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Radiation Risk Modeling of Thyroid Cancer with Special Emphasis on the Chernobyl Epidemiological Data

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Two recent studies analyzed thyroid cancer incidence in Belarus and Ukraine during the period from 1990 to 2001, for the birth cohort 1968 to 1985, and the related ^{131}I exposure associated with the Chernobyl accident in 1986. Contradictory age-at-exposure and time-since-exposure effect modifications of the excess relative risk (ERR) were reported. The present study identifies the choice of baseline modeling method as the reason for the conflicting results. Various quality-of-fit criteria favor a parametric baseline model to various categorical baseline models. The model with a parametric baseline results in a decrease of the ERR by a factor of about 0.2 from an age at exposure of 5 years to an age at exposure of 15 years (for a time since exposure of 12 years) and a decrease of the ERR from a time since exposure of 4 years to a time since exposure of 14 years of about 0.25 (for an age at exposure of 10 years). Central ERR estimates (of about 20 at 1 Gy for an age at exposure of 10 years and an attained age of 20 years) and their ratios for females compared to males (about 0.3) turn out to be relatively independent of the modeling. Excess absolute risk estimates are also predicted to be very similar from the different models. Risk models with parametric and categorical baselines were also applied to thyroid cancer incidence among the atomic bomb survivors. For young ages at exposure, the ERR values in the model with a parametric baseline are larger. Both data sets cover the period of 12 to 15 years since exposure. For this period, higher ERR values and a stronger age-at-exposure modification are found for the Chernobyl data set. Based on the results of the study, it is recommended to test parametric and categorical baseline models in risk analyses.

INTRODUCTION

Thyroid cancer incidence in Ukraine and Belarus was observed to increase significantly in 1990 among subjects 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*). Detrimental health effects of ^{131}I exposures, which formed the main component of post-accident thyroid doses, can be assessed by analyses of epidemiological thyroid cancer data relating to this accident.

The purpose of the present study was to examine the influence of the methods applied for modeling the baseline rates on the age and time effect modifications on the thyroid cancer incidence risk after the Chernobyl accident. A recent study by Jacob *et al.* (*5*) presented a model with the feature of strongly decreasing excess relative risk (ERR) with increasing attained age [see Fig. 6 of ref. (*5*)]. The results were given for various fixed ages at exposure and thus expressed a decrease of the ERR with time since exposure. In contrast to this result, in the study of Likhtarov *et al.* (*6*), a trend of strongly increasing ERR with increasing time since exposure [see Table 6 in ref. (*6*)] was found.

Different types of risk models for the ERR that differ mainly in the numerical treatment of the baseline risk assessment were applied. The baseline forms are either fully parametric as used by Jacob *et al.* (*5*), categorical (i.e. stratified with nuisance stratum parameters), or of a categorical form with a smaller number of subgroups due to the inclusion of interaction effects of attained age and gender (i.e., where each category has an explicit associated fit parameter), as applied by Likhtarov *et al.* (*6*). Comparisons of such models are also made here for the most recent incidence data, covering the period from 1958 to 1998, from the survivors of the A-bombs over Hiroshima and Nagasaki (*7*).

MATERIALS AND METHODS

Chernobyl Data

Data selected for the analysis presented here are the same as applied previously in Jacob *et al.* (*5*) and pertain to 1.62 million children inhabiting 1034 settlements in the countries of Ukraine and Belarus. Only de-identified and aggregated records were used. Individual dose estimates are based on a total of 174,000 measure-

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ments of the ^{131}I content in human thyroids, consisting of at least 10 measurements in each settlement taken during May/June 1986 (*8*). Thyroid doses due to the Chernobyl accident were assessed for the birth years 1968–1985 and relate to thyroid cancers that were surgically removed during the period 1990–2001. The thyroid doses associated with this period cover a wide range from 8 mGy to 18.3 Gy with person-year weighted means of 0.19, 0.17, 0.09, 0.08 and 0.12 Gy for Belarusian males, Belarusian females, Ukrainian males, Ukrainian females and the total cohort, respectively. The data are in grouped form and are categorized on country, settlement, gender, birth year (with intervals of 2 years), and year in which thyroid surgery was performed (also with intervals of 2 years), hereafter referred to as operation year.

The analysis is based on a total of 1089 cases of thyroid cancer and approximately 19.4 million person years (PY). To quantify uncertainties in the modification of risk by age and time in the different models two ratios were considered:

1. The ratio of the ERR at age at exposure 15 years to the ERR at age at exposure 5 years for a fixed time since exposure of 12 years.
2. The ratio of the ERR at time since exposure of 4 years to the ERR at time since exposure of 14 years for a fixed age at exposure of 10 years.

These ratios are well suited, in the sense of falling within and characterizing the range of the main body of data, and form useful tools for comparing the age-at-exposure and time-since-exposure risk modification in the various risk model parameterizations applied here. To facilitate comparisons between the results obtained from the Chernobyl data and from the atomic bomb survivors, a fixed time since exposure of 12 years was chosen for the first ratio. This time is at the end of the observation period for the Chernobyl data and at the start of the observation period for the atomic bomb survivors' cancer incidence data.

A-Bomb Data

Recently released cancer incidence data from the survivors of the WW II A-bombs over Japan were selected for comparison with the Chernobyl data. The A-bomb data cover the period from 1958 to 1998 and contain 18,645 cancers, including 471 cases of thyroid cancer, among 111,952 persons contributing almost 3 million PY. A major analysis of these data can be found in ref. (*7*).

Types of Risk Models Applied to the Chernobyl Data

To summarize the main features associated with the age and time trends indicated by the model fit parameters, optimized against the Chernobyl data, four ERR models are considered with the general form

$$\lambda(c, s, e, a, d) = \lambda_0(c, s, e, a)[1 + \mathrm{ERR}(c, s, e, a, d)], \qquad (1)$$

where λ is the total incidence rate and λ_0 the baseline incidence rate. The covariables are *c*, the country; *s*, the sex; *e*, the age at exposure in years; *a*, the attained age in years; *oy*, the year in which surgery was performed, i.e. operation year; and *d*, the thyroid dose in Gy.

Three specific model types are considered in detail here:

1. Model P, as applied in ref. (*5*)[2] with

$$\lambda_0(c, s, e, a) = \exp[\eta_0 + \eta_c\,\theta_c + \eta_s\,\theta_s + \eta_e(10 - e) + \eta_a \ln(a/20)] \qquad (2)$$

and

$$\mathrm{ERR}(c, s, e, a, d) = [\beta_1\, d + \beta_2\, d^2]\exp[\beta_c\,\theta_c + \beta_s\,\theta_s + \beta_e(10 - e) + \beta_a \ln(a/20)], \qquad (3)$$

where $\eta\ldots$ and $\beta\ldots$ are fit parameters with subscripts denoting the specificity, i.e., *c* for country, *s* for sex etc. θ_c and θ_s are indicator variables for city and gender, respectively, with values of -0.5 for Ukraine, 0.5 for Belarus, -0.5 for males and 0.5 for females.

2. Model C, as in Eq. (3) but recomputed here with a categorical method for dealing with baseline rates, i.e. with baseline stratification on the covariable combination *c*, *s*, *e*, *a* instead of Eq. (2) above. Age at exposure and attained age were categorized in 5-year intervals.
3. Models CS1 and CS2, which are named to indicate their categorical simplified (CS) nature and which have a close correspondence to models 3 and 4 in the paper of Likhtarov *et al.* (*6*) [with parameters given in Table 6 of ref. (*6*)] but refitted to the data set described here. These models both have

$$\lambda_0(oy, c, s, a,) = \exp\{\beta_1 + \Sigma\,\beta_{i=2,3}\,c_{i=1,2} + \Sigma\beta_{i=4,15}\,s_{i=1,2}\,a_{i=1,6} + \Sigma\beta_{i=16,21}\,oy_{i=1,6}\}, \qquad (4)$$

where $oy_{i=1,6}$, $c_{i=1,2}$, $s_{i=1,2}$, $a_{i=1,6}$ and $e_{i=1,6}$ are the categorical variables for *oy* in 2-year intervals; *c*, *s*, *a* and *e* as defined above with the latter two variables in 5-year intervals with

$$\mathrm{ERR}(c, s, e, a, d) = \beta\, d \exp \Sigma\gamma_i Z_i, \qquad (5)$$

where $\Sigma\gamma_i Z_i = \Sigma\,\gamma_{i=1,4}\,e_{i=1,6}$ or $\Sigma\,\gamma_{i=1,4}\,oy_{i=1,6}$ for model CS1 and CS2, respectively. These model forms are generally routinely used in radiation epidemiology, and specifically in Liktarov *et al.* (*6*), and are for interaction effects of dose with either age at exposure (CS1) or time since exposure (CS2).

The regressions for all model types were performed with the AMFIT module of the EPICURE software package (Hirosoft International Corporation, Seattle, WA).

Types of Risk Models Applied to the A-Bomb Data

A recent analysis of thyroid cancer incidence data for the atomic bomb survivors in Hiroshima and Nagasaki (*7*) provided the following gender-averaged excess risk models in terms of weighted thyroid dose, *d*, where the neutron dose component has been multiplied by 10 and added to the γ-ray component:

$$\mathrm{ERR}(d, a, e) = (1 \pm s(0.14 \pm 0.29))\cdot(0.58 \pm 0.26)\cdot d\cdot(a/70)^{(-1.45 \pm 0.82)}\cdot\exp[(-0.037 \pm 0.023)\cdot(e - 30)]. \qquad (6)$$

The gender indicator variable, *s*, is $+1$ for females and -1 for males. Age-related covariables are: age attained, *a*, in years; age at exposure, *e*, in years. The units of *d* are in Sv. The fit parameters with standard errors have been inserted directly into the model forms [see www.rerf.or.jp filename: lss07siteahs.log, page 4 for the relevant EPICURE computer output that contains the results quoted in Eq. (6)].

[2] The Liktarov models and A-bomb models all produce central estimates for the risk that are unweighted with respect to gender and country effect modifiers. To achieve consistency in central risk estimates among all model types considered here, some simple adjustments to the models P and C were necessary. This is because models P and C incorporate the features of a directly fitted ratio of excess risks in Belarus and Ukraine at the same dose and a directly fitted ratio of excess risks in females and males at the same dose. These features are obtained by applying gender and city indicator variables [i.e. θ_s and θ_c in ref. (*5*)] set to either $+0.5$ or -0.5. This method has the effect of causing the fit parameters for the central estimates for models P and C to be means obtained with different weights for the two countries and both genders. Constant multiplication factors of 1.27 and 1.25 may be applied to the central risk estimate fit parameters of models P and C, respectively, to make them directly comparable to the central risk estimates from the other model types considered here.

TABLE 1
Goodness-of-Fit Measures for Model Types Considered and Fitted to the Chernobyl Data

Model	Number of parameters	*df*	Deviance	*AIC*	*BIC*
P	11	107725	3837.9	***3859.9***	***3965.4***
C	54	107682	3772.9	*3880.9*	4398.6
CS1	22	107714	3859.6	3903.6	*4114.6*
CS2	24	107712	3875.0	3923.0	4153.1

Note. The bold numbers indicate the best *AIC* or *BIC*, the italicized numbers indicate the best *AIC* or *BIC* within classes of models with a categorial baseline method [see ref. (*10*) for an explanation of *AIC* and *BIC*].

Additional computations made here involved a replacement of the parametric baseline used in ref. (*7*) by a categorical baseline with stratification of baseline rates on gender, city (Hiroshima or Nagasaki), age attained, age at exposure (both in 5-year intervals), and an indicator variable for participation in the Adult Health Survey (AHS). This later inclusion, also made in ref. (*7*), was necessary because baseline thyroid cancer incidence rates for AHS participants have been estimated to be about 40% higher than those for other cohort members in a recent analysis based on a fully parametric baseline model (*7*).

RESULTS

Quality of Fit of the Chernobyl Data to the Various Models

Table 1 gives the degrees of freedom, the deviance and two indices for the goodness of fit for non-nested models (*9, 10*). The lowest deviance is achieved by the C model (54 parameters), the second best by the P model (11 parameters). The deviance of the CS1 and CS2 models (22 and 24 parameters, respectively) is considerably higher.

According to the Bayesian Information Criterion (*BIC*), there is strong evidence for model P generally fitting the data best. The reason is the smaller number of parameters, which is weighted strongly by the *BIC*. The Aikake Information Criterion (*AIC*) gives more weight to the deviance than the *BIC*. Thus, generally, the criteria for the quality of fit of non-nested models indicate a preference for the fully parametric models with relatively simple and smooth descriptions of the baseline incidence rates. Quality-of-fit criteria for non-nested models may not be totally adequate for intercomparisons between models with parametric and categorical baselines. Among the categorical models, model C is preferable to the CS1 and CS2 models by the AIC; model CS1 is preferred over the C and CS2 models by the BIC; both information criteria disfavor model CS2.

As independent measures of the quality of fit, the numbers of cases predicted for subgroups of the study population (that are deemed to be in the problematical covariable zones, from an examination of Figs. 1–3) are considered. The χ^2 values, given in Table 2, only have the purpose of indicating where the deviations are greatest and so they do not take the number of model parameters into account or form part of a hypothesis-testing procedure. Again, the fully parametric model appears to describe the data best. The categorical models (C and CS1) have particular problems for the subgroups with young attained age (not shown) and young age at exposure. In the latter case, the numbers of cases in the intermediate-dose groups are overpredicted (by more than three standard deviations) and are underpredicted in the high-dose group (by more than two standard deviations). The categorical models (C and CS2) also have particular problems for early and intermediate times since exposure. The numbers of cases in the intermediate dose groups are overpredicted (by more than two standard deviations) and are slightly underpredicted in the high-dose group (by more than one standard deviation). However, the categorical model C actually does better than the P model for the two-dimensional projections into categories of age at exposure and age attained (not shown), where these correspond to the actual strata applied directly in the categorical C model.

In summary, the quality-of-fit criteria give rather more support to the fully parameterized model than the categorical models for young age at exposure and short times since exposure. Information on the parameter values and uncertainty ranges for the models discussed here are given either in refs. (*5, 6*) or in the Appendix (Tables A1–A3).

Excess Relative Risks from the Chernobyl Data

Central estimates of the parametric and categorical models for the ERR at 1 Gy for an age at exposure of 10 years and attained age of 20 years agree quite well. Best estimates with 95% confidence intervals are 22.8 (12.3; 33.3) and 18.0 (9.7; 26.3) for models P and C, respectively. Gender effects and country differences are in agreement between all model types: Females have a lower ERR than males; Ukrainians have a lower ERR than Belarusians.

All models predict a decrease of the ERR with age at exposure (Fig. 1). At 12 years since exposure, the age-at-exposure modification of the risk in the C and CS1 models is not as steep as that predicted by the parametric model P. The reason for the difference is that for young ages at exposure, the number of baseline cases in the exposed groups is considerably higher in the C and CS1 models than in the P model (Table 2). Preference is given here to the age-at-exposure dependences in the parametric model, because all quality-of-fit criteria considered here tend to favor the parametric model. At 12 years since exposure, the ERR after exposure at age 15 is predicted by the parametric model to be a factor of 0.17 (95% CI: 0.05; 0.29) lower than after exposure at age 5 (Table 3).

The age-at-exposure dependence of the ERR, for a fixed time since exposure, is steeper in the model with a parametric baseline than in the categorical models (see

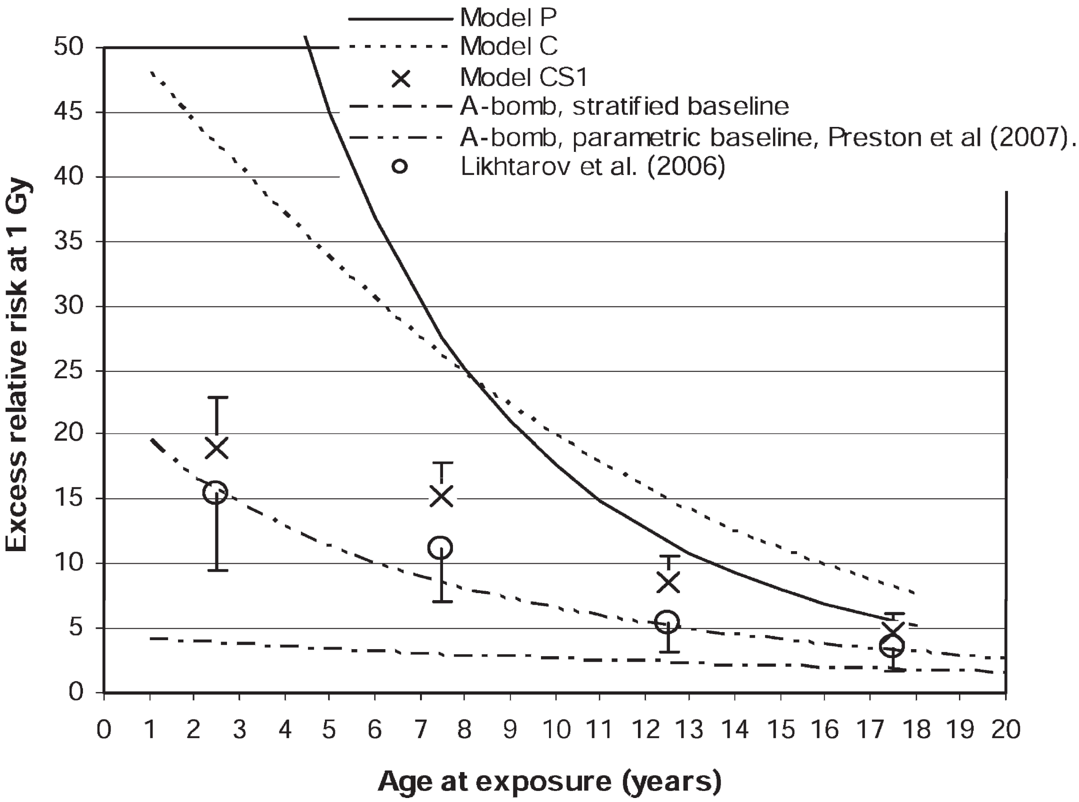

FIG. 1. Time patterns in the Chernobyl data. The effect modification of ERR at 1 Gy by age at exposure for a fixed time since exposure of 12 years. The fit parameters for model CS1 are shown with one standard error. Results of ref. (*7*) for the atomic bomb survivors are shown for comparison.

above), while for fixed attained age, the age-at-exposure modification is steeper in the categorical model than in the parametric model (Fig. 2). Thus, when considering age-at-exposure effects, it is important to state whether time since exposure or attained age is fixed in the consideration.

The parametric model predicts a strong decrease of the ERR with time since exposure, whereas the ERR dependence is either rather flat or even increasing in the categorical models (Fig. 3). Again the difference could be related to a larger number of predicted baseline cases in the categorical models compared to the parametric model (Table 2). Considering the weaker predictions of the categorical models for the time-since-exposure groups (Table 2), the present works tends to favor the decrease of the ERR with time since exposure as predicted by the parametric model. For an age at exposure of 10 years, the parametric model predicts a decrease of the ERR from a time since exposure of 4 years to a time since exposure of 14 years by a factor of 4.4 (95% CI: 0.9; 7.8). The categorical model C predicts an increase (Table 3). In this latter respect, the models yield results that are not consistent, with only slightly overlapping confidence intervals. Though the result of the model CS2 for the data used in the present analysis is intermediate and is statistically compatible with the results of the other two models, the model turns out to be highly unstable when the results are compared to the results obtained in ref. (*6*) for a slightly different data set. The underperformance of the categorical models C and CS2, according to the quality-of-fit considerations (Tables 1 and 2), could be taken to indicate a preference for the result of the parametric model.

The ERR for females was assessed to be consistently lower than for males (by a factor of 0.3).

Excess Relative Risks from the A-Bomb Data

On replacing the fully parametric baseline model of ref. (*7*) with a categorical model that has stratification on gender, city (Hiroshima or Nagasaki), attained age, age at exposure (both in 5-year intervals), and participation in the AHS, i.e. a total of 912 strata, the following results were obtained here:

$$\begin{aligned}\mathrm{ERR}(d, a, e) = {} & [1 \pm s(0.30 \pm 0.31)]\cdot(0.90 \pm 0.35) \\ & \cdot d\cdot\exp[(-0.053 \pm 0.019)\cdot(e-30)]\end{aligned} \tag{7}$$

At 1 Sv, the central ERR estimate of 0.90 ± 0.35, obtained with a stratified baseline, is a factor of 1.6 higher than that of 0.58 ± 0.26 (see Eq. 6), obtained with the parametric baseline of ref. (*7*), and the confidence intervals overlap substantially. A further effect of

TABLE 2
Observed and Predicted Number of Total Cases (with the Number of Predicted Baseline Cases in Parentheses) for Four Models in Various Three-by-Three Covariable Subgroups of the Chernobyl Data

Subgroup/χ^2 value	Observed cases	Predicted cases (baseline cases)		
		Model P	Model C	Model CS1
Covariable subgroups for age at exposure, *e* and thyroid dose, *d*				
$e < 7$; $d < 0.06$	28	24 (12)	29 (18)	27 (15)
$e < 7$; $0.06 \le d < 0.2$	177	208 (35)	228 (66)	225 (77)
$e < 7$; $0.2 \le d < 20$	302	268 (8)	263 (15)	261 (20)
$7 \le e < 13$; $d < 0.06$	138	138 (96)	132 (96)	135 (93)
$7 \le e < 13$; $0.06 \le d < 0.2$	71	67 (26)	63 (26)	66 (29)
$7 \le e < 13$; $0.2 \le d < 20$	73	75 (7)	67 (7)	74 (8)
$13 \le e < 18$; $d < 0.06$	221	222 (199)	214 (188)	211 (184)
$13 \le e < 18$; $0.06 \le d < 0.2$	39	43 (28)	45 (27)	45 (30)
$13 \le e < 18$; $0.2 \le d < 20$	40	42 (10)	49 (10)	45 (11)
χ^2		10	22	19
Covariable subgroups for time since exposure, *tsx* and thyroid dose, *d*				
				Model CS2
$tsx < 7$; $d < 0.06$	67	65 (45)	69 (57)	57 (37)
$tsx < 7$; $0.06 \le d < 0.2$	48	63 (10)	71 (29)	67 (24)
$tsx < 7$; $0.2 \le d < 20$	88	86 (3)	77 (8)	78 (6)
$7 \le tsx < 11$; $d < 0.06$	117	118 (92)	112 (90)	102 (72)
$7 \le tsx < 11$; $0.06 \le d < 0.2$	88	101 (25)	113 (40)	119 (49)
$7 \le tsx < 11$; $0.2 \le d < 20$	148	127 (7)	129 (11)	132 (14)
$11 \le tsx < 15$; $d < 0.06$	203	202 (170)	194 (155)	201 (157)
$11 \le tsx < 15$; $0.06 \le d < 0.2$	151	154 (54)	152 (50)	167 (85)
$11 \le tsx < 15$; $0.2 \le d < 20$	179	172 (15)	172 (13)	166 (24)
χ^2	-	9	18	23
$\Sigma\chi^2$		19	40	42

Notes. χ^2 is a quality-of-fit measure that does not take the number of model parameters into account here. The units of dose, *d*, are in Gy, age at exposure, *e*, and time since exposure, *tsx*, are in years.

applying a stratified baseline here is that the attained-age modification [which had a *P* value of 0.076, according to the score test statistic, with the parametric model, Eq. (6)] has a *P* value of 0.412 and so has been dropped from the model given in Eq. (7) here. The age-at-exposure effect modification found here in Eq. (7) is strongly indicated, with a *P* value of 0.007 according to the score test statistic.

For the ages and times considered here, the ERR estimates in the parametric model are higher than in the categorical model. At the start of the observation period (12 years after exposure), the ERR for age at exposure 5 years is larger than for age at exposure 15 years by a factor of about 3 for the parametric baseline model (Fig. 1). In the first years of observation, the dependence of the ERR on time since exposure was rather flat (Fig. 3).

DISCUSSION

Parametric Compared to Categorical Modeling of the Baseline Thyroid Cancer Rates

Several modeling regimens have been applied to the Chernobyl data to assess the influence of three different methods for dealing with baseline risks. Generally good agreement was found for the central risk estimates and the effect modifiers gender and country.

The main pertinent results here, presented in Figs. 1–3, are that nature of the age-at-exposure and time-since-exposure effect modifications of the central excess relative risks were found to be strongly dependent on the form of the baseline model. A comparison of Figs. 1 and 2 indicates that the steepness of the age-at-exposure effect modification depends both on whether a para-

TABLE 3
Model-Specific Values Tabulated for Two ERR Ratios

ERR model	Baseline model	Data	ERR(e = 15)/ERR(e = 5)	ERR(tsx = 4)/ERR(tsx = 14)
P	parametric	Jacob *et al.* (*5*)	0.17 (0.05; 0.29)	4.37 (0.92; 7.82)
C	categorical	Jacob *et al.* (*5*)	0.33 (0.09; 0.57)	0.57 (0.17; 0.97)
CS1/CS2	categorical, simplified	Jacob *et al.* (*5*)	0.31 (0.12; 0.58)[a]	1.63 (0.09; 4.12)
CS1/CS2	categorical, simplified	Likhtarov *et al.* (*6*)	0.32 (0.08; 1.30)[a]	0.10 (0.03; 0.43)

Notes. The two ratios are the ratio of the ERR at age at exposure 15 years to the ERR at age at exposure 5 years (for a fixed time since exposure of 12 years) and the ratio of the ERR at time since exposure (*tsx*) of 4 years to the ERR at time since exposure of 14 years (for fixed age at exposure of 10 years, all obtained from the Chernobyl data. 95% confidence ranges are quoted in parentheses.

[a] e = 5 and 15 are at the lower bounds of the time intervals in these two cases.

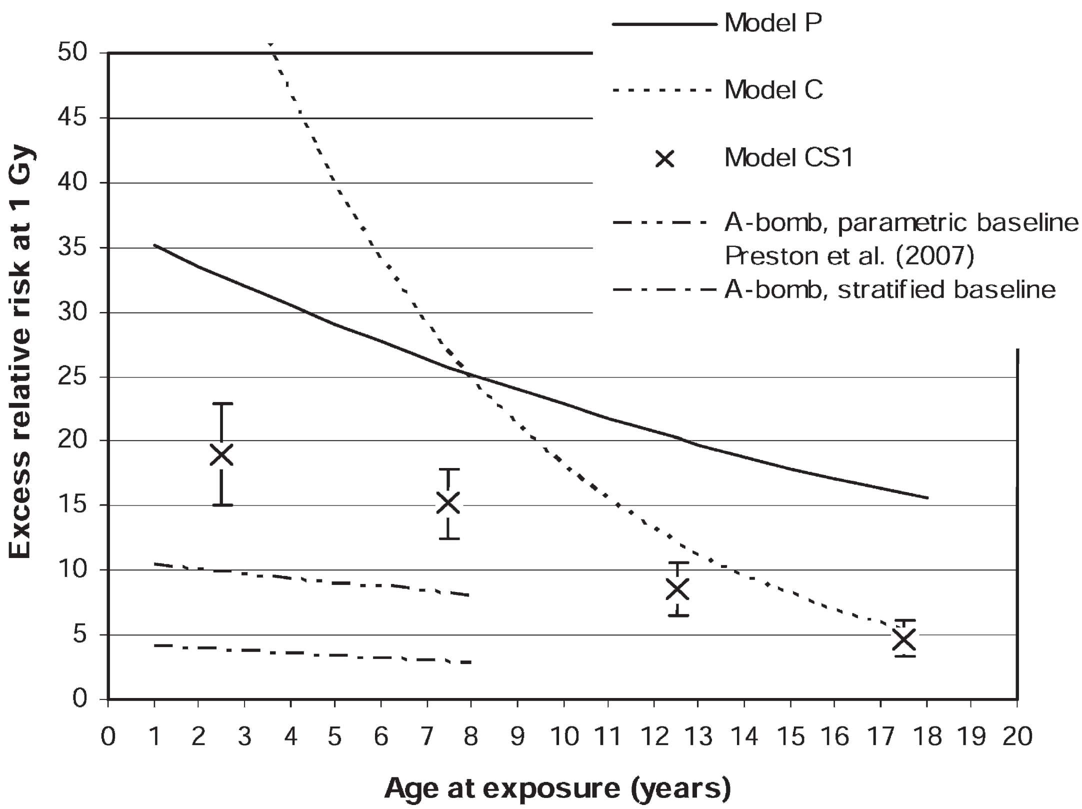

FIG. 2. Time patterns in the Chernobyl data. The effect modification of ERR at 1 Gy by age at exposure for a fixed attained age of 20 years. The fit parameters for model CS1 are shown with one standard error. Results of ref. (*7*) for the atomic bomb survivors are shown for comparison.

metric or categorical baseline model was used and on whether this specific effect modification was considered for fixed time since exposure or for fixed attained age. This effect is pronounced for the Chernobyl data but not for the A-bomb data. Figure 3 indicates that the steepness of the time-since-exposure effect modification also depends on whether a parametric or categorical baseline model was used. Again, this effect is pronounced for the Chernobyl data but not for the A-bomb data.

The type of baseline modeling was also found to considerably influence the ERR results for thyroid cancer incidence among the atomic bomb survivors. Although the central estimate of ERR at 1 Sv for an age at exposure of 30 years, i.e. an adult, is higher with a stratified baseline than with the parametric baseline of ref. (*7*), the situation is reversed for persons exposed as children due to the different effect modifications indicated by the two different baseline methods.

In the case of the present Chernobyl data set, all quality-of-fit tests considered here tended to indicate a preference for the parametric representation of the baseline cancer rates. However, other known confounding risk factors for thyroid cancer such as genetic predisposition, iodine deficiency and iodine prophylaxis at the time of the accident could not be studied because of the current state of the data. Given the differences found in the present work, it is strongly recommended to routinely test excess risk models for sensitivity to the method used for the determination of the baseline rates, and if there are no evident epidemiological indications for one method over another, any resulting differences should be included in the overall uncertainty evaluation.

The results of the present study cannot be taken as evidence that parametric baseline modeling is generally preferable to categorical baseline modeling.

Results for Two Different Chernobyl Data Sets

In the present work, the categorical models of Likhtarov *et al.* (*6*) were applied to the data set of Jacob *et al.* (*5*). Comparing the results obtained with the same models fitted to the data in ref. (*5*), which is for Ukraine and Belarus, and Likhtarov *et al.* (*6*), which is just for the Ukraine, showed generally lower risk estimates associated with the latter data. This is consistent with the country effects on risk estimates obtained from the data in ref. (*5*), which are higher for Belarus than for Ukraine. The reason for this systematic difference is not clear. It may be related to country differences in iodine deficiency (*11*) or to higher incidence rates and possibly to a more intensive surveillance of the thyroid during regular medical examinations in Belarus (*12*). The latter is indicated by a larger fraction of small carcinomas in Belarus compared to Ukraine.

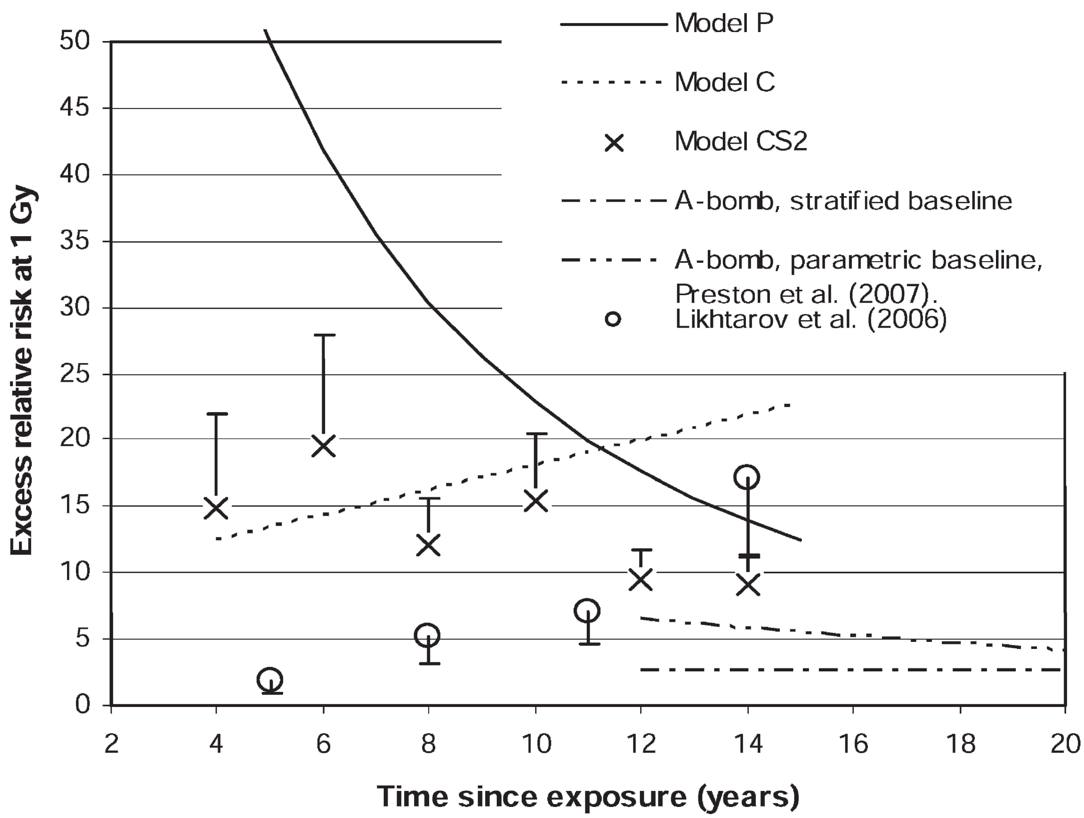

FIG. 3. Time patterns in the Chernobyl data. The effect modification of ERR at 1 Gy by time since exposure, at an age at exposure of 10 years. The fit parameters for model ERR-CS2 are shown with one standard error. Results of ref. (*7*) for the atomic bomb survivors are shown for comparison.

With two exceptions, the results obtained with the two data sets are quite consistent if the country effect is taken into account. The increase of the ERR with time since exposure reported by Likhtarov *et al.* (*6*) is only weakly reproduced by one of the other analyses. Part of the effect may be due to the use of a categorical baseline model, which does not seem to be fully supported by the data. Another possibly related discrepancy between the models of ref. (*6*) and those considered both here and in refs. (*5, 7*) can be found in the attained-age trends in the baseline models. The baseline risk reported by Likhtarov *et al.* (*6*) can be seen [in Table 4 of ref. (*6*)] to decrease with increasing attained age for males but to increase for females. This trend for males contradicts the trends found both here (in Table A2 of the Appendix) and in ref. (*5*) and also in general thyroid cancer incidence rates (*13*) as well as in the latest thyroid cancer incidence data[3] for the A-bomb survivors (*7*).

EAR Estimates

Analogous EAR forms of the ERR models used in this paper were also investigated. In contrast to the ERR results, the EAR estimates and associated trends in effect modification were found to be consistent in the various models. Also, there is a good agreement between refs. (*5*) and (*6*) on a larger EAR for females than for males (factor 1.5) and a decrease of the EAR with age at exposure (factor 0.4 for ages at exposure of 15 and 5 and for an attained age of 20). Thus, for the age-at-exposure and time-since-exposure regimes considered here, EAR values can be estimated with a lower uncertainty and a higher reliability than ERR values. For a thyroid exposure of 1 Gy, the central estimate of the EAR is about 2 cases per 10^4 PY.

Similarities to and Differences from the Atomic Bomb Survivors

The Chernobyl data set and the data set for the atomic bomb survivors overlap in coverage for the period of just over 12 years to 15 years since exposure. For this period, higher ERR values and a stronger age-at-exposure modification are found in the parameteric model for the Chernobyl data. Considering the age-at-exposure modification of the ERR, however, the results for the atomic bomb survivors are generally consistent

[3] The increase in the A-bomb baseline rates with attained age for thyroid cancer incidence rises up to 1.4 and 2.5 cases per 10^4 PY at an age of 70 years for males and females, respectively (for a birth cohort corresponding to $e = 30$ years), according to the parametric baseline model of ref. (*7*).

with the results of the categorical model for the Chernobyl data. The real nature of the age-at-exposure effect modification remains an open question.

It should be noted that the results of the present study are not easily compared to the analysis by Ron *et al.* (*14*) of pooled data from five cohort studies data, because a major part of the pooled data relate to a follow-up time longer than 15 years.

Recommendation on Baseline Modeling

Based on the experience of the study, it is generally recommended to test parametric and categorical baseline models in risk analyses. If quality-of-fit criteria do not clearly favor one kind of model, then deviating results indicate a larger uncertainty of the results than the statistical uncertainty of either method.

APPENDIX

TABLE A1
ERR Best Estimates (Centered at $e = 10$ Years, and $a = 20$ Years) and 95% Confidence Ranges of ERR Fit Parameters for Model C (with Stratum-specific Background Rates)

Model C, fit parameters		
Symbol	Eq. (3)	Meaning
β_1 (Gy^{-1})	15.25 (8.97; 21.52)	Linear term: ERR per unit dose for $a = 20$ and $e = 10$
β_2 (Gy^{-2})	−0.83 (−1.17; −0.49)	Quadratic term: ERR per unit dose squared for $a = 20$ and $e = 10$
$\exp(\beta_c)$	2.18 (1.07; 4.46)	Country ratio
$\exp(\beta_s)$	0.33 (0.14; 0.75)	Sex ratio
β_e (a^{-1})	0.159 (0.100; 0.218)	Slope of the logarithm of ERR with decreasing age-at-exposure
β_a (a^{-1})	1.04 (0.23; 1.85)	Power of a central estimate risk modification

TABLE A2
Rate, Relative Risks and 95% Confidence Intervals for Background Variables (as Optimized with a Simple ERR Model Part that is Linear in Dose) for Models Very Similar to Those in Likhtarov *et al.* (*6*)

Models CS1 and CS2				
Symbol	Variable	Estimate	Lower 95% bound	Upper 95% bound
exp (β_1)	**Constant**	6.47×10^{-6}	3.87×10^{-6}	1.08×10^{-5}
	Country			
exp (β_2)	*Ukraine*	1.0		
exp (β_3)	*Belarus*	1.13*	0.99	1.29
	Age at risk, years			
	males			
exp (β_4)	–	1.0		
exp (β_5)	*10–14*	1.42	0.85	2.38
exp (β_6)	*15–19*	1.01	0.59	1.74
exp (β_7)	*20–24*	0.74	0.42	1.29
exp (β_8)	*25–29*	1.05	0.58	1.93
exp (β_9)	*30+*	1.10	0.55	2.20
	females			
exp (β_{10})	*5–9*	1.51	0.83	2.77
exp (β_{11})	*10–14*	2.49	1.50	4.12
exp (β_{12})	*15–19*	2.01	1.19	3.37
exp (β_{13})	*20–24*	2.26	1.34	3.81
exp (β_{14})	*25–29*	4.10	2.38	7.07
exp (β_{15})	*30+*	4.26*	2.39	7.61
	Calendar time			
exp (β_{16})	*1989–1990*	1.0		
exp (β_{17})	*1991–1992*	1.41	1.06	1.88
exp (β_{18})	*1993–1994*	1.90	1.44	2.52
exp (β_{19})	*1995–1996*	1.81	1.36	2.41
exp (β_{20})	*1997–1998*	2.75	2.08	3.63
exp (β_{21})	*1999–2001*	2.78	2.07	3.72

Notes. The parameters β_1 to β_{21} refer to the fit parameters defined in Eq. (4). *Note that the background fit parameters change somewhat when reoptimized for models CS1 and CS2, with the largest changes associated with the female relative risks. The latter change from having a maximum relative risk of about 4 in the baseline parameters here to a maximum of about 10 or 11 for model CS1 and CS2, respectively. The baseline risk for Belarus relative to Ukraine is also slightly model-dependent.

TABLE A3
Excess Relative Risks and 95% Confidence Intervals for Dose with Various Interaction Effects for Models Very Similar to Those in Likhtarov *et al.* [ref. (*6*) and Eq. (5) of the Main Paper]

Model	Symbol	Variable	ERR/Gy	Lower 95% bound	Upper 95% bound
CS1		Age in 1986, years			
	exp (γ_1)	*1–4*	18.93	11.27	26.60
	exp (γ_2)	*5–9*	15.15	9.78	20.53
	exp (γ_3)	*10–14*	8.56	4.70	12.43
	exp (γ_4)	*15–18*	4.73	1.88	7.58
CS2		Mean calendar year (in each 2-year interval)			
	exp (γ_1)	*1990.5*	14.93	1.34	28.52
	exp (γ_2)	*1992.5*	19.60	3.51	35.70
	exp (γ_3)	*1994.5*	12.01	4.89	19.12
	exp (γ_4)	*1996.5*	15.43	5.72	25.13
	exp (γ_5)	*1998.5*	9.41	4.93	13.88
	exp (γ_6)	*2000.5*	9.18	4.82	13.53

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