

THYROID CANCER INCIDENCE AMONG PEOPLE LIVING IN AREAS CONTAMINATED BY RADIATION FROM THE CHERNOBYL ACCIDENT

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Abstract—As a result of the Chernobyl nuclear power plant accident, massive amounts of radioactive materials were released into the environment and large numbers of individuals living in Belarus, Russia, and Ukraine were exposed to radioactive iodines, primarily ¹³¹I. Iodine-131 concentrated in the thyroid gland of residents of the contaminated areas, with children and adolescents being particularly affected. In the decade after the accident, a substantial increase in thyroid cancer incidence was observed among exposed children in the three affected countries, and compelling evidence of an association between pediatric thyroid cancer incidence and radiation exposure to the thyroid gland accumulated. The data currently available suggest that both the magnitude and patterns of thyroid cancer risk are generally consistent with those reported following external exposure. Based on data from case-control studies, iodine deficiency appeared to enhance the risk of developing thyroid cancer following exposure from Chernobyl. Results from a recent large cohort study, however, did not support these findings. Data on adult exposure are limited and not entirely consistent. Similarly, information on thyroid cancer risks associated with in utero exposure is insufficient to draw conclusions. The lack of information on these two population groups indicates an important gap that needs to be filled. Twenty years after the accident, excess thyroid cancers are still occurring among persons exposed as children or adolescents, and, if external radiation can be used as a guide, we can expect an excess of radiation-associated thyroid cancers for several more decades. Since considerable uncertainties about the long-term health effects from Chernobyl remain, continued follow-up of the exposed populations should provide valuable information. *Health Phys.* 93(5):502–511; 2007

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INTRODUCTION

IN APRIL 1986, the Chernobyl Nuclear Power Plant released about 1,760 PBq of ¹³¹I into the environment.

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These releases were magnitudes larger than the 27 PBq released by the Hanford nuclear site in the 1950's and 1960's and about a third less than the estimated 5,400 PBq released during the nuclear weapons testing at the Nevada Test Site (Beck and Bennett 2002). About five million people living in Belarus and large contaminated regions in Northeast Ukraine and Southwest Russia were exposed to internal radiation from ingesting local milk and, to a much lesser extent, leafy green vegetables, and to external radiation from radionuclides deposited on the ground. Greater than 90% of the thyroid dose was from ingested ¹³²I, which has an 8-d half-life, and <10% was from the shorter-lived radioisotopes, ¹³²I, ¹³³I, and ¹³⁵I (UNSCEAR 2000). Iodine-131 was concentrated primarily in the thyroid gland, with children and adolescents receiving higher doses than adults because the percent of ingested iodine that localizes to the thyroid gland is higher in children compared with adults, children's thyroid glands are smaller, and they drink greater amounts of milk. The dose to the thyroid of a child 5 y old at the time of the accident was about four times larger than for an adult. Individual thyroid doses range from a few milligray to several gray. A discussion of doses to the thyroid gland is presented in this journal by Bouville et al. (2007). To date, thyroid cancer has been the most important medical consequence of the Chernobyl accident. In this paper, I discuss the relationship between radiation exposure from Chernobyl and the risk of developing thyroid cancer, with a focus on results from recently published analytic studies, and compare what has been learned about Chernobyl with what is known about external radiation and thyroid cancer risk.

CHILDHOOD RADIATION EXPOSURE

Within a few years after the accident, physicians noted an increase in the occurrence of childhood thyroid cancer in the contaminated regions, and in 1991 Prisyazhiuk et al. (1991) published a letter in *Lancet* reporting that although no cases of thyroid cancer in

children had occurred in Ukraine between 1981 and 1989, three cases were diagnosed in 1990. The following year, the first report of an unusually high frequency of thyroid cancer in children in Belarus appeared in *Nature* (Kazakov et al. 1992). Soon after, case reports and descriptive studies documented a substantial increase in thyroid cancer incidence among exposed children in the three affected countries (Baverstock et al. 1992; Abelin et al. 1994; Tsyb et al. 1994; Likhtarev et al. 1995; Stsjazhko et al. 1995). In the 8-y period of 1990 to 1998, ~2,000 thyroid cancers were diagnosed among persons <18 y of age in the contaminated areas of Belarus, Russia, and Ukraine (UNSCEAR 2000). Evidence of a meaningful link between the development of pediatric thyroid cancer and dose to the thyroid gland from radioiodines received during childhood continued to accumulate (Buglova et al. 1996; Demidchik et al. 1996; Astakhova et al. 1998; Jacob et al. 1999; Tronko et al. 1999; Heidenreich et al. 2000; Shibata et al. 2001; Kenigsberg et al. 2002) and today it is clear that the association is causal (Bennett et al. 2006; NRC 2006). The most recent data indicate that between 1986 and 2002, close to 4,000 cases of thyroid cancer occurred among persons exposed before age 15 y in Belarus, Ukraine, and the four most contaminated areas in Russia and another 1,000 cases among those exposed between the ages of 15 and 17 y (Bennett et al. 2006; Cardis et al. 2006). The extremely brief time period between radiation exposure and thyroid cancer diagnosis is striking and had not been documented previously. However, few other epidemiologic studies have adequate data to detect such an early effect. The Life Span Study of atomic bomb survivors, which includes ~50,000 people exposed to the bombings before age 20 y, does not have information on cancer incidence for the first 13 y of follow-up (Thompson et al. 1994). Other cohorts are relatively small (Schneider et al. 1993) or include people exposed to very low doses (Ron et al. 1989). Whether the short latency observed following Chernobyl is related to the biology of radiation-related thyroid cancer, accelerated tumor promotion due to iodine deficiency or some other unknown exposure, early detection screening, or the unprecedented number of exposed individuals is unclear.

Ecologic studies

Since ecologic (geographic correlation) studies normally make use of existing data, they are relatively quick and inexpensive and a number of early studies using this design reported a strong association between radioiodine exposure and thyroid cancer incidence (Buglova et al. 1996; Sobolev et al. 1997; Jacob et al. 1999, 2000; Likhtarev et al. 1999; Heidenreich et al. 2000). Several of the ecologic studies provided quantified risk estimates

that were useful in providing a sense of the magnitude of the problem. However, they were burdened by their reliance on group or population level dose and/or disease outcome data. In general, the population group was defined by geography (high exposure areas compared with low exposure areas) or time period (before or after the Chernobyl accident). Because increased medical surveillance and early detection screening were introduced after the accident, comparisons of thyroid cancer incidence before and after the accident can be misleading. Similar problems also may exist when comparing thyroid cancer incidence in areas known to have received high radiation exposure with those receiving little exposure.

Keeping the limitations of ecological studies in mind, a series of quantified relative and absolute excess risk estimates for radiation-related thyroid cancer have been published by Jacob et al. (1999, 2000, 2006). In their latest publication, they studied 577 thyroid cancers diagnosed in 426 settlements in Belarus and 512 thyroid cancer cases in 608 settlements in Northern Ukraine. Cases diagnosed between 1990 and 2001 in the 1968 to April 1986 birth cohort (age 18 y or less at the time of the accident) were ascertained through the Belarus and Ukraine cancer registries. They used 166,012 individual dose estimates for people who had direct instrumental measurements of ^{131}I activity to estimate an average age and sex-specific dose for each settlement, taking into account urban-rural differences. Doses in Belarus were more uncertain than those in Ukraine. The estimated linear coefficient of the excess absolute risk (EAR) per 10,000 person-years (PY) Gy was 2.7 [95% confidence interval (CI) 2.2, 3.1] and the excess relative risk (ERR) per gray was 18.9 (95% CI = 11.1, 26.7), but there was some downward curvature at high doses. The patterns of risk varied depending on the statistical model used. Both the EAR and ERR decreased with age at exposure, but the models differed in other respects. The EAR was higher for females than males and increased with attained age, whereas the ERR was higher for males than females and decreased with attained age. Risks were higher by about 50% in Belarus compared with Ukraine.

In the most recent ecological study, Likhtarov et al. (2006) reported on a population of 301,907 individuals who, at the time of the accident, were between the ages of 1 and 18 y and lived in 1,293 rural settlements in Kyiv, Zhytomyr, or Chernihiv Oblasts in Northern Ukraine. Persons who were <1 y at the time of the accident were excluded from the study because dose estimates for in utero exposure were considered less certain than doses estimated for exposure after birth. Individual thyroid dose estimates largely based on external gamma radiation measurements from radiation detectors placed

against the neck shortly after the accident were available for 26% of the study population. For the rest of the study subjects, dose estimates were based on the thyroid measurements of a person of the same sex and age living in the same or nearby settlement (Likhtarov et al. 2005). The mean dose to the thyroid for the study population was 353 mGy. The rate of ultrasound use over time in the Kyiv, Zhytomyr, and Chernihov Oblasts was used as a proxy measure of the level of medical surveillance. Between 1990 and 2001, 232 histologically confirmed thyroid cancers were diagnosed in the study group. A highly significant linear dose response ($ERR\ Gy^{-1} = 8$; 95% CI = 4.6–15 and EAR per 10,000 PY Gy = 1.5; 95% CI = 1.2–1.9) was demonstrated and the risk estimates were compatible with those reported from other studies of Chernobyl, as well as from studies of childhood exposure to external radiation exposure (Ron et al. 1995; Cardis et al. 2005, Tronko et al. 2006). Both the ERR and EAR decreased with increasing age at exposure, and increased with time since exposure. Using an ERR model, males had a marginally higher risk than females, whereas the reverse was found using an EAR model (Likhtarov et al. 2006).

Case-control studies

Case-control and cohort studies obtain information on an individual level and, therefore, are preferable to ecologic studies. In 1998, Astakhova et al. (1998) published results from the first case-control study. They evaluated 108 thyroid cancer cases diagnosed between 1987 and 1992 in Belarus among persons who were <15 y of age at the time of the accident. They also identified two matched control groups (general population controls and medical controls) of equal size. The controls were matched to cases on age, sex, and whether they lived in a rural or urban area in 1986. Thyroid doses were not reconstructed directly, but were extrapolated from the mean adult doses from the same settlements. The mean thyroid dose among cases was more than two times greater than among either control group ($p < 0.01$). A significant dose response was observed with persons exposed to estimated thyroid doses ≥ 0.3 Gy having an odds ratio of about 5 compared with individuals having estimated doses < 0.3 Gy.

In the last few years, two additional case-control studies have been published. A small population-based case-control study was conducted in Bryansk, Russia (Davis et al. 2004). It included 26 cases (13 women and 13 men) diagnosed between 1991 and 1997, and 52 matched controls, all of whom were <19 y of age at the time of the accident. Cases and controls were matched on age, sex, and region of residence at the time of the Chernobyl accident. Eighty-eight percent of the thyroid

cancers were papillary carcinomas. This was the first study to reconstruct individual thyroid doses from ^{131}I for each subject. A strong dose response was demonstrated ($p < 0.009$), but more detailed analyses were limited due to the study size.

Cardis et al. (2005) recently reported on a large population-based case-control study which was conducted in the Gomel and Mogilev regions in Belarus and the Bryansk, Kaluga, Orel, and Tula regions in Russia. The study included 276 thyroid cancer cases diagnosed between 1992 and 1998, all <15 y of age at the time of the accident. The 1,300 controls were matched to cases on age, sex, and place of residence at the time of the accident. Thyroid doses were reconstructed for cases and controls based on information on residence, food intake and use of stable iodine prophylaxis after the accident obtained from individual questionnaires and on estimated average age-specific doses for each subject's settlement. Thyroid doses were estimated from ^{131}I , short- and long-lived radioiodines and external radiation. The median dose in Belarus was about 10 times higher than in Russia. Thyroid cancer was linked to childhood exposure to ^{131}I specifically and to all radioiodines. Risk increased linearly with dose until ~ 2 Gy, but > 2 Gy risk began to fall off. Based on a linear dose-response model, excluding subjects with doses of 2 Gy or more, the odds ratio at 1 Gy was 5.5 (95% CI = 2.2–8.8), which would be an approximate $ERR\ Gy^{-1}$ of 4.5. Risk estimates were virtually the same when dose from all exposures, all iodine isotopes, or ^{131}I alone were evaluated. Thyroid cancer risks were lower for individuals living in iodine-sufficient regions compared with those living in iodine-deficient regions and also among persons who received stable iodine prophylaxis after the accident compared with those who didn't.

Cohort studies

In the first cohort study of thyroid disease in relation to exposure from Chernobyl, 25,161 people (11,918 in Belarus and 13,243 in Ukraine) who were <18 y of age at the time of the accident are being screened by palpation and ultrasound every 2 y (Stezhko et al. 2004). A unique aspect of this study is that every cohort member had a direct measurement of activity of the thyroid gland performed within 6 wk after the accident. Dose estimates based on these measurements were higher in Belarus than Ukraine. Overall, 44.3%, 27.3%, and 28.4% of the cohort had thyroid doses of < 0.3 Gy, 0.3–0.99 Gy, and ≥ 1 Gy, respectively (Stezhko et al. 2004). Improved individual thyroid dose estimates were reconstructed based on the direct thyroid measurements along with a radioecologic model and interview data (Likhtarov et al.

2005). In the Ukrainian arm of the study, the median thyroid dose was 0.26 Gy. During the first screening cycle in 1998–2000, 45 pathologically confirmed thyroid cancers were diagnosed (Tronko et al. 2006). A strong dose-response relationship ($p < 0.001$) that was approximately linear was demonstrated. The ERR Gy⁻¹ was 5.25 (95% CI 1.7, 27.5) and an estimated 75% (95% CI 50%, 93%) of the cases could be attributed to radiation from Chernobyl. Though not statistically significant, the ERR was higher for females than males and it increased with decreasing age at exposure from about 3.4 for persons exposed at 10–18 y to 9.1 for persons exposed before age 5 y. Although the study region was moderately iodine deficient at the time of the accident (VanMiddlesworth 2002; Tronko et al. 2005), there was no evidence that iodine excretion, as measured at the time of screening, or a history of goiter, a marker of past iodine deficiency, modified the radiation-related risk of thyroid cancer. One of the strengths of this study is that because all cohort members were screened within a 2-y period using the same protocol, risk estimates are not affected by potential problems related to different levels of case ascertainment or screening intensity.

As shown in Table 1, the ERR estimates from the recent Ukrainian ecologic (Likhtarov et al. 2006) and cohort (Tronko et al. 2006) studies and the Cardis et al. (2005) case-control study conducted in Belarus and Russia are compatible with each other and the pooled analysis of external low-linear energy transfer radiation (Ron et al. 1995). EAR estimates are only available from the Chernobyl ecologic studies and they are lower than the ERR reported from the pooled analysis (Ron et al. 1995). The low Chernobyl EAR estimates may be partly due to the shorter follow-up time of the Chernobyl studies (~15 y) compared with the follow-up time for the studies included in the pooled analysis (most >30 y), since the EAR appears to increase with increasing attained age or time since exposure.

ADULT RADIATION EXPOSURE

Information about adults exposed to Chernobyl radiation is minimal (Moysich et al. 2002; Hatch et al.

2005; Bennett et al. 2006). Ivanov and colleagues have studied thyroid cancer incidence among adults living in the contaminated region of Bryansk at the time of the Chernobyl accident. In a descriptive study published in 1999 (Ivanov et al. 1999), they found no evidence of an association between thyroid cancer incidence and radiation dose. In a later study (Ivanov et al. 2003), 769 thyroid cancers were diagnosed between 1991 and 1998 among approximately one million residents of the contaminated region of Bryansk who were between the ages of 15 and 69 y at the time of the accident. The cancers were histologically confirmed for 95% of the cases. Analyses were performed using two methods: comparing thyroid cancer incidence in the exposed study group with national population rates and comparing thyroid cancer incidence within the study population by thyroid dose. Compared to standardized age, sex, and calendar-year-period rates for the whole Russian population, thyroid cancer incidence was about 45% and 90% higher among male and female Bryansk residents, respectively. However, when dose-response analyses were performed using external or internal comparisons, no association was observed. The ERR Gy⁻¹ were -0.6 (95% CI -2.1, 0.8) and 0.0 (95% CI -1.4, 1.7) using external and internal comparisons, respectively. These results suggest that the increased thyroid cancer rates in Bryansk compared with general population rates are due to thyroid cancer screening and better reporting rather than radiation exposure. These findings are consistent with the general lack of an observed statistically significant association between thyroid cancer and adult exposure to either external gamma radiation from the atomic bombings (Thompson et al. 1994) or internal ¹³¹I from diagnostic examinations (Dickman et al. 2003). In contrast, Kenigsberg and Buglova (2005) reported a significantly higher than expected incidence of thyroid cancer in Belarus among both children and persons >19 y at the time of the accident, beginning in about 1993 and continuing until the most recent follow-up in 2002 (Fig. 1). These results indicate the need for further information on adult exposure.

Table 1. Thyroid cancer risk estimates from external radiation and ¹³¹I.

| | Study (reference) | EAR/10 ⁴ person-y Gy | ERR/Gy |
|-----------|---|---------------------------------|----------------|
| External | Pooled analysis (Ron et al. 1995) | 4.4 (1.9, 10) | 7.7 (2.1, 29) |
| Chernobyl | Case-control study in Belarus and Russia (Cardis et al. 2005) | NA ^a | 4.5 (1.2, 7.8) |
| | Cohort study in Ukraine (Tronko et al. 2006) | NA | 5.2 (1.7, 27) |
| | Ecological study in Ukraine (Likhtarov et al. 2006) | 1.5 (1.2, 1.9) | 8.0 (4.6, 15) |
| | Ecological study in Belarus and Ukraine (Jacob et al. 2006) | 2.7 (2.2, 3.1) | 19 (11, 27) |

^aNA = not available.

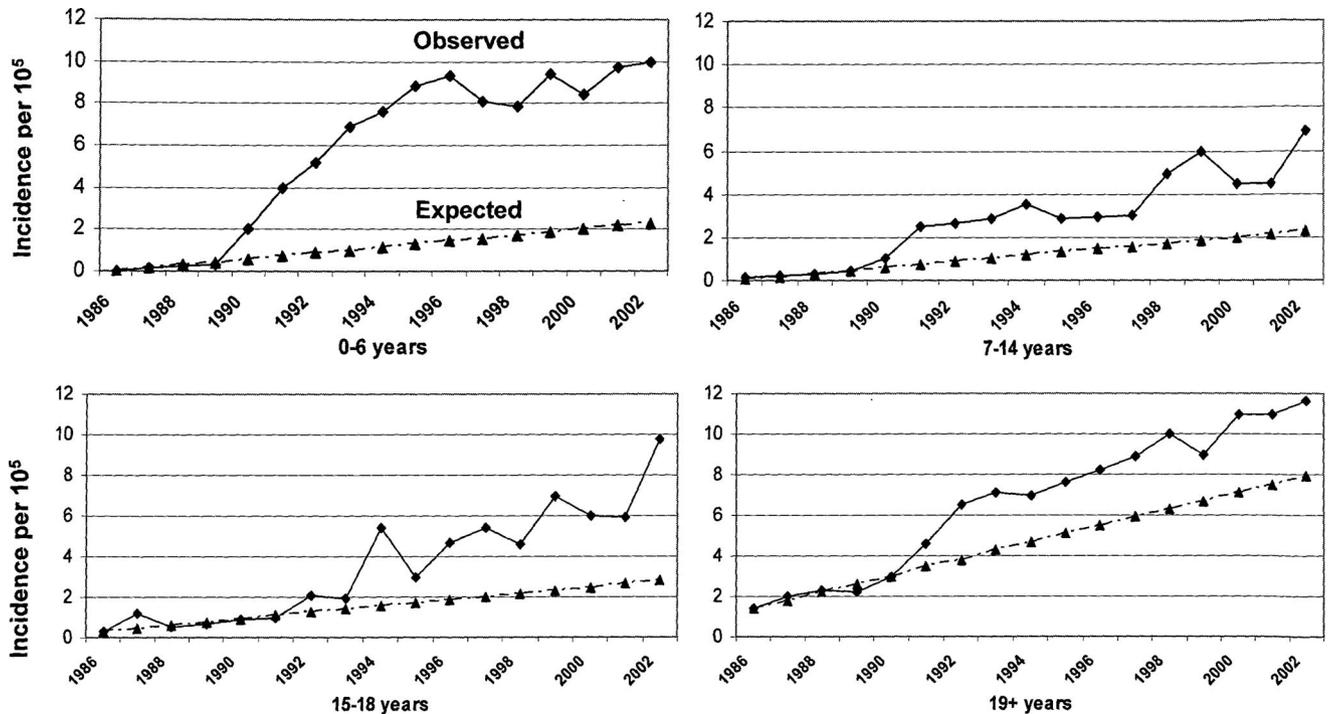


Fig. 1. Observed and expected thyroid cancer incidence by age at the time of the accident (Kenigsberg and Buglova 2005).

IN UTERO RADIATION EXPOSURE

Information on thyroid cancer following in utero ¹³¹I or external radiation exposure is very limited. To date, only a small number of thyroid cancers related to in utero exposure have been reported. One of the few studies providing data on in utero exposure was conducted in Belarus between 1998 and 2000 (Shibata et al. 2001). About 20,000 children living within a radius of 150 km from the Chernobyl plant were screened at school with ultrasound. The children were selected to have been born after the accident (no exposure), between the day after the accident and 31 December 1986 (in utero exposure) and from January 1983 until the day of the accident (childhood exposure). Of the 2,409 children exposed in utero, only one girl developed thyroid cancer (0.09%), whereas 31 cancers (0.49% for girls and 0.15% for boys) were diagnosed among the 9,720 exposed as very young children (<3 y old).

The lower cancer prevalence among the in utero exposed is unexpected given that the proliferative activity of normal human fetal thyroid cells is very high compared with that measured in the thyroid gland of children or adults (Saad et al. 2006). Parshkov (1999) suggested that the mother's physiology may help protect the fetal thyroid gland and, therefore, reduce the amount of radiation-related thyroid cancers. In a more general discussion of radiation exposure in utero, Ohtaki et al.

(2004) suggested that fetal cells may eliminate damaged cells more efficiently than adult cells, possibly through apoptosis or better repair mechanisms. While this hypothesis is intriguing, it is not clear how relevant it is to the thyroid gland. Because the fetal thyroid gland only begins to concentrate iodine at about 10 wk gestation, the reportedly low thyroid cancer rate also may be due to the very small doses received by the thyroid during the early fetal period (Wiersinga and Braverman 2003). A screening study of persons exposed in utero in Ukraine is ongoing and results are expected in the near future. The role of in utero radiation exposure in the etiology of thyroid cancer clearly needs additional research.

MODIFYING FACTORS

Age and time patterns

Current data suggest that thyroid cancer risk decreases with increasing age at the time of the accident in a manner similar to the age at exposure pattern observed following external radiation, although the data are not entirely consistent. In addition, data on adult exposure are sparse and most studies evaluated age at exposure in the narrow age range of 0–18 y. In 2006, three studies were published that discussed effects of age at exposure during childhood and adolescence (Jacob et al. 2006; Likhtarov et al. 2006; Tronko et al. 2006). All reported a trend for the ERR to decrease with increasing age. Jacob

et al. (2006) and Likhtarov et al. (2006) also found that risk decreased with increasing age at exposure using an absolute risk model.

While it is important to know whether the large increase in thyroid cancer incidence seen to date will continue, it is still too early to describe the long-term time trends. Following external radiation, radiation-related cancers were observed more than 40 y after exposure (Ron et al. 1995; Shore and Xue 1999). The question remains, however, whether risks associated with the ^{131}I radiation from Chernobyl will stabilize or whether there will be a downturn over time. Although some studies have suggested that risks were beginning to stabilize among persons exposed as children (Kofler 1999; Tronko et al. 1999; Cardis et al. 2005), the roles of attained age and time since exposure need further clarification. In the ecologic studies conducted in Belarus and Ukraine, Jacob et al. (2006) reported that risk increased with time since exposure only in the absolute risk model, whereas Likhtarov et al. (2006) found that risk increased with calendar time using either relative or absolute risk models. Using data from the Belarus national cancer registry, Mahoney et al. (2004) evaluated thyroid cancer incidence trends for all ages by sex. While this study did not quantify radiation risks, it documented a continuing increase in thyroid cancer incidence. The authors concluded that thyroid cancer incidence rose 775% for males and 1925% for females between 1970 and 2001. The increase in rates was substantially greater in areas with higher exposure from Chernobyl than areas with lower exposure and was most notable among persons diagnosed as children in high exposure areas.

Sex

Thyroid cancer incidence in nonirradiated adult populations is one of the few non sex-specific cancers that occur considerably more frequently among women than men. However, there is little sex-related difference in pediatric thyroid cancer. The effect of sex in radiation-related thyroid cancer is less clear. Following external radiation, the ERR was about two times greater, albeit not statistically significantly so, among women than men (Ron et al. 1995). In Chernobyl, the ERR often was higher in females than males (Heidenreich et al. 1999; Jacob et al. 1999; Tronko et al. 1999, 2006; Davis et al. 2004), but some studies have found the reverse (Buglova et al. 1996; Jacob et al. 2006; Likhtarov et al. 2006). Using an EAR model, females had higher risks than males, but the difference was not always statistically significant.

Iodine status

Iodine plays an essential role in thyroid function and affects thyroid cancer incidence and histology, as well as thyroid dose from ^{131}I exposure. It is, therefore, thought that iodine deficiency could interact with radiation to enhance thyroid cancer risk (Gembicki et al. 1997; Parshkov 1999). In 2003, Shakhtarin et al. (2003) reported a twofold increased ERR for thyroid cancer in highly iodine deficient areas in Bryansk, Russia compared with iodine sufficient areas. Similarly, in the largest case-control study conducted to date (Cardis et al. 2005), the ERR Gy^{-1} was three times greater among study subjects who, at the time of the Chernobyl accident, had resided in settlements that were iodine-deficient compared with people who had resided in settlements with sufficient iodine. In this study, iodine status was defined as the current average level of stable iodine in soil of the subjects' settlement at the time of the accident. Using current average settlement soil measurements is a crude proxy measure of iodine nutrition for an individual study subject at the time of the accident. In the Ukrainian cohort study (Tronko et al. 2006), no effect of current iodine status or diffuse goiter, which generally represents an adaptation to past iodine insufficiency, was observed. Tronko et al. (2006) evaluated iodine deficiency by measuring iodine concentration in each study participant's urine during the period of thyroid screening, i.e., between 1998 and 2000. Although urinary iodine concentration is a good indicator of iodine nutrition, the correlation between iodine levels at the time of screening and at the time of the Chernobyl accident, more than 20 y earlier, is unclear.

CLINICAL FEATURES OF CHERNOBYL-RELATED THYROID CANCERS

Similar to other radiation-associated and sporadic thyroid cancers, the cancers occurring in the Chernobyl-contaminated regions are generally papillary thyroid carcinomas. A solid variant of papillary carcinoma is unusually common in the pediatric cancers and this variant has been documented in childhood thyroid cancer diagnosed in the contaminated areas surrounding Chernobyl (Nikiforov et al. 1997; Williams 2002; Williams et al. 2004). Relatively aggressive thyroid cancers, with high rates of metastases, have been observed among the pediatric cases (Farahati et al. 2000; Reiners et al. 2002), but it is not clear whether these features are characteristic of radiation-related cancers or the relatively young age of the patients at the time of diagnosis (Pacini et al. 1997; Williams et al. 2004). In a comparison of 472 Belarus patients less than 21 y at diagnosis during the period after the accident until 1995, and 369 French and Italian

patients, also less than 21 y at diagnosis, but not exposed to radiation, differences in age distribution, sex ratio, and tumor extent were noted (Table 2) (Pacini et al. 1997). Williams et al. (2004) have shown that cancers currently diagnosed among persons exposed as children are less aggressive than those diagnosed years ago and that age at exposure (within the short range of 0–9 y) is associated with type of tumor differentiation, whereas latency is associated with extent of differentiation. In a comparison of surgically removed thyroid tumors from 311 exposed (cleanup workers, evacuees from restricted areas and residents of contaminated areas) and 2,363 nonexposed adults in Ukraine, Cherenko et al. (2004) noted that the Chernobyl-associated cancers were more often multifocal and had regional metastases than the cancers occurring in nonexposed patients.

The survival rate of both radiation-related and sporadic thyroid cancer is exceptionally high. In the U.S., the 5-y survival rate is over 95% for all ages combined (Ries et al. 2006), and although pediatric thyroid cancer often presents with lymph node involvement, the prognosis for children is even better than it is for adults (Gingalewski and Newman 2006). The number of reported thyroid cancer deaths following the accident has been relatively low (<1%). The most recent report stated that 15 persons have died from Chernobyl-related thyroid cancers (Bennett et al. 2006).

MOLECULAR FEATURES OF CHERNOBYL-RELATED THYROID CANCERS

For years, researchers have been searching for a radiation marker or “fingerprint” that would identify cancers related to radiation exposure. Following radiation exposure DNA double-strand breaks can occur, and if the breaks are not repaired correctly chromosomal rearrangements can result. RET/PTC rearrangements are the most common genetic alteration in radiation-associated papillary thyroid carcinoma. Soon after the accident, RET/PTC, especially PTC3, rearrangements

were relatively frequent in Chernobyl-associated childhood papillary thyroid cancers, particularly the solid variant (Klugbauer et al. 2001; Nikiforov et al. 1997; Smida et al. 1999; Thomas et al. 1999). However, it is uncertain whether the PTC3 rearrangements are linked to radiation exposure, the short latency period, or to the young age of the patients (Powell et al. 2005; Williams et al. 2004), since the frequency of rearrangements was about the same for young thyroid cancer patients whether they were exposed to Chernobyl or were born after the accident (Powell et al. 2005). Current data suggest that the frequency of PTC types changes with latency, so that PTC3 was most frequent within the first 10 y after the accident whereas PTC1 is now becoming more common. Point mutations in the BRAF gene are unusual in Chernobyl-related thyroid cancers, but the BRAF point mutations are most often found in sporadic adult papillary cancers (Cohen et al. 2003; Kimura et al. 2003), and are infrequent in either childhood thyroid cancers (Kumagai et al. 2004; Lima et al. 2004; Powell et al. 2005) or adult cancers which occur subsequent to childhood radiation exposure (Collins et al. 2006). In an analysis of the expression of 2,400 randomly selected genes, similar patterns were seen for sporadic thyroid cancer and Chernobyl-related thyroid cancer (Detours et al. 2005). While these data suggest that the Chernobyl-related cancers do not differ from spontaneous ones on a molecular level, the sample size was small. It remains a challenge to disentangle the effects of the radiation exposure *per se* from those of the young age at diagnosis and short latency.

SUMMARY

Twenty years after the accident, pediatric thyroid cancers no longer occur as a result of the Chernobyl accident since the entire exposed population is now over age twenty; however, excess thyroid cancers are occurring among young adults exposed as children or adolescents. Current data suggest that the shape of the dose-response curve basically is linear, although at high doses there may be a downturn, and that the magnitude of the excess risks and the patterns of modifying effects are largely in agreement with those observed following external radiation exposure. While the long-term risks cannot yet be quantified, if external radiation can be used as a guide, we can expect an excess of thyroid cancers for several more decades. In most analytic studies, thyroid cancer risk appeared to decrease with increasing age at exposure, no significant sex-related differences in radiation-related relative risks were found, but the absolute number of excess thyroid cancers was larger for women than men. Some, but not all, studies have reported that iodine

Table 2. Clinical and demographic features of patients with Chernobyl-related or sporadic thyroid cancers diagnosed between 1986 and 1995 before the age of 21 y (Pacini et al. 1997).

| | Chernobyl-related | Sporadic |
|------------------------|-------------------|------------------|
| Number of patients | 472 | 369 |
| Place of diagnosis | Belarus | Italy and France |
| Female to male ratio | 1.6/1 | 2.5/1 |
| Age at diagnosis (y) | 11.3 ± 3.1 | 14.56 ± 4.2 |
| Tumor histology | | |
| Papillary carcinoma | 94% | 82% |
| Follicular carcinoma | 5% | 15% |
| Tumor extension | | |
| Extrathyroid | 49% | 25% |
| Lymph node involvement | 65% | 54% |

deficiency enhances the risk of thyroid cancer following exposure from Chernobyl. The role of iodine deficiency and iodine prophylaxis requires confirmation. Information on the carcinogenic effects of adult exposure is limited and additional data are needed. Similarly, information on thyroid cancer risks associated with in utero exposure is insufficient to draw conclusions. The lack of information on these two important population groups indicates a key gap that needs to be filled. Further research also is needed in relation to histological, clinical and molecular features of future thyroid cancers. An important remaining question is whether follicular and anaplastic carcinomas will emerge as the exposed populations age and if so, will they have clinical and molecular characteristics representative of these histological types. Long-term follow-up of Chernobyl-exposed populations will help shed light on the many remaining uncertainties regarding future health consequences.

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