

Henry S. Kaplan Distinguished Scientist Award 2003

The crooked shall be made straight; dose–response relationships for carcinogenesis

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Abstract.

Estimates of radiation-induced malignancies come principally from the atomic (A)-bomb survivors and show an excess incidence of carcinomas that is linearly related to dose from about 5 cGy to 2.5 Gy. Above and below this dose range there is considerable uncertainty about the shape of the dose–response relationship. Both the International Commission of Radiation Protection (ICRP) and the National Council of Radiation Protection (NCRP) suggest that cancer risks at doses lower than those at which direct epidemiological observations are possible should be obtained by a linear extrapolation from higher doses. The demonstrated bystander effect for irradiation exaggerates the consequences of small doses of radiation and implies that a linear extrapolation from high doses would underestimate low dose risks. It is possible to make estimates of the cancer risk of diagnostic radiological procedures. Helical computed tomography in children is of particular interest since it is rapidly increasing in use and the doses involved are close to the lower limit of significance in the A-bomb survivors. For example, an abdominal computed tomographic scan in a 1-year-old child can be estimated to result in a lifetime cancer risk of about 1:1000. In the context of radiotherapy, some normal tissues receive 70 Gy, while a larger volume receives a lower dose, but still far higher than the range for which data are available from the A-bomb survivors. Data are available for the risk of radiation-induced malignancies for patients who received radiotherapy, e.g. for prostate or cervical cancer. New technologies such as intensity modulated radiation therapy could result in a doubling of radiation-induced second cancers since the technique involves a larger total-body dose due to leakage radiation and the dose distribution obtained involves a larger volume of normal tissue exposed to lower radiation doses.

1. Introduction

I feel very honoured to receive this award, but also very humble, principally because I knew Henry Kaplan personally. He was a giant, larger than life, in two fields of endeavour. First, he was elected as a member of the National Academy of Sciences for his work on carcinogenesis in the days when the viral aetiology of cancer was in fashion. Second, he was a prominent radiation oncologist, pioneering the treatment of Hodgkin's lymphoma with high-dose radiotherapy and, together with Gilbert Fletcher and Juan Del Regato, founding the American Society for Therapeutic Radiology.

The Kaplan award was established at the interim council meeting of the International Association of Radiation Research (IARR) at Harwell on 6 September 1985. The first recipient was Mort Elkind at Edinburgh in 1987, followed by Rod Withers at Toronto in 1991, Ged Adams at Wurtzburg in 1995 and Jack Little at Dublin in 1999.

It is instructive to ask why, of all the distinguished personages involved with the early development of radiation biology, the only eponymous award of the

IARR should be named in honour of Henry Kaplan. The answer is to be found in the early history of the founding of the Association. In the 1950s, the National Academy of Sciences formed a committee on radiobiology designed to promote the image of radiation research and to advance its funding. Kaplan was a member of that committee as one of the few National Academy members in the field. The committee was determined to hold an international meeting. It approached the newly founded Radiation Research Society, as well as involving leading figures in the UK, Europe and Japan. This led to the first international meeting in Burlington in 1958, attended by over 800 delegates. Therefore, we can see that, more than any other individual, Kaplan was the father of the International Association of Radiation Research (IARR), much as Gino Failla was the father of the Radiation Research Society.

It is a significant challenge to choose an appropriate topic for an eponymous lecture honouring a person with the stature of Henry Kaplan. I chose to discuss the implications to society of the complex shape of the dose–response relationship for radiation-induced carcinogenesis. The title includes a New Testament quote: 'the crooked shall be made straight'. However, after reviewing the evidence, the Old Testament version might be more appropriate: 'that which is crooked cannot be made straight'.

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2. Use of X-rays in medicine

Each year on Earth, 2 billion diagnostic X-ray procedures are performed, usually considered to be 'low dose', while 5.5 million cancer patients receive high doses in the context of radiation therapy. With so many people exposed regularly to an agent that is a known and proven human carcinogen, it is prudent to ask the question 'what is the price tag'.

To begin to answer this question, we must first consider the shape of the dose-response relationship for radiation-induced carcinogenesis. The problem is outlined in figure 1. The data from the Japanese atomic (A)-bomb survivors represent the 'gold standard' and give information on the quantitative risk of radiation-induced cancer from a low dose of about 0.1 Gy to a high dose of about 2.5 Gy. Above and below this dose range, there is considerable uncertainty in the shape of the dose-response relationship. We must first consider the low dose end of the curve. First, there is the adaptive response, whereby exposure to a low level of DNA stress resulting, for example, from a low dose of radiation renders cells resistant to a subsequent exposure. The first reproducible experiments to show an adaptive response to low doses of radiation were reported as a reduction in the number of chromosome aberrations in human lymphocytes (Olivieri *et al.* 1984)

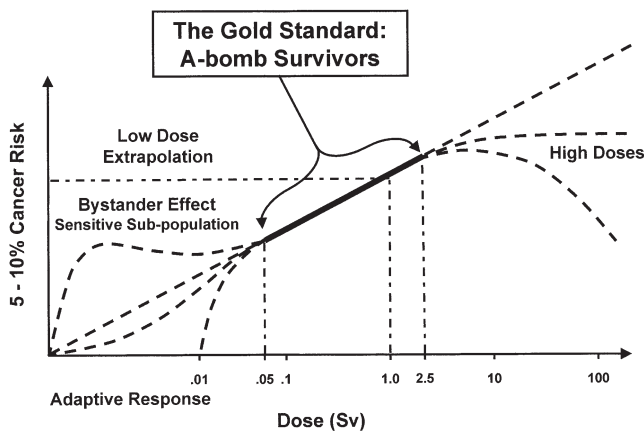


Figure 1. Dose-response relationship for radiation-induced carcinogenesis in humans. The A-bomb data represent the 'gold standard', i.e. the best quantitative data over a dose range from about 0.1 to 2.5 Gy. Above and below this dose range, there is considerable uncertainty. At doses below this range, standard bodies such as the ICRP or the NCRP recommend a linear extrapolation from the high-dose data; however, the bystander effect and existence of radiosensitive subpopulations would suggest this would underestimate risks, while phenomena such as the adaptive response would suggest a linear extrapolation would overestimate risks at low doses. There is equal uncertainty concerning the dose-response relationship at high doses, which is characteristic of radiation therapy.

Subsequent adaptive response studies showed a reduction of micronuclei and sister chromatid exchange in Chinese hamster V79 cells (Ikushima 1987, 1989), a reduction of mutation frequency in human lymphocytes (Sanderson and Morley 1986, Rigaud and Moustacchi 1996), a reduction and an altered spectrum of mutants in human-hamster hybrid A_L cells (Ueno *et al.* 1996), and a reduction in micronucleus formulation in human lymphocytes (Wojewodska *et al.* 1997).

An even more important factor that amplifies the effect of low doses is the 'bystander effect', a term that refers to the induction of biological effects in cells not directly traversed by a charged particle, but which are in close association with cells that are directly exposed.

The plethora of data now available concerning the bystander effect falls into two quite separate categories, and it is not certain that the two groups of experiments are addressing the same phenomenon. First, there are experiments involving the transfer of medium from irradiated cells, which results in a biological effect in unirradiated cells. Second, there is the use of sophisticated single-particle microbeams, which allow specific cells to be irradiated and biological effects studied in their neighbours (Randers-Pehrson *et al.* 2001). This second category of experiments will be discussed in detail since this involves a bystander effect mediated via gap junction communication, which closely mirrors the *in vivo* situation.

3. Bystander effect demonstrated by microbeam experiments

3.1. Micronuclei in normal human fibroblasts

Perhaps the most direct and dramatic demonstration of the bystander effect involves the observation of micronuclei in irradiated human fibroblasts. This is the work of Charles Geard. Cells of one population were lightly stained with cyto-orange, a cytoplasmic vital dye, while cells of another population were lightly stained blue with a nuclear vital dye. The two cell populations were mixed and allowed to attach to the culture dish, and the computer controlling the accelerator was programmed to irradiate only blue-stained cells, with 10 α -particles directed at the centroid of the nucleus. The cells were fixed and stained 48 h later, at which time micronuclei and chromosome bridges were visible in a proportion of the non-hit (i.e. orange-stained) cells (figure 2). This is an astonishing demonstration of the bystander effect because the development of micronuclei implies significant chromosomal damage and rearrangement,

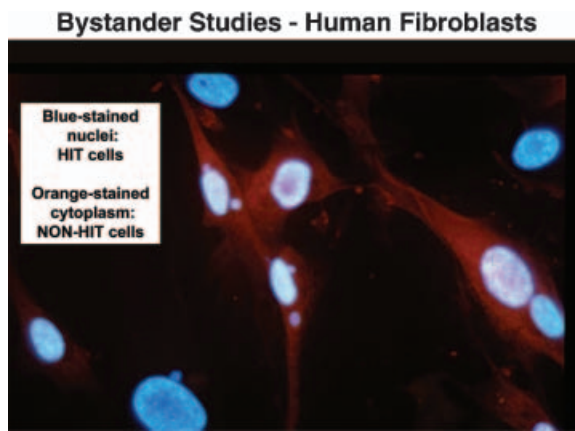


Figure 2. Bystander effect with human fibroblasts. Cells of one population were stained with the vital nuclear dye Hoechst 33342 (blue fluorescence) and cells of another population were stained with the vital cytoplasmic dye cell tracker orange (orange fluorescence) and mixed at a ratio of 1:1. Only blue nuclei were microbeam irradiated with α -particles; the orange cells were thus 'bystanders'. Cells were fixed and stained 44 h after exposure to radiation. A micronucleus is clearly visible in an orange (non-hit) cell. Courtesy of Dr Charles Geard.

which is clearly visible in non-hit cells that have been fixed *in situ*.

3.2. Cell lethality

Lines of hygromycin- and neomycin-resistant V79 cells were produced by transfection into the cells of the appropriate genes. Before exposure, the hygromycin-resistant cells were stained with a low concentration of a vital nuclear dye. They were then plated in microwells in the proportion nine neomycin-resistant for every one hygromycin-resistant cell. The computer was programmed to irradiate only the 10% of cells stained with a nuclear dye with various numbers of α -particles from one to 16, aimed at the centroid of the nucleus. The cells were then removed and cultured for survival in the appropriate growth media, which made it possible to obtain survival curves for hit (open circles) and non-hit (open squares) cells (Sawant *et al.* 2001) (figure 3). There is a considerable degree of cell killing in the non-hit cells, implying a substantial bystander effect. The magnitude of the bystander effect in these studies is much greater than that reported by The Gray Institute for Cancer Research, where only 5–10% lethality is seen in non-hit cells, using protons or soft X-rays in a microbeam. The difference is probably accounted for by the cell density. In The Gray Institute studies, only about 200 cells were seeded in an area of 10×10 mm (Prise *et al.* 1998). The average distance between cells, therefore, was some hundreds of microns, so it is

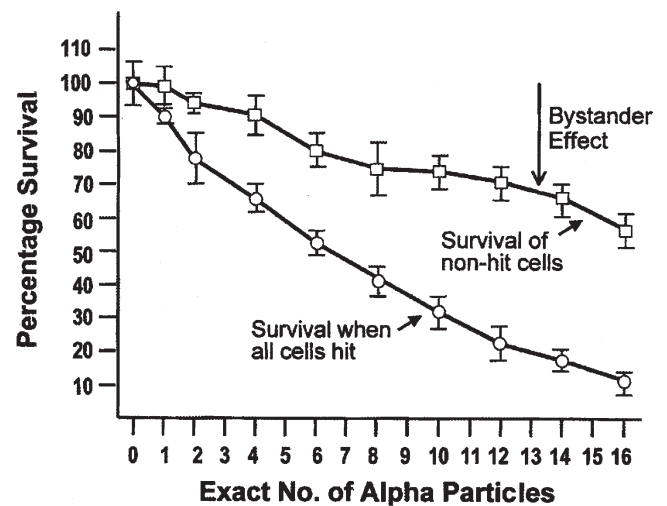


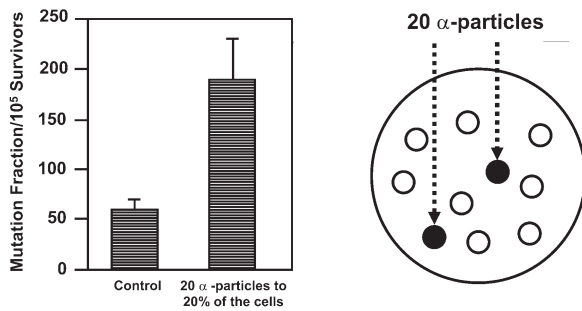
Figure 3. Bystander effect for cell survival in V79 cells. Each datum point on the line with circles refers to the survival of cells when all cell nuclei on each dish were exposed to the same exact numbers of α -particle traversals using the microbeam system. Squares show survival for various numbers of α -particles, from one to 16, traversing 10% of the cell population. The extent to which this falls below the 100% survival for the non-hit cells is an indication of the magnitude of the bystander effect. Each datum point represents the mean \pm SE of the clonogenic survivals from three culture plates. Redrawn from Sawant *et al.* (2002).

likely that communication via gap junctions did not contribute to the effect observed. By contrast, in the studies reported by Sawant *et al.* (2002), 1000–1200 cells were plated in a miniwell of 6.3 mm diameter so that 50–60% of the cells were in close contact, allowing gap junction communication that has been demonstrated to be of importance for the bystander effect in mutation studies with the microbeam.

3.3. Mutagenic effects in human–hamster hybrid cells

In the instances described so far, where the endpoints observed were micronuclei or cell lethality, the hit and non-hit cells could be distinguished by colour staining or separated by selectable markers respectively. For mutation as an endpoint, such techniques are either not possible or not available. In this case, two alternative techniques can be used to demonstrate the bystander effect. In the *first*, a large lethal dose is given to 20% of the cells. The irradiated culture is then assayed for mutations and since the hit cells are all dead, the mutation yield observed must come from the bystanders. Figure 4 shows the results of such an experiment reported by Zhou *et al.* (2000) in which human–hamster hybrid (A_1) cells were exposed to α -particles by use of the Columbia microbeam. After all cells on the dish were identified

Mutations in Bystander A_L Cells



20 α -particles through the nucleus kills the cells that are hit (SF < 1%). Mutations observed therefore come from unhit "bystander" cells.

Figure 4. Bystander effect for mutations at the CD59 locus on human chromosome 11 in human–hamster hybrid (A_L) cells when 20% of the cells receive 20 nuclear traversals by α -particles. There is a substantial incidence of mutations over the background level, despite the fact that less than 1% of the hit cells survive. Most of the mutations, therefore, must arise in bystander cells. Error bars represent \pm SEM. Redrawn from the data of Zhou *et al.* (2000).

and located, the computer was programmed to expose 20% of the cells, randomly selected, to 20 α -particles directed through the centroid of the nucleus. This irradiation allows less than 1% of the

cells to survive, and yet when assayed for mutations in the human chromosome 11 carried in the cells, the mutation yield was four times that of the background (figure 4). These mutations must clearly arise from neighbour cells, not directly exposed, but in close proximity to irradiated cells.

In the second technique to demonstrate a bystander effect for a mutational endpoint, the mutation yield when a fraction of the population (5, 10 or 20%) is exposed to one α -particle is compared with the yield when 100% of the cells are exposed to one α -particle. If mutations are produced only in hit cells, then irradiating, say, 20% of the population should result in a mutation frequency one-fifth of that observed when 100% of the cells are hit. The results of such an experiment reported by Zhou *et al.* (2001) is shown in figure 5a. It is evident that the mutation yield actually observed when only a proportion of the cells are hit by an α -particle is substantially greater than would be predicted based on the assumption that only hit cells can be mutated. The difference is due to bystanders.

This technique can also be used to identify the importance of cell–cell communication via gap junctions as a mechanism of the bystander effect (Zhou *et al.* 2001). When A_L cells were transfected with a dominant negative connexin 43 vector (DN6),

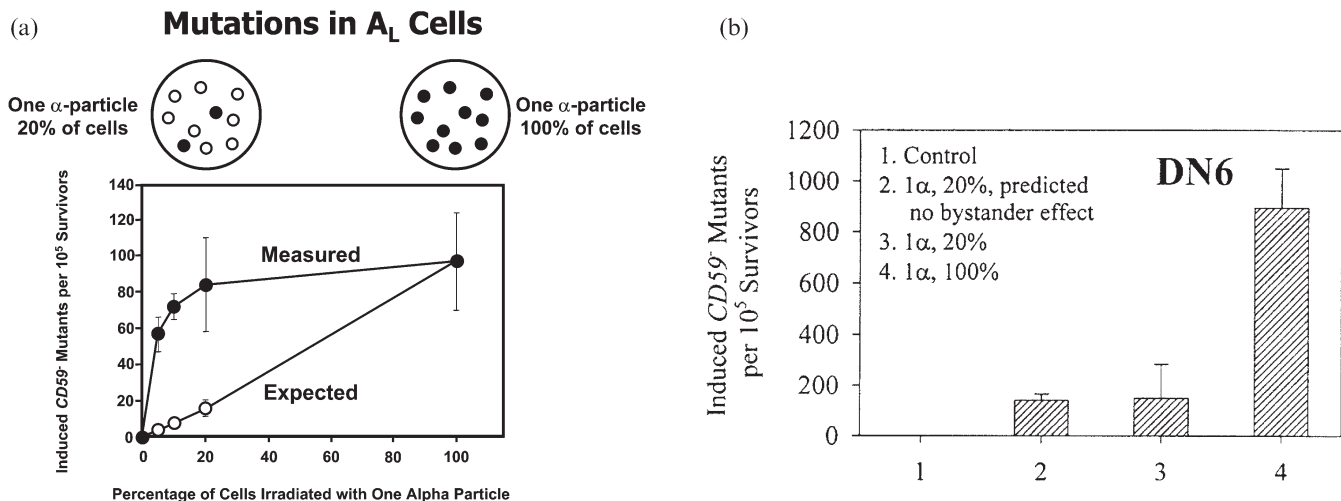


Figure 5. (a) Induced mutations at the CD59 locus on chromosome 11 in human–hamster hybrid A_L cells in which 0, 5, 10, 20 or 100% had been irradiated with exactly one α -particle through its nucleus. The induced mutant fraction is the total mutant fraction minus background incidence; error bars represent \pm SD. If mutations arise only in hit cells, then irradiating 10% of cells should give rise to one-tenth of the mutations produced when all cells are exposed, and so on. The substantially higher number of mutations observed must come from the bystanders. Redrawn from Zhou *et al.* (2001). (b) Induced mutations at the CD59 locus in a population of A_L human–hamster hybrid cells transfected with a dominant negative connexin 43 vector (DN6) that eliminates gap junction communication. In these circumstances, the bystander effect essentially disappears. The error bars represent \pm SD. Column 1 represents unirradiated control cells, which result in an induced mutation rate that is undetectable on this scale; column 4 represents the mutation frequency when all cells are exposed to one α -particle; column 2 is the mutation frequency predicted when 20% of the cells are irradiated and there is no bystander effect; it is simply one-fifth (20%) of column 4; column 3 is the observed mutation frequency when only 20% of the cells are irradiated with a single α -particle. It is indistinguishable from column 2, i.e. the bystander effect is eliminated. Redrawn from the data of Zhou *et al.* (2001).

which eliminates gap junction communication, the bystander effect essentially disappears (figure 5b).

3.4. Oncogenic transformation in mouse fibroblasts

Mouse fibroblast (C3H 10T1/2) cells were plated in a monolayer, and the computer was programmed to irradiate either every cell, or every 10th cell, selected at random with one to eight α -particles directed at the centroid (Sawant *et al.* 2001) of the cell nucleus. The cells were subsequently removed by trypsinization, replated at low density and transformed foci were identified 6 weeks later by their morphological appearance. The results are shown in figure 6 and illustrate that (1) more cells can be transformed by α -particles than were actually traversed by an α -particle and (2) when 10% of the cells on a dish are exposed to two or more α -particles, the resulting frequency of induced oncogenic transformation is indistinguishable from that when all the cells on the dish are exposed to the same number of α -particles.

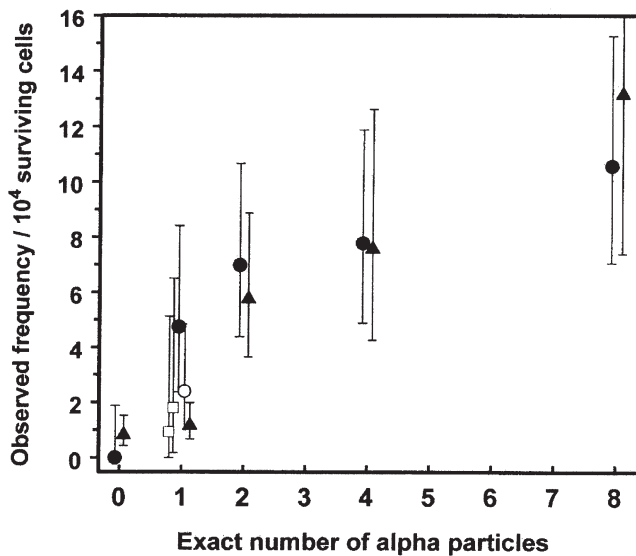


Figure 6. Yield of oncogenically transformed cells per 10^4 surviving C3H 10T1/2 cells produced by nuclear traversals by 5.3 MeV α -particles. Triangles represent the exposure of all cell nuclei on each dish to the exact numbers of α -particles, using the microbeam system. Exactly one α -particle per cell results in a surviving fraction of 0.83. Solid circles represent exposure of one in 10 cell nuclei on each dish to exact numbers of α -particles. Open squares represent subsequent repeats of the experiment in which one in 10 cell nuclei were exposed to exactly one α -particle. An open circle represents combined data for all the experiments in which one in 10 cell nuclei were exposed to one α -particle including these repeat experiments. Standard errors (\pm SD) were estimated assuming an underlying Poisson-distributed number of transformed cells. Redrawn from the data of Sawant *et al.* (2001).

3.5. Implications of a bystander effect

Note that the experimental results discussed here involve laboratory model systems, since bystander experiments with *in vivo* systems, particularly in the human, are clearly not possible at present. However, if these results were applicable *in vivo*, they could have significant consequences in terms of extrapolation of radiation risks from high to low doses, implying that the relevant target for radiation oncogenesis is larger than an individual cell, and that the risk of carcinogenesis would increase more slowly, if at all, at intermediate doses. Thus, a simple linear extrapolation of radiation risk from intermediate doses (where they can be measured) to lower doses (where they must be inferred) would be of questionable validity, at least at high linear energy transfer (LET).

This is shown in figure 7, which combines the data of Zhou *et al.* (2000) in which a proportion of cells were irradiated with a single particle (allowing the bystander effect to be manifest) together with a previous compilation of data by Hei *et al.* (1997) where all cells were exposed to various numbers of particles from one to four. Under these experimental conditions, it is evident that a linear extrapolation of risks from high to low doses (which average less than one particle per cell) would underestimate the risks at low doses. This applies at this stage strictly to α -particles, and it is not known whether it would apply

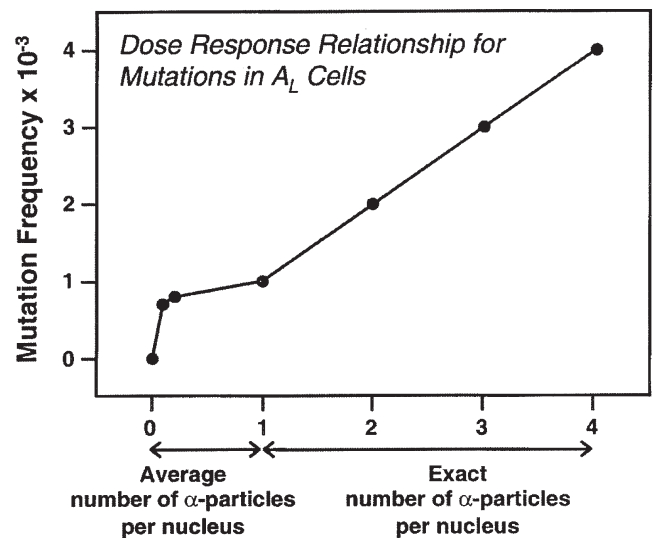


Figure 7. Mutation frequency as a function of the number of α -particles per nucleus (data for the mean number of particle traversals were calculated from cell population in which defined proportion of cells were exposed to a single α -particle). Due to the bystander effect that is evident when only a proportion of the population is exposed, the risk at low doses is higher than predicted by a linear extrapolation from high doses. Based on the data of Zhou *et al.* (2000, 2001).

in an *in vivo* situation, e.g. radon exposure in homes and mines.

4. Cancer risks from diagnostic radiology

Most procedures in diagnostic radiology involve a plain film, e.g. a chest X-ray or an X-ray of the head or extremity. Such procedures result in a very low radiation dose, well below the dose range for which reliable risk estimates are available from the A-bomb survivors. Consequently, any quantitative estimate of the cancer risk must involve some sort of model or assumption to allow an extrapolation to low doses. In other words, it falls onto the 'dotted line' area of figure 1, and so any risk estimate is subject to debate and doubt. There is one very large study, coming from a group in Montreal, that while not purporting to provide quantitative estimate of risk for diagnostic X-rays, it simply shows that when a large number of children receive diagnostic X-rays, there is a price tag! (Infante-Rivard *et al.* 2000). Infante-Rivard *et al.* concentrated only on acute lymphocyte leukaemia (ALL), which has a relatively short latent period, so that a 50-year follow-up (as with the A-bomb survivors) was not necessary. The data are shown in table 1 in terms of the odds ratio (OR) and confidence interval (CI) for girls and boys who had received various numbers of X-ray procedures. It clearly shows a statistically significant excess incidence of acute lymphocytic leukaemia in girls who received two or more diagnostic X-rays; the comparable data for boys was barely significant. The weakness of this study is that it did not distinguish between high dose and low dose radiological procedures. However, it is a clear-cut demonstration that there is a price tag when large numbers of children are exposed to X-rays.

4.1. Helical computed tomographic (CT) scans

One of the most important and exciting developments in diagnostic radiology in the past two decades is the introduction helical CT. This technique provides remarkable diagnostic information, and the

Table 1. Adjusted odds ratios and confidence intervals for the Association of Child's Postnatal Diagnostic X-rays—and acute lymphocyte leukaemia by gender. Adapted from Infante-Rivard *et al.* (2000).

X-rays (<i>n</i>)	Girls		Boys	
	No.	OR (CI)	No.	OR (CI)
None	275	1.00	295	1.00
1	73	1.14 (0.66–1.96)	109	0.94 (0.56–1.55)
≥2	68	2.26 (1.20–4.23)	133	1.39 (0.91–2.14)

scan can be performed so quickly that when used in children, it does not require sedation. Consequently, the use of helical CT is increasing rapidly in children, particularly for the early and accurate diagnosis of appendicitis (Pena *et al.* 1999). The downside is that an abdominal helical CT scan in an infant amounts almost to total-body irradiation and it is not a low-dose procedure (Huda *et al.* 2000).

The doses characteristic of helical CT are comparable with the low-dose range of the A-bomb survivors (figure 8). By estimating the organ doses involved in helical CT and using the Japanese A-bomb data, it is possible to estimate the cancer risks involved in helical CT studies of the head and abdomen in children (Brenner *et al.* 2001). The results are shown in figure 9. A CT scan of the head involves smaller risks because fewer organs prone to carcinogenesis are exposed, but an abdominal helical CT scan in a very young child involves a 1:1000 risk of developing a lethal cancer. This is a small, but not negligible, risk to be weighed against the undoubted benefits of rapid diagnosis.

4.2. Childhood cancer after radiation exposure in utero

In a widely publicized British study, Stewart and colleagues reported an excess of leukaemia and childhood cancer in children irradiated *in utero* because of diagnostic X-ray examinations involving the pelvis of the mother (Giles *et al.* 1956). An

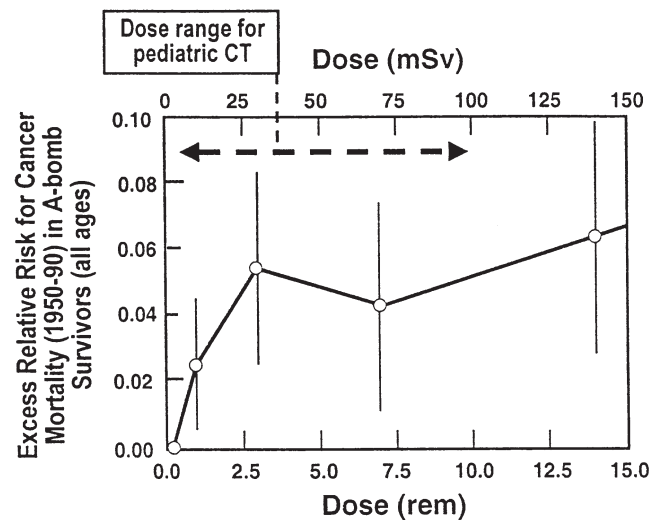


Figure 8. Estimated relative risk, with standard errors, as a function of dose for solid cancer mortality among A-bomb survivors. Only the low-dose data points are shown; taken from Pierce *et al.* (1996). Also shown is the range of organ doses characteristic of a paediatric helical computed tomographic scan of the abdomen. For convenience, doses are expressed in both old (rem) and new (mSv) units. Adapted from Brenner *et al.* (2001).

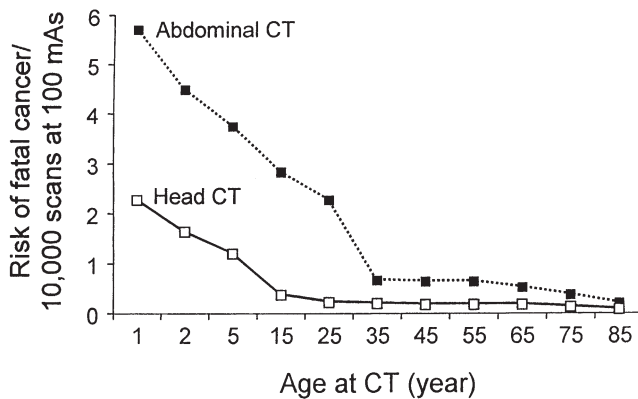


Figure 9. Estimated lifetime attributable cancer mortality risk as a function of age for a single helical computed tomographic examination of the head or abdomen. The numbers shown are for 100 mAs; the risk can be simply scaled for lower or higher mAs values. mAs, milliamperere seconds, the product of the X-ray tube current and the exposure time. Note the rapid increase in risk with decreasing age. Adapted from Hall (2002).

association between leukaemia and X-rays *in utero* was also confirmed in the USA by MacMahon (1962). This has been a highly controversial topic. Doll and Wakeford (1997) summarized all of the available data and concluded that radiation was the causative agent. They concluded the following:

- Low-dose irradiation of the foetus *in utero*, particularly in the last trimester, causes an increased risk of childhood malignancies.
- Obstetric X-ray examination, even though the dose is only about 10 mGy (1 rad), increases the risk of childhood cancer by 40%.
- Excess absolute risk is about 6% Gy⁻¹.

The relative risk of 40% is very high because, of course, cancer is relatively rare in children. The absolute risk works out to be about 6% Gy⁻¹, which is not very different for the cancer risk calculated from the A-bomb survivors following adult exposure, although of course this excess is expressed early in life.

This study lowers the minimum dose at which an excess incidence of cancer has been observed in the human to about 10 mGy.

5. Cancer risks from radiation therapy

In developed countries, rather more than half of all cancer patients receive radiotherapy at some stage in the management of their disease. The fraction is

much lower in developing countries, but is increasing steadily. A radiation-induced second malignancy is, to some extent, the price of success, since if the primary cancer is not cured, or at least controlled, the patient will not live long enough for a second malignancy to develop. In most instances, it is difficult to get a reliable estimate for the incidence of second cancers following radiotherapy because a truly appropriate control group is not available. The two principal exceptions are carcinoma of the cervix in women and prostate in men, since in both examples, surgery and radiotherapy are alternative choices, and so patients treated with surgery constitute the ideal control.

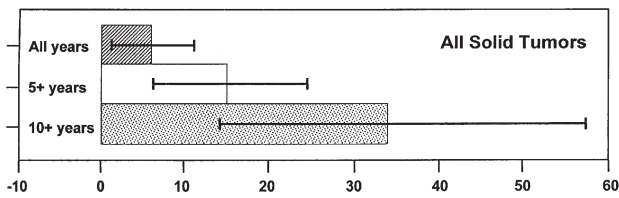
5.1. Second cancers after radiotherapy for prostate cancer

Brenner *et al.* (2000) described a very large study using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. The database contained information on 51 584 men with prostate cancer treated by radiotherapy and 70 539 who underwent surgery. There was no evidence of a difference in the risk of leukaemia for radiotherapy versus surgery patients, but the risk of a second solid tumour at any time post-diagnosis was significantly greater after radiotherapy than after surgery. The increased relative risk became greater with time (figure 10), which also shows the distribution of solid cancers. Note that the increase in relative risk for carcinoma of the lung, which was exposed to a relatively low dose (about 0.5 Gy), is of the same order as that for carcinomas of the bladder, rectum and colon, all of which were subject to much higher doses (typically more than 5 Gy). Overall, one in 70 patients who receive radiotherapy for prostate cancer will develop a second malignancy if they survive for 10 years following treatment.

5.2. Radiation-induced second cancers: the impact of IMRT

The move from three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiation therapy (IMRT) involves more treatment fields, and the dose–volume histograms show that as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of two to three, increasing the total-body exposure, due to leakage radiation. Both factors will tend to increase the risk of second cancers. Before an estimate can be made, one must arrive at a dose–response relationship for radiation-induced cancer.

Percentage Increase in Relative Risk for RT vs. Surgery %



Second Cancers After Prostate RT

% contribution to total number of radiation-induced second cancers (5+ yrs)

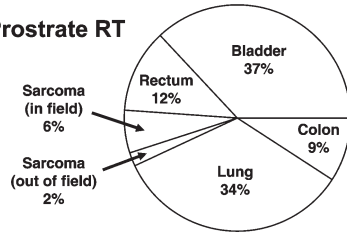


Figure 10. (upper) Percentage increase in the relative risk for all solid tumours as a function of time after radiotherapy. The error bars represent 95% confidence limits. 'All years' refer to all years post-treatment; the standard error is smaller in this case because of the larger number of patients; most did not survive to 5 or 10 years. (lower) Distribution of the principal radiation-induced cancers, namely bladder, lung, rectum and colon. There are also a small number of sarcomas that appear in heavily irradiated areas. Data from Brenner *et al.* (2000). Courtesy Dr David Brenner.

5.3. Dose–response relationship for radiation-induced carcinomas

For single whole-body exposures, the relationship between mortality from solid tumours among the A-bomb survivors is consistent with linearity up to about 2.5 Sv (figure 1).

There is considerable uncertainty concerning the shape of the dose–response relationship for higher doses in the context of radiotherapy, where limited volumes of tissue receive doses of 70 Gy or more, while a much larger volume receives a lower dose because it is exposed to only some of the treatment fields.

Three possibilities can be entertained (figure 11). First, it might be expected that the risk of inducing cancer would fall off at higher doses due to cell killing, on the grounds that dead cells cannot give rise to a malignancy. (The D_0 for cell killing in a fractionated course of 2-Gy fractions is about 3.17 Gy.) However, none of the dose–response curves for radiation-induced cancer in humans have this shape. It must be regarded, therefore, as an extreme possibility. The other extreme possibility, suggested by the data from some human studies, is that the risk of solid tumours shows a levelling off at 4–8 Gy with no decline thereafter. (This would include women irradiated for endometrial cancer in whom the risk for leukaemia reaches a plateau [Curtis

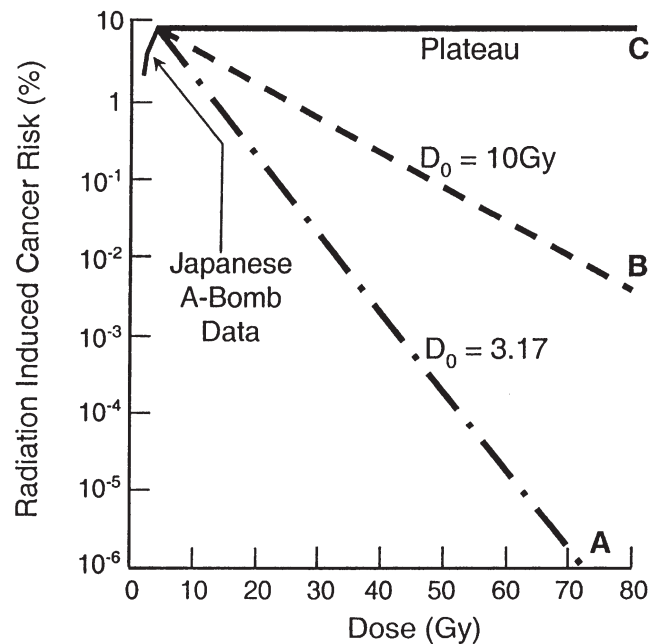


Figure 11. Data from the Japanese A-bomb survivors provide good estimates of the risk of solid tumours for total-body irradiation; up to about 2 Gy, risk is linear with dose reaching about $8\% \text{ Sv}^{-1}$; assuming a dose rate effectiveness factor (DREF) of 2 for a fractionated schedule, the maximum would occur at about 4 Gy. The shape of the dose–response relationship at higher doses is uncertain. Some data in humans and animals indicate a reduction in risk at higher doses, usually attributed to cell killing. Curve A shows what might be expected with cell killing following a D_0 of 3.17 Gy, which is that observed for a fractionated regimen of 2 Gy day^{-1} . This might be described as the predictions of a naïve cell biologist. No *in vivo* data support this shape. Curve B shows a slower fall-off as observed, for example, with leukaemia in women receiving radiotherapy for cervical carcinoma. The fall-off corresponds to a D_0 closer to 10 Gy. Curve C shows no reduction of risk as the dose increases beyond about 4 Gy.

et al. 1994] and children given radiotherapy for cancer in whom the risk for thyroid cancer levels off [Tucker *et al.* 1987, Boice *et al.* 1996].) An intermediate case is represented by women who have been treated with radiation for cervical cancer and have an increased risk of developing leukaemia, but the dose–response relationship is complex: the risk increases with doses up to about 4 Gy and decreases at higher doses but much more slowly than the D_0 of 3.17 Gy assumed above (Day *et al.* 1984, Boice *et al.* 1987, Blettner and Boice 1991). To the extent that the data can be represented in this way at all, the D_0 would be closer to 10 Gy (figure 11).

We thus have three possible dose–response relationships for radiation-induced carcinogenesis. All three are virtually identical at doses up to about 4 Gy in a fractionated protocol, since this represents the solid data from the Japanese A-bomb survivors,

corrected for fractionation. The three dose–response relationships differ widely at high dose since they depend on the assumptions made concerning cell killing. It is difficult to choose the most realistic dose–response relationship for carcinogenesis in general. However, in the case of the induction of carcinoma of the bladder by radiation, an interesting conclusion can be arrived at more easily, which strongly favours curve C. Good data on the incidence of this particular malignancy are available from the A-bomb survivors as well as from patients receiving radiotherapy for prostate cancer and for carcinoma of the cervix. For radiotherapy situations, all of the bladder received quite a large dose of radiation.

The data from the A-bomb survivors indicate a relative risk (RR) for bladder cancer of about 4 at a dose of 2 Gy (Pierce *et al.* 1996). Patients who survive 10 years or more following radiotherapy for prostate cancer show a relative risk of 1.8 for bladder cancer (Brenner *et al.* 2000). (If the patients had lived longer or been younger at the time of irradiation, this RR would certainly be higher.) Dose–volume histograms for prostate cancer treatments indicate a range of doses to the bladder of 48–67 Gy. In the case of patients receiving radiotherapy for carcinoma of the cervix, the RR for bladder cancer was reported to be 5 for an organ dose of 30–80 Gy (Boice *et al.* 1985) (figure 12). A comparison of these data imply comparatively little differences in the relative risk over the dose range from 2 to 80 Gy, thus strongly favouring the flat relationship with little if any fall off attributable to cell killing.

A simple way to compare 3D-CRT and IMRT is to assume as a first approximation that the cancer risk associated with irradiating part of the trunk is directly proportional to the volume irradiated. By a comparison of dose–volume histograms for 3D-CRT and IMRT, it was estimated that IMRT might increase the risk of radiation-induced carcinomas by perhaps 0.5% (Hall and Wu 2003).

Delivery of a specified dose to the isocentre from a modulated field, delivered by either dynamic IMRT or the step and shoot method of IMRT, will, in general, require the accelerator to be energized for longer (hence more monitor units are needed) compared with delivering the same dose from an unmodulated field (Williams and Hounsell 2001).

Some years ago, we made measurements of scattered and leakage radiation using an anthropomorphic ‘Rando’ phantom (Hall *et al.* 1995). Ionization chambers were used to measure the dose to a breast while a four-field technique was used to deliver a dose of 70 Gy to the cervix. Using a 6 MV LINAC the breast dose was 0.25 Gy, while with a 20 MV LINAC the dose consisted of 0.5 Gy X-rays

Relative Risk of Radiation - Induced Bladder Cancer

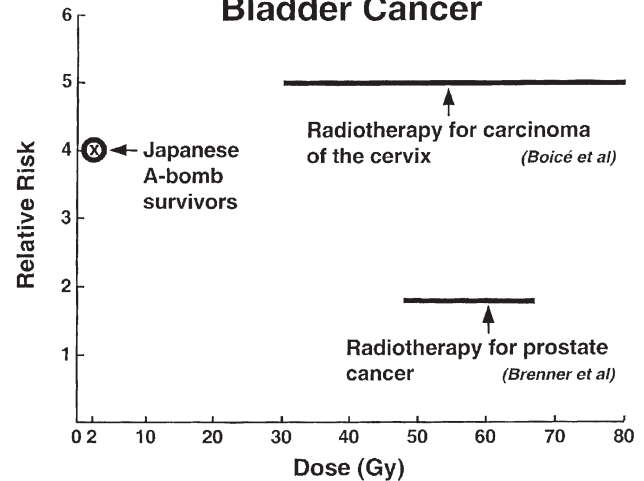


Figure 12. Dependence on dose of the relative risk (RR) of developing a radiation-induced bladder cancer. In the Japanese survivors, RR was 4 at a dose of 2 Gy. Patients who lived 10 years or more following radiotherapy for prostate cancer show an RR of developing a bladder cancer of 1.8 when the bladder received a dose of 48–67 Gy. (Brenner *et al.* 2000). In the case of patients receiving radiotherapy for carcinoma of the cervix, the dose received was 30–80 Gy and the RR of developing bladder cancer was 5 (Boice *et al.* 1985). These data imply that the relative risk of developing bladder cancer varies little with dose over this enormous range; there appears to be little, if any, fall-off attributable to cell killing.

plus a photoneutron component of about 1 cGy. One needs only consider the data for the 6 MV LINAC since higher energies are not usually used for IMRT. The breast dose of 0.25 Gy translates into a risk of radiation-induced cancer of about 0.25%, using a risk estimate of 2%/Gy, appropriate for older patients (International Commission on Radiological Protection 1991).

In summary, the change to IMRT results in an estimated doubling of the incidence of second cancers observed compared with more conventional radiation therapy.

5.4. The bottom line: diagnostic radiology

Plain film techniques, such as a chest X-ray, involve a very low dose of radiation, which is far below the level at which epidemiological data show a risk in humans. This does not imply that there is no risk, but certainly that it must be small. However, even a small risk multiplied by 2 billion can add up to a significant public health problem. CT, and especially helical CT involve a dose that is not so low and in fact is comparable with the lower end of the range of doses for which there are cancer risk

estimates from the A-bomb survivors. In a young child, for example, an abdominal helical CT has an induced cancer risk estimated as 1:1000.

As medical X-rays proliferate, especially helical CT, which is indeed a wonderful diagnostic tool, the concern is that one is creating a public health problem for the future. Bear in mind that the study of the A-bomb survivors states that it takes 50+ years for the carcinogenic legacy of a radiation exposure to be expressed.

5.5. *The bottom line: radiation therapy*

In Western countries, rather more than half of all cancer patients receive radiotherapy at some stage in the management of their disease. Because of the latent period between exposure to radiation and the appearance of a radiation-induced cancer, studies show that the incidence of second malignancies following radiotherapy increases with time after treatment. In patients who survive 10 years, about 1.5% will develop a radiation-induced second cancer. This percentage is likely to be approximately *doubled* by new sophisticated techniques such as IMRT, which deliver a higher curative dose to the primary cancer, but will result in more radiation to adjacent organs and to the whole body.

Second, cancers become an increasing problem as treatment techniques improve, since patients must survive the first cancer to develop a second. It also becomes more of a problem as younger patients become candidates for radiotherapy.

5.6. *The bottom line overall*

It is impossible to imagine the practice of medicine in the 21st century without the ready availability of X-rays. Radiology is a cornerstone of the diagnosis of many human diseases, while radiotherapy is one of the three pillars of cancer treatment. The benefits are obvious and beyond doubt. The purpose of the present paper has been to estimate the possible downside, i.e. the risk of radiation-induced malignancies. The risk is seen to be small, but by no means negligible.

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