Anhang 6

Implications of increased thyroid cancer detection and reporting on risk estimations after the Chernobyl accident

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Abstract. Risk estimates of thyroid cancer from both ecologic studies and cohort studies are analysed for various simulation scenarios after the Chernobyl accident. Based on age and sex-specific dose averages for 669 settlements in the three highly contaminated oblasts of Chernihiv, Zhytomyr and Kyiv and in the city of Kyiv, individual doses have been simulated for 1002706 members of both sexes for the birth cohort 1968-85. For this study population 350 cancer cases have been reported in the period from 1990-99. Two ecologic scenarios have been set up with estimates for regional baseline incidences, screening factors and different correlation patterns for screening and exposure. Using a linear dose response, Poisson regression on the number of cancer cases in a settlement has been performed. The resulting ecologic coefficients for the excess absolute risk and the excess relative risk have been compared with the true mean risk in the population, which has been calculated based on plausible assumptions on baseline incidence and screening regime. Deviations of the ecologic risk from the mean risk were caused by a complex correlation structure of the variables that constitute the dose-response relation. Depending on the scenario, correlations generated a moderate ecologic bias of up to -9 % for the excess absolute risk per unit dose (EARPD) and -15 % for the corresponding relative risk (ERRPD). Based on the simulation of missing information, the observed cases have been sub-divided into spontaneous cases, radiation-induced cases and cases from screening. The EARPD from a scenario for a cohort study overestimated the true risk in the population by a factor of five, owing mostly to more intensive screening. The simulation scenarios comply with many conditions posed by the raw data. They produce consistent results and are able to represent important features of the real situation.

Key words. Thyroid cancer risk, Chernobyl accident, screening effect, ecologic bias, cohort study

1. Introduction

Starting in 1990, the thyroid cancer incidence among the birth cohort 1968-85 increased steeply in areas that were affected by radioactive contaminations due to the accident of the Chernobyl nuclear power plant in 1986. Recent figures are published in Jacob et al. (2004). This increase is partly due to the incorporation of ^{131}I, and partly due to the introduction of ultrasound devices, the public awareness of an increased thyroid cancer risk after the accident, improved systems of case reporting, and dedicated screening programmes.

In this article we address the still open questions, how much the non-radiation part of the increase influences the results of risk studies and how the results of different studies may be interpreted and compared. A number of studies has been carried out with aggregate data (Buglova et al. 1996, Jacob et al. 1998, Jacob et al. 1999, Likhtarev et al. 1999) which may be burdened with an ecologic bias. Numerous reasons for this bias are well known and have been discussed in the literature, a recent summary is given by Wakefield (2004). Here the main contribution can be attributed to screening, which confounds the effect of exposure to radiation.

With simulation calculations for the thyroid cancer incidence in Ukrainian settlements, Kaiser et al. (2004) have developed a methodology to quantify the ecologic bias. Their approach was motivated by previous work (Lubin 1998, Lubin 2002), which focused on the lung cancer risk related to radon exposure confounded by smoking. This problem possesses a similar mathematical structure. But there is a conceptual difference, since lung cancer is caused biologically by both radiation and smoking, whereas screening merely increases the number of detected and reported thyroid cancer cases and has no biological effect.

The simulations of Kaiser et al. (2004) were based on dose estimates for settlements, where more than 10 measurements of the ^{131}I content in the human thyroid had been performed in the period May/June 1986 (Likhtarov et al. 2004). It was shown that correlations between quantities in the dose-response relation are a plausible cause of bias. In the case of thyroid studies, screening is defined as the increase of case detection and reporting by enhanced medical surveillance. It is considered as the main source of such correlations (Ron et al. 1995).

In this work we established scenarios for the increase of the thyroid cancer incidence, and we explored their implications for risk studies. We focus our attention to selected settlements of the three highly contaminated oblasts of Zhytomyr, Kyiv and Chernihiv and to the city of Kyiv with about one million exposed children and adolescents. For two ecologic scenarios the spontaneous and the radiation-induced part of the total risk have been prescribed together with a correlation pattern for exposure and screening. With a linear dose response the ecologic excess risk has been estimated, using settlement-specific Poisson regression on both simulated and real data. It has been compared with the true mean risk in the population, which has been calculated for the assumed decomposition of the risk. Partly based on the simulation of missing information, we quantified the number of spontaneous cases, radiation-induced cases and cases from increased detection and reporting. Finally, we relate the risk estimate from a cohort study to the risk in the population.

Figure 1. Map of Belarus and Ukraine with oblast boundaries, hatched study area includes the Ukrainian oblasts of Chernihiv, Kyiv and Zhytomyr, and the city of Kyiv.

2. Materials and Methods

2.1. Exposure and incidence

The study area consists of the three highly contaminated rural oblasts of Chernihiv, Kyiv and Zhytomyr, and the city of Kyiv. It is shown in the map of Figure 1. From the three rural oblasts 669 settlements have been selected, where measurements of the 131I content in the thyroid have been taken for more than ten persons in May and June 1986. For these settlements and for the city of Kyiv Likhtarov et al. (2004) have estimated age and sex-specifi c doses for each birth year group of the birth cohort 1968-85. For each sex and age group a lognormal dose distribution has been assumed and both its geometric dose mean and standard deviation have been given. The arithmetic mean for the total study population was 0.080 Gy, the maximal measured dose was approx. 10 Gy.

In this study the city of Kyiv is treated as an oblast containing just one settlement. The number of children and adolescents under age 18 in the then 670 settlements at the time of accident was taken from the union-wide census USSR (1991) of the year 1989. The total study

Table 1. Number of settlements, estimated number of exposed children in 1986, and observed number of cases in 1990-99.

region	number of settlements	number of children in 1986	number of cases in 1990-99
Chernihiv o.	222	119712	56
Kyiv city	1	650078	198
Kyiv oblast	203	74296	46
Zhytomyr o.	244	158620	50
total	670	1002706	350

population was 1002706, more than 650000 exposed children lived in Kyiv city. In the rural oblasts the two largest cities were Zhytomyr and Chernihiv with more than 80000 children. The majority of settlements consists of small villages with about 100 children (Figure 2). The oblast-specifi c population data are given in Table 1.

We obtained the cancer cases in the 670 settlements for the observation period 1990-99 from the register of thyroid cancer established at the Ukrainian Institute of Endocrinology and Metabolism of the Academy of Medical Sciences (Tronko et al. 2004). This register contains age and sex-specifi c information for each patient on the date of surgery and the place of residence at the time of the accident. A total of 350 cancer cases have been reported to the registry in 1990-99, the majority of 198 cases was found in Kyiv city (Table 1).

Dedicated screening programmes have been carried out in Belarus and Ukraine after the accident, an overview table is given in Jacob et al. (2004). Notable contributions were registered after 1996 (Nikiforova et al. 2002, Danilyuk et al. 2002). The Ukraine-USA cohort study (Tronko et al. 2003) began in 1998, the majority of cases were reported after 1999. Less than 10 % of the cases in the period 1990-99 can be attributed to the screening programmes in the study area. Here we neglect the impact of such programmes.

2.2. Risk model

We decompose the total number of recorded cancer cases

$$n_c = n_{00} + n_{0s} + n_{r0} + n_{rs} \tag{1}$$

during an observation period ΔT = 10 yr from 1990-99 into four contributions. The n_{00} spontaneous cases would have been found in a situation without an accident and without improved case detection and reporting. The n_{r0} radiation-induced cases would have become clinically relevant after the accident if the surveillance regime had been left unchanged. The additional $n_{0s} + n_{rs}$ spontaneous and radiation-induced cases may be attributed to the effect of improved case detection and reporting starting from the year 1990.

The probability

$$P_{ijk} = 1 - \exp\left(-\int_{t_0}^{t_1} h_{ijk}(t)\,\mathrm{d}t\right) \tag{2}$$

of a person i in a settlement j located in an oblast k to develop a thyroid cancer during the period $\Delta T = t_1 - t_0$ depends on the individual hazard h_{ijk}. Motivated by the decomposition of the total number of recorded cases in Equation (1), this hazard is modelled as

$$h_{ijk} = \left(1+\eta_{ijk}\right) h_{0ijk} + \left(1+\kappa_{ijk}\right) \beta D_{ijk}, \tag{3}$$

where

η_{ijk} is the additional increase factor for the baseline risk, caused by improved case detection and reporting,

h_{0ijk} is the baseline cancer risk without improved detection and reporting,

κ_{ijk} is the additional increase factor for the radiation-induced risk, caused by improved case detection and reporting,

β is the excess absolute risk per unit dose, if there were no improved case detection and reporting (i.e. the unperturbed excess radiation risk), and

D_{ijk} is the individual thyroid dose.

Note, that we consider the increase of the incidence with respect to a reference situation, defined by the hypothetical assumption of an unchanged regime of medical surveillance after the accident. Therefore, the additional increase factors are positive. They reach a maximum value if all cancer cases were detected and reported. However, this value is difficult to estimate because a large number of undetected micro-carcinoma reside in the human thyroid. Since the risk factor β depends on the reference situation, it has no radio-biological meaning. If we assumed that all cancer cancer could be found in principle, we could quantify the reduction of the incidence by undetected cancers with negative 'increase' factors. In this case the coefficient β would indeed describe the radio-biological radiation risk. Although this approach is more intuitive, we forego its application, because the estimation of the input parameters for such a risk model appears very complicated.

For simplification the hazard (3) does not depend on attained age or calendar year. Even if increased linearly by radiation effects, it remains very small. Thus, the probability for contracting thyroid cancer in Equation (2) is well approximated by

$$P_{ijk} = \Delta T \, h_{ijk}. \tag{4}$$

Following the notation of Kaiser et al. (2004), the arithmetic dose mean in a settlement j of an oblast k with N_{jk} persons at risk is

$$\bar{D}_{jk} = \frac{1}{N_{jk}} \sum_i D_{ijk}. \tag{5}$$

The exact expression for the mean settlement-specific hazard becomes

$$\begin{aligned} \bar{h}_{jk} &= \frac{1}{N_{jk}} \sum_i h_{ijk} \\ &= \left(1+\bar{\eta}_{jk}\right) \bar{h}_{0jk} + \mathrm{cov}_{Ijk}(\eta, h_0) \\ &+ \left(1+\bar{\kappa}_{jk}\right) \beta \bar{D}_{jk} + \beta \, \mathrm{cov}_{Ijk}(\kappa, D), \end{aligned} \tag{6}$$

where $\mathrm{cov}_{Ijk}(\eta, h_0)$ and $\mathrm{cov}_{Ijk}(\kappa, D)$ denote the covariances between the individual increase factors and baseline risk or exposure within a settlement j of an oblast k. For example, the covariance

$$\mathrm{cov}_{Ijk}(\kappa, D) = \frac{1}{N_{jk}} \sum_i \kappa_{ijk} D_{ijk} - \bar{\kappa}_{jk} \bar{D}_{jk}. \tag{7}$$

In our scenarios we do not assume correlations between screening and baseline risk within or below the oblast level, whereas correlations between screening and exposure cannot be excluded. Hence, the aggregation of Equation (6) for N_k persons at risk in an oblast k implies for the mean hazard

$$\begin{aligned} \bar{h}_k &= \frac{1}{N_k} \sum_j N_{jk} \bar{h}_{jk} \\ &= (1 + \bar{\eta}_k)\, \bar{h}_{0k} + (1 + \bar{\kappa}_k)\, \beta \bar{D}_k + \beta\, \mathrm{cov}_{Ik}(\kappa, D), \end{aligned} \tag{8}$$

where $\mathrm{cov}_{Ik}(\kappa, D)$ denotes the inner-oblast covariance of exposure and screening.

2.3. Ecologic bias

If all individual information on screening and exposure were available, the mean population-based risk

$$\begin{aligned} \langle h \rangle &= \frac{1}{N_{pop}} \sum_{ijk} h_{ijk} \\ &= \langle h_0 \rangle_{pop} + \beta_{pop} \langle D \rangle \end{aligned} \tag{9}$$

is obtained from the risk model (3) by averaging over all N_{pop} individuals. Then

$$\beta_{pop} = (1 + \langle \kappa \rangle) \beta \left(1 + \frac{\langle \mathrm{cov}_I(\kappa, D) \rangle + \mathrm{cov}_S(\bar{\kappa}, \bar{D})}{(1 + \langle \kappa \rangle) \langle D \rangle} \right) \tag{10}$$

describes the true mean excess absolute risk per unit dose (EARPD) in the study population. The total average is formed in two steps. The first average is built within each settlement, then the average for the total study population is calculated. Consequently, the total covariance between exposure and screening can be decomposed in the mean population-based intra-settlement covariance

$$\langle \mathrm{cov}_I(\kappa, D) \rangle = \frac{1}{N_{pop}} \sum_{jk} N_{jk}\, \mathrm{cov}_{Ijk}(\kappa, D) \tag{11}$$

and the inter-settlement covariance $\mathrm{cov}_S(\bar{\kappa}, \bar{D})$. Expression (10) and the analogous expression for the baseline risk

$$\langle h_0 \rangle_{pop} = (1 + \langle \eta \rangle)\, \langle h_0 \rangle \left(1 + \frac{\langle \mathrm{cov}_I(\eta, h_0) \rangle + \mathrm{cov}_S(\bar{\eta}, \bar{h}_0)}{(1 + \langle \eta \rangle) \langle h_0 \rangle} \right) \tag{12}$$

have been both derived in Kaiser et al. (2004).

The ecologic analysis is based on the mean hazard

$$\bar{h}_{jk,eco} = \langle h_0 \rangle_{eco} + \beta_{eco} \bar{D}_{jk}. \tag{13}$$

in a settlement j of an oblast k. Settlement-specific dose means $\bar{D}_{jk}$ are used to estimate the ecologic EARPD β_{eco} and the mean ecologic baseline risk $\langle h_0 \rangle_{eco}$ for the total study

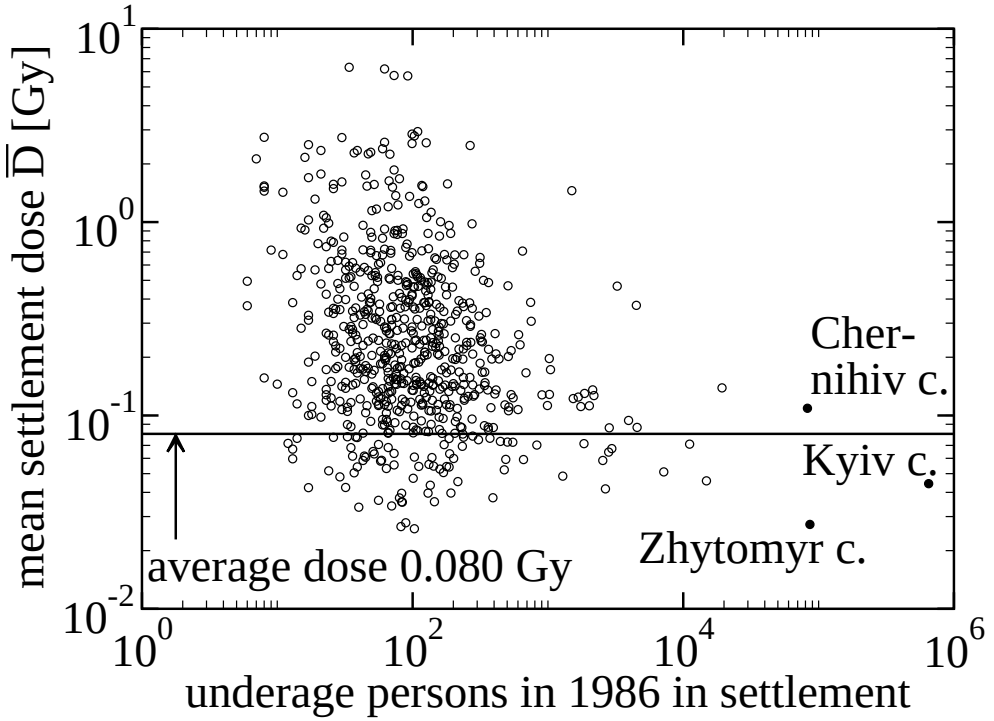

Figure 2. Simulated arithmetic dose means for 670 Ukrainian settlements, cities of Chernihiv, Zhytomyr and Kyiv (●).

population. All correlations and screening information are ignored. With Poisson regression the total mean population-based risk

$$\langle h \rangle = \langle h_0 \rangle_{eco} + \beta_{eco} \langle D \rangle \tag{14}$$

will be reproduced correctly. But the division into the spontaneous risk and the radiation-induced risk will in most cases differ from the true division prescribed by Equation (9). Thus, the ecologic EARPD β_{eco} will not meet the true EARPD β_{pop} in the population. That is the reason for an ecologic bias, measured by the ratio β_{eco}/β_{pop}.

The ecologic excess relative risk per unit dose (ERRPD) is defi ned as $\gamma_{eco} = \beta_{eco} / \langle h_0 \rangle_{eco}$, γ_{pop} is obtained in the same way.

2.4. Simulation of individual dose, screening factor, and health status

In this subsection we explain the assignment of thyroid doses and increase factors to the exposed children. These parameters are required in Equation (3), that forms the basis of the simulations. Then we show how the children receive their health status of either 'case' or 'no case'. Numerical values for oblast-specifi c increase factors and risk parameters of Equation (3) are derived for two scenarios of increased detection and reporting in the following Subsections 2.7 and 2.8.

For each settlement individual doses were drawn from 18 lognormal dose distributions, that were constructed with sex-averaged geometric dose means in the birth groups 1968-85

(Likhtarov et al. 2004). For the geometric standard deviations values between 2.0 and 2.3 have been assumed. The individual doses were grouped into 670 settlement-specific arithmetic dose means (Equation (5)) which were used as Poisson cells in a person year table. The 670 simulated values are shown in Figure 2. The simulated dose distribution is almost lognormally shaped.

To model the enhanced medical surveillance we assume, that a person is either screened or not. Hence, for a person i in a settlement j of an oblast k we set

$$\eta_{ijk} = \eta_{ind}\,\theta_{ijk} \quad \text{with} \quad \theta_{ijk} = \begin{cases} 1 & : \text{ if screened} \\ 0 & : \text{ otherwise.} \end{cases} \tag{15}$$

The individual factor η_{ind} for the additional increase caused by screening and the number of screened persons are chosen so that their product yields the oblast-specific increase factors $\bar{\eta}_k = \eta_{ind}\,z_k$, where z_k denotes the proportion of screened persons in oblast k. In the simulations we assumed values for η_{ind} from 5 to 25. However, the absolute individual values have almost no influence on the results of the simulation scenarios.

For screened persons we introduce the ratio κ_{ind}/η_{ind} which can acquire two values

- $\kappa_{ind}/\eta_{ind} = 1$, if radiation-induced and spontaneous cases were increased by improved detection and reporting in the same way,
- $\kappa_{ind}/\eta_{ind} = 0.2$, if a large number of spontaneous occult cancers were additionally detected.

The lower ratio is motivated by the results of autopsy studies (Franssila and Harrach 1986, Lang et al. 1988), where a large number of occult thyroid cancers have been found. Also the results of the recall and screening programme at the Michael Reese Hospital in Chicago can be explained by assuming an anisotropic ratio $\kappa_{ind}/\eta_{ind} < 1$ (Ron et al. 1992).

After assigning a dose and an increase factor to each individual, its health status must be determined. The probability P_{ijk} of developing a cancer (Equation (2)) is compared with a random number P_r which is evenly distributed between 0 and 1. If $P_{ijk} \geq P_r$, a tumour case is assigned to the individual. Competing risks are not considered because they are very small for young persons below age 31.

2.5. Statistical evaluation of regression results

Now a population data set for 1002706 persons is complete, and Poisson regression on the number of simulated cases in each settlement can be performed with the settlement-specific hazard of Equation (13). For the minimisation of the Poisson likelihood the software package MINUIT (James 1994) from CERNLIB was used. It calculated the point estimates for $\langle h_0 \rangle_{eco}$ and β_{eco}, the corresponding $\pm 2\sigma$ confidence intervals (CI_M) have been calculated with the MINOS routine of MINUIT. They are determined by the shape of the Poisson likelihood near the minimum. To obtain a frequency distribution, either 100 or 1000 population data sets were simulated with the same input parameters. Then the averages of 100 (or 1000) runs for the point estimates *and* for the CI_M were calculated. The confidence intervals, now denoted by CI_D, have also been derived with an alternative method from the distribution of the point

estimates (Figures 3, 4). In all considered cases the averages of the CI_M, calculated by MINOS from the shape of the likelihood, agreed well with the CI_D from the frequency distribution of point estimates.

To assess the ecologic bias we have applied a simple criterion. For the simulation runs it was counted how often the $\pm 2\sigma$ CI_M of a point estimate for the ecologic EARPD β_{eco}, derived from the shape of the likelihood, included the true population-based EARPD β_{pop}. Without any bias this would be the case in 95.4 % of the simulation runs. A notable bias would decrease the counted percentage below this value.

2.6. Analytical solution

Kaiser et al. (2004) have developed an analytical solution method to determine the risk estimates numerically exact from the data on exposure and screening. Hence, Poisson regression is not necessary to calculate the ecologic risk estimates, and the simulation of the individual health status can be omitted. This approach is very fast to generate point estimates of the ecologic risk parameters. However, it cannot produce statistical distributions which are needed to determine confidence intervals. The analytical solution is used to cross-check the simulation results and to calculate the ecologic bias. Sometimes this bias is very small and can only be detected with the more accurate analytical solution.

2.7. First scenario of increased detection and reporting

Increased case detection and reporting. For the settlement-specific analysis we chose the observation period 1990-99. Jacob et al. (2004) separated all oblasts of Belarus and Ukraine into three groups with different baseline incidence. Chernihiv oblast, Kyiv city and Kyiv oblast belong to the high incidence group, Zhytomyr oblast falls into the middle group. The baseline incidence I_{0k}^P for a calendar period P in an oblast k was computed with the empirical relation

$$I_{0ks}^P = c_{ks}^P + d_{ks}^P \, a^{e_s} \tag{16}$$

of Jacob et al. (2004) with the fit parameters c_{ks}^P d_{ks}^P and e_s for sex s. Instead of using the actual age distribution of the birth cohort 1968-85, this relation was evaluated here with the mean age of 18 yr in the period 1990-99. The incidence for both sexes was the mean of the two sex-specific incidences. The values for the increase factors

$$\bar{\eta}_k^{90-99} = \frac{4\,I_{0k}^{90-93} + 4\,I_{0k}^{94-97} + 2\,I_{0k}^{98-01}}{10\,I_{0k}^{86-89}} - 1, \tag{17}$$

are listed in Table 2. In Equation (17) the calendar periods are weighted according to their duration. The factors measure the increase with respect to the period 1986-89. Assuming a lag time of three years between the time of exposure and the detection of a thyroid cancer, the incidence in this period can be considered unperturbed by neither radiation effects nor screening activities.

Table 2. Estimates of the baseline risk $\bar{h}_{0k}$ from the total incidence I_k^{90-99} with increase factors $\bar{\eta}_k^{90-99}$, dose estimates $\bar{D}_k$ and an ERRPD γ of 10 Gy^{-1} (variant 1) and 20 Gy^{-1} (variant 2).

region	total incidence I_k^{90-99} [10^{-6} PY^{-1}]	increase factor $\bar{\eta}_k^{90-99}$	arithmetic dose mean $\bar{D}_k$ [Gy]	baseline risk for variant 1 $\bar{h}_{0k}$ [10^{-6} PY^{-1}]	variant 2
Chernihiv o.	46.8	1.1	0.080	12.4	8.6
Kyiv city	30.5	1.1	0.044	10.1	7.7
Kyiv oblast	61.9	1.1	0.113	13.8	9.0
Zhytomyr o.	31.5	0.5	0.122	9.5	6.1
mean	34.9	1.0	0.080	10.5	7.7

The oblast-specifi c baseline risk

$$\bar{h}_{0k} = \frac{I_k^{90-99}}{(1+\bar{\eta}_k^{90-99})(1+\gamma\bar{D}_k)}, \tag{18}$$

has been estimated from the total incidence I_k^{90-99} by division of factors, that describe the effects of both radiation exposure and screening. This baseline risk determines the hypothetical risk in the birth cohort 1968-85 for the period 1990-99 without the accident and without enhanced medical surveillance. It depends on the increase factor, the mean dose, and on the ERRPD γ. Estimates for increase factors and doses are given in Table 2. For the ERRPD we consider the two values 10 Gy^{-1} (variant 1) and 20 Gy^{-1} (variant 2), that are motivated by the results of Ron et al. (1995) and Jacob et al. (1999).

Table 3. Mean population-based EARPD β_{pop}, ERRPD γ_{pop}, and baseline risk $\langle h_0 \rangle_{pop}$ for the variants 1 and 2.

vari-ant	EARPD β_{pop} [10^{-4} (Gy PY)$^{-1}$]	ERRPD γ_{pop} [Gy^{-1}]	baseline risk $\langle h_0 \rangle_{pop}$ [10^{-6} PY^{-1}]
1	1.70	8.0	21.2
2	2.41	15.6	15.5

Risk factors. With the estimates of $\bar{h}_{0k}$ and $\bar{\eta}_k^{90-99}$ from Table 2 the mean population-based baseline risk $\langle h_0 \rangle_{pop}$ of Equation (12) is fi xed. Also the radiation-induced excess risk is fully determined in Equation (9), because we decided to keep the total risk in accordance with the total number of observed cases. By dividing this risk by the population-based dose average of 0.08 Gy (Likhtarov et al. 2004) we obtain the EARPD β_{pop}. Values of $\langle h_0 \rangle_{pop}$, β_{pop} and γ_{pop} for the two considered variants are given in Table 3.

The individual assignment of cancer cases in a simulation is based on Equation (3). Now the last missing quantity is the unperturbed risk factor β for the hypothetical situation without enhanced surveillance after the accident. It is determined from Equation (10). The

population-based means for the increase factors and the dose can be taken from Table 2. The covariance $\mathrm{cov}_S(\overline{\kappa}, \overline{D})$ between settlements is calculated with the settlement-specific dose estimates of Likhtarov et al. (2004). The mean covariance $\langle \mathrm{cov}_I(\overline{\kappa}, \overline{D}) \rangle$ vanishes, because in this scenario no correlations are assumed inside settlements. Numerical values are listed in Table 4. Owing to a constant radiation-induced risk, β increases for $\kappa_{ind}/\eta_{ind} = 0.2$. The covariance $\mathrm{cov}_S(\overline{\kappa}, \overline{D})$ is negative, because the screening intensity is lower in Zhytomyr oblast with the highest dose mean.

2.8. Second scenario of increased case detection and reporting

Shinkarev et al. (2004) have estimated that about 1 % of the children of Minsk city and Gomel city were living in highly contaminated rural areas at the time of accident. Their doses are about 3–10 times larger than the city average. Anxious about their high exposure, these children have their thyroids examined more frequently.

The second ecologic scenario is based on this estimation. In towns with more than 1000 children at risk in 1986 a fraction of 1 % is selected with an arithmetic dose mean five times larger than the town mean. This fraction possesses a lognormal dose distribution with a standard deviation similar to the standard deviation of the town. To half of these children the enhanced increase factors of a cohort study from Table 9 are assigned. Thereby approx. 4600 children from 29 towns have been selected, the majority of 70 % came from Kyiv city. Compared to the first scenario, all settlement-specific dose distributions are identical. Also the oblast-specific baseline risks, the increase factors (Table 2) and the population-based risk factors (Table 3) remain unchanged.

Hence, the covariance $\mathrm{cov}_S(\overline{\kappa}, \overline{D})$ is still determined by the values of Table 4. Additionally, exposure and screening are positively correlated in the 29 selected towns, the corresponding mean covariance $\langle \mathrm{cov}_I(\kappa, D) \rangle$ of Equation (11) can only be determined by simulations. Results are shown in Table 6. Consequently, the unperturbed risk factor β, calculated from Equation (10), drops slightly below the values of the first scenario to keep the number of radiation-induced cases.

2.9. Scenario for a cohort study

The Ukraine-USA cohort study (Tronko et al. 2003) is carried out in the highly contaminated oblasts of Kyiv, Chernihiv and Zhytomyr. It yielded 21 cancer cases among 11571 members in the second screening period, which started in 2001 and lasted 2.5 years. This means a total incidence of 726×10^{-6} PY^{-1}. The arithmetic mean dose of this cohort is approx. 0.65 Gy (Stezhko et al. 2004). We only consider the first variant of oblast-specific baseline risks, where according to Tables 1 and 2, the mean baseline risk $\langle h_0 \rangle$ for the three oblasts is 11.4×10^{-6} PY^{-1}.

For the cohort scenario the following assumptions are made. If all cohort members receive the same medical examinations, their increase factors η_{ind} and κ_{ind} for enhanced detection and reporting are the same within the cohort. The identical treatment of all cohort

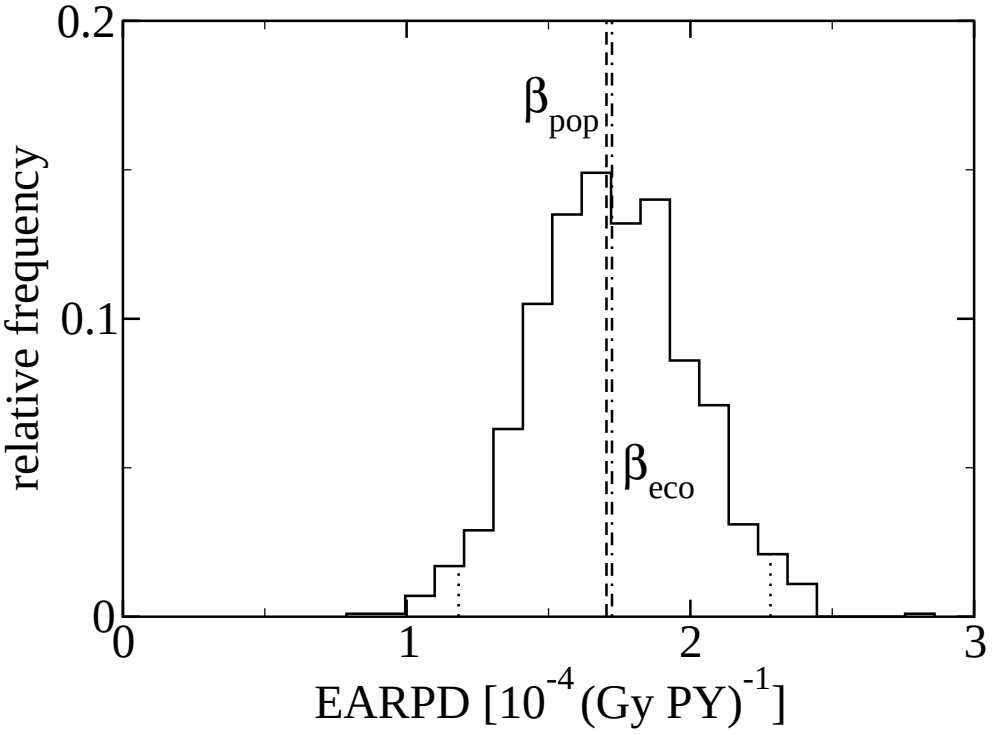

Figure 3. First scenario (variant 1): relative frequency distribution of the EARPD β_{eco} for $\kappa_{ind}/\eta_{ind} = 0.2$, arithmetic mean (— · —) with $\pm 2\sigma$ intervals (· · · · · ·) and mean population-based EARPD β_{pop} (– – –).

members prohibits any correlations of risk parameters, exposure and screening. Hence, the baseline risk and EARPD of a cohort are

$$\langle h_0 \rangle_{coh} = (1+\eta_{ind})\,\langle h_0 \rangle \quad \text{and} \quad \beta_{coh} = (1+\kappa_{ind})\,\beta, \tag{19}$$

and the ERRPD $\gamma_{coh} = \beta_{coh}/\langle h_0 \rangle_{coh}$. Note, that with Equation (19) we consider the increase with respect to the incidence for the reference period 1990-99 in a hypothetical situation without notable effects of enhanced medical surveillance after the accident. By fixing the total incidence, the baseline incidence and the unperturbed risk factor β (Table 4), the increase factors η_{ind} and κ_{ind} are prescribed for this scenario. Their values are given in Table 9.

3. Results

3.1. First scenario of increased case detection and reporting

In Figure 3 1000 point estimates of the ecologic EARPD β_{eco} for variant 1 and $\kappa_{ind}/\eta_{ind} = 0.2$ have been grouped into 20 equidistant bins between minimum and maximum value. The shape of the resulting frequency distribution is nearly symmetric. The simulated mean value of the ecologic EARPD β_{eco} lies close to the true EARPD β_{pop} (Table 3), that has been calculated with the input data from Tables 1 and 2. Owing to the small fluctuations of the total mean dose and the oblast-specific increase factors, the difference of the simulated values of β_{pop} to the value of Table 3 is negligible.

Table 4. First scenario: results for the covariance $\mathrm{cov}_S(\bar{\kappa},\bar{D})$ between settlements, the ecologic EARPD β_{eco}, ecologic bias and fraction of simulation runs where the CI_M of β_{eco} included β_{pop}; unperturbed excess absolute risk β is simulation parameter for Equation (3).

vari-ant	ratio κ_{ind}/η_{ind}	covariance $\mathrm{cov}_S(\bar{\kappa},\bar{D})$ [10^{-3} Gy]	β	EARPD [10^{-4} (Gy PY)$^{-1}$] [a] β_{eco}	[b] β_{eco}	ecologic bias [b] β_{eco}/β_{pop}	frac. of runs with β_{pop} in CI_M of β_{eco}
1	0.2	-1.5	1.44	1.7 (1.2;2.3)	1.74	1.02	96 %
1	1	-7.4	0.89	1.6 (1.1;2.2)	1.60	0.94	93 %
2	0.2	-1.5	2.04	2.4 (1.8;3.0)	2.37	0.98	96 %
2	1	-7.4	1.26	2.2 (1.6;2.8)	2.20	0.91	90 %

[a] average of 1000 runs with $\pm 2\sigma$ CI_D.
[b] exact numerical solution.

All simulation results for the EARPD are shown in Table 4. For a cross-check the mean value of 1000 simulated point estimates for the ecologic EARPD β_{eco} has been compared with the value of a numerically exact solution (Kaiser et al. 2004). The difference between the two values was always less than a percent. For both variants of the unperturbed baseline risk of Table 2 the ecologic bias comes out very small. For the ratio $\kappa_{ind}/\eta_{ind} = 0.2$ it almost disappears. Here the contribution of radiation-induced cases found by screening is smaller.

The statistical criterion, that has been introduced in Subsection 2.5, suggests that there is no bias if $\kappa_{ind}/\eta_{ind} = 0.2$. For $\kappa_{ind}/\eta_{ind} = 1.0$ a small bias becomes visible because the fraction of runs, where the CI_M of β_{eco} included β_{pop}, drops slightly below 95.4 %.

Correlations of screening and exposure within settlements are not present in this scenario. Correlations between settlements determine the value of the covariance $\mathrm{cov}_S(\bar{\kappa},\bar{D})$. This covariance is already included in the definition (9) of the true population-based EARPD β_{pop}. Hence, it does not cause any bias. However, there exist even more complicated correlations between the four individual parameters of Equation (3). Actually, these hidden correlations cause the deviation of β_{eco} from β_{pop} (Kaiser et al. 2004).

The ecologic ERRPD γ_{eco} was calculated in 1000 runs by Poisson regression using the equation corresponding to Equation (13). Figure 4 shows the distribution of 1000 point estimates for the ERRPD γ_{eco}. The distribution is skewed to the left. Numerical values for the ERRPD are given in Table 5. The agreement of the simulated mean for the ERRPD and the value from a numerically exact calculation is still very good. Again, a negligible bias appears for $\kappa_{ind}/\eta_{ind} = 0.2$.

An ecologic fit to the raw data yielded the EARPD β_{raw} = 1.7 (1.4;2.2) $\times$ 10^{-4} (Gy PY)$^{-1}$ and the ERRPD γ_{raw} = 8.4 (5.9;12) Gy^{-1}. The point estimates meet those of the first variant for the ratio $\kappa_{ind}/\eta_{ind} = 0.2$. But also the point estimates for $\kappa_{ind}/\eta_{ind} = 1$ lie very close to the estimates of the raw fit, so that an equal increase of reported cases cannot be ruled out. The $\pm 2\sigma$ CI_M of the raw fit are slightly smaller and they exclude the point estimates of the second variant. Therefore, in the following this variant will be left out for the analysis.

The estimates for the mean ecologic baseline risk $\langle h_0 \rangle_{eco}$ came out identical in the simulations for both the EARPD and the ERRPD. For the first variant the value was

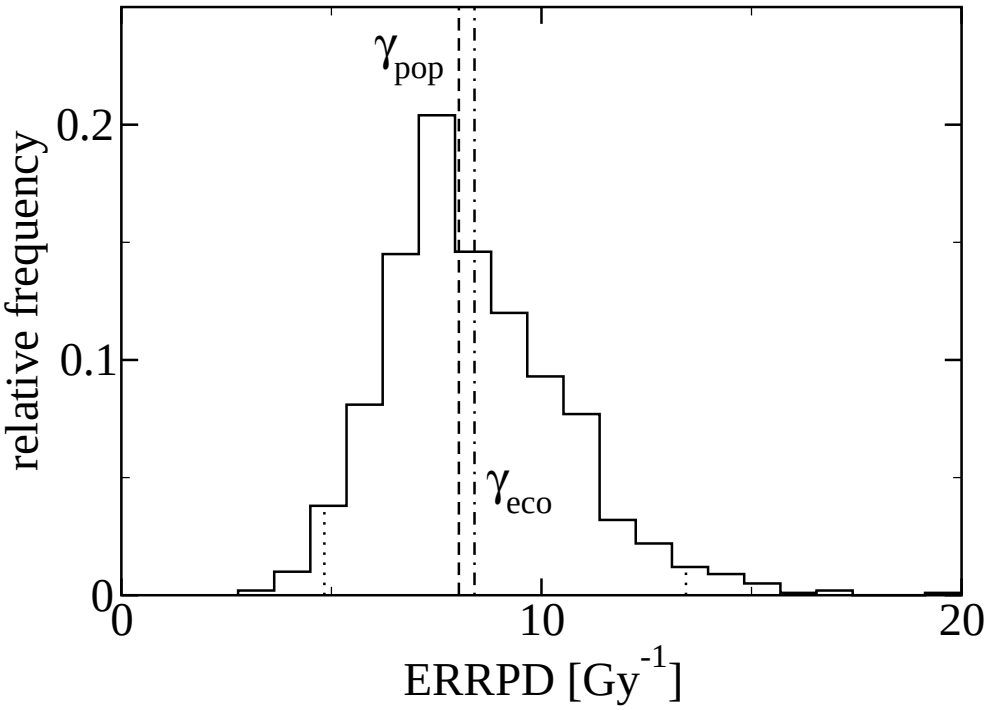

Figure 4. First scenario (variant 1): relative frequency distribution of the ERRPD γ_{eco} for $\kappa_{ind}/\eta_{ind} = 0.2$, arithmetic mean (— · —) with $\pm 2\sigma$ intervals (· · · · · ·) and mean population-based ERRPD γ_{pop} (– – –).

Table 5. First scenario: results for the ecologic EARPD γ_{eco}, ecologic bias and fraction of simulation runs where the CI_M of γ_{eco} included γ_{pop}.

vari-ant	ratio κ_{ind}/η_{ind}	ERRPD [Gy^{-1}] [a] γ_{eco}	[b] γ_{eco}	ecologic bias [b] $\gamma_{eco}/\gamma_{pop}$	frac. of runs with γ_{pop} in CI_M of γ_{eco}
1	0.2	8.4 (4.8;13)	8.3	1.02	96 %
1	1	7.4 (4.1;12)	7.3	0.90	93 %
2	0.2	15.3 (9.0;26)	15.0	0.96	95 %
2	1	13.3 (7.3;22)	12.7	0.82	88 %

[a] average of 1000 runs with $\pm 2\sigma$ CI_D.
[b] exact numerical solution.

21 (16;26) $\times 10^{-6}$ PY^{-1}. The distribution of $\langle h_0 \rangle_{eco}$ is symmetric.

3.2. Second scenario of increased case detection and reporting

For this scenario it is not possible to perform the numerical exact calculation simply with the input data of Tables 1 and 2, because now additional inner-settlement correlations arise in the 29 larger towns. Therefore, 100 data sets have been simulated to calculate the 670 settlement-specific inner covariances $\mathrm{cov}_{Ijk}(\kappa, D)$ as means of the simulation runs. Of course, only the 29 covariances pertaining to the larger towns are significantly different from zero.

Table 6. Second scenario (variant 1): results for the mean inner covariance $\langle \mathrm{cov}_I(\kappa, D)\rangle$, the ecologic EARPD β_{eco}, ecologic bias and fraction of simulation runs where the CI_M of β_{eco} included β_{pop}; unperturbed excess absolute risk β is simulation parameter for Equation (3).

ratio κ_{ind}/η_{ind}	covariance $\langle \mathrm{cov}_I(\kappa, D)\rangle$ $[10^{-3}$ Gy]	β	EARPD $[10^{-4}$ (Gy PY)$^{-1}]$ [a] β_{eco}	[b] β_{eco}	ecologic bias [b] β_{eco}/β_{pop}	frac. of runs with β_{pop} in CI_M of β_{eco}
0.2	4.3	0.84	1.7 (1.1;2.3)	1.69	0.99	93 %
1	9.3	1.38	1.5 (1.0;2.1)	1.54	0.91	92 %

[a] average of 100 runs with $\pm 2\sigma$ CI_D.
[b] exact numerical solution.

Table 7. Second scenario (variant 1): results for the ecologic ERRPD γ_{eco}, ecologic bias and fraction of simulation runs where the CI_M of γ_{eco} included γ_{pop}.

ratio κ_{ind}/η_{ind}	ERRPD $[\mathrm{Gy}^{-1}]$ [a] γ_{eco}	[b] γ_{eco}	ecologic bias [b] $\gamma_{eco}/\gamma_{pop}$	frac. of runs with γ_{pop} in CI_M of γ_{eco}
0.2	8.0 (4.1;13)	7.9	0.99	96 %
1	7.1 (3.5;11)	6.9	0.85	92 %

[a] average of 100 runs with $\pm 2\sigma$ CI_D.
[b] exact numerical solution.

Table 8. Subdivision of the 350 recorded cases for the two scenarios of increased case detection and reporting (variant 1).

ratio κ_{ind}/η_{ind}	spontaneous cases total	from screening	radiation-induced cases total	from screening scen. 1	scen. 2
0.2	213	107	137	21	26
1	213	107	137	66	70

The total covariance for this scenario consists of the sum of mean population-based $\langle \mathrm{cov}_I(\kappa, D)\rangle$, defined in Equation (11), and $\mathrm{cov}_S(\bar{\kappa}, \bar{D})$. Based on input data of Tables 1 and 2 and the simulated mean covariance $\langle \mathrm{cov}_I(\kappa, D)\rangle$, the ecologic risk coefficients have been calculated numerically exact. The results are shown in Tables 6 and 7 only for the first variant. Again, the numerically exact values agree well with the mean of the point estimates obtained by Poisson regression on the number of simulated cases. Compared to the first scenario, the ecologic risk coefficients come out smaller. Hence, by adding inner-settlement correlations the bias increases but remains still moderate.

3.3. Expected cases

With our choice of the risk model (3) the separation of all 350 recorded cases according to Equation (1) into spontaneous cases, radiation-induced cases and cases from enhanced

Table 9. Scenario for a cohort study (variant 1): increase factors, EARPD and ERRPD.

ratio κ_{ind}/η_{ind}	spont. inc. fac. η_{ind}	rad.-ind. inc. fac. κ_{ind}	EARPD β_{coh} $[10^{-4}\ (\mathrm{Gy\ PY})^{-1}]$	β_{coh}/β_{pop}	ERRPD γ_{coh} $[\mathrm{Gy}^{-1}]$	$\gamma_{coh}/\gamma_{pop}$
0.2	21	4.1	7.4	4.3	3.0	0.37
1	9.5	9.5	9.3	5.5	7.8	0.98

detection and reporting is straightforward. Table 8 shows the numbers for the two ecologic scenarios. About half of the spontaneous cases were found by screening because the mean population-based increase factor $\langle\eta\rangle \cong 1$ and the correlation of the oblast-specific baseline risks and increase factors is negligible.

For the ratio $\kappa_{ind}/\eta_{ind} = 1$ the fraction of radiation-induced cases from screening drops slightly below 50 % for the first scenario, owing to a small negative covariance of exposure and screening. For the second scenario the net correlation is positive, which increases the fraction of cases from screening scantly above 50 %. For the ratio $\kappa_{ind}/\eta_{ind} = 0.2$ the fraction of radiation-induced cases from screening is reduced to 15 % for the first scenario and to 21 % for the second scenario. Comparing both scenarios, some 4-5 radiation-induced cases have been found additionally by intensified screening of highly exposed children in large towns.

3.4. Scenario for a cohort study

The estimates of increase factors, EARPD and ERRPD for a cohort study are shown in Table 9. The increase factor of η_{ind} = 9.5 for an equal detection increase of spontaneous and radiation-induced cases agrees well with the factor of 7.4 for the increase of a recall and screening programme at the Michael Reese Hospital in Chicago (Ron et al. 1992), where patients have been irradiated for benign head and neck diseases. The factors of Table 9 describe the increased incidence in a cohort study for the birth cohort 1968-85 in the period 2001-02 relative to the period 1990-99. In 2001-02 the mean age of the cohort was 24 years, whereas for the period 1990-99 the mean age was 18 years. Hence, part of the increase must be attributed to the ageing of the cohort rather than to intensified screening. Using the empirical Equation (16) to compare incidence rates at the two different ages for the period 1986-89, we estimate that the contribution of ageing to the baseline risk ranges between 20 % and 30 %.

Of course, a comparison of an ecologic study with a cohort study based on incidence rates of the same time period would exclude the contribution of ageing. However, for the period 2001-02 a large number of cases has been reported by the Ukraine-USA screening programme, so that the derivation of an unperturbed baseline risk according to Subsection 2.7 is not reliable.

It is more instructive to compare directly the coefficients for the radiation-induced risk. Mostly owing to more intensive screening, the EARPD is about 4-5 times higher in the cohort than in the population. For $\kappa_{ind}/\eta_{ind} = 1$ the ERRPD of the cohort and of the population are almost equal because the effect of enhanced case detection and reporting cancels. If more

spontaneous cases are found by screening, i.e. $\kappa_{ind}/\eta_{ind} = 0.2$, the ERRPD in the cohort is reduced to 37 % of the value in the population.

4. Discussion

Although a steep rise of the thyroid cancer incidence in the birth cohort 1968-85 has occurred after the Chernobyl accident, it remains difficult to separate the contributions of radiation exposure on one side and improved case detection and reporting on the other side. In this article we made an attempt with simulation scenarios, that were based on real Chernobyl data on cancer incidence and radiation exposure. Increase factors have been roughly determined by comparing the estimates for baseline incidence of subsequent time periods.

If all individual information on exposure, incidence and screening were available, the mean population-based excess risk could be calculated directly and would describe the true risk in the population. In reality, it will be impossible to collect all necessary individual data. However, with our simulations we generated these data under the constraint, that they were compatible with available exposure and incidence data.

On the settlement-specific level enough incidence and exposure data has been gathered to perform an ecologic study. The ecologic risk is obtained from a fit to the data with complete negligence of screening information. Therefore, the ecologic risk may differ from the true risk, giving rise to an ecologic bias. The size of this bias is generally not known, which is a reason to criticise the reliability of ecologic studies. However, in our simulation scenarios we are able to quantify the bias with high accuracy. We invented two ecologic scenarios, which were investigated with two variants for the regional baseline risk. Furthermore, the effect of equal or notably higher detection increase of spontaneous cancer cases with respect to radiation-induced cases (i.e. κ_{ind}/η_{ind} = 1 or 0.2) has been tested.

In both ecologic scenarios the first variant produces a lower bias than the second variant. Here the majority of cases is radiation-induced in contrast to the first variant. In the first ecologic scenario the bias arises from the inhomogeneous regional distribution of increase factors, baseline risks and exposure. In the second scenario the bias is slightly enlarged by small correlations between exposure and screening within large towns. The maximal observed bias is -9 % for the EARPD and -15 % for the ERRPD.

Generally, the bias of the excess risk is caused by complex correlations between risk coefficients, increase factors and exposure, which can arise if individual data is aggregated. However, if all individuals were selected at random for screening and without any regional variation of the baseline risk, no correlations were generated. In this case no bias would appear with a linear risk model.

The bias decreases, if a higher detection increase for spontaneous cases is assumed, because radiation effects become less important.

In all considered cases, a larger bias was observed for the ERRPD than for the EARPD. The potential for bias is higher in a relative risk model, owing to its more complex correlation structure. Already without screening acting as a confounder a relative risk model produces a covariance term on an aggregate level, because baseline risk and exposure interact by

multiplication. A pure specification bias arises, owing to the different forms of the hazard on the individual level and on the aggregate level (Wakefield 2004). The addition of absolute risks does not produce such a bias.

An independent ecologic fit to the raw settlement-specific data yielded estimates for risk coefficients, that match almost exactly those of the first ecologic scenario for the first variant and the ratio $\kappa_{ind}/\eta_{ind} = 0.2$. This result supports an assumption of a higher detection probability for spontaneous cases than for radiation-induced cases. Also autopsy studies suggest an anisotropic ratio $\kappa_{ind}/\eta_{ind} < 1$. This accordance may be purely coincidental. However, if it were true, the value of approx. 20 Gy^{-1} from Jacob et al. (1998) for the population-based ERRPD does not seem applicable to the observation period 1990-99 that has been considered here. Values between 8-10 Gy^{-1} appear more plausible in line with the findings of Ron et al. (1995). By extending the period of observation the birth cohort becomes older and the mean baseline risk is increased. This effect can provide a plausible explanation for the different ERRPD of Ron et al. (1995) and Jacob et al. (1998).

The incidence of the Ukraine-USA cohort study is about 20 times higher than the incidence in 1990-99 among all exposed children of the study area. This increase has three causes: a higher exposure of the cohort members, an enhanced screening intensity and an older mean age of the cohort. It appears difficult to quantify all three contributions. With our assumptions we find that the EARPD of a cohort study is about 4-5 times higher than the mean risk in the study population. This difference is mostly due to the high screening intensity within a cohort. Thus, with the EARPD from a cohort study the incidence in the population is overestimated. Depending on the amount of occult spontaneous cancers detected by screening, the ERRPD in a cohort is either similar or notably lower than the ERRPD in the population.

To conclude, the results of the simulation scenarios exhibit a remarkably consistent view, and we are convinced, that they render important features of the real situation. The observed bias remained moderate. However, other sources of bias have not been discussed here. They may arise from individual measurement errors, from incomplete measurements within settlements, and from a non-linear dose-response relation. Their impact can also be assessed using systematic simulation studies.

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