the additional increase after 1990 is independent of the particular 25-year age-group. This can also be seen in-

Table 2. Model information for the synoptic linear logistic change-point regression model for age-specific incidence data for females (Figure 3), deviance=87.5, degrees of freedom=88.

Variable	Estimate	Std. error	p-value	Odds ratio
Age group (25 to 49)	1.837	0.063	<0.0001	6.276
Age group (50 to 74)	2.437	0.062	<0.0001	11.437
Age group (≥75)	2.806	0.067	<0.0001	16.540
Time (t)	0.026	0.004	<0.0001	1.026
Interaction (t*d _{90-99'} broken stick)	0.026	0.007	0.0003	1.027
Interaction (t*age-group (<25))	0.024	0.009	0.0081	1.024
Interaction (t*age-group (≥75))	-0.016	0.005	0.0018	0.984

abbreviations and variables: see Table 1.

directly from Tables 2 and 3, which do not contain 3-way effects of the form time*age group*d_{90-99'}, because these 3-way effects were non-significant (p>0.2). However, in the 5-year age groups the trends are considerably more variable.

From 1976 to 1990, for females, according to our synoptic model for the age-specific data (Table 2 and Figure 3), the global annual increase for the two middle age groups together (25–74) comes to 2.6% per year (p<0.0001). From 1990 on, there is a highly significant additional increase of another 2.6% per year (p=0.0003), probably due to Chernobyl. For the youngest and oldest females, age turned out to be an effect modifier. This can be seen from the significant interactions of age with time in Table 2. The accelerated increase of an additional 2.4% (p=0.0081) in young females may be, at least partly, a consequence of the decline in the birth rate, resulting in a higher-than-average demographic aging of this group, and the very strong positive association of thyroid cancer incidence with age.

Because the male thyroid cancer incidence is only one-third of the female incidence, we would expect less precise results from the analysis of the male data. However, applying the model for the female data in Table 2 to the male data yields model parameter estimates compiled in Table 3 that are qualitatively consistent with the estimates obtained from the female data. From 1976 to 1990, for males (Table 3 and Figure 4), the annual increase for the two middle age groups (25–74) measures 2.1% per year (p=0.0022). From 1990 on, there is a non-significant additional increase of the male thyroid cancer incidence of 1.0% per year (p=0.5222). As for young females, the accelerated increase in young males may also be a result of the decline in the birth rate. The basic time trend parameters derived from the analysis of the male data are, therefore, broadly con-

Table 3. Model information for the synoptic linear logistic change-point regression model for age-specific incidence data for males (Figure 4), deviance=97.2, degrees of freedom=88

Variable	Estimate	Std. error	p-value	Odds ratio
Age group (25 to 49)	1.770	0.121	<0.0001	5.871
Age group (50 to 74)	2.860	0.117	<0.0001	17.456
Age group (≥75)	3.459	0.131	<0.0001	31.771
Time (t)	0.021	0.007	0.0022	1.022
Interaction (t*d _{90-99'} broken stick)	0.010	0.015	0.5222	1.010
Interaction (t*age-group (<25))	0.022	0.017	0.1994	1.022
Interaction (t*age-group (≥75))	-0.012	0.010	0.2369	0.988

abbreviations and variables: see Table 1.

sistent with the corresponding parameters for the female synoptic age-specific model.

In summary, male thyroid cancer incidence in the Czech Republic is only one-third of the female incidence, and basic annual increases for both genders are nearly identical. The hypothetical Chernobyl effect is only weakly dependent on age, at least from the viewpoint adopted in this paper. This effect for males is only one-third the effect for females. Effect modification of the annual growth rates by age is similar but somewhat weaker for males compared to females.

DISCUSSION

We investigated annual age and gender-specific incidence proportions of thyroid carcinoma in the Czech Republic for the years 1976–1999, with emphasis on a possible impact of the Chernobyl disaster on data from 1987 on. To assess the underlying gender-specific time trends of the age-standardized and age-specific incidence proportions, as well as possible trend disturbances as a consequence of the Chernobyl accident, we developed parsimonious trend models based on linear logistic regression. In the Czech Republic as a whole, we observed unexpectedly strong and significant annual increases in the thyroid cancer incidence proportions for both males and females even before the Chernobyl accident. Only 4 years after the Chernobyl accident the growth rate of the age standardized overall thyroid cancer incidence significantly increased, from 2.0% per year to 4.6% (=2.0+2.6) per year (p=0.0003). This effect seems to be related to the Chernobyl accident, all the more as it is gender specific (females being affected nearly three times as much as males), while improved gender-specific medical surveillance and reporting after the Chernobyl accident is hardly conceivable. The additional increases from

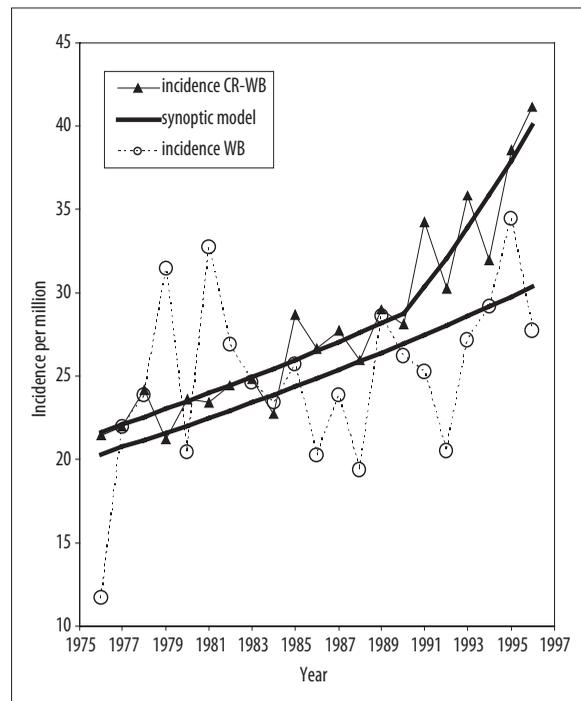


Figure 5. Age-standardized incidence of thyroid cancer in the Czech Republic for West Bohemia (WB) and the remainder of the Czech Republic (CR-WB, cf. Figure 1)

1990 on are essentially independent of age, although age is an effect modifier for both the baseline levels (intercepts) and the general annual increases in thyroid cancer incidence in the age categories. It is generally considered that x-ray exposure produces thyroid cancer with a 15–20-year latency. With this in mind, and assuming that the latency time will have an approximate normal distribution, it comes as no surprise that thyroid cancer would start to rise within 4 years of the accident.

One strength of our study is its large number of person-years observed: 247,384,706. By comparison, the pooled analysis of seven studies, including the atomic bomb survivors investigated by Ron and Lubin et al., accounts for only 3 million person-years [25]. However, one weakness of our investigation is the lack of a stratification of the data according to levels of I-131 contamination. Field measurements of radio-iodine can be used only when performed within the first days after an accident, because of the short half-life of I-131. Although it is known that iodine fallout did not strongly parallel cesium deposition, a certain association of iodine and cesium is to be expected. Therefore, we recommend stratifying the Czech thyroid cancer incidence data by, say, two to five regions according to levels of Cs-137 deposition. If the additional increases in the thyroid cancer incidence were different in differently contaminated regions, this would eventually strengthen the evidence of a causal relationship. In ecological studies one should consider iodine deficiency as a confounder, because iodine deficiency could exacerbate thyroid uptake of radioactive iodine. Positive and significant correlations of the thyroid cancer incidence with measured or reconstructed I-131 deposition have been reported previously [2,15,26,27]. A motivating example for a spatial-temporal approach is shown in Figure 5. In

the less contaminated West Bohemia ([3], Figure 1) no significant broken-stick effect is found, whereas in the remainder of the Czech Republic, in 1990, the trend of thyroid cancer incidence changes its slope significantly.

CONCLUSIONS

Our investigation shows an additional increase of thyroid cancer incidence in the Czech Republic four years after the Chernobyl accident. This effect is dependent on gender, but essentially independent of age. Our findings complement previous results by others, which were mainly confined to children and adolescents. However, this type of study based on highly aggregated data has weaknesses with respect to causal interpretation. Independent evidence can perhaps be obtained from other national cancer registries of moderately or highly contaminated countries in eastern or northern Europe, as for example Poland [28].

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