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Thyroid Cancer Risk in Areas of Ukraine and Belarus Affected by the Chernobyl Accident

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The purpose of the present study was to analyze the thyroid cancer incidence risk after the Chernobyl accident and its degree of dependence on time and age. Data were analyzed for 1034 settlements in Ukraine and Belarus, in which more than 10 measurements of the ^{131}I content in human thyroids had been performed in May/June 1986. Thyroid doses due to the Chernobyl accident were assessed for the birth years 1968–1985 and related to thyroid cancers that were surgically removed during the period 1990–2001. The central estimate for the linear coefficient of the EAR dose response was 2.66 (95% CI: 2.19; 3.13) cases per 10^4 PY-Gy; for the quadratic coefficient, it was −0.145 (95% CI: −0.171; −0.119) cases per 10^4 PY-Gy^2. The EAR was found to be higher for females than for males by a factor of 1.4. It decreased with age at exposure and increased with age attained. The central estimate for the linear coefficient of the ERR dose response was 18.9 (95% CI: 11.1; 26.7) Gy^{-1}; for the quadratic coefficient, it was −1.03 (95% CI: −1.46; −0.60) Gy^{-2}. The ERR was found to be smaller for females than for males by a factor of 3.8 and decreased strongly with age at exposure. Both EAR and ERR were higher in the Belarusian settlements than in the Ukrainian settlements. In contrast to ERR, EAR increases with time after exposure. At the end of the observation period, excess risk estimates were found to be close to those observed in a major pooled analysis of seven studies of childhood thyroid cancer after external exposures.

INTRODUCTION

Thyroid cancer incidence in Ukraine and in Belarus started to increase significantly in 1990 among those who were children or adolescents at the time of the Chernobyl accident in April 1986 (*1*, *2*). Since then, the incidence rate has increased further (*3*, *4*). Analyses of thyroid cancer after the Chernobyl accident have a large potential for improving the understanding of the detrimental health effects of ^{131}I exposures, which were the main cause of thyroid doses after the accident.

Two case-control studies found an association of the increase in thyroid cancer incidence with radiation exposure due to the Chernobyl accident (*5*, *6*). These studies have limitations in deriving risk estimates due to large dose uncertainties.

A cohort study is being performed here based on data for 25,161 Belarusian and Ukrainian children who had the ^{131}I content of the thyroid measured in May/June 1986 (*7*). Due to the intensive screening of the cohort members, the prevalence is considerably higher than in the general population. Consequently, estimates of the excess absolute risk (EAR) per dose for cohort members will not be the same as in the general population. It remains an open question as to what degree the intensive screening will influence excess relative risk (ERR) estimates.

Ecological studies have been performed for settlements in Belarus, Russia and Ukraine with relatively good dosimetry (*8*, *9*). There is a general concern whether quantitative risk values can be derived with such an ecological study design (*10*, *11*). Therefore, extensive simulation studies have been performed to explore the potential of ecological studies of thyroid cancer incidence in areas highly contaminated by the Chernobyl accident.[3] A main problem here is the potential for correlations between thyroid dose and increased case detection between the settlements. These simulations indicate that the ecological bias is relatively small in studies in which the ecological units are age groups in settlements with measurements of the ^{131}I content in the human thyroid. The reasons include:

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[3] J. C. Kaiser, P. Jacob, M. Blettner and S. Vavilov, Implications of increased thyroid cancer detection and reporting on risk estimations after the Chernobyl accident. Manuscript submitted for publication.

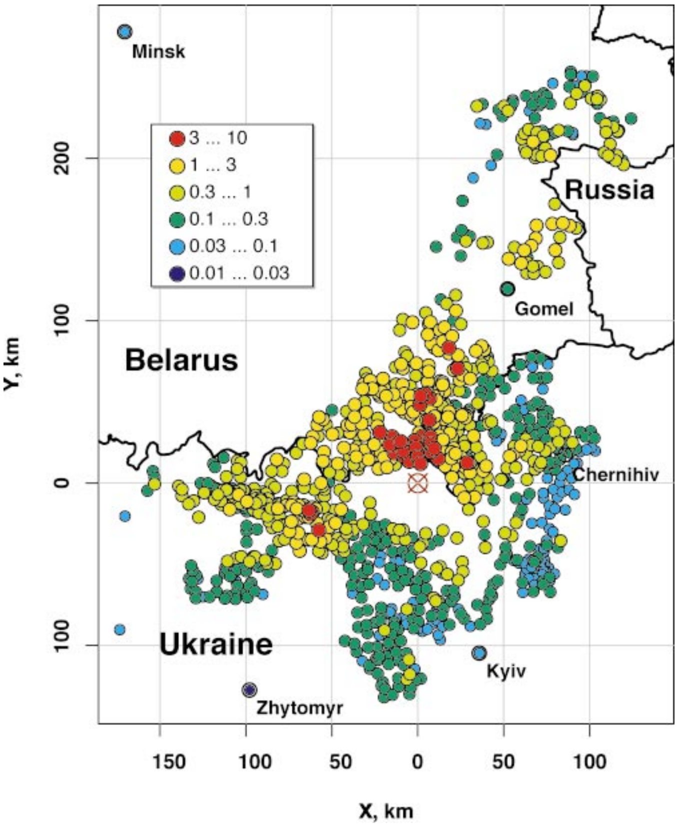

FIG. 1. Average thyroid dose (Gy) of the birth cohort 1968–1985 in the 608 Ukrainian and 426 Belarusian study settlements. The Chernobyl nuclear power plant is indicated in the center of the map.

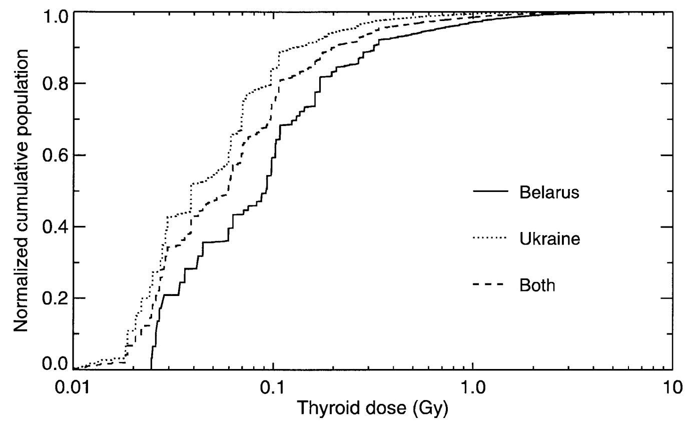

FIG. 2. Population weighed distribution of age-gender specific doses in the 608 Ukrainian and 426 Belarusian study settlements.

1. There is a unique database of more than 200,000 measurements of the ^{131}I content in the human thyroid that were performed in May/June 1986 (*12*, *13*).
2. Radiation is the dominant cause of thyroid cancer among those who were children or adolescents in the highly contaminated areas at the time of the accident, where the thyroid measurements were performed.
3. In general, there is no evidence for a correlation of thyroid dose and the main confounding factor, an increase in case detection and reporting, within the ecological units. In larger towns, there was a potential for such a correlation. Simulation calculations showed, however, that the ecological bias due to such a correlation is very small.[3]
4. There is no indication that the dose response for thyroid cancer after exposures during childhood is nonlinear in the dose range of 0.05–1.0 Gy (*9*, *14*).

The purpose of this study was to derive risk estimates for those who were children or adolescents at the time of the Chernobyl accident and were living in settlements in which more than 10 measurements of the ^{131}I content in the human thyroid were performed in May/June 1986 (study settlements). Compared to earlier reports (*8*, *9*) the risk analysis presented here is based on improved dose estimates and a longer follow-up (until the end of 2001), which allows an evaluation of the degree of dependence on time. Relationships between the uncertainty of dose estimates, the variability of individual doses within the age-gender groups in the single settlements, and the range of average doses of the ecological units are discussed, because these are considered important criteria for the validity of the ecological study.

MATERIALS AND METHODS

The analysis presented here is based on registry data on thyroid cancer. To guarantee the privacy of the persons involved, the registry data were merged before analysis into groups of 2-year intervals of birth year and 2-year intervals of year of surgery. In total, the study uses data for 18,612 ecological units, which are defined by nine birth-year groups in the period 1968–1985, both genders, and 1034 study settlements (Fig. 1). For each of the ecological units, there are thyroid cancer data for six year-of-surgery groups in the period 1990–2001.

Dosimetry

Individual thyroid doses due to ^{131}I exposures were derived from measurements of the ^{131}I activity in the human thyroid that had been performed during the first few weeks after the Chernobyl accident. Short-lived radionuclides contributed less than 10% to the total thyroid dose (*15*). The doses were calculated as a product of the time-integrated activity in the thyroid, and a conversion factor, absorbed energy per ^{131}I decay and per thyroid mass (*16*).

Ukraine. Age-gender specific doses in 608 settlements were derived from a total of 75,313 individual dose estimates (*17*). Time-integrated activities in the thyroid were assumed to be the product of an average time-integrated activity in the settlement and age- and gender-dependent factors. Different factors were used for rural and urban areas. The 95% range of average age-gender specific thyroid doses was 0.014–0.33 Gy (Fig. 2). There were a few small settlements with considerably higher doses, up to 16 Gy for 1–2-year-old boys. Typically, the individual time-integrated activities within the ecological units (age-gender groups in the single settlements) had a coefficient of variation (CV) of 1.1, corresponding in a lognormal distribution to a geometric standard deviation (GSD) of 2.3. The spread of their distributions is a combined effect of the variability of the true individual doses and the uncertainties of the dose estimates.

Belarus, age-dependent doses. Previous estimates of individual thyroid dose estimates, based on measurements of the ^{131}I activity in the human thyroid (*13*), have been reviewed and improved (*18*). One main result of this new analysis was that the ingestion pathway dominates the time dependence of the radioiodine intake not only for rural settlements but also for most of the inhabitants of the large cities Minsk and Gomel. Age-dependent thyroid doses were derived for 426 study settlements in Belarus based on 90,699 re-evaluated individual time-integrated activities. Typically, the individual time-integrated activities within the age groups of the single settlements had a CV of 1.2 (corresponding to a GSD of 2.6) (*19*). Uncertainty of the average integrated activities in the ecological units depends on the number and the quality of measurements in the settlement. It was assessed to correspond on average to a CV of 0.5 (GSD of 1.6). This value also applies to the dose estimates, because the uncertainty of the average value of the conversion factor is small compared to the uncertainties of the iodine measurements.

Belarus, age-gender dependent doses. Only estimates of gender-averaged doses were available for Belarus, so the following procedure was applied to estimate the gender specific doses. The gender-specific doses in Kyiv City (which was the Ukrainian city with the largest number of ^{131}I measurements) were used to derive gender-specific doses, $D^{\mathrm{city}}_{s,i}$, for the birth cohort i in Minsk and Gomel City according to

$$D^{\mathrm{city}}_{s,i} = D^{\mathrm{city}}_{av,i} \cdot D^{K}_{s,i}/D^{K}_{av,i}, \quad \text{with} \tag{1}$$

$$D^{K}_{av,i} = (PY^{K}_{f,i}D^{K}_{f,i} + PY^{K}_{m,i}D^{K}_{m,i})/(PY^{K}_{f,i} + PY^{K}_{m,i}), \tag{2}$$

where PY is person-years, the index s can be either f for females or m for males, and the index K stands for Kyiv. In the same way, gender-specific doses for the rural settlements of Belarus were derived using the doses in Chernihiv Oblast (which was the Ukrainian oblast with the largest number of ^{131}I measurements). The 95% range of average age-gender specific doses in the 426 Belarusian study settlements was 0.025–1.11 Gy (Fig. 2). There were a few small settlements with considerably higher thyroid doses, of up to 18 Gy for 1–2-year-old boys.

Both countries. For settlements close to the boundary of the two countries, comparable values have been derived by the dosimetric approaches used for the two countries (Fig. 1). The distribution of the estimated individual doses within the ecological units was slightly wider in Belarus than in Ukraine because of a larger uncertainty of the measurements. The measurements in Ukraine were performed with collimators, which were less prone to error than the measurements taken without collimators for Belarus. Also, there were generally better measurement conditions in Ukraine (e.g., measurements were taken inside houses rather than outside, subjects were wearing clean clothes rather than contaminated ones, and subjects were asked to wash before measurements were taken). The 95% range of average age- and gender-specific thyroid doses in the 1034 settlements was 0.018–0.65 Gy (Fig. 2). The ratio of the two limiting percentiles of the range is 36 corresponding to a CV of 1.15 (GSD of 2.5) for a lognormal distribution.

Population

Ukraine. The age-gender structure according to the census data for 1989 and age-gender specific death rates were used to estimate the demographic structure in the study settlements in 1986 (*20, 21*). A linear interpolation of the census data for 1979 and 1989 gave similar results (*20, 22*), which was considered to be a confirmation of the method. Information on the total population in the study settlements in the years 1992–1994 was obtained from local authorities. Information on the population of the Ukrainian oblasts for 1991 and 1994 was received from the Ministry of Statistics of Ukraine (*23*). It was assumed that the number of inhabitants of each settlement changed during 1986–1994 proportionally to the changes in the whole rural/urban population of the oblast in which the settlement is located and that the age-gender structure also remained the same. In total, there were 997,000 children and adolescents in 1986 in the 18 age and gender groups of the 608 Ukrainian study settlements. Most of the children and adolescents (694,000) lived in Kyiv City.

Belarus. The derivation of the age-gender structure of the population in the Belarusian study settlements in 1986 is similar to the Ukrainian study settlements and has been described elsewhere (*24*). In total, there were 623,000 children and adolescents in 1986 in the 18 age and gender groups of the 426 study settlements. Most of the children and adolescents lived in either Minsk City (418,000) or Gomel City (132,000) at the time of the accident.

Both countries. The loss of follow-up during the period 1986 to 2001 was neglected because it was considered to be small compared to the other sources of uncertainties in the risk analysis. The loss of person-years due to death was relatively small because the members of the cohort were quite young during the period of observation. The loss of follow-up and cases due to migration was also considered to be small, because thyroid cancers of people who were exposed as children or adolescents by the Chernobyl accident and who underwent surgery in Belarus, Russia or Ukraine should be reported to the registry of the country where the person lived at the time of the accident. Migration to other countries has been neglected.

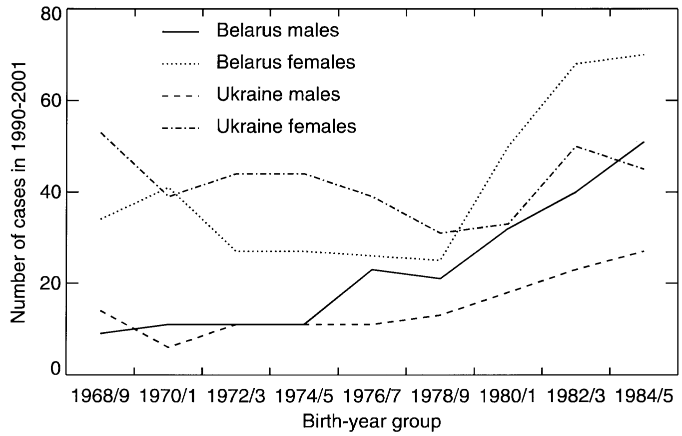

FIG. 3. Number of thyroid cancer cases in the period 1990–2001 in nine birth-year groups in the 608 Ukrainian and 426 Belarusian study settlements.

Thyroid Cancer Cases

Data on thyroid cancer cases in the period 1990–2001 for the birth cohort 1968–1985 were used. These data files contain the place of residence at the time of the accident for all cases. For some of the cases, only the year of birth was available; for this reason, only birth years were used for all cases here, and age at surgery is defined by the difference of the year of surgery and the birth year.

Ukraine. The clinical-morphological register at the Institute of Endocrinology and Metabolism of the Academy of Medical Sciences of Ukraine has been described elsewhere (*3*). According to the *Order of the Ministry of Public Health on the Improvement of Endocrinological Help to the Population* from 1992, all thyroid cancer cases among subjects who were up to 18 years old at the time of the Chernobyl accident and who were operated on in Ukraine must be reported to the register. The data were cross-checked with the Ukrainian Cancer Registry, and a few missing cases were added. For the 608 Ukrainian study settlements, 512 thyroid cancer cases were reported, 378 cases among females and 134 among males. There is no clear dependence of the cases among females on birth year (Fig. 3). For males, the incidence in the birth cohort 1984/1985 is larger than in the birth cohort 1968–1977 by a factor of 2.5. For both genders together, the incidence rate is 52 cases per 10^6 person-years for the youngest subjects (birth years 1982–1985), and about 40 cases per 10^6 person-years for the other birth-year groups. The ratio of female to male cases is about 2 for the younger subjects (1978–1985) and about 4 for the older subjects (birth years 1968–1977). There is a continuous increase of the incidence rate in the subsequent years (Fig. 4) compared to the first years after the accident. The screening of the Ukraine-American cohort started in 1998 (*25*). Up to the end of 2000, 43 cancer cases

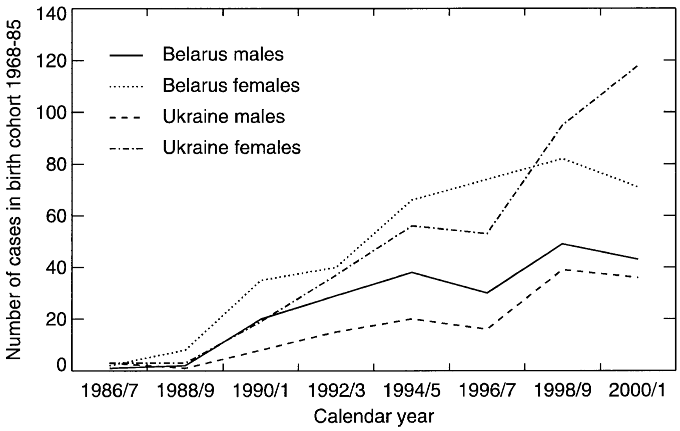

FIG. 4. Number of thyroid cancer cases for nine calendar-year periods in the birth-year cohort 1968–1985 in the 608 Ukrainian and 426 Belarusian study settlements.

were detected, which contributed 20% to the number of cases in 1998–2000 in our 608 study settlements.

Belarus. A data exchange of the following three registers was performed, which resulted in consistent data sets in the registers:

1. The Belarusian State Chernobyl Register, which was established in 1993 according to a decree of the Council of Ministers of Belarus, containing data on liquidators and citizens of areas with ^{137}Cs contaminations exceeding 555 kBq m^{-2}.
2. The Belarusian Cancer Register, which was established in 1953 according to a directive from the Ministry of Public Health of the USSR. The register does not contain information about the place of residence at the time of the Chernobyl accident.
3. The medical history records of patients treated in the National Scientific and Practical Center of Thyroid Tumors in Minsk, where all thyroid cancers of Belarusian children are treated.

For the 426 Belarusian study settlements, 577 thyroid cancer cases have been reported, 368 cases among females and 209 among males. In contrast to the Ukrainian study settlements, the incidence among young subjects is considerably greater than for the older subjects (Fig. 3). The incidence rate is 133 cases per 10^6 person-years for the youngest (birth years 1984–1985), where this rate decreases initially with age at exposure and then has an approximately constant value of about 55 cases per 10^6 person-years for the birth-year cohorts of 1978–1969. The ratio of female to male cases is about 1.6 for the youngest subjects (1980–1985) and 1.2 for the birth-year cohort (1976–1979) and increases to 4 for the older subjects (birth years 1968–1971). As in Ukraine, the incidence rate increases continuously since the first years after the accident (Fig. 4).

Data Analysis

Poisson regressions were performed with EAR models,

$$\lambda(c, s, aae, age, d) = \lambda_0(c, s, aae, age) + \alpha(c, s, aae, age, d), \quad (3)$$

and with ERR models

$$\lambda(c, s, aae, age, d) = \lambda_0(c, s, aae, age)[1 + \alpha(c, s, aae, age, d)], \quad (4)$$

where λ is the total incidence rate, λ_0 the baseline incidence rate, α the EAR, β the ERR, c the country, s the gender, *aae* the age at exposure (birth year − 1986), *age* the age attained (calendar year − birth year), and d the thyroid dose. The baseline risk was modeled by

$$\lambda_0(c, s, aae, age) = \exp[\eta_0 + \theta_c\eta_c + \eta_s\theta_s + \eta_{aae}(10 - aae) + \eta_{age}\ln(age/20)], \quad (5)$$

the EAR by

$$\alpha(c, s, aae, age, d) = (\alpha_1 d + \alpha_2 d^2)\exp[\alpha_c\theta_c + \alpha_s\theta_s + \alpha_{aae}(10 - aae) + \alpha_{age}\ln(age/20)], \quad (6)$$

and the ERR by

$$\beta(c, s, aae, age, d) = (\beta_1 d + \beta_2 d^2)\exp[\beta_c\theta_c + \beta_s\theta_s + \beta_{aae}(10 - aae) + \beta_{age}\ln(age/20)], \quad (7)$$

where $\alpha_{\ldots}$, $\beta_{\ldots}$ and $\eta_{\ldots}$ are fit parameters, θ_c is −0.5 for Ukraine and 0.5 for Belarus, and θ_s is −0.5 for males and 0.5 for females.

The regressions were performed with the program AMFIT of the software package EPICURE (Hirosoft International Corporation, Seattle, WA). Results for subgroups were considered to be different if the 95% confidence range for the corresponding fit parameters did not include the value for equality.

RESULTS

Baseline Incidence Rate

The estimates of the baseline incidence rate in the EAR and the ERR models are nearly identical (Table 1). The central estimate of the baseline incidence rate is 14 cases per 10^6 PY. No significant difference is observed between the Ukrainian and the Belarusian settlements. The rate is assessed to be larger for females than for males by a factor of 5.9. For the same age attained, the baseline incidence rate in the year 2001 is estimated to be larger than in 1990 by a factor of 1.9. For fixed age at exposure, the rate increases with age attained to the power of 3.8 (Fig. 5). This increase is due to aging and to an improvement in case detection and reporting during the period of observation.

Excess Absolute Risk

The central estimate for the linear coefficient of the EAR dose dependence is 2.66 (95% CI: 2.19; 3.13) cases per 10^4 PY-Gy; for the quadratic coefficient, it is −0.145 (95% CI: −0.171; −0.119) cases per 10^4 PY-Gy^2 (Table 1). Thus the dose–response curve has a downward curvature for very high doses. The EAR is assessed to be higher in the Belarusian study settlements than in the Ukrainian settlements by a factor of 1.4 and higher for females than for males by a factor of 1.5.

For fixed attained age, EAR decreases with increasing *aae*, for a difference of 8 years in *aae* by a factor of 0.4 (Fig. 6, upper panel).

For fixed *aae*, EAR increases (a bit more than) proportionally with age attained. A non-parametric analysis indicates that the increase flattens with time after exposure (*26*). Models with quadratic terms in ln(*age*/20) in Eqs. (5) and (7), however, did not improve the quality of the fit.

TABLE 1
Best Estimates and 95% Confidence Intervals of Fit Parameters According to Equations (3–7)

	Excess absolute risk model		Excess relative risk model	
	Fit parameter	Value	Fit parameter	Value
Baseline incidence rate for age at exposure 10 and attained age 20	$\exp(\eta_0)$	14.0 (10.5; 18.7) $(10^6$ PY$)^{-1}$	$\exp(\eta_0)$	14.0 (10.5; 18.6) $(10^6$ PY$)^{-1}$
Ratio of baseline incidence rates in Belarusian and Ukrainian study settlements	$\exp(\eta_c)$	0.83 (0.64; 1.08)	$\exp(\eta_c)$	0.83 (0.63; 1.08)
Ratio of baseline incidence rates of females and of males	$\exp(\eta_s)$	5.93 (4.01; 8.77)	$\exp(\eta_s)$	5.97 (4.03; 8.84)
Slope of the logarithm of the baseline incidence rate with decreasing age at exposure[a]	η_{aae}	0.058 (0.010; 0.106) a^{-1}	η_{aae}	0.058 (0.010; 0.106) a^{-1}
Exponent of attained-age dependence of baseline incidence rate	η_{age}	3.76 (2.84; 4.69) a^{-1}	η_{age}	3.77 (2.84; 4.69) a^{-1}
Linear coefficient of dose response of excess risk	α_1	2.66 (2.19; 3.13) $(10^4$ PY Gy$)^{-1}$	β_1	18.9 (11.1; 26.7) Gy^{-1}
Quadratic coefficient of dose response of excess risk	α_2	−0.145 (−0.171; −0.119) $(10^4$ PY Gy$^2)^{-1}$	β_2	−1.03 (−1.46; −0.60) Gy^{-2}
Ratio of excess risks in Belarusian and Ukrainian study settlements with same dose	$\exp(\alpha_c)$	1.36 (1.12; 1.66)	$\exp(\beta_c)$	1.64 (1.14; 2.37)
Ratio of excess risks of females and of males for the same dose	$\exp(\alpha_s)$	1.55 (1.29; 1.86)	$\exp(\beta_s)$	0.260 (0.162; 0.415)
Slope of the logarithm of excess risk with decreasing age at exposure[b]	α_{aae}	0.106 (0.075; 0.137) a^{-1}	β_{aae}	0.048 (0.015; 0.111) a^{-1}
Exponent of attained-age dependence of excess risks	α_{age}	1.05 (0.71; 1.40) a^{-1}	β_{age}	−2.71 (−3.76; −1.67) a^{-1}

[a] Equal to the slope of the logarithm of the baseline incidence rate with calendar year of observation.
[b] Equal to the slope of the logarithm of the excess risk with calendar year of observation.

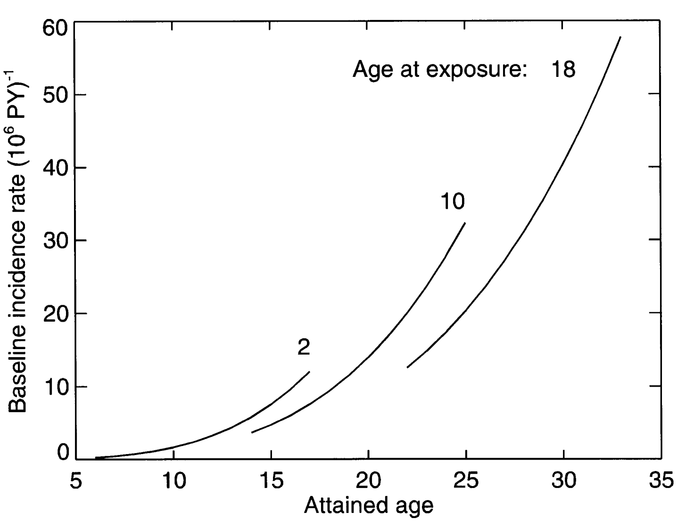

FIG. 5. Estimated baseline thyroid cancer incidence for different ages at exposure (birth year − 1986) in the 1034 study settlements.

Excess Relative Risk

The central estimate for the linear coefficient of the ERR dose dependence is 18.9 (95% CI: 11.1; 26.7) Gy^{-1}; for the quadratic coefficient, it is −1.03 (95% CI: −1.46; −0.60) Gy^{-2} (Table 1). The ERR is assessed to be higher in the Belarusian settlements than in the Ukrainian settlements by a factor of 1.6 and lower for females than for males by a factor of 3.8.

ERR depends mainly on age attained, with a small dependence on *aae* (Fig. 6, lower panel). In a period in which age attained doubles, ERR decreases by a factor of 6.5.

Results for Subpopulations

The numbers of baseline, excess and total cases predicted by the EAR and ERR models for the entire study population and for subgroups of the study population are similar (Table 2). For males in the Belarusian settlements, the ratio of excess to baseline cases, i.e. the excess relative risk, is estimated to be 8.5. For females in the Belarusian settlements and males in the Ukrainian settlements, it is about 2.2 and for females in the Ukrainian settlements 0.6.

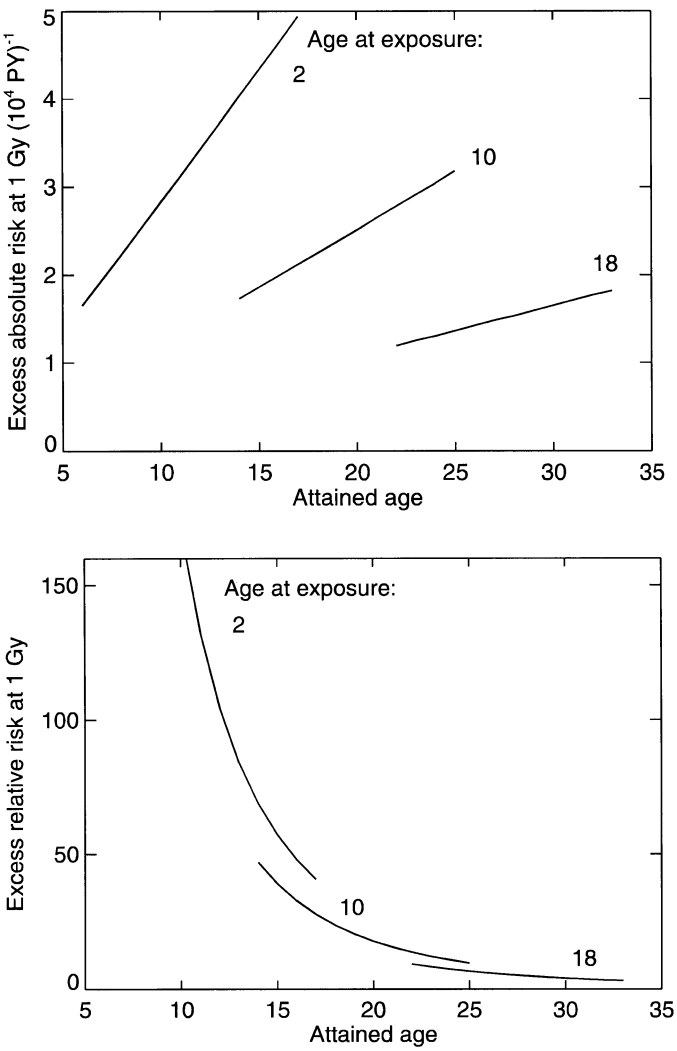

FIG. 6. Central estimate of EAR (upper panel) and of ERR (lower panel) after an exposure to 1 Gy for different ages at exposure (birth year − 1986) in the 1034 study settlements.

Separate risk analyses were performed in subpopulations. Best estimates of excess risks in towns with more than 10,000 children and adolescents and in the remaining smaller villages agree within 10% (results not shown).

DISCUSSION

Criteria for Quality Assessment of the Ecological Study

Average doses in the ecological units were estimated based on 166,012 individual dose estimates for persons with measurements of the ^{131}I activity in the thyroid. Thus, although the study is not based directly on individual dose estimates, there are on average nine individual dose estimates per ecological unit. There are 150 settlements with less than 18 individual dose estimates. Therefore, some ecological units have only one or even no individual dose estimate. The dose estimates for the ecological units, however, are based on at least 11 individual dose estimates and a generic age-gender dependence of the thyroid dose.

The range of average doses for the ecological units (GSD = 2.5) is larger than the uncertainty of the average dose in the ecological units (GSD = 1.6) and similar to the range of true individual doses within the ecological units (GSD of 2.1 to 2.6; see Appendix). Ideally, the range of average doses for the ecological units should exceed the other two ranges. The present study is close to fulfilling these conditions.

The major concern, that an ecological bias may exist in the present study, is due to an observed correlation of screening level and dose. Ecological studies have been simulated for four screening scenarios for thyroid cancer in settlements, in which the ^{131}I activity in the human thyroid was measured in May/June 1986 after the Chernobyl accident.[3] These simulations indicate that the ecological bias is small in the present study.

Dependence of Risk Estimates on Time after Exposure

In an earlier study (*27*) of Belarusian settlements with relatively good dosimetry, the EAR per dose was 2.8 (95% CI: 1.3; 6.0) cases per 10^4 PY-Gy for females and 1.7 (95% CI: 0.8; 3.6) cases per 10^4 PY-Gy for males in the period 1994–1996. This is in very good agreement with the results of the present work. In the birth-year cohort 1968–1985, the EAR increases and the ERR decreases with time after exposure. This is explained by a faster increase in the spontaneous thyroid cancer incidence than of the radiation-in-

TABLE 2
Baseline, Excess and Total Cases According to the EAR and ERR Models Compared with Observed Cases and Estimates of Average Dose

		Ukrainian settlements			Belarusian settlements			All settlements		
Cases	Model	Males	Females	Both	Males	Females	Both	Males	Females	All
Baseline	EAR	40.9	237.1	278.0	21.8	121.2	143.0	62.6	358.4	421.0
	ERR	40.7	238.1	278.8	21.7	122.0	143.7	62.4	360.1	422.5
Excess	EAR	97.8	136.2	234.0	185.1	249.3	434.4	282.9	385.5	668.4
	ERR	96.9	135.0	231.9	184.1	248.4	432.5	281.0	383.4	664.4
Total	EAR	138.7	373.3	512.0	206.8	370.6	577.4	345.5	743.9	1089.4
	ERR	137.6	373.1	510.7	205.7	370.5	576.2	343.3	743.6	1086.9
Observed cases		134	378	512	209	368	577	343	746	1089
Average dose (Gy)		0.083	0.075	0.079	0.189	0.171	0.180	0.124	0.112	0.118

duced incidence. The spontaneous thyroid cancer incidence increased due to the aging of the cohort and due to an increasing case detection and reporting rate.

The increase in the EAR with time after exposure occurs mainly before 1998 (*26*). It may be concluded that the additional cases detected in the cohort study (*7*), in which the screening started in 1998, have only a minor effect on the results of the present study. The continuing increase in the annual number of excess cases in the study settlements underlines the importance of longer-lasting studies of thyroid cancer in populations that have been exposed by the Chernobyl accident.

Dose Uncertainties

The risk analysis presented here does not take dose uncertainties into account. For a linear dose response and an additive classical error structure, an underestimation of the excess risk is expected if the dose uncertainty is neglected in the Poisson regression (*28*). This underestimation is expected to be small in the present analysis as indicated by the following two observations:

1. The dose uncertainty is small compared to the range of average doses used for the ecological units.
2. In an earlier analysis, calculations were performed that were similar from the methodological point of view to the present analysis (*9*). Results were compared with an independent method, a risk calculation with a Monte Carlo method, which took dose uncertainties into account. No large bias of the results was observed. Indeed, the EAR was found to be 10% higher in the Monte Carlo calculation than in the Poisson regression.

In summary, the bias on the risk estimates caused by neglecting the dose uncertainties in the analysis is not expected to be large. However, the confidence intervals are too small, and this should be kept in mind in the evaluation of the significance of differences discussed in the Results section.

Comparison with Risks after External Exposures

A pooled study of thyroid cancer after external exposures during childhood resulted in estimates of the EAR per dose of 4.4 (95% CI: 1.9; 10.1) cases per 10^4 PY-Gy and of the ERR per dose of 7.7 (95% CI: 2.1; 28.7) Gy^{-1} (*14*). The pooled study includes cohorts with observation times that extend to several decades after exposure. The observation period of the present study was 4 to 15 years after exposure. Results for the end of the observation period (central estimate for linear coefficient of EAR in 2001 is 3.4 cases per 10^4 PY-Gy and of ERR is 10.3 Gy^{-1}) are in good agreement with the results for external exposures.

APPENDIX

Combined Variability and Uncertainty of Estimated Individual Doses within the Ecological Units

The CV of the estimated time-integrated activities of the individuals within the ecological units has been estimated as 1.1 for Ukraine and 1.2 for Belarus. The variability of the dose factor that relates the time-integrated activity and the thyroid dose has been estimated to correspond to a GSD of 1.8 (*29*). Assuming a lognormal distribution of the dose factor, error propagation leads to a CV in the range of 1.4–1.6 for the estimated individual doses within the ecological units.

Variability of True Individual Doses within the Ecological Units

Main factors influencing the variability of true individual doses of a group of given age and gender in a study settlement are the variability in the thyroid mass, the ^{131}I concentration in milk, and the rate of consumption of contaminated milk.

Typically, these factors can be described by lognormal distributions with GSDs of 1.8, 1.3–1.8 and 1.6, respectively (*15*). Combination of these three sources of variability leads to distribution for the true doses with GSDs of 2.1 to 2.6, or coefficients of variability (CV) of 0.9 to 1.2. This is consistent with the range of estimated individual thyroid doses within the ecological units (see above), since the latter distribution is broadened by the uncertainties of the individual dose estimates.

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