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Biologically-based risk estimation for radiation-induced chronic myeloid leukemia

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Abstract Radiation cancer risks are typically determined by the use of simple statistical descriptions of epidemiological data. It is important in risk assessment in general, however, to attempt to incorporate as much biological information into the risk models as possible. We illustrate this by presenting a biologically-based linear-quadratic-exponential (LQE) incidence rate model for radiation-induced chronic myeloid leukemia (CML). The model consists of a linear-quadratic dose-response for the induction of BCR-ABL, a waiting time distribution between BCR-ABL formation and detection of CML, and an exponential cell-killing term that multiplies both the background and induced incidence rates. Using data exclusive of the A-bomb survivor cohort, Bayesian priors are defined for each of the nine parameters in this LQE model. The priors are based on chromosomal translocations in lymphocytes, hematopoietic stem cell survival experiments, CML waiting times in women irradiated for benign disease, the background CML incidence rate in the U.S. population, and genomic DNA target sizes of BCR and ABL. Fixing three of the LQE model parameters to the means of their priors, maximum likelihood estimates of the remaining six parameters were obtained using A-bomb survivor incidence data for Hiroshima males. The likelihood estimates and the corresponding six prior distributions, both approximated as multivariate normal, were then used to form Bayesian posteriors for the six parameters not fixed. With these posteriors the LQE model yields $Q_\gamma^*=0.0042\ \mathrm{Gy}^{-1}$ where Q_γ^* is the upper 95% confidence bound of the lifetime CML risk per person-gray in the limit of low doses of gamma-rays. This value is slightly less than $Q_\gamma^*=0.0049\ \mathrm{Gy}^{-1}$ obtained from likelihood estimates of the LQE parameters, and substantially less than $Q_\gamma^*=0.0158\ \mathrm{Gy}^{-1}$ obtained for a simple statistical model linear in dose for kermas less than 4 Gy.

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Introduction

The advantage of biologically-based cancer models, relative to purely statistical models, is their potential to bring biological considerations to bear on epidemiological risk estimates. Biological considerations can affect risk estimates through both the structure and the parameter values of the model. This paper demonstrates biologically-based modeling for a specific example of radiation carcinogenesis.

In epidemiological studies, cancer endpoints with similarities are often pooled together. For example, acute myeloid leukemia (AML) is usually given as a single disease entity even though it really consists of many subtypes [1, 2]. In general, it cannot be assumed that cancer subtypes arise via the same mechanism, nor can it be assumed that they arise from within the same target cell population. Cancer endpoints are thus difficult to model as groups, and, due to low numbers of cases, difficult to model as individual subtypes. Chronic myeloid leukemia (CML) is exceptional in this regard. Almost all cases of CML are associated with a BCR-ABL chromosomal translocation [3], and the CML incidence rate is high enough that induction by ionizing radiation can be detected epidemiologically [4, 5, 6]. Furthermore, there is evidence that ionizing radiation induces BCR-ABL formation [7, 8, 9] and that BCR-ABL causes CML [10, 11, 12] and other leukemias [13]. These properties make radiation-induced CML attractive for biologically-based cancer risk modeling.

There are two paths by which biological information can exert an impact on cancer risk estimates. One is the constraint of model structures to plausible forms, the other is the constraint of parameter values to reasonable ranges. To estimate the separate impacts attributable to each of these paths, three models of radiation-induced CML risk will be compared. In the first model, neither the structure nor the parameter values are constrained to be biologically plausible. Risk estimates based on this linear dose-response model depend on epidemiological data alone. The other two models have dose-response structures constrained to a biologically plausible linear-quadratic-exponential (LQE) form. In the second model six of the nine LQE parameter values are free in the sense that they are determined by the likelihood function (i.e., A-bomb data) alone. In the third model these parameter values are determined not only by the likelihood function, but also by the 'soft' constraints of informative Bayesian priors (i.e., A-bomb exclusive data). The three models of CML risk allow us to assess the separate and combined impacts of biologically plausible model structures and parameter ranges.

Bayesian methods

Aspects of Bayesian methods [14, 15] central to this paper will now be described. Suppose we have vectors of model parameters θ and observed data *X*. Bayes theorem

$$P(\theta \mid X) = \frac{L(X \mid \theta)P(\theta)}{\int_\theta L(X \mid \theta)P(\theta)d\theta} \tag{1}$$

then states that the posterior distribution $P(\theta|X)$ equals the normalized product of the likelihood function $L(X|\theta)$ and the prior distribution $P(\theta)$. Assuming, and we shall throughout, that the prior and likelihood estimates of θ are multivariate normal, denoted $\mathrm{MVN}(\mu_p, \Sigma_p)$ and $\mathrm{MVN}(\mu_l,\Sigma_l)$, respectively, the posterior distribution is also multivariate normal, denoted $\mathrm{MVN}(\mu, \Sigma)$; this follows from Eq. (1) because the log-posterior is then the sum of a quadratic log-likelihood and a quadratic log-prior, which, upon completing the squares, yields a quadratic log-posterior with

$$\Sigma = \left(\Sigma_l^{-1} + \Sigma_p^{-1}\right)^{-1} \quad \text{or} \quad \Sigma^{-1} = \Sigma_l^{-1} + \Sigma_p^{-1} \tag{2}$$

and

$$\mu = \Sigma\left(\Sigma_l^{-1}\mu_l + \Sigma_p^{-1}\mu_p\right) \quad \text{or}$$

$$\mu = \left(\Sigma_l^{-1} + \Sigma_p^{-1}\right)^{-1}\left(\Sigma_l^{-1}\mu_l + \Sigma_p^{-1}\mu_p\right). \tag{3}$$

Viewing the matrix Σ^{-1} as information, these equations state that the posterior information equals the likelihood information plus the prior information, and that the posterior mean is the information-weighted average of prior and likelihood means. By symmetry we see that likelihoods and priors are treated equivalently in forming posteriors. At times, however, it is useful to view them asymmetrically in the context of optimization theory [16]. In this setting the quadratic log-likelihood becomes the objective function and the quadratic log-prior becomes a penalty function or 'soft' constraint. Posterior parameter estimates then become maximum likelihood estimates optimized under the soft constraints of Bayesian priors.

Models

Three models for the expected number of CML cases among A-bomb survivors are presented. The first has the linear dose-response structure of Preston et al. [4], the second and third have a biologically plausible LQE dose-response structure. Common to all three models, the expected number of background cases equals person-years multiplied by an incidence rate that increases exponentially with age [17], and a waiting-time distribution

$$w(t) = \frac{k_t^3 t^2}{2} e^{-k_t t} \tag{4}$$

describes the time *t* between formation of the BCR-ABL translocation and development of CML; the structure of $w(t)$ is arbitrary except that it must vanish within 15 years [5]. Among differences between the models, dose in Sv is used in the linear model while separate gamma and neutron doses are used in the LQE models, and the LQE models include cell killing while the linear model does not.

Linear model

Based on A-bomb survivor data alone, Preston et al. [4] concluded that a linear dose-response model adequately describes the risk of radiation-induced CML. We modified the model of Preston et al. [4] so that the waiting time distribution is more realistic between t=0 and 5 years, and so that the background incidence age structure is consistent with the U.S. population [17]. The result is

$$m_i = \left(e^{c_1 + k a_i} + D_i t_i^2 e^{c_2 - k_t t_i}\right) P_i \tag{5}$$

where the parameters c_1, k, c_2 and k_t are obtained by maximizing the Poisson log-likelihood

$$\sum_i O_i \log(m_i) - m_i. \tag{6}$$

Here m_i, O_i, a_i, P_i, D_i and t_i denote the expected number of CML cases, the observed number of CML cases, the average age, the person-years, the average marrow dose in Sv, and the average number of years since exposure, respectively, for the *i*th grouped data cell.

Linear-quadratic-exponential model

Assuming that the BCR-ABL translocation causes CML [10, 11, 12], that the dose-response of BCR-ABL translocations in CML target cells is proportional to the dose-response of total translocations in lymphocytes, and that CML target cells have survival dose-responses similar to murine hematopoietic stem cells, a biologically plausible LQE dose-response structure for expected CML cases is

$$m_i = P_i\left[e^{c_1+ka_i} + \left(D_{\gamma i} + (\beta/\alpha)D_{\gamma i}^2 + (\alpha_n/\alpha)D_{ni}\right)t_i^2 e^{c_2-k_t t_i}\right] \cdot e^{-\left(\alpha_k D_{\gamma i}+\beta_k D_{\gamma i}^2+\alpha_{kn}D_{ni}\right)} \qquad (7)$$

where m_i, O_i (Eq. 6), a_i, P_i and t_i are defined as in the linear model, $D_{\gamma i}$ and D_{ni} are the average gamma and neutron marrow doses for the ith grouped data cell, $\alpha D_{\gamma i}+\beta D^2_{\gamma i}+\alpha_n D_{ni}$ is the expected total number of chromosomal translocations per target stem cell, and $\alpha_k D_{\gamma i}+\beta_k D^2_{\gamma i}+\alpha_{kn} D_{ni}$ is the expected number of lethal hits per target stem cell. The biological basis of this model is as follows. Let N be the number of CML target cells [17], and let $P(ba|T)$ be the probability that a cell has BCR-ABL given that it has a translocation [18]. Substituting into Eq. (7) the expression

$$e^{c_2} = NP(ba\,|\,T)\alpha\frac{k_t^3}{2} \qquad (8)$$

the LQE model becomes

$$m_i = P_i\left[e^{c_1+ka_i} + NP(ba\,|\,T)\left(\alpha D_{\gamma i} + \beta D_{\gamma i}^2 + \alpha_n D_{ni}\right)w(t_i)\right] \cdot e^{-\left(\alpha_k D_{\gamma i}+\beta_k D_{\gamma i}^2+\alpha_{kn}D_{ni}\right)} \qquad (9)$$

Here

$$NP(ba\,|\,T)\left(\alpha D_{\gamma i} + \beta D_{\gamma i}^2 + \alpha_n D_{ni}\right)e^{-\left(\alpha_k D_{\gamma i}+\beta_k D_{\gamma i}^2+\alpha_{kn}D_{ni}\right)} \qquad (10)$$

is the probability that the exposure causes BCR-ABL in a target stem cell not killed by the exposure. In our model this is also the probability that an exposed individual eventually develops CML (in the absence of competing risks). Multiplying this expression by $w(t_i)\Delta_i$, where Δ_i is the length of the observation time for the ith data cell, the result is the probability that an exposed individual develops CML within a Δ_i interval t_i years after the exposure (again in the absence of competing risks). Finally, multiplying this result by P_i/Δ_i, the number of exposed people still in the study during this observation window, and cancelling the Δ_i's, the result is Eq. (9) or Eq. (7). Note that by using P_i/Δ_i, rather than the number of people entering the study in 1950, we are controlling for competing risks. Also note that, because exponentiation tends to normalize parameter estimates, Eq. (7), rather than Eq. (9), should be used in the optimization routines that maximize Eq. (6).

The LQE model assumes that CML induction is a one-stage process, i.e., that any additional events necessary for CML are common enough to always occur within 15 years of the rate-determining step of BCR-ABL formation. The LQE model also assumes that the target cell population size is not regulated to return to its pre-irradiation level. Thus, the exponential cell killing term multiplies not only the induced incidence rate, but also the background incidence rate.

Data sets

Likelihood data

Our likelihood function is based on only the Hiroshima male portion of the A-bomb survivor incidence data. Exclusion of the remaining A-bomb survivor data is rationalized in this section.

Of the 59 cases of CML among the A-bomb survivors, only 6 are from Nagasaki. It is not known why CML is essentially absent in Nagasaki. It is known that adult T-cell leukemia (ATL) is unusually high in Nagasaki (22 cases), compared to Hiroshima (1 case), and that ATL does not show a dose-response [4]. These observations suggest that perhaps the human T-cell leukemia virus (HTLV) precludes the development of CML. Consistent with this notion is the observation that 3 of the 4 Nagasaki male cases were ages 11, 13, and 24 at diagnosis, and that the seroprevalence of HTLV increases with age and is higher in females than in males [19].

Based on A-bomb exclusive data, it was our prior belief that the excess risk of radiation-induced CML peaks about 8 years after irradiation and vanishes after about 15 years [5, 6]. Consistent with this, we note that the three adolescent Nagasaki male cases were probably radiation-induced (background rates are low at these ages) and that their exposure-to-CML waiting times were 8 years, 11 years and 11 years, respectively. Thus, the Nagasaki data does lend some credence to our prior beliefs.

Among Hiroshima females, only 7 out of 25 cases arrived within 15 years of the exposure, compared to 15 out of 28 for males. Furthermore, it is clear from the high dose portion of the Hiroshima female data (Table 1) that some of the induced cases are arriving much later than expected [5, 6], i.e., that we are not simply missing induced cases. Related to this, Table 1 shows that only 3 female cases were diagnosed before the age of 40, compared to 10 male cases. These inconsistencies suggest that either we do not understand CML well enough to model it mechanistically, or that, for some reason, the Hiroshima female data is (at least in part) not representative of the processes that normally underlie radiation-induced CML. We adopt this latter view (the Nagasaki data proves that it can happen) and thus exclude the Hiroshima female data from our analysis. In contrast, Tables 1and 2 show that the Hiroshima male data is highly consistent with the prior data (see Discussion section). Thus, the Hiroshima male data alone is used to form the likelihood function.

Bayesian prior data

Priors corresponding to β/α, α_n/α, and c_2 of the LQE model (Eq. 7) are given in Table 3 (see Appendix for details regarding c_2). These priors were formed using dicentric yield parameters α and β, and α_n for lymphocytes exposed to gamma-rays [20] and neutrons [21], respectively. Thus, we have assumed that either translocations

Table 1 Hiroshima CML cases by age, sex and dose in Sv (*O* observed cases, *E* expected background cases based on U.S. incidence rates [17], *tsx* average of the times since exposure for the cases)

Age[a] (years)	0.2 Sv≤D				0.2 Sv<D≤1 Sv				1 Sv<D			
	Males		Females		Males		Females		Males		Females	
	O (E)	tsx	O (E)	tsx	O (E)	tsx	O (E)	tsx	O (E)	tsx	O (E)	tsx
1–10	0 (0.02)		0 (0.01)		0 (0.00)		0 (0.00)		0 (0.00)		0 (0.00)	
10–20	0 (0.15)		0 (0.09)		1 (0.02)	8.4	0 (0.01)		2 (0.00)	9.6	0 (0.00)	
20–30	0 (0.38)		1 (0.28)	13.9	1 (0.05)	13.9	0 (0.05)		1 (0.01)	6.2	0 (0.01)	
30–40	1 (0.71)	22.9	0 (0.64)		2 (0.11)	12.1	0 (0.10)		2 (0.03)	7.3	2 (0.02)	18.1
40–51	1 (1.32)	17.9	0 (1.29)		1 (0.17)	32.9	1 (0.20)	10.9	2 (0.05)	7.3	1 (0.04)	22.9
50–60	3 (1.83)	24.2	1 (2.06)	22.9	2 (0.26)	14.6	4 (0.33)	9.2	0 (0.08)		0 (0.07)	
60–70	3 (2.18)	22.2	4 (2.57)	26.6	1 (0.33)	10.9	4 (0.41)	19.2	1 (0.09)	13.9	1 (0.08)	27.9
>70	4 (3.76)	33.6	4 (4.44)	32.4	0 (0.56)		1 (0.69)	37.8	0 (0.11)		1 (0.09)	27.8
Total	12 (10.4)		10 (11.4)		8 (1.50)		10 (1.79)		8 (0.38)		5 (0.32)	

[a] Age at diagnosis

Table 2 Parameter estimates for the LQE dose-response model of Eq. (7)

Parameter	Point estimate (95% confidence interval)		
	LQE prior	LQE likelihood	LQE posterior
c_1	–13.04 (–13.21, –12.87)	–12.6338 (–14.69, –10.58)	–13.034 (–13.200, –12.867)
k (years^{-1})	0.042 (0.040, 0.045)	0.040 (0.006, 0.073)	0.042 (0.040, 0.045)
k_t (years^{-1})	0.377 (0.014, 0.74)	0.4220 (0.22, 0.63)	0.391 (0.224, 0.559)
c_2	–10.47 (–16.06, –4.81)	–9.5505 (–11.41, –7.69)	–9.673 (–11.227, –8.119)
α_k (Gy^{-1})	0.290 (0.251, 0.329)	0.3044 (–0.034, 0.643)	0.2900 (0.251, 0.329)
β_k (Gy^{-2})	0.068 (0.054, 0.082)	0.0238 (–0.098, 0.146)	0.0673 (0.054, 0.081)

arise as frequently as dicentrics [22] – a topic of debate [23], or, less restrictively, that their dose-response parameters differ by at most a common factor.

Blast crisis of CML can be either lymphoid or myeloid [24]. This suggests that CML target cells are primitive hematopoietic stem cells. Bayesian prior distributions for the LQE cell killing parameters in Eq. (7) should therefore be based on hematopoietic stem cell survival experiments. Since human survival data for primitive hematopoietic stem cells are unavailable, the priors will be estimated from murine data. Specifically, for 1 MeV fission neutrons, α_{kn} has been estimated using the marrow repopulating ability assay [25], and for gamma-rays, α_k and β_k have been estimated using the day-35 cobblestone area forming cell assay [26], see Table 3.

In addition to α and $P(ba|T)$, the prior for c_2 depends on the number of CML target cells in adult males, denoted N, and the waiting time distribution parameter k_t, see Appendix and Eq. (8). A combination of SEER (Surveillance, Epidemiology, and End Results) data [27] and translocation data [28, 29] allows estimation of N [17], and a fit of Eq. (4) to the excess CML risk following treatment of benign gynecological disease (see Fig. 2 of Inskip et al. [5]), yields k_t in Table 3. This k_t estimate compares favorably with the likelihood estimate in Table 2. Thus, males and females appear to have similar treatment-to-CML waiting times. In contrast, Preston et al. [4] suggest that the waiting time constant is seven-fold slower in females than in males.

Table 3 Bayesian prior distributions for the LQE model of Eq. (7) (*S.E.* standard error, *N.R.* not relevant since parameter is fixed)

Parameter	Mean	S.E.[a]	References
c_1	–13.04	0.0854	[17][a]
k	0.042 years^{-1}	0.0013	[17][a]
k_t	0.3770 years^{-1}	0.1850	[5, 17]
c_2	–10.47	2.7987	[5, 17, 13, 32, 20][a]
α_k	0.2900 Gy^{-1}	0.0200	[26]
β_k	0.0680 Gy^{-2}	0.0070	[26]
β/α	0.055/0.0107 Gy^{-1}	N.R.	[20]
α_n/α	0.8/0.0107	N.R.	[20, 21]
α_{kn}	2.3 Gy^{-1}	N.R.	[25]

[a] These results correspond to the “note added in proof” of [17])

Priors for the background parameters c_1 and k were estimated using 1992–1996 SEER data [27] with CML identified by the ICD-O code 9863. The ICD-9 CML code 205.1 was not used here because it includes chronic myelomonocytic leukemia, a disease not associated with BCR-ABL. Since the A-bomb survivor cohort probably contains far fewer cancer treatment survivors than the SEER populations, and since cancer treatments cause CML [5, 6, 30, 31], use of the SEER data was restricted to first cancers and adjustments based on survival times were made so that person-years derive from populations without previous cancers. Fitting an exponential age structure to the resulting SEER males yields priors for c_1 and k given in Table 3.

Table 4 Poisson regression parameter estimates for the linear CML dose-response model of Eq. (5)

Parameter	Point estimate	95% Confidence interval
c_1	–12.7895	(–14.7947, –10.7842)
k	0.0407 years^{-1}	(0.0091, 0.0723)
k_t	0.4039 years^{-1}	(0.2099, 0.5980)
c_2	–8.3886	(–10.1926, –6.5846)

Results

Linear model

Maximizing Eq. (6) using the linear model of Eq. (5) and only the Hiroshima male CML incidence data with kermas less than 4 Gy, the parameter estimates given in Table 4 and the covariance matrix

$$\Sigma = \begin{pmatrix} 0.0098 & 0.0862 \\ 0.0862 & 0.8472 \end{pmatrix} \tag{11}$$

for k_t and c_2 were obtained. The lifetime excess CML risk per person-Sv in the absence of competing risks

$$R = \int_0^\infty t^2 e^{c_2 - k_t t} dt = \frac{2e^{c_2}}{k_t^3} \tag{12}$$

could thus be estimated using bivariate normal random samples of k_t and c_2. This resulted in R=0.0075 Sv^{-1} with 95% confidence interval (0.0039, 0.0158), consistent with R=0.0088 Sv^{-1} obtained using the linear model of Preston et al. (see [18]). Assuming a neutron RBE of 10 as in Preston et al. [4], we let $D=D_\gamma+10D_n$ in Eq. (5) to obtain

$$R_\gamma^* = 0.0075\,\text{Gy}^{-1} \quad \text{and} \quad Q_\gamma^* = 0.0158\,\text{Gy}^{-1} \tag{13}$$

for the mean and upper 95% confidence bound, respectively, of the lifetime CML risk per person-Gy in the limit of low doses of gamma-rays.

LQE likelihood model

The second model considered has the LQE structure of Eq. (7) and six of its nine LQE parameters determined by the Hiroshima male data. The remaining three parameters (β/α, α_n/α and α_{kn}) were fixed to their prior means (Table 3) because the Hiroshima male data is not powerful enough to estimate all five of the LQE dose-response shape parameters. Thus, we optimized the LQE log-likelihood surface (Eq. 6) with three of the dose-response shape parameters fixed, and this resulted in $\{c_1, k, k_t, c_2, \alpha_k, \beta_k\}=\theta \sim \text{MVN}(\mu_l,\Sigma_l)$ where

$$\mu_l = \begin{pmatrix} -12.63 \\ 0.04 \\ 0.42 \\ -9.55 \\ 0.30 \\ 0.02 \end{pmatrix} \text{ and } \Sigma_t = \begin{pmatrix} 1.096 & -0.017 & 0.023 & 0.090 & 0.102 & -0.020 \\ -0.017 & 0.0003 & -0.0003 & -0.001 & -0.002 & 0.0003 \\ 0.023 & -0.0003 & 0.011 & 0.090 & 0.003 & -0.0003 \\ 0.090 & -0.001 & 0.090 & 0.900 & -0.005 & -0.007 \\ 0.102 & -0.002 & 0.003 & -0.005 & 0.030 & -0.005 \\ -0.020 & 0.0003 & -0.0003 & -0.007 & -0.005 & 0.004 \end{pmatrix} \tag{14}$$

as summarized in Table 2. Using bivariate normal random samples of k_t and c_2, the lifetime excess CML risk per person-Gy in the limit of low doses of gamma-rays becomes

$$R_\gamma = \frac{2e^{c_2}}{k_t^3} = 0.0021\,\text{Gy}^{-1} \qquad 95\%\ CI\ (0.0008, 0.0049) \tag{15}$$

and thus, for the LQE likelihood model we have Q^*_γ=0.0049 Gy^{-1}.

LQE bayesian model

The third model uses information contained in both the likelihood and the priors. Specifically, it uses Eqs. (2) and (3) to form the posterior distribution $\theta \sim \text{MVN}(\mu, \Sigma)$ as a combination of the maximum-likelihood distribution $\text{MVN}(\mu_l, \Sigma_l)$ and the prior distribution $\text{MVN}(\mu_p, \Sigma_p)$. Here, μ_l and Σ_l are given by Eq. (14), μ_p is specified by Table 3, and the matrix Σ_p is non-zero only on its main diagonal and in the two positions defined by $\text{cov}(c_1, k)=-1.04\times10^{-4}$ – the main diagonal of Σ_p contains the squares of the standard errors in Table 3. The posterior distributions are summarized in Table 2. Using bivariate normal random samples of k_t and c_2 (Σ not shown)

$$R_\gamma = \frac{2e^{c_2}}{k_t^3} = 0.0022\,\text{Gy}^{-1} \qquad 95\%\ CI\ (0.0011, 0.0042) \tag{16}$$

and hence, for the LQE Bayesian model we have Q^*_γ=0.0042 Gy^{-1}.

Discussion

Our main results are Q^*_γ=0.0158 Gy^{-1} and R_γ=0.0075 Gy^{-1} for the linear model, Q^*_γ=0.0049 Gy^{-1} and R_γ= 0.0021 Gy^{-1} for the LQE likelihood model, and Q^*_γ= 0.0042 Gy^{-1} and R_γ=0.0022 Gy^{-1} for the LQE posterior model. Thus, structure had a strong impact on mean risk estimates and priors had only a slight impact on risk uncertainty.

In view of the independence of the prior (A-bomb exclusive) and likelihood (Hiroshima male) data, the agreement between the mean values of the LQE prior and likelihood parameter estimates (see Table 2) is extremely encouraging. It tells us that the prior and likelihood data sets are consistent with one another, as they should be since presumably they describe the same fundamental process in nature. Meanwhile, the Hiroshima female data, the Nagasaki male data, and the Nagasaki female data, each have inconsistencies with the prior data. We question how representative these other A-bomb data are of normal radiation-induced CML. Furthermore, the value of applying Bayesian methods to inconsistent prior and likelihood data sets is unclear; intuitively, additional inconsistent data tells us that we really know less than we previously thought, but the Bayesian approach tells us that we know more (the Bayesian approach does not take into consideration that we expect and desire consistency between the likelihood and prior data sets). Thus, the Hiroshima male data alone was used to form the likelihood. Although this may seem objectionable, our view is that the exclusion of inconsistent data constitutes yet a third path for transferring prior knowledge to risk estimates, the constraints on structures and parameter values being the other two paths.

The confidence intervals of the parameter estimates in Table 2 tell us that the prior and likelihood data sets are complementary sources of information. Prior data is the main source of information for the background parameters c_1 and k, and the dose-response shape parameters α_k and β_k; it is the complete source of information for the three fixed dose-response shape parameters β/α, α_n/α, and α_{kn}. Meanwhile, the likelihood data contains very little dose-response shape information, but it is the main source of information for the waiting time parameter k_t and the dose-response amplitude parameter c_2. Since it is k_t and c_2 that determine the low-dose risk (see Eq. 12), and since priors contribute little to their estimates, it is not at all surprising that priors had little impact on risk.

In general, estimates of upper bounds are less robust than estimates of mean values. Furthermore, since the LQE log-likelihood surface is nearly flat in several directions, upper bounds generated by this surface are expected to be particularly unstable. Supporting this claim, minor alterations in the optimization algorithm that were inconsequential to all other risk estimates caused up to two-fold increases in Q^*_γ of the LQE likelihood model. We therefore caution that impact of priors on risk uncertainty may be greater than suggested by our results.

The a2 intron of ABL is unusually large at about 300 kb [13]. This provides a large target for BCR-ABL translocations which, after splicing out the intron, produce the same chimeric protein product and thus the same clinical disease. This may explain why CML is somewhat unique in being both prevalent and homogeneous. In this study, prevalence was needed to use the A-bomb data and homogeneity was needed to use endpoint-specific molecular data. Extensions of our methodology to other cancer endpoints that are not both homogeneous and prevalent, may therefore be difficult. Nevertheless, as the mechanisms of carcinogenesis continue to unfold, and as clinical diseases become more and more molecularly defined, the prospects of applying our approach to other cancer endpoints will only improve.

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Appendix

The mean and standard error of $c_2=\log(NP(ba|T)\alpha k_t^3/2)$ were computed using $P(ba|T)=3.4\times10^{-10}$ from [18], $\alpha=0.0107$ (0.007, 0.015) from [20], $N=1.5*1.93\times10^8$ ($1.2*1.3\times10^8$, $2.7*2.9\times10^8$) adjusted for $w(t)$ as in [17], and k_t as in Table 3. Here standard errors define the parenthetic limits for α, and, to crudely compensate for unknown uncertainty in $P(ba|T)$, 95% confidence limits are used for N. Thus, the mean of c_2 was taken to be $\log(0.0107*(.377)^3*1.5*1.93\times10^8*3.4\times10^{-10}/2)=-10.47$, and the standard error of c_2 was taken to be the average difference between -10.47 and the bounds $\log(0.007*(0.192)^3*1.2*1.3\times10^8*3.4\times10^{-10}/2)=-13.54$ and $\log(0.015*(.562)^3*2.7*2.9\times10^8*3.4\times10^{-10}/2)=-7.95$. This average equaled 2.7987.

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