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Does Chernobyl Accident Have Any Effect on Thyroid Cancers in Turkey? a Retrospective Review of Thyroid Cancers from 1982 to 2006

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Abstract. Besides the genetic and environmental factors, radiation is an important aetiological cause in the occurrence of thyroid cancer (TC), particularly papillary carcinoma. Chernobyl disaster led to a dramatic increase in the frequency of TC in Eastern Europe. We aimed to determine the data of TC in our unit from 1982 to 2006 and whether Chernobyl disaster has a possible effect on TC distribution. The data of 351 patients with TC are reviewed retrospectively. The dates at diagnosis were classified in five time periods. The ratios of TCs in our unit were concordant with the literature. Comparing the five 5-year periods, there was a significant decrease in the ratio of follicular carcinoma ($p<0.01$) although the ratio of other thyroid cancers did not change ($p>0.05$). The ratio of papillary microcarcinoma increased ($p<0.01$) while the ratio of classical form decreased ($p<0.01$). The differences between the time periods and the mean ages at diagnosis for each TCs were not significant ($p>0.05$). If Chernobyl disaster had any effect, the mean age at diagnosis would be younger. The decrease in the ratio of follicular carcinoma in our study may be due to iodine supplementation. The higher ratio of papillary microcarcinoma can be related to increased diagnostic scrutiny. Epidemiological studies are necessary to determine TC incidence in Turkey.

Key words: Chernobyl disaster, Retrospective review, Thyroid cancers

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BESIDES the genetic and environmental factors, radiation is an important aetiological cause in the occurrence of TC, particularly papillary carcinoma [1, 2]. The thyroid gland is highly sensitive to radiation-induced oncogenesis. The studies that investigate the effects of ionizing radiation on oncogenesis have showed that exposure to moderate-to-high levels can cause TC as well as other most common forms of cancer, leukaemia, breast and lung cancers [3].

The exposure to radiation in childhood is more important for the occurrence of TC, since the thyroid gland in children is especially vulnerable to the carcinogenic action of ionizing radiation. A close relationship between the exposure to ionizing radiation and the risk of TC was first suggested in 1950 in children who received X-ray therapy in infancy for an enlarged thymus. More conclusive evidence was obtained from several large studies following radiation treatment to the scalp or neck, and showing a dose-dependent increase in relative risk for development of TC [2]. Current knowledge about the effect of radiation on man is largely based on the studies of the population exposed to the effects of the atomic bomb explosions in Japan in 1945 [4].

Chernobyl nuclear accident in 1986 was also one of the most serious environmental disasters. It led to a dramatic increase in the frequency of TC in children. The first evidence of an increase in TC frequency came in 1990, when physicians in the capitals of Belarus and Ukraine noticed increased numbers of TC in children, only 4 years after the accident [5]. Later, the epidemiological studies that explore the association between

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Table 1. Time period-distributions of TCs

Histological Type	Period 1 n (%)	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	Period 5 n (%)	Total n (%)
Papillary	12 (70.6%)	32 (78%)	57 (79.2%)	64 (85.3%)	122 (83.6%)	287 (81.8%)
Follicular	5 (29.4%)	7 (17.1%)	6 (8.3%)	4 (5.3%)	9 (6.1%)	31 (8.8%)
Hurthle cell	0 (0%)	0 (0%)	1 (1.4%)	4 (5.3%)	1 (0.7%)	6 (1.7%)
Medullary	0 (0%)	0 (0%)	3 (4.2%)	1 (1.3%)	7 (4.8%)	11 (3.1%)
Anaplastic	0 (0%)	1 (2.4%)	5 (6.9%)	2 (2.7%)	4 (2.7%)	12 (3.4%)
Others	0 (0%)	1 (2.4%)	0 (0%)	0 (0%)	3 (2.1%)	4 (1.2%)

Table 2. Time period-distributions of papillary carcinomas

Papillary Subtype	Period 1 n (%)	Period 2 n (%)	Period 3 n (%)	Period 4 n (%)	Period 5 n (%)	Total n (%)
Classical	8 (66.7%)	18 (56.3%)	33 (57.9%)	35 (54.7%)	44 (36.1%)	138 (48.1%)
Microcarcinoma	2 (16.7%)	10 (31.3%)	16 (28.1%)	17 (26.6%)	59 (48.3%)	104 (36.2%)
Follicular	2 (16.7%)	4 (12.5%)	8 (14%)	8 (12.5%)	15 (12.3%)	37 (12.9%)
Others	0 (0%)	0 (0%)	0 (0%)	4 (6.3%)	4 (3.3%)	8 (2.8%)

Chernobyl disaster and thyroid cancer incidence have showed the effect of radioactive iodines (particularly I-131) on the large populations in many Eastern European countries. There is a controversial debate concerning a possible effect of the radioactive iodines on the increase of TCs in Western Europe where the exposure was less [6, 7]. Some studies from several Western countries mention that this increase is due to augmented detection of microcarcinoma via developed diagnostic tools rather than radiation [6, 8–10]. However, the factors explaning this increase have not been clearly established.

There are not enough data whether Chernobyl disaster has an effect on the incidence of TC in Turkey. In a hospital-based study of 518 cases with thyroidectomy, Taneri and colleagues [11] reported an apparent rise of thyroid malignancies in Turkey. They have emphasized that Chernobyl disaster could have a contribution to this increase. We aimed to determine the data of thyroid cancers in our unit from 1982 to 2006 and whether the exposure to radioactive iodines due to Chernobyl nuclear accident has a possible effect on TC distribution. Our unit is one of the reference centers in Aegean region of Turkey. For this reason, we think that our data may represent the distribution of TC in Aegean region.

Method

The data of the patients who are diagnosed as thyroid cancer in Endocrinology department from 1982 to 2006 are reviewed retrospectively. Demographic features, histological types which were determined after surgery and the date of diagnosis for 351 patients with TC were recorded from outpatient records. The dates at diagnosis were classified in five time periods as 1982–1986 (period 1), 1987–1991 (period 2), 1992–1996 (period 3), 1997–2001 (period 4), and 2002–2006 (period 5).

SPSS 14.0 for windows (SPSS Inc. Chicago USA) was used for statistical analysis of the results. The statistical evaluations included the chi-square test with level of significance $p<0.05$.

Results

321 (91.5%) of patients with TC were from Aegean region. The mean age was 43.3 ± 13, 47 years (range: 15–87). The patients consisted of 274 (78.1%) female and 77 (21.9%) male; M/F ratio of 1:3, 6. 351 TCs included 287 (81.8%) papillary, 31 (8.8%) follicular, 6 (1.7%) hurthle cell, 11 (3.1%) medullary, 12 (3.4%) anaplastic /undifferentiated carcinomas and 4 (1.2%) others (1 unclassified — differentiated cancer, 1 angiosarcoma, 1 lymphoma, 1 metastasis of adeno cancer). Time period-distributions of TCs are showed in Table 1. The subtypes of papillary carcinoma included 138 (48.1%) classical papillary, 104 (36.2%) microcarcinoma, 37 (12.9%) follicular variant, 8 (2.8%) others (oxyphilic, diffuse sclerosing, tall cell and poorly dif-

Table 3. The mean age of patients at the time of diagnosis

Histological Type	Period 1	Period 2	Period 3	Period 4	Period 5
Papillary	35 ± 12.6	40.3 ± 13.3	41.8 ± 13.9	41.4 ± 11.8	44.5 ± 12.1
	n: 12	n: 32	n: 57	n: 64	n: 122
Follicular	27.6 ± 8.6	47.1 ± 13.3	45.3 ± 15.8	37.7 ± 7.4	40.8 ± 11.9
	n: 5	n: 7	n: 6	n: 4	n: 9
Hurthle cell	—	—	39	52.1 ± 7.7	62
	n: 0	n: 0	n: 1	n: 4	n: 1
Medullary	—	—	34.3 ± 2.0	51	44 ± 20.7
	n: 0	n: 0	n: 3	n: 1	n: 7
Anaplastic	—	63	54.6 ± 17.7	70 ± 0	64.7 ± 11.1
	n: 0	n: 1	n: 5	n: 2	n: 4
Others	—	58	—	—	71.5 ± 2.1
	n: 0	n: 1	n: 0	n: 0	n: 3

Table 4. The mean age of patients at the time of accident

Histological Type	Period 2	Period 3	Period 4	Period 5
Papillary	36.9 ± 12.9	33.8 ± 14.0	29.4 ± 12.1	26.9 ± 11.8
	Range: 16–67	Range: 9–78	Range: 1–64	Range: 1–53
	n: 32	n: 57	n: 63	n: 120
Follicular	47 ± 8.9	37 ± 16.8	25.2 ± 9.1	22.3 ± 12.3
	n: 7	n: 6	n: 4	n: 9
Hurthle cell	—	39	37.7 ± 10.6	39
	n: 0	n: 1	n: 4	n: 1
Medullary	—	26 ± 3	37	26.14 ± 20.5
	n: 0	n: 3	n: 1	n: 7
Anaplastic	58	45.8 ± 19.1	57.5 ± 2.12	47.5 ± 11.6
	n: 1	n: 5	n: 2	n: 4
Others	54	—	—	47.3 ± 8.80
	n: 1	n: 0	n: 0	n: 3

ferentiated). Time period-distributions of papillary carcinomas are showed in Table 2.

Comparing the five 5-year periods, there was a significant decrease in the ratio of follicular carcinoma ($p<0.01$) although the ratio of other thyroid cancers did not change ($p>0.05$). When the association between the subtype ratio of papillary cancers and the five periods of time was examined, the ratio of papillary microcarcinoma increased ($p<0.01$) while the ratio of classical form decreased ($p<0.01$). It was not determined any differences in the ratio of follicular form ($p>0.05$). The mean age of the patients at diagnosis and Chernobyl accident are showed in Table 3 and Table 4. The patients who were born after the accident and diagnosed before the accident were not included. The differences between the time periods and the age of patients at diagnosis for each TCs were not significant ($p>0.05$).

Discussion

The most frequent types of thyroid carcinoma are differentiated forms (papillary and follicular). Other forms such as anaplastic and medullary carcinomas, lymphomas, and secondary cancers are rare [1]. We found that the ratios of TCs in our unit were concordant with the literature [11, 12]. Our results showed a decreasing ratio of follicular carcinoma in comparison with other TCs. In several studies, it has been reported that the ratio of papillary to follicular carcinoma increased in iodine defficient areas after iodine prophylaxis [1]. Turkey is a region of endemic goitre. For this reason legislation for mandatory iodization of household salt was passed in July 1999 [13]. The decrease in the ratio of follicular carcinoma in our institution may be due to iodine supplementation.

No significant variability between the ratios of papil-

lary carcinoma among time intervals was found, there was an inverse relation between the ratio of classical form and microcarcinoma. Microcarcinoma's ratio increased as classical form's decreased. Papillary thyroid carcinoma is the most common type of differentiated thyroid carcinoma and those with diameters ≤1 cm have been named as papillary microcarcinoma by the World Health Organization [14]. These lesions are frequently detected as incidental findings on autopsy or in surgical specimens. On examination of the thyroid glands in 408 consecutive autopsy cases, Yamamoto and colleagues found an incidence of 11.3% for papillary microcarcinoma [15]. Moreover, Harach and colleagues systematically sectioned the thyroid glands from 101 consecutive autopsies in 2- to 3-mm width and found that 35.6% of autopsy cases had one or more foci of papillary carcinoma [16].

The incidence of TCs, particularly papillary forms, has been increasing sharply for many years in Western countries. Similarly, the data from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program database showed an increase of TC incidence in the United States (US) [9, 17]. It was found that the incidence of TC in the US showed a two fold increase over the past 30 years and 87% of the increase was due to the diagnosis of small papillary cancers [9]. The radiation was not responsible for the increased incidence of TC according to the authors. Recently, common opinion about this higher incidence of TC is increased diagnosis of papillary microcarcinoma with the advent of improved methods of diagnostic evaluation, especially high resolution ultrasound and ultrasound guided fine needle aspiration biopsy (FNAB) [6, 8–10].

The wider use of neck imaging is contributed to the incidence of thyroid nodules [18]. Thyroid ultrasonography is more sensitive than physical examination and scintigraphy in detection of thyroid nodules [19]. It often reveals additional useful features which may help in the clinical management of thyroid nodule. Irregular margin, increased vascularity, and the presence of calcification increase the likelihood of cancer. But none of these features are not pathognomonic of thyroid cancer and FNAB is the first approach in the management of thyroid nodules and the selection of patients for surgery [18, 20, 21]. Diagnostic accuracy of FNAB is improved with ultrasound guidance, especially for impalpable nodules due to the common use of imaging techniques. The prevalence of small impalpabl thyroid nodule found incidentally in an asymptomatic patient has increased. The prevalence of thyroid cancer in such lesion is thought to be low. Although a recent publish suggests that the rate of malignancy may be as high as 12% [22], general acceptance is that small (<1 cm), impalpable nodules in patients are not in a high risk category for thyroid cancer [21]. In our center, ultrasound guidance FNAB has been performed on any nodule more than 10 mm in diameter or in nodules as small as 6 mm with higly suspicious ultrasonographic features for last decade. It may be possible that the higher ratio of papillary microcarcinoma is related to increased diagnostic scrutiny.

Whether Chernobyl disaster has any effect on the distribution of TC in our center is doubtful for some reasons like geographic location of Turkey. Due to prevailing winds at time of the meltdown, radioactive materials were preferentially carried northward and westward. Since Turkey is further south than Chernobyl, the likelihood of TC incidence in our country being affected from this disaster may be less.

Papillary carcinoma is most prevalent type of TC in both children and adults with radiation-induced or sporadic cancer [2, 23]. There are differences among papillary thyroid carcinoma variants in histological appearance, tumor behavior and latency period. Solid variant is less differentiated and more aggressive than classical and follicular variants. Although classical papillary morphology is often observed in tumors diagnosed in older children, the solid variant of papillary TC occurs with an elevated frequency in younger patient. Because solid variant has been associated more typically with shorter post-Chernobyl latency (≤10 years). Most post-Chernobyl papillary carcinomas in children aged 14 years or younger at the time of surgery included solid and solid-follicular variants has been revealed [23]. Our results did not reveal any increase the ratio of papillary cancer and these radiation induced variants. This finding does not support the hypothesis of the effect of Chernobyl disaster on the distribution of TC in Aegean region.

It has been reported that the histology of post-Chernobyl papillary TC detected predominantly by ultrasound screening has been changing with longer latency in a recent study from Ukraine [24]. Although the largely solid-follicular variant consisted of 79% of the all thyroid tumors in a previous study of exposed Ukrainian children, the predominant subtypes were mixed or follicular, and only 34.9% of tumors have a

significantly solid component in this report. Microcarcinoma (≤10 mm) has comprised 23.3% of papillary TCs, and most of those have been more differentiated. It has been emphasized that there is no unique histologic signature for these carcinomas. The ratios of subtypes also changed with time periods in our center. There was an increase in the ratio of microcarcinoma despite of classical form. It may not be appropriate to decide whether Chernobyl disaster has any effect on TC incidence in our region with only evaluation of histological variants' frequency. For this reason, molecular studies may be helpful for evaluation of radiation effect on TC occurrence. Gene rearrangements are prevalent in childhood thyroid carcinomas whereas point mutation are rare. Genetic analysis of post-Chernobyl papillary TCs in children implicated the RET oncogene in the pathogenesis of these tumors. RET activation in papillary carcinomas occurs through chromosomal recombination resulting in illegitimate expression of a fusion protein consisting of the intracellular tyrosine kinase (TK) domain of RET coupled to the N-terminal fragment of a heterologous gene, giving rise to the RET/PTC oncoproteins. RET/PTC1 and RET/PTC3 are the common rearragements. RET/PTC3 is related to a solid morphology and fast-growing tumors with short latency, RET/PTC1 is characterized of carcinomas with typical papillary architecture [2, 23].

The influence of age at irradiation has been assessed in a pooled analysis of seven studies of radiation-induced thyroid cancer [25]. The excess relative risk began to decline about 30 years after exposure but was still elevated at 40 years. Risk also decreased significantly with increasing age at exposure, with little risk apparent after age 20 years. We determined that the mean ages at diagnosis of TCs especially papillary carcinoma for each time periods were stable . If the disaster had any effect, the mean age of patients at diagnosis would be expected to be younger.

There are some limitations in our study. There is not any extensive epidemiolocigal data related to yearly TC incidence in Turkey in literature. So, we could not compare our results to those in other geographic regions of Turkey. Because of the retrospective epidemiological data review of 351 patients, molecular tests could not be performed appropriately to clarify whether radiation has any effect on distribution of TC.

In conclusion, whether Chernobyl disaster has an impact on the occurrence of TC in our country has not been known enough. The incidence of TC can be affected by increased diagnostic scrutiny as well as genetic and environmental factors. Epidemiological and molecular studies are necessary to determine the incidence and pathogenesis of TCs in Turkey.

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References

1. Feldt-Rasmussen U (2001) Iodine and cancer. *Thyroid* 11(5): 483–486.
2. Fagin JA, Nikiforov YE (2006) Radiation-induced thyroid cancer: Lessons from Chernobyl. In: Mazzaferri EL, Harmer C, Mallick UK, Kendall-Taylor P (eds). Practical Management of Thyroid Cancer: A Multidisciplinary Approach. *Springer*, 321–326.
3. Wakeford R (2004) The cancer epidemiology of radiation. *Oncogene* 23(38): 6404–6428.
4. Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M, Shimaoka K (1994) Thyroid diseases among atomic bomb survivors in Nagasaki. *JAMA* 272(5): 364–370.
5. Williams ED (2006) Chernobyl and thyroid cancer. *J Surg Oncol* 94(8): 670–677.
6. Scheiden R, Keipes M, Bock C, Dippel W, Kieffer N, Capesius C (2006) Thyroid cancer in Luxembourg: a national population-based data report (1983–1999). *BMC Cancer* 6: 102.
7. But A, Kurttio P, Heinavaara S, Auvinen A (2006) No increase in thyroid cancer among children and adolescents in Finland due to Chernobyl accident. *Eur J Cancer* 42(8): 1167–1171.
8. Burgess JR, Tucker P (2006) Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. *Thyroid* 16(1): 47–53.
9. Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 295(18): 2164–2167.
10. Colonna M, Guizard AV, Schvartz C, Velten M, Raverdy N, Molinie F, Delafosse P, Franch B, Grosclaude P (2007) A time trend analysis of papillary and follicular cancers as a function of tumour size: a study of data from six cancer registries in France

(1983–2000). *Eur J Cancer* 43(5): 891–900.
11. Taneri F, Kurukahvecioglu O, Ege B, Yilmaz U, Tekin E, Cifter C, Onuk E (2005) Prospective analysis of 518 cases with thyroidectomy in Turkey. *Endocr Regul* 39(3): 85–90.
12. Busnardo B, De Vido D (2000) The epidemiology and etiology of differentiated thyroid carcinoma. *Biomed Pharmacother* 54(6): 322–326.
13. Erdogan G, Erdogan MF, Emral R, *et al.* (2006) Iodine status and goiter prevalence in Turkey before mandatory iodization. *J Endocrinol Invest* 25(3): 224–228.
14. Hedinger C, Williams ED, Sobin LH (1989) WHO histological classification of thyroid tumors: a commentary on the second edition. *Cancer* 63(5): 908–911.
15. Yamamoto Y, Maeda T, Izumi K, Otsuka H (2006) Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases. *Cancer* 65(5): 1173–1179.
16. Harach HR, Franssila KO, Wasenius VM (2006) Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 56(3): 531–538.
17. Hayat MJ, Howlader N, Reichman ME, Edwards BK (2006) Cancer Statistics, Trends, and Multiple Primary Cancer Analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist* 12(1): 20–37.
18. Polyzos SA, Kita M, Avramidis A (2007) Thyroid nodules — stepwise diagnosis and management. *Hormones (Athens)* 6(2): 101–119.
19. Schneider AB, Bekerman C, Leland J, Rosengarten J, Hyun H, Collins B, Shore-Freedman E, Gierlowski TC (1997) Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. *J Clin Endocrinol Metab* 82(12): 4020–4027.
20. Gharib H, Goellner JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med* 118(4): 282–289.
21. Perros P (2006) Thyroid nodules. In: Mazzaferri EL, Harmer C, Mallick UK, Kendall-Taylor P (eds). Practical Management of Thyroid Cancer: A Multidisciplinary Approach. *Springer* 75–81.
22. Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB, Shong YK (2004) Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clin Endocrinol (Oxf)* 60(1): 21–28.
23. Yamashita S, Saenko V (2007) Mechanisms of disease: molecular genetics of childhood thyroid cancers. *Nat Clin Pract Endocrinol Metab* 3(5): 422–429.
24. Bogdanova TI, Zurnadzhy LY, Greenebaum E (2006) A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: pathology analysis of thyroid cancer cases in Ukraine detected during the first screening (1998–2000). *Cancer* 107(11): 2559–2566.
25. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD Jr (1995) Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 141(3): 259–277.