RADIATION RESEARCH **159**, 656–662 (2003)
0033-7587/03 $5.00

A Biologically Based Model for Liver Cancer Risk in the Swedish Thorotrast Patients

W. F. Heidenreich,[a,1] Ullakarin Nyberg[b] and P. Hall[b]

[a] *GSF—Institute for Radiation Protection, 85764 Neuherberg, Germany; and* [b] *Department of Medical Epidemiology, Karolinska Institutet, S-17177 Stockholm, Sweden*

Heidenreich, W. F., Nyberg, U. and Hall, P. A Biologically Based Model for Liver Cancer Risk in the Swedish Thorotrast Patients. ***Radiat. Res.*** **159, 656–662 (2003).**

Data on liver tumors among 416 Swedish patients who were exposed to Thorotrast between 1930 and 1950 were analyzed with the biologically based two-step clonal expansion (TSCE) model. For background data, the Swedish Cancer Register for the follow-up period 1958 to 1997 was used. Effects of radiation on the initiating mutation and on the clonal expansion rate explained the observed patterns well. The TSCE model permits the deduction of several kinetic parameters of the postulated tumorigenesis process. Dose rates of 5 mGy/year double the spontaneous initiation rate. The clonal expansion rate is doubled by 80 mGy/year, and for females it reaches a plateau at dose rates beyond 240 mGy/year. For males the plateau is not significant. The magnitude of the estimated promoting effect of radiation can be explained with a moderate increase in the cell replacement probability for the intermediate cells in the liver, which is strikingly similar to the situation in lung tumorigenesis. **© 2003 by Radiation Research Society**

INTRODUCTION

Patients injected with the radiographic contrast agent Thorotrast (*1*) were exposed to the α-particle emitter ^{232}Th, which is excreted very slowly by the body, giving a biological half-life of about 400 years. Persons injected with Thorotrast are exposed to α-particle radiation for the rest of their lives at an approximately constant dose rate. The thorium is stored in several organs, one of which is the liver. Therefore, one of the primary effects of Thorotrast is liver cancer. All Thorotrast studies have reported significantly elevated risks of primary liver cancer (*2–6*). In Sweden, 432 individuals exposed to Thorotrast through cerebral angiography were compared to the general population by computerized linkage with the Cancer Register available for all Swedish citizens. A total of 65 cancers of the liver and gallbladder were found in the Thorotrast-exposed patients, while less than two cases were expected (*7*). The biologically based two-stage clonal expansion (TSCE) model was used to analyze the data on liver cancers. This model is a generalization of Knudson's recessive oncogenesis model (*8*) and can be thought of as a mathematical formalization of the initiation-promotion-progression paradigm of carcinogenesis. It allows separation of the effects of exposures on the various steps of carcinogenesis. Radon has been found to act not only on initiation, but also on promotion in the induction of lung tumors in humans and rats (*9, 10*). This implies that the growth advantage of intermediate cells may be increased by radiation, but this mechanism of action can never be conclusively proven from cancer incidence data. A more direct test would be to study the size distribution of premalignant clones of intermediate cells, such as the foci of altered hepatocytes in the liver (*11*). Therefore, one of the motivations for this work was to study whether a promoting effect of radiation could be seen in liver cancer incidence data.

[1] Address for correspondence: GSF-Institute for Radiation Protection, 85764 Neuherberg, Germany; e-mail: heidenreich@gsf.de.

MATERIALS AND METHODS

Data Set

The study cohort of 433 exposed persons used here is a subset of the 1,117 patients considered by Martling *et al.* (*7*). Cohort members had to be alive in January 1958, when the Swedish Cancer Register was started. In all, 684 individuals were excluded from the initial study cohort, 361 because of death within 1 year after the examination with Thorotrast, 62 lost to follow-up, and 261 who died prior to 1958. The amount of injected Thorotrast was not known for all persons. When only the number of injections was known, the average volume of one injection was multiplied by the number of injections to obtain an estimate. For 17 persons (among whom there was one case of liver cancer), this was not possible. These people were excluded from the analysis, leaving 416 exposed persons to be considered. The end point primary liver cancer (ICD-7 code 1550) was taken from the Swedish Cancer Register (*12*). This end point was preferred over the wider code 155, because most of the cases in the Thorotrast cohort belonged to this subtype (Table 1). Using code 155 would dilute the resulting relative risks; the problem of distinguishing between the subtypes was judged to be less severe. Patients were followed until diagnosis of liver cancer, death or December 31, 1993. The distribution of birth years, age at injection, and the follow-up period can be seen in Fig. 1; the range and mean values are given in Table 2. In the study group, 53 primary liver tumors were found during the follow-up period. The volumes of injected Thorotrast ranged from 2 to 49 ml. Frequent exposures were 8.5 ml and 16.5 ml. The cumulative injected Thorotrast volume was used to estimate the dose rate, which is assumed to

TABLE 1
Observed Number of Cancers in Various ICD-7 Codes among the 416 Persons in the Thorotrast Cohort and for the Swedish Population at Two Times

		Swedish population	
ICD-7 code	Thorotrast	1960	1995
155	64	881	884
1550 (primary liver)	53	421	398
1551 (gallbladder)	6	249	290
Other 155	5	211	196

be constant from the date of injection for life, by using 0.4 Gy/year for 25 ml of Thorotrast (*13*).

As a control group, incidence data from the Swedish Cancer Register were used. Male and female primary liver cancer (ICD-7 code 1550) rates in 5-year intervals (until the age of 85, older persons are in one group) for each of the years 1958–1997 were used. The background rates are plotted in Fig. 2. This approach is suggested, because the collection probability for liver cancer in exposed and control individuals is identical. None of the exposed persons were treated for liver diseases; their disease status had no influence on their liver tumor risk. The reason for examinations using Thorotrast was suspicion of intracranial disorders. The most frequent symptom was seizures. There were 15,057 primary liver cancers in the control group, an average of 376 per year. The cases in the cohort of Thorotrast patients were not deleted from the control group, since this would have only a negligible effect.

The TSCE Model

The TSCE model has a long history (*14, 15*). A sketch of the model is given in Fig. 3. Intermediate cells are created with the initiation rate ν from normal cells. The initiation rate is dependent on the number of the cells at risk and the initiating rate per cell. An intermediate cell can

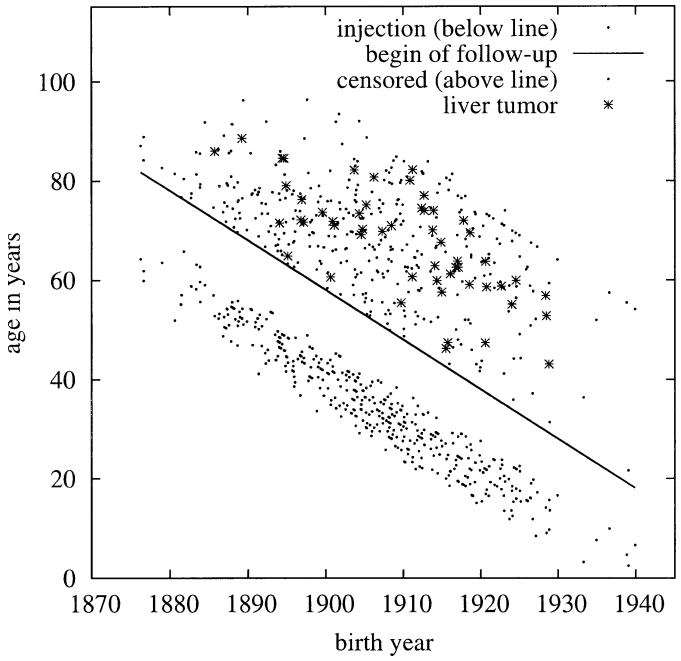

FIG. 1. Scatter plot giving for each of the 416 exposed persons the date and age of injection, beginning and end of follow-up, and the end point of liver tumor or other outcome.

TABLE 2
Characteristics of the Thorotrast Cohort

Characteristic	Range	Mean
Birth year	1876.3–1939.9	1906.5
Age at injection	2.5–65.7	34.1
Years after injection	14.7–60.5	34.3
Amount injected (ml)	2–49	12.8

divide into two intermediate cells with rate α, die or differentiate with rate β, and divide into an intermediate cell and a malignant cell with transformation rate μ. The progression from a malignant cell to an observable tumor is described with a lag time. Not all of these parameters can be determined from incidence data (*16, 17*). Therefore, identifiable parameters are used here. We investigated the influence of ionizing radiation on initiation, promotion and transformation; these effects can be separated by fitting the model to sufficiently powerful data.

The ratio of the initiation rate for exposure rate d over the spontaneous initiation rate is assumed to be linear,

$$\frac{\nu(d)}{\nu(0)} = 1 + \nu_1 d. \tag{1}$$

The parameter ν_1 is the inverse of the exposure rate, which doubles the

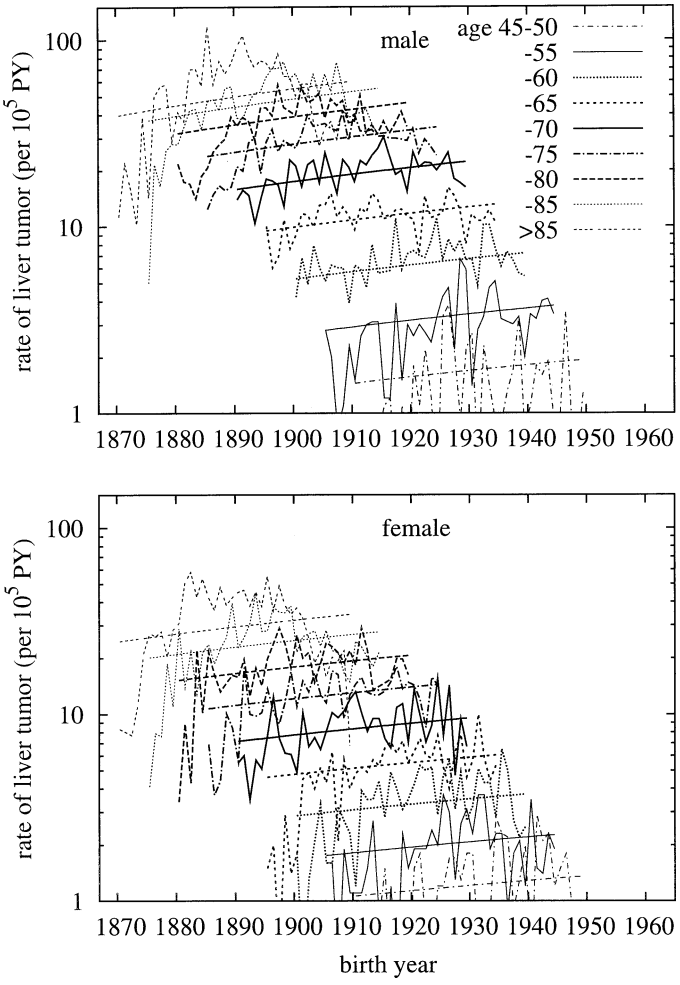

FIG. 2. Rates of liver tumors for the older age groups on a year-by-year basis. The straight lines are estimates with the IP model as described in the text. For the younger groups, too few cases are observed to allow creation of this type of plot.

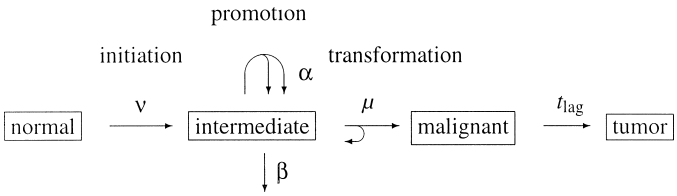

FIG. 3. Sketch of the TSCE model.

initiation rate. The effective clonal expansion rate $\gamma(d) \equiv \alpha(d) - \beta(d) - \mu(d)$ is allowed to be dependent on the exposure rate such that it is linear with coefficient γ_{lin} at low rates and reaches a plateau at γ_{level} at high rates. Such a form worked well with statistically more powerful data sets with radon-induced lung tumors (*18*). Exactly the same form was used in ref. (*10*):

$$\gamma(d) = \gamma_0 + \gamma_{level}(1 - e^{-(\gamma_{lin}/\gamma_{level})d}). \quad (2)$$

γ_0 is the spontaneous clonal expansion rate. For the ratio of the transformation rate over the spontaneous rate, a linear dependence is again assumed:

$$\frac{\mu(d)}{\mu(0)} = 1 + \mu_1 d. \quad (3)$$

Various subsets of the five parameters in the equations above are estimated, in addition to three parameters which affect only the background: The product $Y_0 \equiv \nu(0)\mu(0)$ of the spontaneous initiation and transformation rates is identifiable. The data in Fig. 2 suggest a birth-year effect. To keep things simple, two values of Y_0 were estimated, one for the year 1876 and one for 1976, with linear dependence in between. The stochastic parameter q was used that gives a leveling of hazard to Y_0/q at high age.[2] The model as formulated allows a calculation of the hazard for the first malignant cell. To allow for a finite time before the observable liver cancer, a lag time t_{lag} of 5 years is introduced.

Cancer incidence differs between the sexes. Therefore, two sets of parameters need to be estimated, one for males and one for females; some of the values may not be significantly different. To test for gender differences, the ''sex factor'' was calculated as the ratio of the value for females divided by the geometric mean value for women and men combined.

Likelihoods and Quality of Fit

The mathematical formulation of the TSCE model allows a calculation of the hazard and the survival probability S (i.e. the probability that no liver cancer occurred) for each age, and of the hazard $h = -d(\ln S)\,dt$. Model fitting was done by maximizing a log-likelihood that has two parts. The individual information on the exposed patients is entered in

$$\ln L_{indiv} = \sum_{\text{no cancer}} \ln S_i + \sum_{\text{cancer}} \ln(h_i S_i). \quad (4)$$

The hazard is calculated at the age of cancer diagnosis; the survival is calculated for the follow-up period. The background information from the population-based register is entered in a Poisson likelihood

$$\ln L_{Poisson} = \sum_i \left(n_i - \Lambda_i + n_i \ln \frac{\Lambda_i}{n_i} \right). \quad (5)$$

The sum is over all classes of the register data, stratified by age (in 5-year intervals), calendar year, and sex. As usual, n_i is the observed number of cases, and Λ_i is the expected number in each of the i classes. It is calculated from the model, using the center of each age interval, and the age 87.5 for the oldest group of >85 years. The youngest age at follow-up was 20 years (see Fig. 1). For the Poisson likelihood estimation, only groups with an age of above 20 years were used, to avoid possible problems with childhood cancers.

The deviance was

$$\text{Dev} = -2(\ln L_{indiv} + \ln L_{Poisson}) \quad (6)$$

for the maximum. Parameter uncertainties were calculated using Wald-based errors and by profile likelihood techniques. These calculations were done with the function minimizer MINUIT from CERN (*19*).

Two data sets and common estimated parameters were used before in applications of the TSCE model: Moolgavkar *et al.* (*20*) used the Colorado miners and the data on the British doctors in a combined analysis. Case–control data were combined with population data for lung cancer in one likelihood (*21*). The combination of the likelihood of a large set of stratified data (the Swedish population) and a likelihood that uses the individual information from a group of patients into one likelihood as in Eq. (6) in an application of the TSCE model is new to our knowledge.

As a means for judging the quality of fit, the numbers of expected cases were calculated for various groups of patients by summing over all group members the cumulative hazard of each patient during the follow-up. The groups were defined similarly to the groups in ref. (*7*).

RESULTS

The deviances of some of the model fits are given in Table 3. All models have the eight parameters that determine the background model. These parameters were estimated effectively from the Swedish cancer data using the Poisson regression part of the likelihood, since there are many more cases in these data than in the exposed group.

[2] In terms of the spontaneous biological parameters $q = \frac{1}{2}(-\gamma + \sqrt{\gamma^2 + 4\alpha\mu})$ (*17*).

TABLE 3
Comparison of Various Models Showing their Deviance, and the Number of Fitted Parameters

Model	Deviance	Number of parameters	Radiation-sensitive parameters
IP model, sex-dependent	2366.2	14	ν_1, γ_{lin}, γ_{level} and sex factors
IP model	2367.0	13	As above, with sex factor 1 for γ_{lin}
IP model, sex-independent	2376.0	11	As above, sex factors 1
IT model, sex-dependent	2381.4	12	ν_1, μ_1 and sex factors
IT model	2381.5	10	As above, sex factor 1
I model, sex-dependent	2389.5	10	ν_1 and sex factor
I model	2389.5	9	As above, sex factor 1
No dose	2789.6	8	None

Notes. The ''no dose'' model described the spontaneous risk. All models include the eight parameters that describe the spontaneous hazard (Y_{1876}, Y_{1976}, γ_0 q, and their respective sex factors.

TABLE 4
Maximum Likelihood Estimates (MLE) for all Parameters of the IP Model, and their Confidence Intervals

Parameter	MLE	CI (68%)	Sex factor	CI (68%)
Y_{1876} (10^{-8} year^{-2})	0.527	(0.478, 0.582)	1.60	(1.45, 1.76)
Y_{1976} (10^{-8} year^{-2})	1.09	(1.01, 1.18)	1.50	(1.39, 1.63)
ν_1 [(ml)$^{-1}$]	3.23	(2.56, 4.10)	1.61	(1.32, 1.99)
γ_0 (year^{-1})	0.126	(0.124, 0.128)	0.87	(0.86, 1.99)
γ_{lin} (ml^{-1})	0.026	(0.020, 0.033)	1	Fixed
γ_{level} (year^{-1})	0.49	(0.37, 1.45)	0.51	(0.18, 0.67)
q(10^{-4} year^{-1})	0.116	(0.108, 0.125)	1.71	(1.59, 1.84)
		IT model		
ν_1 (ml^{-1})	48	±72	1	Fixed
μ_1 (ml^{-1})	0.32	±0.57	1	Fixed
		I model		
ν_1 (ml^{-1})	260	(225, 300)	1	Fixed

Notes. With the exception of γ_{level}, the errors are close to symmetrical. The sex factor was calculated for each parameter as the ratio of the value for females divided by the geometric mean of the two genders. The radiation-specific parameter values are given for the IT and the I models. The data are not good in separating the initiating and transforming actions of radiation. Therefore, profile-likelihood uncertainties could not be calculated for the IT model; the standard Wald-based errors are given instead. The parameters omitted for the IT and the I models are very close to the IP model, since they influence the background, which is effectively estimated from the statistically very powerful registry of data.

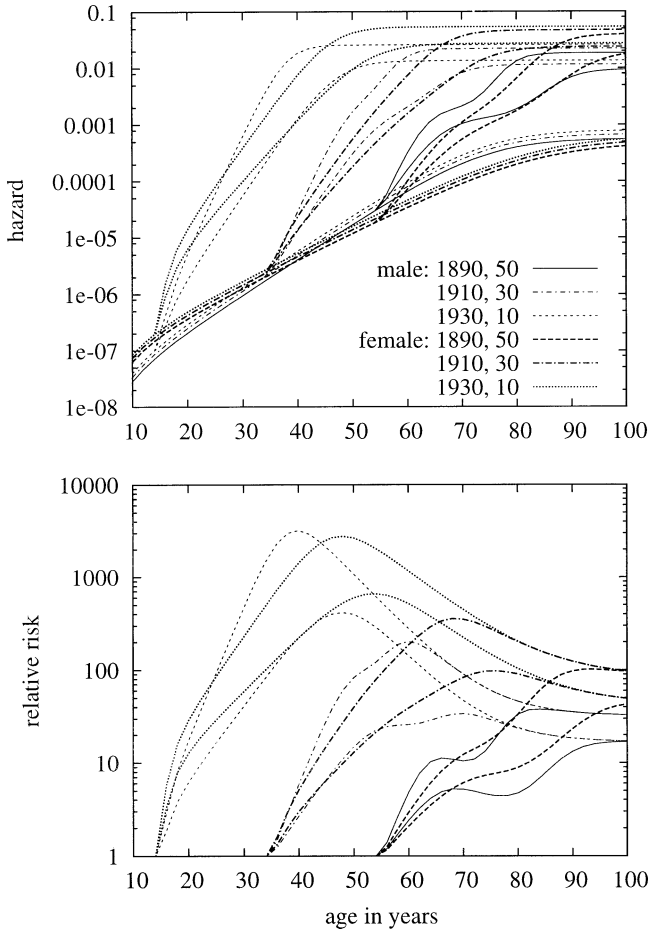

FIG. 4. Hazards and relative risks for the IP model for different birth years and ages at injection. In each case the lower line gives the risk for an injection of 8 ml, the upper the risk for 16 ml. The upper panel also shows the estimated background hazard.

Because of the large database, they were estimated reliably. The other parameters could play a role only in the exposed group. When exposure effects were allowed, two local maxima of the likelihood were found, both with an influence of radiation on initiation. In addition, radiation affected either promotion (IP model) or transformation (IT model). Neither model could be improved significantly by making the other radiation effect nonvanishing. The barrier in the log-likelihood between the IP and the IT models, which prevents the IT model from moving to the IP model if the promotion parameters are released, presumably has to do with the very restricted exposure pattern available in the data set.

Also estimated are the parameters of a model with radiation affecting only initiation (I model). When the sex-dependent versions of the models are compared, the IT model has two more parameters but an improvement of 8 points in the deviance. The IP model has four more parameters and an improvement of 23 points in the deviance. Compared to the IT model, it has 2 more parameters and an improvement of 15 points in the deviance. Note, however, that the IT and IP models are not nested. For each of these models, the deviance is also given, when the radiation-relevant parameters are assumed to be independent of the sex. For the I and IT models, the sex dependence of the radiation-related parameters is not significant. The same applies to the linear component γ_{lin} of promotion in the IP model. The version with this parameter constant at 1 is called the IP model.

The IP model is described in more detail. All of its estimated parameters are given in Table 4. In Fig. 2, the liver cancer rates of the IP model are plotted for control groups. In Fig. 4, the hazard functions and the relative risk functions of the IP model are plotted for some typical exposure patterns. In Table 5, the observed and expected numbers of cases are given for the IP model for different groups of patients (*7*). The agreement is good; even the largest discrepancy, in the group with age at injection 40–50 years, may be due to statistical fluctuations.

The resulting effect of exposure on promotion can be seen in Fig. 5. The parameters γ_{level} of the promoting effect differs substantially between the sexes: There is pronounced leveling for females but only minor leveling for males. For this reason the dose response in Fig. 4 is stronger for males than for females. We assume that the data set for males only is not strong enough at high dose to estimate a leveling.

For the I model and the IT model, the radiation-related parameters only are given in Table 4. The other parameters

TABLE 5
Case Stratified with Respect to Several Risk-Related Characteristics

	Observed			Expected: IP			Expected	
Gender	Cases	Background	SIR	Cases	Background	RR	IT cases	I cases
Male	26	0.439	59.2	27.1	0.433	62.6	26.0	26.2
Female	27	0.217	124.3	26.2	0.220	119.2	26.3	26.4
Age (years) at injection								
<20	11	0.040	274.1	12.8	0.039	324.8	13.6	13.4
20–<30	21	0.151	138.9	23.3	0.147	158.2	24.3	24.4
30–<40	8	0.195	41.1	11.9	0.184	64.5	10.0	10.4
40–<50	11	0.167	65.7	4.1	0.165	24.9	3.4	3.5
≥50	2	0.103	19.5	1.2	0.116	10.1	1.1	0.9
Years since injection								
<20	0	0.046	0.0	1.1	0.072	15.8	1.3	1.1
20–<30	11	0.193	56.9	11.6	0.209	55.3	8.3	7.3
30–<40	24	0.237	101.1	22.2	0.202	110.2	16.7	15.6
≥40	18	0.180	100.3	18.3	0.170	107.9	26.0	28.6
Injection (ml)								
<10 (mean 8.3)	21	0.446	47.1	17.0	0.441	38.5	19.5	27.6
10–<20 (mean 16.1)	20	0.172	116.4	24.8	0.173	143.6	22.5	19.5
≥20 (mean 28.3)	12	0.038	313.5	11.5	0.038	299.3	10.4	5.5
Age (years) at diagnosis								
<50	5	0.010	509.2	6.3	0.017	379.0	5.2	4.5
50–<60	18	0.073	245.2	15.4	0.080	191.2	12.4	10.9
60–<70	18	0.229	78.7	18.4	0.224	82.0	17.0	17.2
≥70	12	0.344	34.9	13.2	0.332	40.0	17.7	20.0
Calendar year								
<1968	7	0.172	40.7	8.3	0.211	39.4	6.6	5.8
1968–<1978	20	0.231	86.7	19.9	0.207	96.2	14.2	13.0
1978–<1988	21	0.186	112.7	18.8	0.163	115.1	20.1	20.2
≥1988	5	0.067	74.4	6.2	0.071	87.7	11.4	13.6

Notes. The observed background and the SIR are calculated using data from the Swedish Cancer Register. For an accredited model, the observed cases would be Poisson-distributed around the expected cases.

are very similar to those of the IP model. The IT model has an initiation parameter that is more than an order of magnitude larger than that in the IP model. It is also much larger than the transformation parameter. The symmetry between the action of radiation on initiation and transformation, which would be expected if the simplest version of the two-mutation hypothesis of the TSCE model were applicable, is not present. The uncertainties of the two given parameters in the IT model are large. This indicates that the data are not very good for separating the initiating and transforming actions of radiation. For the I model, the initiation parameter is again larger by more than a factor of 5. The estimated magnitude of the initiating effect of radiation depends strongly on whether an additional action of radiation is considered.

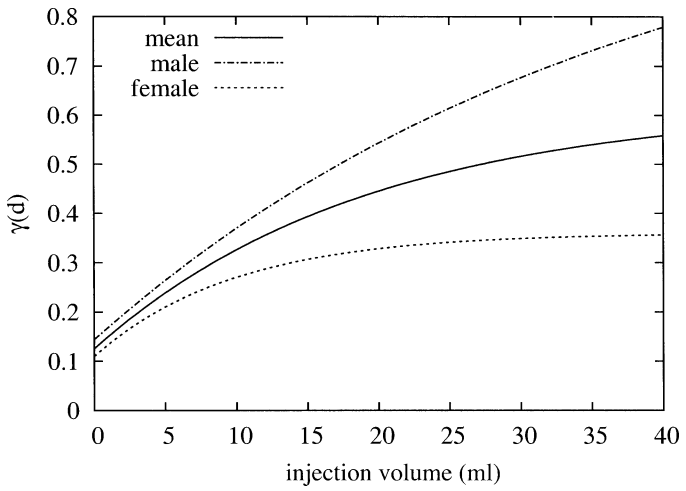

FIG. 5. Dependence of promotion on injection volume in the IP model.

The expected numbers of cases calculated with the I and the IT models are included in Table 5. Their agreement with the data is in general inferior to that of the IP model. These observations are in agreement with the substantially lower deviance of the IP model when compared to the IT and the I models.

DISCUSSION

The IP model, which assumes that radiation acts both on initiation and promotion, describes the data well (see Table 5). It performs substantially better than the models where

radiation is assumed to act only on initiation, or on initiation and transformation. This is also seen by comparing the estimated deviance in Table 3. The model could not be improved by also assuming a transforming action of radiation. This data set is not ideal for testing for a promoting action of radiation since no data after the end of exposure can exist. The effects of age at exposure and time since exposure favor a promoting action over a transforming one (*22*) and give a strong indication that initiation alone is not sufficient to describe the data. An experiment looking for foci of altered hepatocytes in the liver might provide additional insights.

The radiation-related parameters are chosen such that they are in principle observable in experiments. The volume of treatment can be converted into a dose rate by assuming that an injection of 25 ml of Thorotrast gives a dose rate of about 0.4 Gy/year (or 8 Sv/year when an RBE of 20 for α particles is used) to the liver (*13*). For the IP model, the kinetic parameters can be described as follows: The doubling dose rate for initiation is about 5 mGy/year or 100 mSv/year. The doubling dose rate for promotion is about 80 mGy/year or 1.6 Sv/year. For females the effect reaches a plateau at about 15 ml, or 240 mGy/year, or 4.8 Sv/year. For males a leveling is not estimable. For females the leveling is at a factor of about 3 above the spontaneous clonal expansion rate.

Most of the dose from Thorotrast is due to the α particles from ^{232}Th. This also holds for radiation from radon and its progeny to the lung. Therefore, it may be of interest to compare the numbers from the last paragraph with results from an analysis of lung tumors in the Colorado miners: Initiation doubled at 700 mSv/year, promotion doubled at 125 mSv/year, a plateau occurred from a dose rate of 1 Sv/year, at a factor of 4 above the spontaneous clonal expansion rate (*15, 18*). Although there are many uncertainties in such a comparison, the liver may be more sensitive to initiation and less sensitive to promotion than the lung if equivalent doses are used. The differences are not dramatic if one considers the large potential errors. The order of magnitude of the exposure response is plausible. We are aware that this is not proof that the effect of Thorotrast in the induction of liver cancer results entirely from ionizing radiation. A chemical effect of the thorium on the liver cannot be excluded.

In a recent paper, the promoting action of radiation in the lungs was proposed to be connected to an advantage of the intermediate cells when cells inactivated by radiation in the neighborhood are replaced (*23*). A similar calculation is possible for the liver. An α particle from Thorotrast hitting a liver cell nucleus deposits an energy of about 200 mGy. This number can be calculated using an energy of 4 MeV for the α particles from ^{232}Th, the corresponding stopping power of about 1000 MeV cm^2/g (*24*), and the diameter of a liver cell nucleus, which is assumed to be spherical, of about 10 μm. The liver is exposed evenly to the α particles (*25*). Therefore, at a dose rate of 200 mGy/year, a cell nucleus in the liver is hit on average once a year, inducing an inactivation rate $\beta = 0.3$ per year, if about 30% of cells with nuclei that are hit by α particles are killed (*23*). Such a dose rate occurs after an injection of 12 ml Thorotrast. The estimated linear component γ_{lin} in Table 4 gives for this dose rate a promoting effect of the radiation with a clonal growth advantage of $\gamma = 0.3$ per year. The cells in the liver are distributed in three dimensions, so we assume that each target cell has on average $N = 12$ nearest neighbors. Using $\gamma = gN\beta$ from Eq. (1) in ref. (*23*), an excess replacement probability $g = 0.08$ for intermediate cells is needed to model the promoting effect of radiation in the liver. This value agrees well with the estimates for lung cells: $g = 0.04$ if secretory cells are the target and $g = 0.15$ if basal cells are the target. These calculations may provide motivation for studies of the effect of radiation on the proliferation of premalignant cells.

ACKNOWLEDGMENT

This work was supported by the EU under contract number FIGH-1999-00005.

Received: July 31, 2002; accepted: November 18, 2002

REFERENCES

1. H. D. Abbatt, History of the use and toxicity of Thorotrast. *Environ. Res.* **18**, 6–12 (1979).
2. M. Andersson, K. Juel and H. H. Storm, Pattern of mortality among Danish Thorotrast patients. *J. Clin. Epidemiol.* **46**, 637–644 (1993).
3. M. Andersson, B. Carstensen and H. H. Storm, Mortality and cancer incidence after cerebral arteriography with or without Thorotrast. *Radiat. Res.* **142**, 305–320 (1995).
4. T. Mori, Y. Kato, H. Matsudaira, R. Machinami, Y. Akita and K. Fukutomi, Recent results in the first series of the Japanese follow-up study of Thorotrast patients and their relationships with statistical analyses of autopsy series. In *Health Effects of Internally Deposited Radionuclides* (G. van Kaick, A. Karaoglou and A. M. Kellerer, Eds.), pp. 181–191. World Scientific, Singapore, 1995.
5. G. van Kaick, H. Wesch, H. Luehrs, D. Liebermann and A. Kaul, Epidemiological results and dosimetric calculations—an update of the German Thorotrast study. In *Health Effects of Internally Deposited Radionuclides* (G. van Kaick, A. Karaoglou and A. M. Kellerer, Eds.), pp. 53–67. World Scientific, Singapore, 1995.
6. L. B. Travis, C. E. Land, M. Andersson, U. Nyberg, M. B. Goldman, L. K. Gaul, E. Berger, H. H. Storm, P. Hall and J. D. Boice, Jr., Mortality after cerebral angiography with or without radioactive Thorotrast: An international cohort of 3,143 two-year survivors. *Radiat. Res.* **156**, 136–150 (2001).
7. U. Martling, A. Mattsson, L. B. Travis, L. E. Holm and P. Hall, Mortality after long-term exposure to radioactive Thorotrast: A forty-year follow-up survey in Sweden. *Radiat. Res.* **151**, 293–299 (1999).
8. A. G. Knudson, Mutation and cancer: Statistical study of retinoblastoma. *Proc. Natl. Acad. Sci. USA* **68**, 820–823 (1971).
9. E. G. Luebeck, S. B. Curtis, F. T. Cross and S. H. Moolgavkar, Two-stage model of radon-induced malignant lung tumors in rats: Effects of cell killing. *Radiat. Res.* **145**, 163–173 (1996).
10. W. F. Heidenreich, P. Jacob, H. G. Paretzke, F. T. Cross and G. E. Dagle, Two-step model for fatal and incidental lung tumor risk in rats exposed to radon. *Radiat. Res.* **151**, 209–217 (1999).
11. S. Ober, H. Zerban, A. Spiethoff, K. Wegener, M. Schwarz and P. Bannasch, Preneoplastic foci of altered hepatocytes induced in rats

by irradiation with α-particles of Thorotrast and neutrons. *Cancer Lett.* **83**, 81–88 (1994).

12. *Cancer Incidence in Sweden 1997*. Technical report, National Board on Health and Welfare, Stockholm, 1999.
13. A. Kaul, Biokinetic models and data. In *Health Effects of Internally Deposited Radionuclides* (G. van Kaick, A. Karaoglou and A. M. Kellerer, Eds.), pp. 53–67. World Scientific, Singapore, 1995.
14. S. H. Moolgavkar, Carcinogenesis models: An overview. In *Physical and Chemical Mechanisms in Molecular Radiation Biology* (W. A. Glass and M. N. Varma, Eds.), pp. 387–395. Plenum Press, New York, 1991.
15. W. F. Heidenreich and H. G. Paretzke, Biologically based models of radiation-induced cancer. *Radiat. Res.* **156**, 678–681 (2001).
16. W. F. Heidenreich, On the parameters of the clonal expansion model. *Radiat. Environ. Biophys.* **35**, 127–129 (1996).
17. W. F. Heidenreich, E. G. Luebeck and S. H. Moolgavkar, Some properties of the hazard function of the two-mutation clonal expansion model. *Risk Anal.* **17**, 391–399 (1997).
18. E. G. Luebeck, W. F. Heidenreich, W. D. Hazelton, H. G. Paretzke and S. H. Moolgavkar, Biologically based analysis of the Colorado uranium miners cohort data: Age, dose and dose-rate effects. *Radiat. Res.* **152**, 339–351 (1999).
19. F. James, *MINUIT Function Minimization and Error Analysis, Version 94.1*. CERN, Geneva, 1994.
20. S. H. Moolgavkar, G. Luebeck, D. Krewski and J. M. Zielinski, Radon, cigarette smoke, and lung cancer: A re-analysis of the Colorado plateau uranium miner's data. *Epidemiology* **4**, 204–217 (1993).
21. W. F. Heidenreich, J. Wellmann, P. Jacob and H. E. Wichmann, Mechanistic modelling in large case–control studies of lung cancer risk from smoking. *Statist. Med.* **21**, 3055–3070 (2002).
22. W. F. Heidenreich, Signals for a promoting action of radiation in cancer incidence data. *J. Radiol. Prot.* **22**, A71–A74 (2002).
23. W. F. Heidenreich, M. Atkinson and H. G. Paretzke, Radiation-induced cell inactivation can increase the cancer risk. *Radiat. Res.* **155**, 870–872 (2001).
24. ICRU, *Stopping Powers and Ranges for Protons and Alpha Particles*. Report 49, International Commission on Radiation Units and Measurements, Bethesda, MD, 1993.
25. A. Goto, Y. Takebayashi, D. Liu, L. Li, T. Saiga, T. Mori, A. Yamadera and M. Fukumoto, Microdistribution of alpha particles in pathological sections of tissue from Thorotrast patients detected by imaging plate autoradiography. *Radiat. Res.* **158**, 54–60 (2002).