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NONLYMPHATIC LEUKEMIAS AND ADULT EXPOSURE TO DIAGNOSTIC X-RAYS: THE EVIDENCE RECONSIDERED

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Abstract—It has recently been suggested that the relatively small radiation exposures involved in diagnostic X-ray procedures performed on adults may pose a health hazard because they significantly increase the risk of contracting non-lymphatic leukemias (Be77; Be78). The present investigation examines the models advanced in support of this hypothesis and reviews the results of other studies which consider the possibility of leukemia induction by diagnostic X-rays. This examination demonstrates that the contention that a few rads of diagnostic X-ray exposure significantly increases leukemia risk is not supported by any of the available data. There is some indication that relatively high diagnostic X-ray exposures (> 20 rad) are associated with increased leukemia risk. The nature of this association is, however, complicated by the fact that it may be a case of X-rays being caused by chronic illness associated with an undiagnosed leukemia rather than a direct cause effect relationship (St73; St69; Kn71). Further studies are needed to determine the true risks and benefits associated with diagnostic X-rays.

INTRODUCTION

Epidemiologic studies of persons exposed to high doses of radiation such as the Hiroshima/Nagasaki survivors (Bi66; Br62) or persons undergoing radiation therapy (Co57) convincingly demonstrate that such high radiation doses can induce leukemia. More recently, Bertell (Be77; Be78) has suggested that the relatively small doses of radiation involved in diagnostic X-ray procedures performed on adults may considerably increase their risk of contracting nonlymphatic leukemias. This finding, which is particularly alarming because of the prevalence of such procedures, has caused Bertell (Be77; Be78) to call for a drastic and immediate reduction in legal X-ray exposure limits. The purpose of this present discussion is to examine Bertell's assertions, in light of the available data, to better determine the extent to which diagnostic X-rays may increase leukemia risk in adults, and thus pose a threat to human health.

BERTELL'S ANALYSES

Bertell's analyses (Be77; Be78) are based on the incidence of nonlymphatic leukemias in males over 45 yr of age as determined from the data gathered in the Tristate Leukemia Survey (Gr63; Gi72). Bertell's contention is based on two lines of argument. The first (Be77) is that X-rays can be shown to have an "aging" effect that is proportional to the number of rads of X-ray exposure. The hypothesis that an aging effect exists is based on two observations. The first is that the leukemia rate increases with the age of the population at risk. This is well known (Do65). The second is that the nonlymphatic leukemia rate increases with the amount of diagnostic X-ray exposure.

To describe the effect of natural aging,

Bertell proposes the equation

$$X = (1.06)^t \quad (1)$$

where X is the risk of contracting leukemia at age $15 + t$ relative to the risk of developing leukemia at age 15 and t is the number of years lived beyond age 15. Risk at age 15 is taken as 1. This equation appears to fit the data quite well. To describe the effect of diagnostic X-ray procedures Bertell proposes the following equation

$$X = (1.06)^{t+Kr} \quad (2)$$

where X and t are defined as above, r is exposure to diagnostic X-rays in rads and K is a constant which converts rads exposure to years natural aging. The amount of "aging" caused per rad diagnostic X-ray exposure was then evaluated, by taking a value of K such that the mean age/dose adjusted risk of males over 45 yr of age receiving more than 5 rad diagnostic X-ray exposure was equal to the mean age adjusted relative risk of males over 45 yr of age receiving less than 5 rad diagnostic X-ray exposure. This adjustment procedure deserves some consideration. The observed mean relative risk of males over 45 yr of age is given by

$$\bar{X}_0 = R_{45+}/R_{15} \quad (3)$$

where R_{45+} and R_{15} are the leukemia rates for males over 45 yr of age and persons of age 15 respectively. The calculated mean relative risk for males over age 45 taking only age into account is

$$\bar{X}_{cl} = \left[\sum_{i=1}^{N} (1.06)^{t_i}\right] \Big/ N \quad (4)$$

where t_i is the number of years lived beyond age 15 by the ith person and N is the number of males over age 45 in the population of interest. Similarly a calculated mean relative risk that takes both age and X-ray dose into account is given by

$$\bar{X}_{cld} = \left[\sum_{i=1}^{N} (1.06)^{t_i+Kr_i}\right] \Big/ N \quad (5)$$

where r_i is the X-radiation dose in rads of the ith person and K is an arbitrary constant. An adjusted risk (either age or age/dose) is given by

$$\bar{X}_a = \bar{X}_0/\bar{X}_c \quad (6)$$

where $\bar{X}_0$ is the observed relative risk and $\bar{X}_c$ is some calculated relative risk.

The original analysis of the Tri-state Leukemia Survey data which dealt with diagnostic X-ray exposure showed that males exposed to more than 5 rad diagnostic trunk X-ray had a high mean age adjusted risk of leukemia relative to a group of controls (Gi72), and by definition they had higher X-ray exposure. Perusal of equations (3)–(6) should convince the reader that, since the value of $\bar{X}_{cld}$ (equation 5) can be made arbitrarily large by increasing the value of K, it is necessarily true that at some positive value of K the age/dose adjusted mean risk of those exposed to more than 5 rad X-ray will become equal to the age adjusted mean risk of those exposed to less than 5 rad diagnostic X-ray. Offering this necessary relationship as proof of an aging effect of diagnostic X-ray is the logical equivalent of saying that, since habitually driving one's car 100 m.p.h. decreases life expectancy and growing older decreases life expectancy, habitually driving one's car 100 m.p.h. causes premature aging. Though true in an actuarial sense it does not reflect any biological reality. One might suggest that if the age adjusted risk of developing nonlymphatic leukemia increases exponentially with X-ray exposure, as suggested by equation (2), the aging process would provide at least a useful analogy. The possible existence of such a relationship was, however, not considered by Bertell (Be77) and indeed appears doubtful in light of the available data.

Her second argument (Be78) is that the leukemia rate increases gradually with the number of X-ray films per individual that are taken. In support of this she gives four tables based on the Tristate data which apparently show an increase in incidence of leukemia with number of films X-ray exposure. These tables are reproduced in their entirety in

Tables 1–4. The main point of interest is that Bertell's presentation uses overlapping exposure ranges. That is, one cannot determine whether, for example, persons exposed to 26–30 X-ray films show a higher leukemia rate than those exposed to no X-ray films. It is, however, possible to back calculate non-overlapping dose range rates with fair precision. The leukemia rate is given by

$$R = C/P \times 10^5 \tag{7}$$

where C is the number of cases, P is the number of persons at risk and R is the leukemia rate per 100,000 persons. Rearranging (7) we get

$$P = C/R \times 10^5. \tag{8}$$

Now, we know the number of cases and the incidence rate per 100,000 in say the range 0–10. Likewise we know the number of cases and incidence rate in the range 0–15. Taking C_i, P_i and R_i as the number of cases, population size at risk and leukemia rate in the range 11–15, and taking C_t, P_t, R_t and C_k, P_k, R_k to represent similar quantities in the ranges 0–10 and 0–15 films, respectively, we can back calculate our non-overlapping values (C_i, P_i, R_i) as follows:

$$C_i = C_k - C_t \tag{9}$$

$$P_i = ((C_k/R_k) - (C_t/R_t)) \times 10^5 \tag{10}$$

$$R_i = C_i/P_i \times 10^5. \tag{11}$$

Using the values presented for these ranges in Table 1 as a numerical example we have

$$C_i = 65 - 58 = 7 \tag{12}$$

$$P_i = ((65/2.04) - (58/2.99)) \times 10^5 = 271701 \tag{13}$$

$$R_i = 7/271701 \times 10^5 = 2.58. \tag{14}$$

All of the rates shown in Tables 1–4 under

Table 1. Nonlymphatic leukemia rates by X-ray exposure: males 45–64 yr of age. Trunk (chest or abdomen) exposure given as no. of plates

Bertell Calculations* (overlapping Ranges)			Corrected Calculations (Non-overlapping Ranges)		
Exposure Range	Cases	Rate/10^5/yr.	Exposure Range	Cases	Rate/10^5/yr.
0-2	30	1.59	0-2	30	1.59
0-5	40	1.63	3-5	10	1.76
0-10	58	1.99	6-10	18	3.91
0-15	65	2.06	11-15	7	2.58
0-20	74	2.14	16-20	9	3.31
0-25	81	2.26	21-25	7	5.55
0-30	82	2.24	26-30	1	1.30
0-40	84	2.21	31-40	2	1.43
0-50	89	2.32	41-50	5	14.16
0-70	91	2.376	> 50	4	12.37
0-80	92	2.378			
0-120	93	2.404			

*Reproduced from Bertell (1978).

Table 2. Nonlymphatic leukemia rates by X-ray exposure: males 45–64 yr of age. Trunk (chest or abdomen) + 1/4 extremities (dental + limbs) exposure given as no. of plates

Bertell Calculations* (Overlapping Ranges)			Corrected Calculations (Non-overlapping Ranges)		
Exposure Range	Cases	Rate/10^5/yr.	Exposure Range	Cases	Rate/10^5/yr.
0-2	17	1.34	0-2	17	1.34
0-5	34	1.79	3-5	17	2.70
0-10	53	1.97	6-10	19	2.40
0-15	63	2.03	11-15	10	2.42
0-20	69	2.08	16-20	6	2.81
0-25	77	2.20	21-25	8	4.38
0-30	80	2.21	26-30	3	2.50
0-40	84	2.22	31-40	4	2.44
0-50	88	2.23	> 40	9	10.62
0-60	90	2.35			
0-70	91	2.376			
0-80	92	2.378			
0-120	93	2.404			

*Reproduced from Bertell (1978).

Table 3. Nonlymphatic leukemia rates by X-ray exposure: males 65 yr of age or older. Trunk (chest or abdomen) exposures given as no. of plates

Bertell Calculations* (Overlapping Ranges)			Corrected Calculations (Non-overlapping Ranges)		
Exposure Range	Cases	Rate/10^5/yr.	Exposure Range	Cases	Rate/10^5/yr.
0-10	72	6.80	0-10	72	6.80
0-15	87	7.32	11-15	15	10.38
0-20	99	7.55	16-20	12	11.12
0-25	107	8.05	21-25	8	44.61
0-30	108	8.01	26-30	1	5.23
0-40	110	7.85	31-40	2	3.78
0-50	114	8.14	> 40	11	†
0-60	116	8.28			
0-70	118	8.42			
0-80	119	8.49			
0-100	121	8.64			

*Reproduced from Bertell (1978).
†Roundoff error prevents further calculation. See text for further explanation.

Table 4. Nonlymphatic leukemia rates by X-ray exposure: males 65 yr of age or older. Trunk (chest or abdomen) + 1/4 extremities (dental + limbs) exposures given as no. of plates

Bertell Calculations* (Overlapping Ranges)			Corrected Calculations (Non-overlapping Ranges)		
Exposure Range	Cases	Rate/10^5/yr.	Exposure Range	Cases	Rate/10^5/yr.
0-10	67	6.91	0-10	67	6.91
0-15	81	6.83	11-15	14	6.47
0-20	93	7.30	16-20	12	13.63
0-25	102	7.76	21-25	9	22.24
0-30	108	8.01	26-30	6	17.70
0-40	110	7.85	31-40	2	3.78
0-50	114	8.14	> 40	11	†
0-60	116	8.28			
0-70	118	8.42			
0-80	119	8.49			
0-100	120	8.57			
0-110	121	8.64			

*Reproduced from Bertell (1978).

†Roundoff error prevents further calculation. See text for further explanation.

the heading "corrected calculations" were produced in this manner. These rates are not suitable for calculation of dose response functions because of a lack of age standardization [this is also true of the rates given by Bertell (Be78)] and round off error generated by the fact that the rates were reported to only 3 significant digits. Nonetheless it is readily apparent that the general positive association which was claimed to exist is somewhat dubious. In fact, the only striking feature of the data is a very great increase in leukemia rate for males exposed to over 40 X-ray films. This, as will be seen, is a feature similar to the findings of three prior leukemia studies involving diagnostic X-rays.

PREVIOUS STUDIES

The first of the studies considered here is that of Stewart *et al.* (St62). This study involved 483 cases of nonlymphatic leukemia, as well as 496 cases of lymphatic leukemia, 956 cases of "other cancers" and 956 controls. The study concluded that only nonlymphatic leukemias showed an excess rate of diagnostic X-ray exposure. This excess, which was present to a greater degree in males than in females, was attributable to a very marked excess (1.8 × controls) of persons who had had 10 or more trunk X-rays within 5 yr prior to diagnosis of leukemia. The authors originally calculated that some 8% of nonlymphatic leukemias were X-ray induced. Other studies, however, show that preleukemics have an inordinately high risk of developing infectious diseases (St69; Kn71) such as pneumonia which would themselves result in an increased rate of exposure to diagnostic X-rays. This finding cast sufficient doubt on the cause-effect relationship that the senior author subsequently retracted her earlier estimate (St73).

A later study in New Zealand also considered the possibility of a positive relationship between leukemia and diagnostic X-ray procedures (Gu64). This study, which in-

cluded 355 cases of acute leukemia, 78 cases of chronic granulocytic (myeloid) leukemia, 157 cases of chronic lymphocytic leukemia, and 712 controls matched for age and sex, showed a positive relationship between X-rays and chronic granulocytic leukemia. However, all of the excess exposure was attributable to a total of 4 individuals who had received more than 20 R skin dose during a ten year period prior to diagnosis. Because the vast majority of leukemia cases showed no excess X-ray exposure the authors concluded that, at most, 1% of the leukemias were induced by exposure to diagnostic X-ray.

The final study to be considered is the original analysis of the Tristate Leukemia Survey data (Gi72). This study, which included 1370 controls and 1414 cases of leukemia, found that diagnostic X-ray exposure was associated with significantly elevated age adjusted relative risks of chronic myeloid and acute myeloid leukemias in males. No significantly elevated risks were found for females or for any other leukemia types. Here too, the bulk of the X-ray exposure reported was within a 10-yr period prior to diagnosis. The relevant male data are reproduced in Tables 5 and 6. There appears to be a generally increasing risk of leukemia with X-ray exposure, especially in the case of trunk X-rays. The data however are presented in overlapping intervals. Thus, individuals who were exposed to more than 41 trunk X-rays are included in all other categories (i.e. an individual who has had more than 41 trunk X-rays has also had more than 11 trunk and more than 41 total X-ray exposures). Such individuals have a very greatly increased age standardized risk of contracting leukemia, which tends to inflate relative risk statistics in the other dose categories. Looking at the relative risks of contracting acute myeloid leukemia in the case of trunk X-rays for example, one finds that the relative risk of those exposed to more than 40 trunk X-rays (41+) is 5.06, while those exposed to more than 20 (21+) trunk X-rays have a risk of 1.88. Considerations of simple arithmetic dictate that, since those in the 41+ category have a risk of 5.06 and those in the 21+ category, have a risk of 1.88, those in the 21–41 dose range must have a risk of somewhat less than 1.88.

Because of the age standardization procedure used in the original analysis (Gi72; Sh66) precise calculation of relative risks for non-overlapping dose ranges would require access to the original raw data. If, however, one takes X_i as the relative risk for a given overlapping dose range Y_i as the number of cases in the dose range, and Z_i as the number of controls an ordinary least squares regression of X_i against Y_i/Z_i gives a rather good fit (see Tables 5 and 6).

This fit, moreover, is much better than that obtained from calculating unstandardized relative risk values.

Since different case populations, and thus different age standardizations, are involved in each table, separate regressions given in Tables 5 and 6, were calculated for each leukemia type/radiation site combination. Relative risks for non overlapping dose categories are obtained by taking the difference between the cumulative case or control values (i.e. [No. of cases 21–40] = [No. of cases 21+] − [No. of cases 41+]), taking their quotient, and applying this in the appropriate regression equation. Though no defense is offered for this *ad hoc* procedure, it does give some idea of the corresponding properly calculated values.

Perusal of the predicted age standardized relative risk values in Tables 5 and 6 suggests that the main source of excess risk is indeed those men exposed to more than 41 trunk X-rays. This is especially true since the "all sites" sub-category includes the "trunk" subcategory, but is still generally lower (i.e. if "all sites" shows a lower risk than "trunk", then those persons in "all sites" but not "trunk" must have a still lower relative risk). Of further interest is the apparent absence of any general upward trend with dose. This parallels the result developed from Bertell's (Be78) leukemia rate calculations derived from the same data base. Further, in the New Zealand study (Gu64) greatly increased risk of chronic granulocytic (chronic myeloid) leukemia was associated with X-ray doses of more than 2 rad. A fair rule of thumb is that

Table 5. Acute myeloid leukemia relative risks by number of plates—males. Non-overlapping values in parentheses

No. of Plates	Number of Persons Exposed		Relative Risk
All sites	Cases	Controls	
11 + (11-20)	59(26)	185(97)	[1.14]1.13(.93)*
21 + (21-40)	33(17)	88(62)	[1.36]1.37(.95)*
41 + (41+)	16(16)	26(26)	[2.34]2.34(2.34)*
			X = 0.162 + 4.07 (Y/Z)
Trunk			
11 + (11-20)	33(16)	82(51)	[1.42]1.36(1.19)*
21 + (21-40)	17(8)	31(26)	[1.81]1.88(1.18)*
41 + (41+)	9(9)	5(5)	[5.07]5.06(5.07)*
			X = 0.377 + 2.61 (Y/Z)

*The standardization procedure employed by the authors precludes exact back calculation of non overlapping relative risks. Overlapping range predicted risk values are shown in brackets.

Table 6. Chronic myeloid leukemia relative risks by number of plates—males. Non-overlapping values in parentheses

No. of Plates	Number of Persons Exposed		Relative Risk
All Sites	Cases	Controls	
11 + (11-15)	56(15)	185(59)	[1.60]1.60(1.36)*
16 + (16-20)	41(10)	126(38)	[1.71]1.73(1.41)*
21 + (21-40)	31(16)	88(62)	[1.85]1.83(1.38)*
41 + (41+)	15(15)	26(26)	[2.96]2.96(2.96)*
			X = 0.103 + 4.95 (Y/Z)
Trunk			
11 + (11-15)	39(11)	82(28)	[2.33]2.22(2.10)*
16 + (16-20)	28(6)	54(23)	[2.45]2.33(1.73)*
21 + (21-40)	22(11)	31(26)	[2.99]3.26(2.19)*
41 + (41+)	11(11)	5(5)	[7.17]7.14(7.17)*
			X = 0.998 + 2.81 (Y/Z)

*The standardization procedure employed by the authors precludes exact back calculation of non overlapping relative risks. Overlapping range predicted risk values are shown in brackets.

1 trunk X-ray = 0.5 rad skin dose (US66). Thus, the two studies are in substantial agreement.

DISCUSSION

The data surveyed here do not indicate the exponential increase in leukemia risk with increased X-ray exposure suggested by Bertell (Br77; Be78). Rather they suggest that, while a high relative risk of contracting non-lymphatic leukemia is associated with having an inordinately large number of diagnostic X-ray procedures within a 5–10-yr period, somewhat lower doses (< 40 trunk X-rays) result in little increased risk.

Bertell's aging model, illustrated in Fig. 1, supports the conclusion that there is little or no excess risk of leukemia associated with

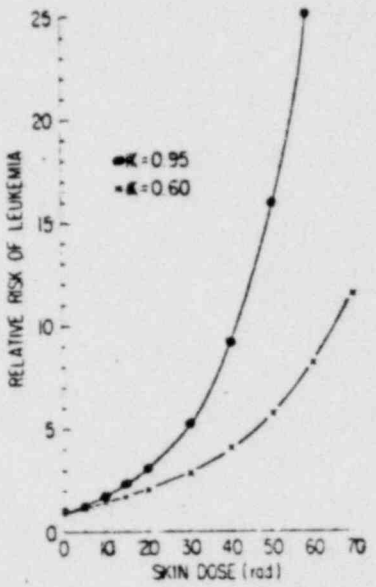

FIG. 1. Bertell's (Be77) X-ray dose-leukemia relative risk models (equation 2) for values of K calculated for those with 5 + rad X-ray exposure ($K = 0.60$) and 10 + rad X-ray exposure ($K = 0.95$). These quite different functions were proposed by Bertell (Be77) as alternative descriptions of the same data set.

moderate numbers of diagnostic X-ray exposures. As expected from the exponential form of the model (equation 2), risk rises very rapidly at high dose. This accounts for the fact that it is very successful in equalizing the high risk of those exposed to say 30 rad [≈ 60 films (US66)]. However, the value of K, which converts rads exposure to years natural aging (equation 5), required to reduce the average age/dose adjusted risk to one is 0.95 for those exposed to 10 or more rads (10 +) but only 0.60 if those exposed to 5 or more rads (5 +) (which includes those exposed to 10 + rad) are taken as the affected group (Be77). Figure 1 shows that these are quite different functions.

Further, this discrepancy demonstrates that, for the 5 + rad exposure group, the calculated value of K (0.60) reduces the age/dose adjusted risk of those persons exposed to from 5 to 10 (5–10) rad to somewhat less than 1 and reduces the age/dose adjusted risk of those persons exposed to 10 + rad to somewhat more than 1. This is necessarily the case because we know that when only the 10 + rad range is considered one must assume a higher value of K (0.95) to get an average age/dose adjusted relative risk of 1. Thus, for $K = 0.60$, the average age/dose adjusted relative risk of the 10 + rad exposure group must be greater than 1 (equations 5 and 6). Now, we also know that the overall average age/dose adjusted risk of the 5 + exposure group, which is in turn an average of the age/dose adjusted risks of the 5–10 and 10 + rad exposure groups, equals 1 for $K = 0.60$. Since it is impossible to have two numbers greater than 1 whose average equals 1, it follows that the age/dose adjusted risk of the 5–10 rad exposure group must be less than 1 when $K = 0.60$.

Returning to Fig. 1 we see that for $K = 0.60$ the 5–10 rad exposure group would be expected to have age adjusted relative risks of from 1.2 to 1.4 in the absence of dose adjustment. However, dose adjustment results in relative risks of less than 1 for this group. Therefore, the true age adjusted relative risk of the group is even smaller (i.e. approx. 1) which supports the idea that the apparent excess risk of nonlymphatic leukemia associated with diagnostic X-ray procedures is primarily attributable to a relatively small number of individuals who had an inordinately large number of X-rays.

Nonetheless, one might assume that Bertell's model has some merit for high X-ray dose. In this regard a study of patients receiving radiation treatments for ankylosing spondylitis (Cl67) is of interest. These individuals received trunk X-ray exposures of several hundred rad. Bertell's model would, taking equation (2) with $K = 0.60$, predict that, minimally, 1 out of every 20 persons so treated would develop nonlymphatic leukemia. The observed value was approx. 1 in 270 (Mi70). Thus, the model does not fit well for high doses either. Likewise, it cannot be said to describe the situation in females since the original analysis of the Tristate data (Gi72) found no significant excess risk associated with diagnostic X-rays in this group.

The remaining question then is whether or not the greatly increased leukemia risks

shown by at least some individuals exposed to high doses of diagnostic X-rays indicates the hypothesized cause effect relationship. It is a truism that diagnostic X-ray procedures are generally performed on persons with some medical complaint and, given that the critical dose seems to be on the order of 40 or more trunk exposures within a 10-yr period, the medical complaint in question must be chronic. It may be that a preleukemic state, which would in any case result in leukemia, also results in chronic infections that cause symptoms requiring diagnostic X-rays (St73). In this scenario leukemia causes X-rays rather than vice versa. On the other hand, it may be that chronic disease causes X-rays which in turn cause leukemia. These alternatives would not seem to be resolvable in the light of present data.

Further, even if it could definitely be shown that a large number of diagnostic X-ray exposures can cause leukemia, the desirability of taking steps to reduce exposure to diagnostic X-rays remains problematical. It is true that the large numbers of diagnostic exposures per individual which are associated with definite increases in the risk of contracting leukemia might be eliminated by increased restrictions on the use of diagnostic X-rays. However, as noted above, such large numbers of diagnostic X-ray exposures would seem to imply a chronic disease state affecting a small number of persons. The risk/benefit ratio involved in such a situation is uncertain in that diagnostic X-rays also convey information vital to the treatment of disease. Thus, if steps were taken to further limit diagnostic X-ray exposures, it might be that any reduction in the death rate resulting from decreased leukemia risk, would be more than offset by deaths resulting from inappropriate diagnosis or treatment of other diseases. Again, the data which would support or refute the preceding conjecture are yet to be gathered.

In summary then, the available data do not support the idea that leukemia risk increases gradually with the number of X-ray exposures. Likewise there seems little reason to suggest that X-ray exposures cause premature aging. What the data do suggest is that a large number of diagnostic X-ray procedures (> 40) within a 10-yr period is associated with a significantly elevated risk of nonlymphatic leukemia. However, it is not clear that this association necessarily indicates that diagnostic X-rays cause leukemia. Finally, even if such a cause-effect relationship were clearly demonstrated, there is insufficient information regarding the overall risk-benefit picture to justify new regulatory decisions regarding diagnostic X-rays. Further research is needed to determine whether a problem indeed exists, and if it does exist, what steps should be taken to correct it.

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