Infant leukaemia after *in utero* exposure to radiation from Chernobyl

E. Petridou*†, D. Trichopoulos*, N. Dessypris†, V. Flytzani†, S. Haidas‡, M. Kalmanti§, D. Koliouskas||, H. Kosmidis¶, F. Piperopoulou# & F. Tzortzatou☆

* Harvard Center for Cancer Prevention, 677 Huntington Avenue, HSPH3-901 Boston, Massachusetts 02115, USA
† Department of Hygiene and Epidemiology, Athens University Medical School, Athens 115 27, Greece
‡ Department of Paediatric Haematology–Oncology, Agia Sophia Children's Hospital, Athens 115 27, Greece
§ Department of Paediatric Haematology–Oncology, University Hospital, Heraklion 715 00, Greece
|| Department of Paediatric Haematology–Oncology, Hippokrateion Hospital, Thessaloniki 546 42, Greece
¶ Department of Paediatric Haematology–Oncology, Aglaia Kyriakou Children's Hospital, Athens 115 27, Greece
# Department of Paediatric Haematology–Oncology, Ahepa Hospital, Thessaloniki 546 36, Greece
☆ Oncology Unit, First Department of Paediatrics, University of Athens, Agia Sophia Children's Hospital, Athens 115 27, Greece

THERE has been no documented increase in childhood leukaemia following the Chernobyl accident. However, different forms of childhood leukaemia may not be equally susceptible to radiation carcinogenesis. Infant leukaemia is a distinct form associated with a specific genetic abnormality. Outside the former Soviet Union, contamination resulting from the Chernobyl accident has been highest in Greece and Austria and high also in the Scandinavian countries[1–4]. All childhood leukaemia cases diagnosed throughout Greece since 1 January 1980 have been recorded. Here we report that infants exposed *in utero* to ionizing radiation from the Chernobyl accident had 2.6 times the incidence of leukaemia compared to unexposed children (95% confidence interval, 1.4 to 5.1; $P \approx 0.003$), and those born to mothers residing in regions with high radioactive fallout were at higher risk of developing infant leukaemia. No significant difference in leukaemia incidence was found among children aged 12 to 47 months. Preconceptional irradiation had no demonstrable effect on leukaemia risk at any of the studied age groups.

The Chernobyl accident, which occurred on 26 April 1986, has led to widespread radionuclide contamination. In Belarus and Ukraine an increase in the incidence of thyroid cancer has been reported[5,6], but no increase in childhood leukaemia has been documented so far either in these[6,7] or any other European country[2,8,9], including Greece[4]. However, different forms of childhood leukaemia may differ in susceptibility to radiation carcinogenesis. Evidence has emerged that infant leukaemia is a distinct entity associated, in more than two-thirds of cases, with a specific genetic abnormality in the 11q23 chromosome band[10,11]. Moreover, the relevant exposure period for infant leukaemia is likely to be during the intrauterine life, when susceptibility to the carcinogenic effects of ionizing radiation is assumed to be particularly high[12,13].

All childhood leukaemia cases diagnosed throughout Greece from 1980 have been recorded by a national network of childhood oncologists[4,14]. At the time of our analysis, the records were complete to 31 December 1994. For every leukaemia case, gender, date of birth, date of diagnosis, type of leukaemia, and maternal residence are available. Fallout radiation from the Chernobyl accident has been measured by other investigators in more than 1,000 samples of surface soil from 42 of the 52 administrative divisions of Greece; the remaining 10 administrative divisions were exposed to a lesser extent for meteorological reasons (measurements summarized in ref. 4). Fallout radioactivity from Chernobyl was estimated by taking the arithmetic mean of the measurements in every division and is expressed in Bq kg^{-1} of ^{137}Cs in surface soil. The administrative divisions were then combined into 3 categories, with fallout radioactivity 1,000 or more Bq kg^{-1}; 999–100 Bq kg^{-1}; and below 100 Bq kg^{-1}.

Exposure of the Greek population to Chernobyl radiation started soon after the accident and was notable for about a year; average exposure has been estimated at about 2 mSv (ref. 1). Therefore, children born during the second half of 1986, the first half of 1987, and most of those born during the second half of 1987 were considered as exposed to Chernobyl irradiation *in utero*, whereas those born from 1 January 1980 to 31 December 1985 (6 years) and those born from 1 January 1988 to 31 December 1990 (3 years) were considered unexposed (Table 1). We have not classified children born during the first half of 1986, because those born before the end of April were clearly unexposed, whereas those born in May and June were only exposed during the last pregnancy months, when the risk of radiation-induced carcinogenesis is unknown.

Our analysis was based on estimation of age-adjusted leukaemia rates (as in ref. 15), calculated until the end of the fourth year of life, because data beyond that age were not available for the children born during 1990. The results are summarized in Table 1. Comparison of leukaemia rates between the two unexposed birth cohorts (born before 31/12/85 or after 1/1/88), provides no indication of any difference in incidence (for infants, $X^2 = 0.39$, $P = 0.53$; for children 12 to 47 months, $X^2 = 0.02$, $P = 0.90$). There is also no difference in the incidence of leukaemia at ages from 12 to 47 months between children exposed and unexposed *in utero* to Chernobyl radiation ($P \approx 0.56$). In contrast, *in utero*-exposed infants have 2.6 times the incidence of leukaemia compared to nonexposed infants ($P \approx 0.003$). Changing the operational definition of exposure by 6 months had no discernible effect.

The incidence of infant leukaemia among unexposed children was 27.9 per 10^6 person-years (95% confidence interval, CI, 18.9–39.5). Among children exposed *in utero* the corresponding incidence rates were 32.2 (CI 1.6–159.8) for those born in low radioactivity administrative divisions (only 1 case); 71.4 (CI 31.2–141.3) for those born in intermediate radioactivity divisions (7 cases); and 116.6 (CI 37.0 to 281.3) for those born in high radioactivity divisions (4 cases). The latter two incidence rates are significantly higher than that among children who were unexposed *in utero* (two tailed P values 0.02 and 0.004, respectively; two tailed P for trend 0.0005).

Several molecular rearrangements in 11q 23 (the MLL gene) are far more common in infant leukaemia than in leukaemia of older children or adults[16–19], and they are likely to originate from mutations during pregnancy[20]. Ionizing radiation is an established cause of acute lymphoblastic leukaemia and the intrauterine life represents a period of increased susceptibility[12,21]. As infant leukaemia is likely to have prenatal origin of non-constitutive nature[19,20,22] ionizing radiation *in utero* becomes a highly plausible cause of this disease.

Previous studies have not specifically examined infant leukaemia, but in a Swedish study[23] three infants that were *in utero* at the time of the accident developed leukaemia. Studies evaluating the effect on childhood cancer of prenatal exposure to diagnostic X-ray examinations did not indicate that infant leukaemia is differentially susceptible to radiation carcinogenesis[21,24,25]. However, prenatal diagnostic X-rays are almost always undertaken during the last months of pregnancy and in discrete sessions. It is possible that the early pregnancy period, the time of exposure to radiation in our study, represents a high-risk stage or contains a window of increased susceptibility. Data concerning dated X-rays in pregnancy at different stages of intrauterine development are remarkably consistent with this view[25], although they do not specifically indicate that infant leukaemia is differentially susceptible to early fetal irradiation.

Our study also provides evidence against the hypothesis[26] that paternal exposure to ionizing radiation increases the risk of either

TABLE 1 Children of specified birth cohorts who developed leukaemia in Greece

Birth cohort	Liveborn	Characterization	Number of cases grouped by age at diagnosis (months)*				
			−5	6–11	12–23	24–35	36–47
1/1/80 to 31/12/85	801,175	unexposed	8	14	55	64	68
1/7/86 to 31/12/87	163,337	exposed	4	8	8	19	16
1/1/88 to 31/12/90	311,391	unexposed	3	6	17	36	26
Incidence rate (per 10^6 person-years)		exposed	49.0	98.0	49.0	116.3	98.0
		unexposed	19.8	36.0	64.7	89.9	84.5
Rate ratio			2.6			1.1	
95% confidence interval			1.4–5.1			0.8–1.5	
P (2-tailed)			$P \approx 0.003$			$P \approx 0.56$	

* Follow-up is 0.5 year in the first 2 columns, 1 year in the last 3.

infant leukaemia or leukaemia at ages 12 to 47 months, and supports the counter-arguments advanced in this context[27,28]. Thus, leukaemia rates were almost identical among children born between 1/1/80 and 31/12/85 and those born between 1/1/88 and 31/12/90.

In conclusion, we provide evidence that infant leukaemia may be caused by very low level intrauterine exposure to ionizing radiation; that fallout from the Chernobyl explosion may have increased the incidence of infant leukaemia among Greek children exposed *in utero*, perhaps by as much as 2 to 3 fold; and that low-level preconceptional radiation has no demonstrable effect on leukaemia risk. □

Received 4 April; accepted 3 June 1996.

1. Papastephanou, C., Manolopoulou, M. & Charalambous, S. J. *Envir. Radioact.* **7,** 49–64 (1988).
2. Auvinen, A. *et al. Br. med. J.* **309,** 151–154 (1994).
3. International Chernobyl Project *Technical Rep.* (IAEA report number: ISBN 92-0-129191-4, Vienna, 1992)
4. Petridou, E. *et al. Scand. J. Soc. Med.* **22,** 127–131 (1994).
5. Abelin, T. *et al. Soz. Präventivmed.* **39,** 189–197 (1994).
6. Kuchuk, A. A. *Tox. Lett.* **72,** 213–217 (1994).
7. Vanchieri, C. *J. natn. Cancer Inst.* **84,** 1616 (1992).
8. Hjalmars, U., Kulldorff, M. & Gustafsson, G. *Br. med. J.* **309,** 154–157 (1994).
9. Parkin, D. M. *et al. Euro. J. Cancer* **29,** A87–95 (1992).
10. Cimino, G. *Blood* **82,** 544–546 (1993).
11. Cortès, J. E. & Kantarjian, H. M. *Cancer* **76,** 2393–2416 (1995).
12. U.S. National Academy of Sciences Committee on Biological Effects of Ionizing Radiation. *BEIR-V Rep.* (U.S. N.A.S. Washington, 1990).
13. Hoshimoto, Y., Kato, H. & Schull, W. J. *RERF Technical Report* 4–88 (Radiation Effects Research Foundation, Hiroshima, 1988).
14. Petridou, E. *et al. Br. J. Cancer* (in the press).
15. Rothman, K. J. & Boice, J. D. Jr Publication 79–1649 (National Institutes of Health, 1979).
16. Ross, J. A., Davies, S. M., Potter, J. D. & Robison, L. L. *Epidemiol. Rev.* **16,** 243–271 (1994).
17. Clearly, M. L. *New Engl. J. Med.* **329,** 958–960 (1993).
18. Canaani, E., Nowell, P. C. & Croce, C. M. *Adv. Cancer Res.* **66,** 213–234 (1995).
19. Pui, C.-H., Kane, J. R. & Crist, W. M. *Leukemia* **9,** 762–769 (1995).
20. Ford, A. M. *et al. Nature* **363,** 358–360 (1993).
21. Monson, R. R. & MacMahon, B. in *Radiation Carcinogenesis: Epidemiology and Biological Significance* (eds Boice, J. D. & Fraumeni, J. F. Jr) 97–105 (Raven, New York, 1984).
22. MacMahon, B. & Levy, M. A. *New Engl. J. Med.* **270,** 1082–1085 (1964).
23. Ericson, A. & Kallen, B. *Envir. Res.* **67,** 149–159 (1994).
24. Bithell, J. F. & Stewart, A. M. *Brit. J. Cancer* **31,** 271–287 (1975).
25. Mole, R. H. *Brit. J. Cancer* **62,** 152–168 (1990).
26. Gardner, M. J. *et al. Br. med. J.* **300,** 423–429 (1990).
27. MacMahon, B. *Cancer Causes Contr.* **3,** 283–288 (1992).
28. Doll, R., Evens, H. J. & Darby, S. C. *Nature* **367,** 678–680 (1994).

ACKNOWLEDGEMENTS. We thank B. MacMahon for his constructive presubmission review of this paper. This study was supported in Greece by the 'Europe Against Cancer' programme of the European Union, and in Boston by a grant to Harvard University from G. S. Livanos.

CORRESPONDENCE and requests for materials should be addressed to D.T. (e-mail: epetrid@atlas.uoa.ariadne-t.gr).

Correct *Hox* gene expression established independently of position in *Caenorhabditis elegans*

Deborah Cowing & Cynthia Kenyon

Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, California 94143-0554, USA

THE *Hox* genes are expressed in a conserved sequence of spatial domains along the anteroposterior (A/P) body axes of many organisms[1]. In *Drosophila*, position-specific signals located along the A/P axis establish the pattern of *Hox* gene expression[2–4]. In the nematode *Caenorhabditis elegans*, it is not known how the pattern of *Hox* gene expression is established. *C. elegans* uses lineal control mechanisms and local cell interactions to specify early blastomere identities[5,6]. However, many cells expressing the same *Hox* gene are unrelated by lineage, suggesting that, as in *Drosophila*, domains of *Hox* gene expression may be defined by cell-extrinsic A/P positional signals. To test this, we have investigated whether posterior mesodermal and ectodermal cells will express their normal posterior *Hox* gene when they are mispositioned in the anterior. Surprisingly, we find that correct *Hox* gene expression does not depend on cell position, but is highly correlated with cell lineage. Thus, although the most striking feature of *Hox* gene expression is its positional specificity, in *C. elegans* the pattern is achieved, at least in part, by a lineage-specific control system that operates without regard to A/P position.

In *C. elegans*, homologues of the *Drosophila* genes *Sex combs reduced*, *Antennapedia* and *Abdominal-B* are expressed in consecutive domains along the A/P body axis[7,8]. Cells that express a particular *Hox* gene have only position in common; they are unrelated by cell type or lineal origin (Fig. 1). To begin to understand how the *Hox* gene expression pattern is established, we have mispositioned cells that are normally located in the posterior body region, and have investigated whether they would still express the posterior-specific *Hox* gene, the *Antennapedia* homologue *mab-5*.

A mesodermal cell called M is unusual in that it migrates a long distance from its anterior origin into the posterior body region[9] (Fig. 2*a*). As it reaches the posterior, it begins to express *mab-5* (Fig. 2*c–e*). In contrast, cells closely related to M by lineage remain in the anterior and do not express *mab-5* (ref. 9, and data not shown). Thus it seemed likely that M switches on *mab-5* expression because it encounters a signal located in the posterior body region. To change the position of this cell, we blocked its migration by using cytochalasin D, which blocks actin polymerization, or colchicine, which depolymerizes microtubules[10,11]. If M

which the free energy is truly minimized.

Under appropriate conditions, qualitatively similar and equally rugged landscapes characterize the penetration of magnetic flux into type-II superconductors[1], the packing of granular materials[2], the folding of proteins[3] and the assembly of atomic clusters into amorphous structures[4]. Even the so-called travelling salesman problem (see figure) is not merely of academic interest, as it resembles problems encountered in the efficient routing of telephone connections, and in the placement of elements on an integrated circuit.

What makes these systems alike? Are there specific microscopic features, common to each, which underlie the existence of highly convoluted landscapes? This question seems to have been largely answered already, by developments in the theory of spin glasses[5]. A spin glass is a disordered material, the basic dynamics of which arise from the interactions of many magnetic moments. An example is a dilute solid solution of magnetic manganese atoms in copper. The random distribution of the manganese atoms causes the interactions between different pairs of atoms to be dissimilar. Some pairs have minimum interaction energy when parallel, others when antiparallel. As a result, the system struggles to find a unique configuration of lowest energy, and instead wanders between a large number of different but statistically similar 'near ground state' configurations. The inability of the system to find a unique ground state is referred to as 'frustration'.

So — frustrated dynamics lead to rugged landscapes. The next goal is to identify generic qualitative and quantitative features which might be exhibited by all frustrated systems.

On the theoretical front, one approach is to study simple mathematical models of rugged landscapes which are motivated by archetypal systems, and constructed on the basis of very general assumptions. In this way it is possible to derive, for 'typical' landscapes, the number of local minima and the expected time required for the system to evolve from its initial configuration to the nearest local minimum[6,7], where its evolution is arrested (A. Perelson and C. Macken, Los Alamos National Lab.). These results account well for the temporal evolution of antibodies during immune system response.

Studies of model atomic clusters[4] (R. S. Berry, Univ. Chicago) suggest that energy landscapes can be usefully classified according to their topographies. Glass-forming materials appear to have many local minima (disordered metastable states) of roughly equal energy. On the other hand, in simple proteins and materials that form crystals, the landscapes are characterized by frequent large differences in energy between 'neighbouring' local minima. Whereas the former topography leads to the amorphous structures seen in glasses, the latter produces directed evolution towards the more 'focused' structures of crystals, and the specific compact folded states of proteins. In fact, the landscapes associated with proteins often appear to have funnel-like, self-similar structures (P. G. Wolynes, Univ. Illinois, and J. N. Onuchic, Univ. California, San Diego) which help to guide the dynamical evolution rapidly towards the correct folded state.

It remains to be seen whether further work along these lines will lead to the development of a general theory of frustrated systems. But just as Feynman diagrams, developed originally in quantum electrodynamics, subsequently became essential tools in other fields such as statistical mechanics and fluid turbulence, so has the notion of the rugged landscape become a standard working image for physicists talking about atomic clusters, as well as for biologists speaking of protein folding. □

Mark Buchanan is an assistant editor at Nature.

1. Fisher, M. P. A. *Phys. Rev. Lett.* **62**, 1415–1418 (1989).
2. Liu, C.-H. *et al. Science* **269**, 513–515 (1995).
3. Wolynes, P. G., Onuchic, J. N. & Thirumalai, D. *Science* **267**, 1619–1620 (1995).
4. Ball, K. D. *et al. Science* **271**, 963–966 (1996).
5. Binder, K. & Young, A. P. *Rev. Mod. Phys.* **58**, 801–976 (1986).
6. Perelson, A. S. & Macken, C. A. *Proc. Natl Acad. Sci. USA* **92**, 9657–9661 (1995).
7. Kauffman, S. A. *Origins of Order, Self Organization and Selection in Evolution* (Oxford Univ. Press, 1993).

EPIDEMIOLOGY

Links in childhood leukaemia

Sarah C. Darby and Eve Roman

LEUKAEMIA is the major malignancy of childhood in developed countries, accounting for around a third of all cancers diagnosed in children. Its incidence has a distinctive shape, with a marked peak at ages 2–3 followed by a steady decline (see figure overleaf). This pattern is consistent with the notion that exposures before birth and early in life may be important determinants of disease. For most cases the cause of the disease is uncertain. But recent scientific work has given rise to several hypotheses, and a paper by Petridou *et al.* (page 352 of this issue[1]) points to another.

Genetic abnormalities, such as Down's syndrome, and also chemotherapy and radiotherapy, are well established causes of leukaemia. No more than 5% of leukaemias occurring in childhood can, however, be ascribed to such causes. In addition, there is considerable evidence from case–control studies, where the exposure of people with and without disease is compared, that diagnostic X-ray of the mother's abdomen during pregnancy can cause leukaemia; by contrast, cohort studies, where the disease rate in exposed and nonexposed individuals is compared, have failed to confirm this association, perhaps because of their low statistical power[2]. Nowadays, it seems unlikely that *in utero* X-ray exposure could account for more than 1% of childhood leukaemias, because pregnant women are X-rayed less frequently and doses are much lower than in the past.

As well as the causes listed above, for which risk estimates can be quantified directly, *in utero* and postnatal exposures to an ever-growing list of biological, physical and chemical agents have been suggested as risk factors for childhood leukaemia; among the suspects are electromagnetic radiation, hydrocarbons, pesticides, vitamin K and a variety of infections. Indeed, the epidemiological evidence that infectious agents are involved is considerable[3,4], but as yet no definite, or even candidate, agents have been identified.

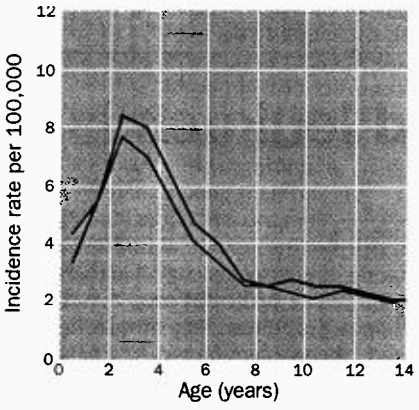
It seems reasonable also to postulate that natural background radiation may cause a fraction of childhood leukaemias. The proportion that can be attributed to such radiation cannot, however, be estimated directly, because most children are exposed at very similar dose rates. Indirect estimates, based on extrapolation from data on survivors of the Japanese bombings, who were exposed at much higher doses and dose rates, indicate that around 7% of childhood leukaemias could be caused by postnatal exposure to background radiation, and risk estimates from studies of the effects of X-rays in pregnancy indicate that perhaps another 7% might be due to *in utero* exposure[5–7].

Occasionally, following events such as the accident at the Chernobyl nuclear plant in 1986 and the atmospheric nuclear weapons tests in the early 1960s, some populations receive much more low-dose-rate radiation than others. Until now, such studies have not reported evidence to contradict the estimates based on extrapolations from exposure to medical or atomic-weapon sources of radiation[8,9]. But none has specifically examined infant leukaemia categorized by *in utero* exposure.

This is what Petridou *et al.* have done, focusing on the incidence of infant leukaemias in Greece following the

accident at Chernobyl. Because of local weather conditions at the time, northern Greece experienced some of the highest levels of contamination from the accident outside the former Soviet Union. Estimates of the resulting average population dose during the following year are of the order of 1 millisievert (refs 10, 11), similar to that received annually from natural background radiation. If the risk estimates based on extrapolation are wrong, and a substantial proportion of infant leukaemias are caused by natural background radiation, then one would expect the Chernobyl exposure to cause an approximate doubling of risk in Greece.

That is indeed what is reported by



Incidence of childhood leukaemia in England and Wales, showing the peak at ages 2–3 and a steady decline thereafter (purple, male; red, female). In Europe, about 1 in 2,000 children develop leukaemia before their fifteenth birthday, but the cause of the vast majority of cases is unknown. (Source: Leukaemia Research Fund, University of Leeds.)

Petridou *et al.* — infants aged up to 1 year old who were exposed *in utero* to Chernobyl irradiation have a 2.6-fold increase in leukaemia compared with children born earlier or later. In addition, among Greek children exposed *in utero* to Chernobyl radiation, those born to mothers living in high radioactivity areas had higher rates than children born to mothers living in low radioactivity areas.

It is important, however, not to assume that the reported association is causal. First, there is no *a priori* reason to suppose that leukaemia in infants is more readily induced by *in utero* radiation than leukaemias in older children, and no increase was observed in older Greek children exposed *in utero* to Chernobyl radiation. Second, although there is a gradient in incidence of childhood leukaemia from low through medium to high radioactivity areas, the question arises as to whether those living in high radioactivity areas would actually have received the highest doses, since the majority of the Chernobyl exposure came from ingestion of contaminated foodstuff; moreover, no account is taken of the fact that exposures from Chernobyl lasted several years, so that children born after the period defined as 'exposed' would also have received some Chernobyl exposure.

Third, the results depend on only 12 cases of infant leukaemia occurring in children who were *in utero* during the high exposure period, of whom only four were born to mothers living in the high radioactivity areas at the time of diagnosis. Finally, cytogenetic techniques suggest that infant leukaemia constitutes a distinct subset of childhood leukaemias, with approximately 80% of cases having an abnormality at position 23 on the long arm of chromosome 11 (11q23)[12]. But no diagnostic data are given on the type of leukaemia, or on how many children actually had the defect at 11q23.

It is to be hoped that Petridou *et al.* will be able to present at least some of this additional information elsewhere. Even if they do, however, as is usual in epidemiology, observational data from a single study cannot be regarded as any more than hypothesis-generating. Corroborating evidence is needed, for example from other groups of children exposed *in utero* to different levels of environmental radiation, before any firm conclusions can be drawn.

For all the drawbacks and difficulties of their study, Petridou and colleagues have provided a welcome contribution to the literature. The causes of childhood leukaemia are likely to prove many and complicated. The more data and hypotheses we have with which to attack the problem, the better. □

Sarah C. Darby is in the Imperial Cancer Research Fund Cancer Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, UK. Eve Roman is in the Leukaemia Research Fund Centre for Clinical Epidemiology, 17 Springfield Mount, Leeds LS2 9NG, UK.

1. Petridou, E. *et al. Nature* **382,** 352–353 (1996).
2. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UN, New York, 1988).
3. Greaves, M. F. & Alexander, F. E. *Leukaemia* **7,** 349–360 (1993).
4. Kinlen, L. J. *Br. J. Cancer* **71,** 1–5 (1996).
5. Darby, S. C. in *Origins of Human Cancer: A Comprehensive Review* (eds Brugge, J. *et al.*) 183–190 (Cold Spring Harbor Laboratory Press, NY, 1991).
6. US National Academy of Sciences Committee on Biological Effects of Ionizing Radiation *BEIR-V Rep.* (US NAS, Washington, DC, 1988).
7. Bithell, J. F. & Stiller, C. A. *Stat. Med.* **7,** 857–864 (1988).
8. Parkin, D. M. *et al. Br. J. Cancer* **73,** 1006–1012 (1996).
9. Darby, S. C. *et al. Br. Med. J.* **304,** 1005–1009 (1992).
10. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UN, New York, 1994).
11. Papastephanou, C., Manolopoulou, M. & Charalambous, S. *J. Envir. Radioact.* **7,** 49–64 (1988).
12. Pui, C.-H., Kane, J. & Crist, W. M. *Leukaemia* **9,** 762–769 (1994).