Original Article

Thyroid Cancer Incidence in Bulgaria Before and After The Introductıon of Universal Salt Iodization- An Analysis of National Cancer Registry Data

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Background: Thyroid cancer (TC) is the most common malignancy of the endocrine system and has become the fastest increasing cancer among women. Increased exposure to ionizing radiation during childhood, environmental pollutants, possible iodine deficiency, and excessive iodine exposure are among the suspected risk factors.
Aims: The study aimed to analyze thyroid cancer (TC) incidences between 1980 and 2013 in Bulgaria and to study the incidence rate before and after the introduction of universal salt iodization in 1994 in regions with different iodine deficiency levels.
Study Design: Retrospective analysis of the total number of cases with all histological types of thyroid cancer in Bulgaria (TC, ICD10 code C73) diagnosed between 01/01/1980 and 31/12/2013 retrieved from the anonymous cancer registry database of the Bulgarian National Cancer Registry (BNCR Age-standardized rates (ASR) of thyroid cancer per 100,000 of the population were calculated for each year of the periods mentioned below by sex and age utilized the WHO world reference populations with a special statistical module of the BNCR's software CancerRegBG, 2011. Incidence rates (IR) were reported by age, sex, and period of diagnosis (1980-86, 1987-93, 1994-99, 2000-2006, 2007-2013). Trends among males and females were analyzed separately, as well as by age category: 0-19, 20-44, 45-64, and 65+. Annual percentage changes (APCs) of age-standardized incidence rates were analyzed to determine trends using Joinpoint regression, by a Joinpoint statistical software SEER * Stat Software, Version 4.1.1, 2014.
Results: The ASR of TC in Bulgaria has been increasing since 1990 being higher among women compared to men (4.68 vs 2.81). The highest ASR of TC was observed in women in the period 2007 to 2013. The only significant joinpoint was recorded in 1990 for females and in 1991 for males. The highest IR was in Smolyan district, a region with historically existing iodine deficiency and relatively high post-Chernobyl radiation exposure.
Conclusion: In Bulgaria, thyroid cancer incidence rates have increased since 1990 following global trends. The reasons might be improved diagnostics and registration, pre-existing iodine deficiency, and post-Chernobyl radiation exposure. Our results showed ASR of TC in different regions - endemic and non-endemic - largely differed depending on the Chernobyl accident-induced radiation dose, but the previously existing iodine deficiency might have also played a role as it increased also the risk in areas with relatively low exposure. The role of iodine intake in thyroid cancer remains uncertain but iodine deficiency could be a contributing factor to increased risk of thyroid cancer.
Keywords: Bulgaria, Cancer, Epidemiology, Incidence, Thyroid

Introduction

Thyroid cancer (TC) is the most common malignancy of the endocrine system and was ranked ninth among women in EU countries in 2012, according to the EUCAN. The estimated incidence of thyroid cancer in European women was 9.3, threefold more prevalent compared to that in men (1).

Since the end of the last century, thyroid cancer has become the fastest increasing cancer among women especially in developed countries. In Europe thyroid cancer incidence has been raising between 1973-1977 and 1998-2002 for most of the populations except for Sweden and Norway where the incidence rate decreased for both males and females (2, 3,4).

A significant increase of thyroid cancer has been observed not only in Europe but also in many other countries around the world during the past several decades (4). In the past three decades the incidence of thyroid cancer in the United States has been more than twice higher

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among the individuals with high socioeconomic status (5). In Canada since 1970 age-standardized thyroid cancer incidence rates have increased in women from 3.9 to 23.4 per 100000 and in men from 1.5 to 7.2 per 100 000 while the mortality rates have remained stable (6). Similar trends of increasing of thyroid cancer incidence existed in certain European countries– Italy, Lithuania, Croatia, Denmark and Finland regardless of the socioeconomic status, diet and overall morbidity (7).

The reason behind the increased incidence of TC worldwide is still unclear but most likely there is no single risk factor related to this tendency (8). Improved screening and diagnostic technologies, increased healthcare accessibility and utilization, increased exposure to ionizing radiation, especially during childhood, obesity and metabolic syndrome, environmental pollutants and possibly iodine intake are among the suspected risk factors. The relationship between iodine intake and thyroid cancer remains unclear but both iodine deficiency and excessive iodine exposure may contribute to thyroid cancer although the extents of these contributions are still not resolved (9, 10). Iodine deficiency may induce an increasing incidence of benign thyroid conditions but high iodine intake also affects thyroid function and possibly TC risk (11). Since the "universal iodine supplementation" has been introduced in many countries and the iodine status of the population has improved, it is still under discussion if the iodine supplementation contributed to increased incidence of cancer and has been a topic of controversy and public concern.

Bulgaria is a country with recognized iodine deficiency (12). For the first time preventive measures to control iodine deficiency were initiated in the late fifties, but they were not sustainable and in the 1980s iodine deficiency re-emerged as a public health problem (13). In 1994 universal salt iodization (USI) was implemented on the whole territory of Bulgaria and the country was proclaimed as an "iodine deficiency free country" in 2005 (14). Up to this moment, there are no studies on the incidence of thyroid cancer before and after the introduction of the USI and the effect of iodine supplementation on the dynamics of TC in regions with different iodine status in Bulgaria.

The aim of our study was to analyze thyroid cancer incidence (TC) during the period 1980 - 2013 in Bulgaria and to study the incidence of thyroid cancer in Bulgaria before and after the introduction of universal salt iodisation. in regions with different levels of iodine deficiency before the introduction of universal salt iodization.

MATERIALS AND METHODS

The cancer related data of the total number of thyroid cancer in Bulgaria (TC, ICD10 code C73) patients diagnosed with all histological types between 01/01/1980 and 31/12/2013 were retrieved from the anonymous cancer registry database of the Bulgarian National Cancer Registry (BNCR). : The BNCR is population-based, covers the whole country and regularly receives information on new cancer cases (ICD10 codes C00-C96, D00-D09 and D37-D48) from the 13 Regional Cancer Registries (RCRs). The RCRs collect information on cancer patients, diagnosed and treated in hospitals, clinics, centers, and other health establishments within their region. Each RCR is responsible for one, two or three from all 28 administrative districts in the country. In the RCRs information for cancer cases is extracted, coded and recorded in a specialized registration information system (CancerRegBG) which complies with international classifications and standards. RCRs use two methods of data collection passive and active which has been more prevalent in recent years. Each RCR maintains regional databases containing information on registered cases. Regularly these regional databases are sent to the BNCR to be combined into a national database. (15) Data after 2013 were not included in the study, as there is a tendency to a sharp decline in the number of newly registered cases of cancer (total, by site, gender, age groups, etc.), as well as the rough and standardized frequency and mortality which due to regulatory and financial problems leading to incomplete registration of malignant diseases in the country.

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Incidence rates (IR) per 100 000 were reported by age, sex and period of diagnosis (1980-86, 1987-93, 1994--99, 2000-2006, 2007-2013). Trends among men and women were analyzed separately and by age category 0-19, 20-44, 45-64, and 65+.
Age groups were determined based on the number of cases and standardized incidence rates (world standard) in men and women at a 5-year interval. The groups are combined because there are single cases in the age group 0-19 year, 20-44 are the group with the highest incidence rates for women and 45-65 - for men. After the 65 years, the incidence rates have declined significantly.
Basic descriptive statistics were performed. Age-standardized rates (ASR) of thyroid cancer per 100 000 population were calculated for each year of the periods, mentioned below by sex and age utilized the WHO world reference populations (16) and were calculated using a special statistical module of the BNCR's software CancerRegBG, 2011. Standard errors for the ASRs were calculated as described by Boyle and Parkin [17]. Ninety-five percent confidence intervals (95 % CI) of IR were estimated using Microsoft Excel version, 2013. The average ASR over each of the five calendar periods (1980-86, 1987-93, 1994--99, 2000-2006, 2007-2013) were calculated using Microsoft Excel version, 2013.
Annual percentage changes (APCs) of age-standardized incidence rates were analyzed to determine trends using Joinpoint regression, by an Joinpoint statistical software SEER * Stat Software, Version 4.1.1,2014 (https://seer.cancer.gov/seerstat/. The software takes trend data (e.g. cancer rates) and fits the simplest Joinpoint model that the data allow and is used for calculation of cancer trends. Joinpoint regression analysis identify points where a statistically significant change over time occurred in the linear slope of the trend. Adjacent segments join at points called join points, which indicate statistically significant changes in the time trend ($p<0.05$) (17). A comparison of the confidence intervals are used to compare the age groups and time categories. When 95% confidence intervals of the means of two independent populations do not overlap, there is a statistically significant difference between the means (at a significance level of 0.05) (18).

RESULTS

The incidence of TC in Bulgaria has been increasing since 1990. It almost doubled between 1987-1993 and 2007-2013. The TC incidence rates - total and distinguished by sex from 1980 to 2013 are presented in Table 1. The overall, age-adjusted rate (WHO age- standardized rate – (ASR) increased from 1.74 cases per 100 000 population in 1994-1999 to 3.05 in 2007–2013, with average annual percentage change (APC) of 4.20 from 1990 to 2013, being higher among women compared to men (4.68% and 2.81%, respectively) (Table 1). The comparison of ASR before and after 1986 showed a statistically significant increased incidence rate since 1986 ($p< 0.05$).
Some differences in the incidence trends over the studied period from 1980 to 2013 were observed. The only one significant Joinpoint was identified in 1990 for females and in 1991 for males during the entire period 1980 - 2013, when the APC (-3.87%) from negative over 1980-1990 became steadily growing during the next period of time - from 1990 to 2013 for both sexes. (Fig 1, Fig 2, and Fig.3).
The highest ASR of TC was observed in women from 2007 to 2013 (ASR 4.86, 95% CI: 4.61-5.10) and in men for the same time period (ASR 1.21, 95% CI: 1.09-1.33). During the whole period under analysis the ASR of women was higher than that of men - three times in 1980-1986 (2.46/ 0.84 per 100 000, respectively) and four times in 2007 (4.86/ 1.21 per 100 000, respectively). (Table 1) The increase was statistically significant for each of the monitored time periods both in the whole population and in the female group. The age-adjusted incidence rate of TC was most pronounced in the age group of 20-44 years and especially among women and the increase was statistically significant compared to the previous age group 0-19 year for all time intervals. (Table. 2.).

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We compared the total ASR of TC from 1993 to 2013 in four geographically separated populations each with different historical prevalence of iodine deficiency (Pleven and Dobrich, non-endemic and Smolyan and Vratsa, endemic regions) after the introduction of universal salt iodization in 1994 (Table 3.). A significant difference was observed in the incidence of TC between the selected regions, endemic or non-endemic. The total incidence of thyroid cancer tended to be higher in endemic areas than in non-endemic ones. When the results were broken down by sex, this trend was not so obvious.

The region with the highest prevalence of TC was Smolyan (a region with a long history of iodine deficiency), not only the total rate, but also the rate by male/female compared to other regions of the country (Table 3.). The established prevalence of TC in Smolyan among women was the highest in Bulgaria for the overall observed period since 1993. The endemic region of Vratsa, also with history of iodine deficiency, ranked second. Although Dobrich and Pleven are known as non-endemic areas, a high incidence of cancer, especially among women was also registered.

DISCUSSION

The TC is the most common malignant disease of the endocrine system. The incidence rate has steadily increased in developed countries (19, 4, 8, 20). The same trend was observed in Bulgaria since the early 1990s. Bulgaria as an iodine deficient country adopted the mandatory salt iodization in 1994 shortly after the Chernobyl accident. During Chernobyl fallout, the prevention of iodine deficiency was vague and the population was left without any supplementation with iodine (13, 14). The steady increase of the incidence of thyroid cancer in Bulgaria in both sexes started in 1990-1991 and is still going on, showing a trend of increase over different time periods. Joinpoint analysis showed that there was only one point of significant refraction of cancer incidence where the downward trend turned into ascending in 1990 (males) and in 1991 (females). While in the period 1987-1986 the ASR of the total population was 1.73, in 2007-2013 it reached 3.05, which represented a 2.5-fold increase over a relatively short time. This steady trend was consistent with the overall global trend towards increased thyroid cancer in the recent decades (7, 21, 22, 11).

The upward trend in Bulgaria since 1990 could be attributed, as in many other developed countries, partially to the improved early detection of smaller nodules (< 2 cm), better reporting and registration, introduction of more accurate equipment and a broader coverage of the population with ultrasound detection and fine needle aspiration biopsies (23).

Bulgaria is among the countries with relatively low incidence of thyroid cancer in Europe. The average IR of TC in Bulgaria is twice lower than the European average, 3.05 vs. 6.3 per 100 000 population in 2012, with large regional differences observed in Europe. The incidence of TC was lower compared to Lithuania (15.5), Italy (13.5), and Austria (12.4) but the positive trend of increase is alarming (1).

As in most countries, in Bulgaria the incidence of TC cancer was more common in women, approximately three to four times higher than that in men, that corresponded to the general trend for the female population to be at higher risk of thyroid diseases including neoplasms (24, 25, 22). The age trend showed a reversed U-shaped effect, with the highest incidence among women aged 20-44 in 2007-2013. This differed from most data showing that the highest incidence of TC was among women at the age group of 45-60 years (23). Some suspected risk factors for TC included radiation exposure, especially during childhood, environmental pollution, history of thyroid diseases, and low or high iodine intake (10). The effect of radiation from Chernobyl disaster on the iodine deficient youngest population in 1986 could be the reason of the relatively higher ASR in the female age group 20-44 year from Bulgaria (ASR 2,22) compared with the older population groups 45-64 and 65+ (2,08 and 0,35). We assume that this is a Chernobyl accident effect on the iodine deficient children's population, which in 1986 was under the age of 10, particularly sensitive to

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radiation. The much higher effective dose of exposure of thyroid gland to ^{131}Iodine in children compared with adults in Bulgaria was established in 1988, two years after the accident (0.50 vs 0.17 mSv). The greatest exposures were in regions of higher altitudes above the sea level, as well as in those where the fallout density was highest (settlements above 0.8 km altitude) and some others on the path of the radioactive cloud. Smolyan and Dobrich were such cities where the highest incidence of TC in both sexes was found. (25, 27, 28). Although a significant part of the territory of Bulgaria was affected by the radiation cloud, Chernobyl effect on the incidence of cancer in the period 1990-2003 in regions with different radioactive contamination has not been proven. (28). Our results on the incidence of TC over a longer period of time, 1993-2013, showed a significantly higher incidence in Smolyan, Dobrich and Pleven compared to Vratsa, where the total effective dose was the lowest.
The highest incidence of TC among women in Smolyan **was probably** the result of radiation exposure against the background of a long-lasting iodine deficiency, thyroid diseases and low environmental selenium availability (29). Although the population of Vratsa had received relatively low radiation dose in 1986 the overall incidence of cancer and that among women was considerable (24). This **might be** the effect of radiation on an iodine deficient population exposed to industrial environmental pollution.

CONCLUSION

In Bulgaria, thyroid cancer incidence rates have increased since 1990 following global trends but still remain moderate on the European map. The reasons might be improved diagnostics and registration, pre-existing iodine deficiency and post-Chernobyl radiation. The role of iodine intake in thyroid cancer remains uncertain but iodine deficiency could be a contributing factor to increased risk of thyroid cancer. The results of our analyzes showed that thyroid cancer in the different regions - endemic and non-endemic - differed depending on the radiation dose during Chernobyl, but the previously existing iodine deficiency may also play a role as it also increased the risk in areas with relatively low exposure.
The comparison of the total incidence of TC between the endemic and non-endemic regions after the introduction of universal iodization showed that the highest incidence was observed in Smolyan and Vratsa, both regions with a pre-existing deficiency.
Currently, the iodine deficiency in Bulgaria is under control because of the universal iodization of salt. More detailed comprehensive studies are needed to identify trends in the incidence and the subtype of TC in a population without iodine deficiency.

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References

1. European Network of Cancer Registries, ENCR Factsheets, January 2017. www.encr.eu
2. Smailyte G, Miseikyte-Kaubriene E, Kurtinaitis J. Increasing thyroid cancer incidence in Lithuania in 1978–2003. BMC Cancer. 2006; 6: 284. published online 2006 Dec 11. doi: 10.1186/1471-2407-6-284
3. Kilfoy BA, Zheng T, Hollord TR et al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes Control, 2009; 20,:525-31.
4. Vučemilo L. Thyroid Cancer Incidence and Mortality Trends in Croatia 1988-2010. Acta clinica Croatica, 2015; Vol. 54, 1: 30-36.
5. Li N, Xianglin L Du, Lorraine R et al. Impact of Enhanced Detection on the Increase in Thyroid Cancer Incidence in the USA: Review of Incidence Trends by

Socioeconomic Status Within the Surveillance Epidemiology, and End Results Registry, 1980-2008. THYROID, 2013; Vol 23, 1, 103-9**.**

6. Topstad D, Dickinson J. Thyroid Cancer Incidence in Canada: a national cancer registry analysis. CMAJ Open 2017. DOI:10.9778/cmajo.20160162
7. Pellegriti, G, Frasca F, Regalbuto C et al. Worldwide Increasing Incidence of Thyroid Cancer: Update on Epidemiology and Risk Factors. J of Cancer Epidem, Volume 2013, Article ID 965212, 10 pages
8. Liu Y, Lei S, Haipeng X. Review of Factors Related to the Thyroid Cancer Epidemic. Int J Endocrin., Volume 2017, Article ID 5308635, 9 pages doi: 10.1155/2017/5308635
9. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics 2002, CA: Cancer Journal for Clinicians 2005; 55, 2, March/April: 74-108.
10. Zimmermann MB, Galetti V. Iodine Intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Research 2015; 8, 8. doi: 10.1186/s13044-015-0020-8.
11. Dal Maso L. Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control 2009 Feb; 20, 1:75-86.
12. Pentchev, I et al. In: Endemic goiter in Bulgaria, Med. I fizk, 1961 (Bulga)
13. Peneva L, Lozanov B, Koev D. Status of Iodine Nutrition in Bulgaria. In: Iodine Deficiency in Europe, Delange F , ed, Plenum Press, New York, 1993:415-19.
14. Van der Haar F, van Ingen JWE, Laurberg P. Review of Progress towards Sustained Optimal Iodine Nutrition in Bulgaria. Report by a team of experts on behalf of the Network for Sustained Elimination of Iodine Deficiency. Ministry of Health of Bulgaria, UNICEF, 2006.
15. Bulgarian National Cancer Registry.http://www.sbaloncology.bg/Bulgarian-cancer-registry.htm.
16. Ahmad OB, Boschi-Pinto C, Lopez AD et al. Age standardization of rates: a new WHO standard. GPE Discussion Paper Nr.31 WHO 2001.
17. Cancer Registration: Principles and Methods. Edited by O.M. Jensen, D.M. Parkin, R. MacLennan, C.S. Muir and R.G. Skeet // IARC Scientific Publications No. 95. - Lyon: IARC, 1991.
18. Altman GD, Bland MJ. How to obtain the P value from a confidence interval. BMJ 2011;343:d2304 doi: 10.1136/bmj.d2304.
19. Bray, F. Ren, Masuyer E, Ferlay J, Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132: 1133-45.
20. Pathac KA, Leslie WD, Klonsch ThC et al. The changing face of thyroid cancer in a population-based cohort. Cancer Medicine, open access, 2013, doi:10.1002/cam4.103.
21. Vigneri R, Malandtino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing?. Curr Opin Oncol 2015; Jan, 27(1):1-7.
22. Lukas J, Drabek J, Lukas D, Dusek L, Gatek J. The epidemiology of thyroid cancer in the Czech Republic in comparison with other countries. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2013; Sep, 157(3): 266-75.
23. Salamanca-Fernandez, E, Rodriguez-Barranco M, Yoe-Ling, Chang-Chan et al. Thyroid Cancer Epidemiology in South Spain: a population-based time trend study. Endocrine, online 2018. https://doi.org/10.1007/s12020-018-1681-6 . Pathac KA, Leslie WD, Klonsch ThC et al. The changing face of thyroid cancer in a population-based cohort. Cancer Medicine, open access, 2013, doi:10.1002/cam4.103.
24. Nagataki S, Nystroem E. Epidemiology and primary prevention of thyroid cancer. Thyroid, 2002; Oct, 12(10): 889-96.

Uncorrected proof

25. Li N, Xianglin L Du, Reitzel LR, et al. Impact of Enhanced Detection on the Increase in Thyroid Cancer Incidence in the United States: Review of Incidence Trends by Socioeconomic Status Within the Surveillance Epidemiology and End Results Registry, 1980-2008. Thyroid 2013; Vol 23, 1:103-9.
26. Vasilev G. Bayrakova A. Predicted health effects in Bulgaria from the Chernobyl NPP accident: Objective assessments and public reactions.One decade after Chernobyl: Summing up the consequences of the accident. Poster presentations, 1997, IAEA, INIS, https://inis.iaea.org/search/Search.aspx?q=28073810
27. Drozdovitch1 V, Bouville A, Chobanova N et al. Radiation Exposure to the population of Europe following the Chernobyl Accident. Radiation Protection Dosimetry 2007; 123(4): 515-528
28. Chobanova N, Vukov M, Yagova1 A, Ivanova R. Epidemiological Study on 2006; vol. XI № 2: p 86-94.
29. Lozanov B, Tzachev K, Kirilov G et al. Selenium and Thyroid Status in Children Living in an Endemic Region with adequate iodine supplementation. Endocrinologia, vol. XI 2006; 4: p 213-23.

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TABLE 1. Age-standardized incidence rates (ASR) with 95% Confidence Interval (95% CI) and p-value of thyroid cancer by sex and time periods in Bulgaria, using Joinpoint analysis for the period 1980-2013

All thyroid	Time period (year)	ASR	SE (ASR)	95 % CI	p-value
Total	1980-1986	1.73	0.05	1.64-1.83	
	1987-1993	1.41	0.04	1.32-1.50	<0,0001
	1994-1999	1.74	0.05	1.64-1.85	< 0.0001
	2000-2006	2.23	0.06	2.12-2.34	<0.0001
	2007-2013	3.05	0.07	2.92-3.19	<0.0001
	< 1986	1.73	0.05	1.64-1.83	
	>1986	2.09	0.03	2,04-2.14	<0.0001
Male	1980-1986	0.84	0.05	0.75-0.94	
	1987-1993	0.78	0.04	0.69-0.87	0,35447
	1994-1999	0.83	0.05	0.73-0.94	0,44329
	2000-2006	0.96	0.05	0.86-1.10	0,06559
	2007-2013	1.21	0.06	1.09-1.33	0,00142
Female	1980-1986	2.46	0.08	2.30-2.63	
	1987-1993	2.02	0.08	1.87-2.17	000114

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	1994-1999	2.63	0.09	2.44-2.91	<0.0001
	2000-2006	3.44	0.10	3.24-3.64	<0.0001
	2007-2013	4.86	0.12	4.61-5.10	<0.0001
SE: standard error					

TABLE 2. Age-standardized incidence rates (per 100 000, world standard) of thyroid cancer by age groups and time periods in Bulgaria

	ASR (95% CI)					
Age group (year)/time period	0 - 19	20 - 44	45 - 60	65+	Total	P***
Total						
1980-1986	0.09 (0.02-0.16)	0.68 (0.49-0.87)**	0.69 (0.39-0.98)	0.27 (-0.18-0.72)	0.09 (-0.002-0.19)	
1987-1993	0.03 (-0.004-0.065)	0.63 (0.44-0.81)**	0.54 (0.27-0.80)	0.21 (-0.16-0.58)**	1.41 (1.32-1.85)*	<0.0001
1994-1999	0.11 (0.02-0.19)	0.71 (0.49-0.92)**	0.70 (0.36-1.03)	0.22 (-0.18-0.62)**	1.74(1.64-1.85)	
2000-2006	0.07 (-0.006-0.14)	0.89 (0.66-1.11)**	0.98 (0.61-1.34)	0.29 (-0.12-0.71)**	2.23 (2.11-2.34)*	<0.0001
2007-2013	0.12 (0.01-0.22)	1.32 (1.04-1.61)**	1.32 (0.89-1.75)	0.29 (-0.12-0.69)**	3.05 (2.91-3.18)*	<0.0001
	0 - 19	**20 - 44**	**45 - 60**	**65+**	**Total**	
Male						
1980-1986	0.04 (-0.02-0.10)	0.25 (0.09-0.41)**	0.36 (0.05-0.66)	0.19 (-0.38-0.76)**	0.84 (0.75-0.93)	
1987-1993	0.02(-0.03-0.07)	0.22(0.07-0.37)**	0.35 (0.04-0.65)	0.18 (-0.34-0.72)**	0.78(0.69-0.86)	
1994-1999	0.04(-0.04-0.13)	0.24(0.06-0.41)	0.38(0.023-0.74)*	0.17(-0.35-0.69)	0.83(0.73-0.94)	
2000-2006	0.03(-0.04-0.09)	0.32 (0.12-0.5)	0.44(0.08-0.80)	0.18 (-0.32--.68)	0.96(0.86-1.060)	
2007-2013	0.05(-0.05-0.14)	0.47(0.23-0.70)	0.50(0.12-0.88)	0.19(-0.33-0.72)	1.20(1.08-1.32)*	0.00257
Female						
1980-1986	0.15(0.02-0.27)	1.1(0.77-1.45)**	1.0(0.50-1.50)	0.19(-0.37-0.76)**	2.46(2.3-2.62)	
1987-1993	0.07(-0.02-0.16)	1.04(0.70-1.37)**	0.72(0.29-1.16)	0.18 (-0.34-0.71)**	2.02(1.87-2.16)**	0.00007
1994-1999	0.17(-0.007-0.3)	1.19(0.79-1.59)**	0.99(0.44-1.54)	0.26(-0.31-0.84)**	2.62(2.44-2.81)**	<0.0001
2000-2006	0.11((-0.02-0.25)	1.48(1.05-1.89)**	1.47(0.84-2.09)	0.37(-0.24-0.99)**	3.43(3.2-3.63)**	<0.0001
2007-2013	0.19(-0.004-0.39)	2.22(1.69-2.76)**	2.08(1.33-2.83)	0.35(-0.23-0.94)**	4.86 (4.61-5.1)**	<0.0001

- * significant differences by time period, p< 0.05

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- **Significant difference by age, p < 0.05)
- *** significant differences for the total group. The p-values in the last column refer only to the comparison of the last age group (65+) with the Total group.

TABLE 3. Age-standardized incidence rates (ASR) with 95% Confidence Interval (CI) of thyroid cancer by sex and endemic/non-endemic regions in Bulgaria for the period 1993-2013			
Region	Sex	ASR (95% CI)	p
	Total		
Pleven (non-endemic) Smoljan (endemic)		1.95 (1.62-2.28) 3,09 (2.51-3.66)*	0.00079
Dobrich (non-endemic) Smoljan (endemic)		2.19 (1.80-2.58) 3,09 (2.51-3.66)*	0.01109
Pleven (non-endemic) Vratza (endemic)		1.95 (1.62-2.28) 2.70 (2.10-3.31)*	0.03264
Dobric (non-endemic) Vratza (endemic)		2.19 (1.80-2.58) 2.70 (2.10-3.31)	0.16564
	Male		
Pleven (non-endemic) Smoljan (endemic)		0,77(0.50-1.04) 1,17 (0.68-1.65)	0.15842
Dobrich (non-endemic) Smoljan (endemic)		1.02 (0.65-1.39) 1,17 (0.68-1.65)	0.64263
Pleven (non-endemic) Vratza (endemic)		0,77(0.50-1.04) 0,84 (0.51-1.17)	0.76046
Dobrich (non-endemic) Vratza (endemic)		1.02 (0.65-1.39) 0,84 (0.51-1.17)	0.48633
	Female		
Pleven (non-endemic) Smoljan (endemic)		3,17(2.55-3.77) 4,95 (3.90-5.99)*	0.00398
Dobrich (non-endemic)		3, 34(2.64-4.03)	0.01188

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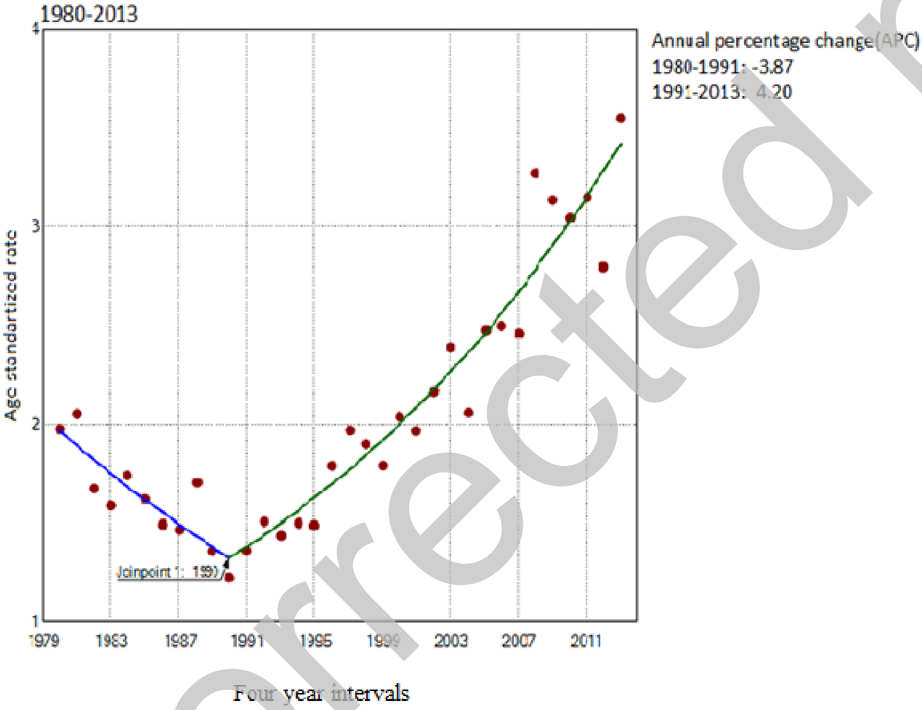
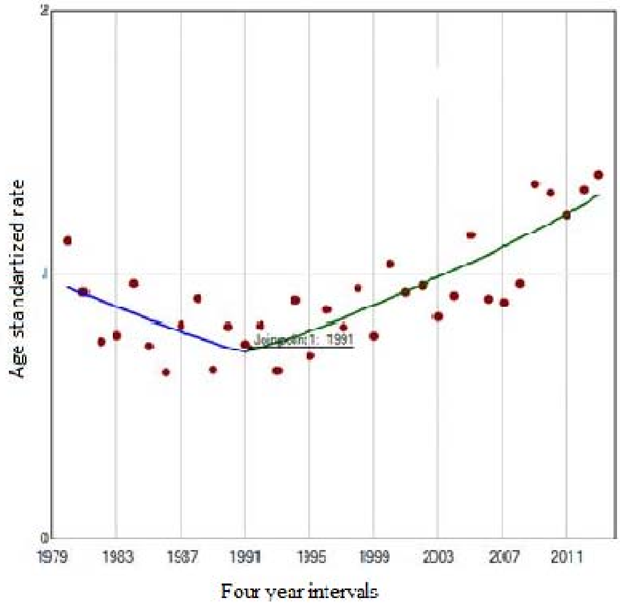
Smoljan(endemic)		4,95 (3.90-5.99)*	
Pleven (non-endemic) Vratza (endemic)		2,71(2.10-3.31)	0.29803
Dobrich (non-endemic) Vratza (endemic)		3, 34(2.64-4.03) 2,71(2.10-3.31)	0.18125
• * $p< 0.05$			

Fig.1 Total incidence of thyroid cancer in Bulgaria using Joinpoint analyses for the period 1980-2013



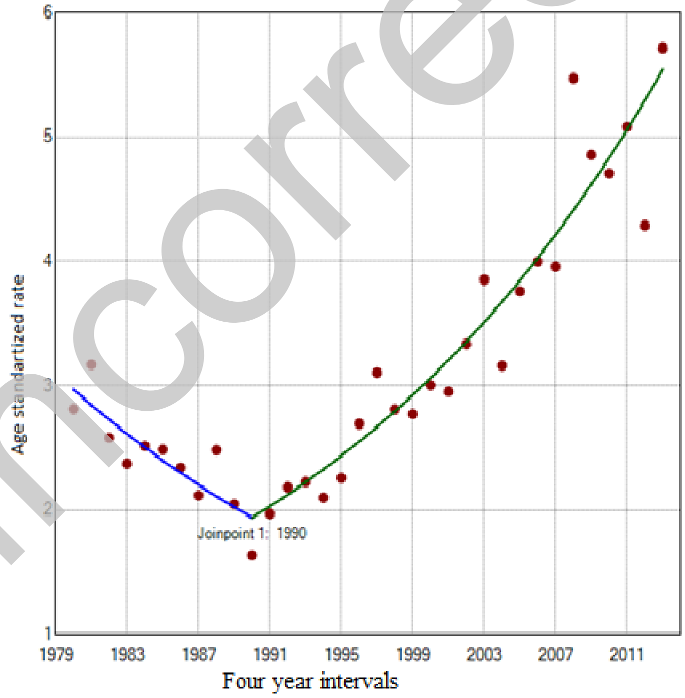
uncorrected proof

Fig.2.Incidence of thyroid cancer in male
in Bulgaria using Joinpoint analyses for the period
1980-2013



Annual percentage change(APC)
1980-1991: -2.63
1991-2013: 2.81

Fig. 3. Incidence of thyroid cancer in female
in Bulgaria using Joinpoint analyses for the period
1980-2013



Annual percentage change(APC)
1980-1991: -4.17
1991-2013: 4.67

uncorrected proof