Cancer Risk from Low-Level Radiation

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In recent years, much work and substantial monetary expenditures have been devoted to reducing radiation exposure from radiography and other medical procedures. This effort is motivated by the often-repeated assertion that any radiation dose, no matter how small, can cause cancer. The basis for that statement is the linear no-threshold theory of radiation carcinogenesis. According to that theory, if 1 Gy (100 rad) of exposure gives a cancer risk R, the risk from 0.01 Gy (1 rad) of exposure is $R / 100$, the risk from 0.00001 Gy (1 mrad) is $R / 100,000$, and so on. Thus the cancer risk is not 0 regardless of how small the exposure.

However, a strong sentiment has recently developed in the community of radiation health scientists to regard the risk estimates in the low-dose region that are based on the linear no-threshold theory as being grossly exaggerated or completely negligible. For example, the 6000-member Health Physics Society, the principal organization for radiation protection scientists, has issued a position paper stating, "Below 10 rad...risks of health effects are either too small to be observed or are non-existent" [1]. In fact, substantial evidence exists that low-level radiation may even be protective against cancer—a view known as hormesis.

The purpose of this article is to review the basis for the linear no-threshold theory and to present some of the emerging information that has caused this recent shift in sentiment.

Basis for the Linear No-Threshold Theory

The original basis for the linear no-threshold theory, as that theory emerged in the mid twentieth century, was theoretic and very simple. A single particle of radiation hitting a single DNA molecule in the nucleus of a single cell of the human body can initiate a cancer. The probability of such a cancer initiation is therefore proportional to the number of such hits, which is proportional to the number of particles of radiation, which is proportional to the dose. Thus the risk is proportional to the dose: this is the linear no-threshold theory.

The problem with this simple argument is that factors other than initiating events affect the cancer risk. Human bodies have biologic defense mechanisms that prevent almost all initiating events from developing into a fatal cancer [2, 3]. This article will present some of the most important examples of these defenses, including how they are affected by low-level radiation. Our bodies produce enzymes that repair DNA damage with high efficiency (99.99% for single-strand breaks and 90% for double-strand breaks [2, 3]). Low-level radiation can be shown to stimulate production of these repair enzymes. Apoptosis, a process by which damaged cells "commit suicide," is stimulated by low-level radiation [4]. The immune system is important for preventing mutations from developing into a cancer; low-level radiation stimulates the immune system, but high radiation levels depress it. Many cancers are initiated by corrosive chemicals; processes exist for scavenging these out of cells, and low-level radiation stimulates these scavenging processes [5]. Radiation can alter cell cycle timing, extending the time before the next cell division (mitosis). Damage repair is effective only until the next mitosis, so changing this available time can be important (Elkind M, personal communication). Because all of these biologic defense mechanisms require consideration, the basis for the linear no-threshold theory is far too simple.

Direct and obvious evidence also exists for failure of the simple argument. The number of initiating events is roughly proportional to the mass of the animal: more DNA targets mean more hits. Thus, the simple theory predicts that the cancer risk should be approximately proportional to the mass of the animal. But the cancer risk in a given radiation field is very similar for a mouse weighing 30 g and a human weighing 70 kg. Our very definition of dose would be misleading if only the total number of hits (which is proportional to the number of initiating events) was relevant regardless of the target mass, because the definition of dose is based on the energy absorbed per unit mass of tissue, which is proportional to the number of radiation hits per unit of target mass.

Many aspects of the problem are now understood on the molecular level [2, 3]. DNA damage events naturally induced by corrosive chemicals

TABLE I	Effects of Preexposure to Radiation on Chromosome Aberration in Human Lymphocyte Cells Induced by X-Ray Exposure 6 Hr Later			
Donor	Dicentrics and Rings		Deletions	
	400 cGy	(5 + 400) cGy	400 cGy	(5 + 400) cGy
1	136	92	52	51
2	178	120	62	46
3	79	50	39	15
4	172	42	46	34
5	134	106	58	41

Note.—Study used preexposure dose of 5-cGy X rays and later exposure of 400 cGy. Data are from [6].

TABLE 2	Effects of Radiation on Immune Response in Mice		
Test	Response to Exposure [a]		
	2.5 cGy	5 cGy	7.5 cGy
Plaque-forming cell reaction	110	143	174
Mixed lymphocyte culture [b] reaction	109	133	122
Reaction to concanavalin A [c]	191	155	530
Natural killer cell [d] activity	112	109	119
Antibody dependant cell mediated cytotoxicity [e] activity	109	128	132

Note.—Data are from [16].

[a] Percentage of response in unexposed mice compared with response in exposed mice.

[b] Used as test of T-cell function.

[c] Lectin that stimulates T-lymphocytes.

[d] Cells that recognize and kill tumor cells.

[e] Assists in natural killer cell activity.

and thermal processes occur roughly a million times per day in each of the trillions of cells in our bodies, but only about one per cell per day remains unrepaired and survives as long-term mutations; it is these mutations that are normally responsible for human cancers. The DNA damage from radiation is, on average, more severe than damage from chemicals or thermal processes. However, a dose of 0.1 Sv (10 rem), which is near the upper limit of low-level radiation, is estimated to cause only 0.004 long-term mutations per cell [2, 3], a trivial addition to the one mutation per cell per day resulting from natural processes.

Taking all this into account, it is evident that cancer-initiating events are not the controlling factor in determining the dose–response relationship for radiation in the low-level radiation region, as was assumed in the linear no-threshold theory. The principal effect of radiation is in modifying the biologic defense mechanisms, rather than in providing initiating events.

Effects of Low-Level Radiation on Biologic Defense Mechanisms

Several examples can be given of how low-level radiation affects biologic defense mecha-

nisms. Cancers are initiated by genetic damage in a cell nucleus. One type of genetic damage that has been widely studied is chromosome aberrations, and it was long ago recognized that a high dose of radiation increases the number of these aberrations. However, Table 1 presents an in vitro example of data from Shadley and Dai [6] showing how that process is affected if a low dose of radiation is given a few hours earlier than the high dose. In this case, the number of chromosome aberrations caused by the high dose is substantially reduced.

As an example of an in vivo experiment, Cai and Liu [7] reported that exposure of mouse cells to 65 cGy (65 rad) caused chromosome aberrations in 38% of bone marrow cells and in 12.6% of spermatocytes. If these exposures are preceded 3 hr earlier by an exposure to 0.2 cGy, the percentages of aberrations are reduced to 19.5% and 8.4%, respectively. Many other examples of such experiments, both in vitro and in vivo, are found in the literature, and the findings are usually explained as the result of stimulated production of repair enzymes by low-level radiation. These are examples of what is called "adaptive response" [8]; the body adapts to effects of ra-

diation by developing protective responses. Recent evidence of this behavior has been documented in human exposures, on the basis of comparing residents of an area of high background radiation (1 cGy/year) with those in an area of normal background radiation (0.1 cGy/year) in Iran [9]. When lymphocytes from these groups were exposed to 1.5 Gy (150 rad), the mean frequency of chromosome aberrations per cell was 0.098 ± 0.012 for the former versus 0.176 ± 0.017 for the latter, a 4-SD difference presumably caused by adaptive response induced by radiation in residents of the high-radiation background area.

Another type of experiment that reveals effects of adaptive response involves detection of genetic mutations. In an in vitro experiment, it was found that an X-ray exposure of 300 cGy to human lymphocytes induced a frequency of mutations at the *hprt* locus of 15.5×10^{-6}, but if this large exposure was preceded 16 hr earlier by an exposure of 1 cGy, this frequency was reduced to 5.2×10^{-6} [10]. As an in vivo example, it was found that the percentage of dominant lethal mutations in offspring resulting from exposures of female drosophila to 200 cGy of X rays before mating was substantially reduced by preceding this high dose with an exposure to 2 cGy [11]. For various strains of drosophila and different oocyte maturities, these percentages were reduced from 42% to 27%, from 11% to 4.5%, from 40% to 36%, from 32% to 12.5%, from 42% to 30%, and from 51% to 22% [11].

A technique has been developed for directly observing repair of DNA base damage [12]. These researchers found that preceding an exposure to 2 Gy of gamma radiation with an exposure 4 hr earlier to 0.25 Gy reduced the time for 50% DNA lesion removal from 100 min to 50 min.

One might consider the possibility that adaptive response is effective only against large doses of radiation, but data exist regarding its effectiveness against spontaneous transformation to malignancy in cells with a predisposition to such transformation. This was shown for exposures of C3H 10T1/2 mouse cells, in which the rate of spontaneous neoplastic transformation was reduced by 78% 1 day after exposure to low doses of radiation [13]. In a similar experiment with HeLa x skin fibroblast cells, the transformation reduction was by 55% [14]. In both of these studies, the results had high statistical significance.

This may be understood on a more basic level from effects of radiation on corrosive oxidants that normally cause the cancer-initiating DNA damage and the antioxidants that scav-

enge them out of cells. A study of rat cells indicated that 50 cGy of X-ray exposure increases the amount of an antioxidant (superoxide dismutase) by approximately 25% and decreases the amount of lipid peroxide (oxidized cell members) by approximately 20% [15]. At much higher doses, these effects are reversed [15].

The effects of low-level radiation on the immune system are relevant because it destroys cells that have persistent DNA damage and is thus important in resisting the development of cancer. A summary from the work of Liu [16] of such effects on several different measurements of the immune response is presented in Table 2. In each of these measurements, the immune response is increased by low-level radiation.

One study of this effect over a wide range of radiation doses [17] reported increases in immune response by 80% in vitro and by 40% in vivo at about 20 cGy and a rapid decrease in immune response to well below the unirradiated level at doses greater than 50 cGy in both in vitro and in vivo exposures.

The immune system provides resistance to metastasis of tumors. When tumor cells are transplanted into the groins of mice, the rate of their metastasis into the lung is cut approximately in half by total body irradiation with 15–30 cGy 12 days after the transplantation [18]. Doses greater than 50 cGy, on the other hand, reduce the immune response, leading to increased rates of metastasis. A study in rats [19] showed that irradiation of the whole body—but not tumor irradiation—with low-level radiation reduces the rate of metastasis and increases infiltration into the tumor of killer lymphocytes [20]. The latter effect was

known much earlier [17]. Total-body irradiation with low-level radiation doses has also been shown to reduce tumor size [17, 21]. Clearly, total-body irradiation with low-level radiation stimulates the immune system.

Risk-Versus-Dose Data from Human Exposures

The principal data that have been cited by those in influential positions to support the linear no-threshold theory are from studies reporting solid tumors (all cancers except leukemia) among the Japanese atomic bomb survivors [22], and findings of an International Association for Research on Cancer study of occupational doses to radiation workers [23]. Data drawn from Pierce et al. [22] are shown in Figure 1, in which the error bars represent 95% confidence limits (2 SD). If error bars are ignored, the points suggest a linear relationship with intercept near-zero dose. But the data themselves give no statistically significant indication of increased incidence of cancer for doses of less than 25 cSv. In fact, considering the three lowest dose points alone, the slope of the dose–response curve has a 20% probability of being negative (risk decreasing with increasing dose) [23].

The International Association for Research on Cancer study of 95,673 monitored radiation workers in the United States, the United Kingdom, and Canada found 3830 deaths for all cancers except leukemia but no deaths exceeding what was expected [24]. The risk is reported as –0.07/Sv with 90% confidence limits (–0.4/Sv, +0.3/Sv). No support for the linear

no-threshold theory can be found here. However, for the 146 leukemia deaths, Cardis et al. [24] do report a positive risk-versus-dose relationship and claim that this finding supports the linear no-threshold theory. Their data are listed in Table 3. It is obvious from those data that there is no indication of an excess risk below 40 cSv (even the excess for > 40 cSv is by only 1.4 SD). The authors' conclusion that the positive risk-versus-dose relationship supports the linear no-threshold theory is based on an analysis that arbitrarily discards the data (Table 3) for which the ratio of observed to expected deaths is less than unity. They thus discard three of the seven data points.

Therefore, the solid tumor data on atomic bomb survivors and the leukemia data on monitored radiation workers are said to support the linear no-threshold theory (although the leukemia data on the former group and the solid-tumor data on the latter group do not), but several studies seem to contradict that theory. The data regarding leukemia among atomic bomb survivors [22] are shown in Figure 2, with error bars indicating 95% confidence limits. These data strongly suggest a threshold greater than 20 cSv.

A similar behavior is found for breast cancer among Canadian women exposed to X-ray fluoroscopic examinations for tuberculosis [25], the data for which are shown in Figure 3. Here again, there seems to be a decrease in risk with increasing dose—at least up to 20 cSv. The data on lung cancer among these Canadian women [26], and also a one-point study of 10,000 individuals in Massachusetts [27], are shown in Figure 4. Again, we see a decrease in the low-dose region,
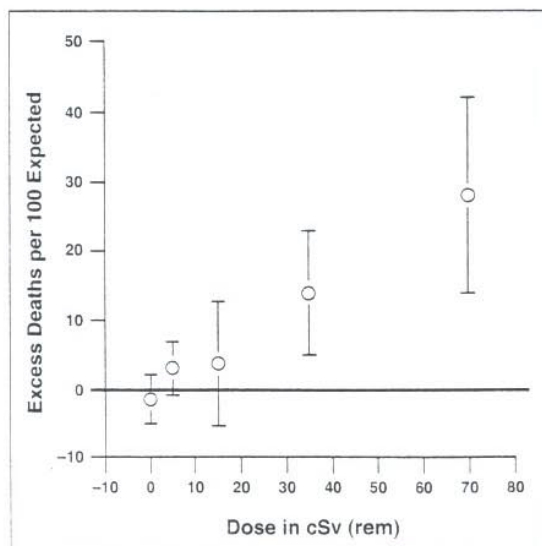

Fig. 1.—Plot shows number of deaths from solid tumors per 100 in excess of expected deaths among Japanese atomic bomb survivors (1950–1990) versus their dose. Error bars show 95% confidence limits. Plot data are drawn from [22].

TABLE 3	Leukemia Deaths Among Nuclear Industry Workers in Three Countries		
Dose (cSv)	No. of Deaths		
	Observed (n = 146)	Expected (n = 145.9)	Ratio[a]
0–1	72	75.7	0.95
1–2	23	21.2	1.08
2–5	20	21.8	0.92
5–10	12	11.3	1.06
10–20	9	7.8	1.15
20–40	4	5.5	0.73
>40	6	2.6	2.3

Note—Data are from findings in [24], a study of 95,673 monitored radiation workers in the United States, the United Kingdom, and Canada.

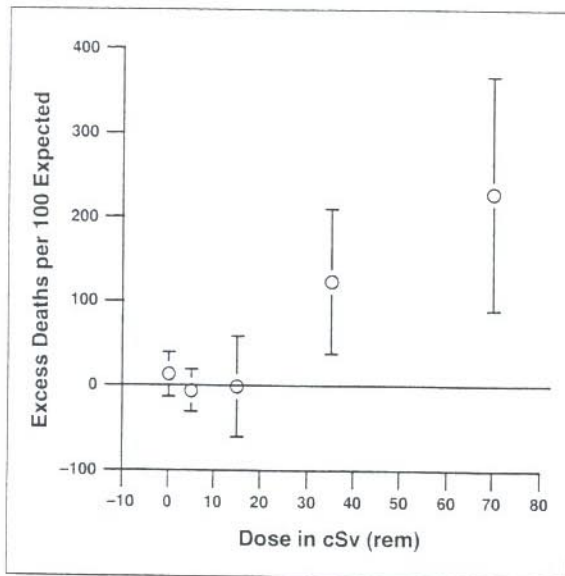[a] Observed deaths to expected deaths.

Fig. 2.—Plot shows number of deaths from leukemia per 100 in excess of expected deaths among Japanese atomic bomb survivors (1950–1990) versus their dose. Error bars show 95% confidence limits. Plot data are drawn from [22].
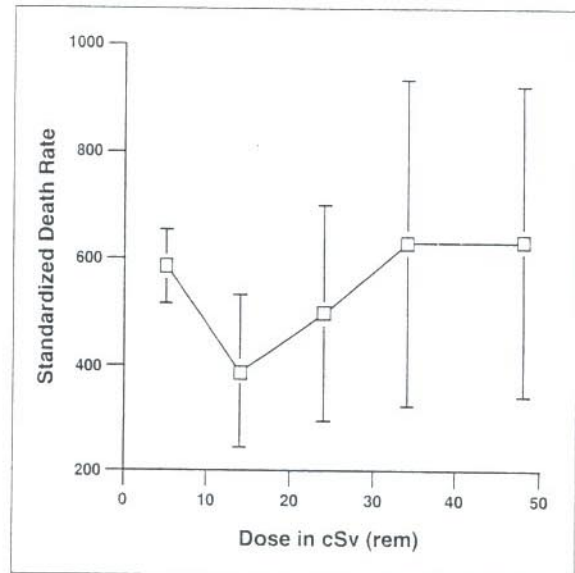
Fig. 3.—Plot shows standardized rates of death from breast cancer per million person-years among Canadian women after irradiation in fluoroscopic examinations versus their radiation dose. Error bars show 95% confidence limits. Plot data are drawn from [25].

in this case extending at least up to 100 cSv. In Figure 4, these data are compared with lung cancer data for the Japanese atomic bomb survivors, and the difference between the two data sets is statistically significant: the atomic bomb survivor data gives a much higher risk at all doses. This can perhaps be explained by the difference between the very high dose rate in the atomic bomb survivors and the lower dose rate

for protracted fluoroscopic examinations extending over several years. In any case, one must consider the data in Figure 4 before accepting the widely practiced approach of using atomic bomb survivor data to predict risks from low-level radiation at low dose rates.

In 1957, an explosion occurred in an incredibly mismanaged radioactive waste–storage facility, the Mayak nuclear weapons complex in

the eastern Urals of Siberia, then part of the Soviet Union. The explosion caused large radiation exposures to people in some nearby villages. A follow-up study of 7852 exposed villagers [28] found that their rate of subsequent cancer mortality was much lower than that of unexposed villagers. The ratio for exposed to unexposed was 0.27 for 4 cGy exposure, 0.39 for 12 cGy, and 0.28 for 50 cGy; for
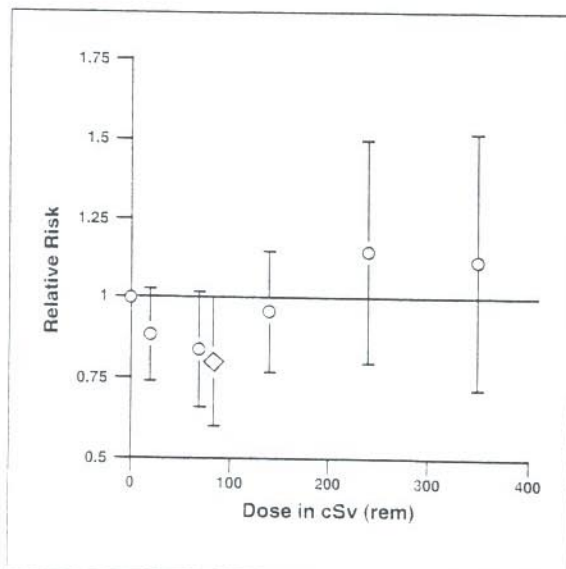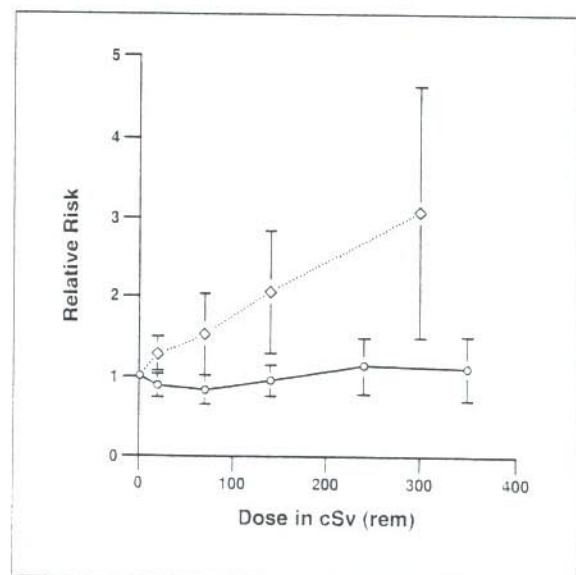
Fig. 4.—Plots show relative risk of mortality from lung cancer versus dose to lung, with 95% confidence limits.
A. Plot with expanded vertical scale shows data from [26] (circles) and data from [27] (diamond).
B. Plot shows data drawn from [26]; solid line connects data from Canadian fluoroscopy patients, and dashed line connects data from atomic bomb survivors.

the latter two groups, the differences are outside the 95% statistical confidence limits.

A $10 million study of shipyard workers involved in servicing United States Navy nuclear-propelled ships compared those who were and were not occupationally exposed to radiation [29]. In the former group, workers had exposures greater than 0.5 cSv (0.5 rem) and average exposures of 5 cSv, whereas the latter group had exposures of less than 0.5 cSv. The exposed workers had a cancer mortality rate that was only 85% of that for the unexposed workers, a difference of more than 4 SDs. Hiring procedures, medical surveillance, job type, and other factors were the same for both groups, so the often-used explanation of "the healthy worker effect" does not apply here.

Stimulation of the immune system by low-level radiation is being used on an experimental basis for medical treatment of non-Hodgkin's lymphoma via total-body and half-body irradiation. This radiation is administered to one group of patients ("irradiated" group), but not to an otherwise similar control group, before both groups are given other, similar, standard treatments such as chemotherapy with or without accompanying high-radiation doses to tumors. In one such study [18], after 9 years, 50% of the control group but only 16% of the irradiated group had died. In a study published in 1976 that used different standard treatment, the 4-year cancer survival rate was 70% for the irradiated group versus 40% for the control group [30]. Another study that was conducted during the same period but used a more advanced chemotherapy technique found the 4-year survival was 74% for the irradiated group versus 52% for the control group [31].

Probably the most significant data on low-level radiation exposure in humans is still in the research stage, but preliminary results are interesting. In Taipei and other areas of Taiwan, 1700 apartment units were built using steel contaminated with cobalt-60, exposing 10,000 occupants for 16 years to an average, according to preliminary estimates, of 4.8 rem in the first year and 33 rem in total [32]. From national Taiwan statistics, 173 cancers and 4.5 leukemias would be expected from natural sources, and according to the linear no-threshold theory, there should have been 30 additional leukemias. However, a total of only five cancers and one leukemia have occurred among these people [32].

The data described earlier deal with radiation by X rays and gamma rays (and some

neutrons for the atomic bomb survivors). There are also impressive relevant data from radiation with alpha particles. One such study is of bone and head cancers among dial painters, chemists, and others occupationally exposed to ingested radium [33]. No tumors were found among those with exposures of less than 1000 cGy, but for dose ranges centered about 1800, 3500, 7500, and 20,000 cGy, 25–38% in each category developed tumors. Elaborate analyses of these data show that a linear no-threshold fit is statistically unsupportable and a threshold behavior is strongly suggested.

Several studies have reported that workers who inhaled plutonium, resulting in sizable radiation exposures to their lungs, have lower lung cancer mortality rates than those not thus exposed [34–36]. Contrary to impressions generated by the media, no record exists of cancer deaths resulting from human exposure to plutonium.

Very strong evidence against the linear no-threshold theory is provided by an extensive study of lung cancer rates compared with the average radon exposure in homes for 1729 counties in the United States (more than half of all counties in the nation, with 90% of the population) [37]. Plots of age-adjusted rates are shown in Figures 5A and 5C. Rather than showing individual points for each county, the plot shows points grouped into intervals of radon exposure (shown on the baseline along with the number of counties in each group). The points are plotted as the mean value of m for each group, with SD indicated by the error bars. Also plotted are the first and third quartiles of the distribution. Figures 5B and 5D show these data corrected for prevalence of cigarette smoking. When a large number of counties are represented in an interval, the SD of the mean is quite small. Figure 5 reveals a clear tendency for lung cancer rates to decrease with increasing radon exposure—with or without correction for smoking prevalence. These findings are in sharp contrast to the increase expected from the supposition, based on the linear no-threshold theory, that radon can cause lung cancer, shown by the line labeled "Theory." These data have been analyzed for more than 500 possible confounding factors, including socioeconomic, geographic, environmental, and ethnic associations [38], but the conclusion remains firm that the linear no-threshold theory fails badly by grossly overestimating the cancer risk from low-level radiation.

Cancer Risk-Versus-Dose Data from Animal and Other Studies

In the 1960s and 1970s, many animal studies were conducted on cancer risk versus dose, using X rays, gamma rays, and beta rays with both external exposures and injection of radioactive materials [39]. Nearly all of these studies indicated, with high statistical significance, that the linear no-threshold theory overestimates the cancer risk from low-level radiation.

Ingenious experimental techniques have been developed for observing the effects of a single alpha particle hitting a single cell. Miller et al. [40] found that the probability for transformation to malignancy from N particle hits on a cell is much greater than N times the probability for transformation to malignancy from a single hit. This is a direct violation of the linear no-threshold theory, indicating that estimated effects based on extrapolating the risk from high exposure, represented by N hits, greatly exaggerates the risk from low-level exposure as represented by a single hit.

Dependence of the Latent Period on Dose

A substantial body of data, both on animals and on humans, indicates that the latent period between radiation exposure and cancer death increases with decreasing exposure; these data are reviewed by Cohen [39] (older data) and Raabe [41] (more recent data). These data lead to the obvious conclusion that for low-enough exposures, the latent period exceeds the normal life span, so no actual cancers develop. Thus, an effective threshold does exist. Even in the absence of all considerations discussed previously, this effect alone would invalidate the linear no-threshold theory as applied to low-level radiation.

Conclusion

The evidence presented in this review leads to the conclusion that the linear no-threshold theory fails badly in the low-dose region because it grossly overestimates the risk from low-level radiation. This means, for example, that the cancer risk from diagnostic radiography is much lower than is given by usual estimates, and may well be zero.
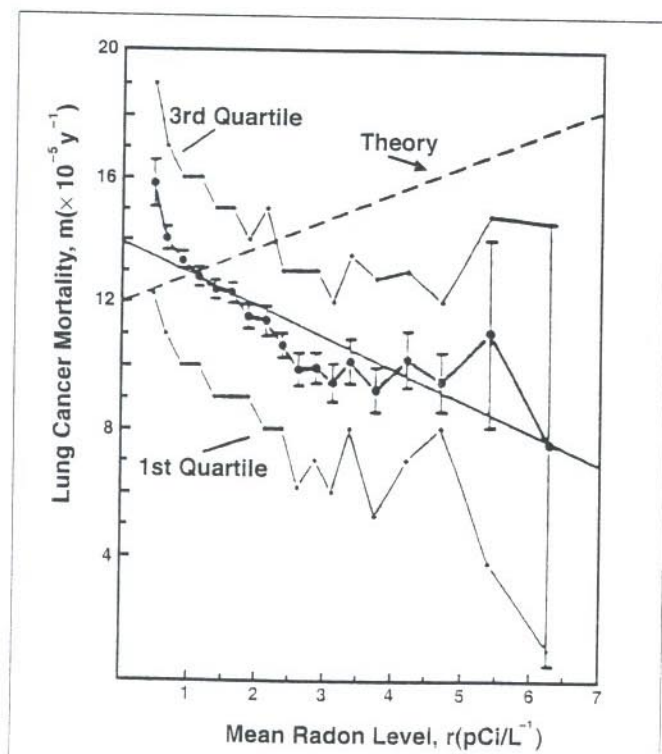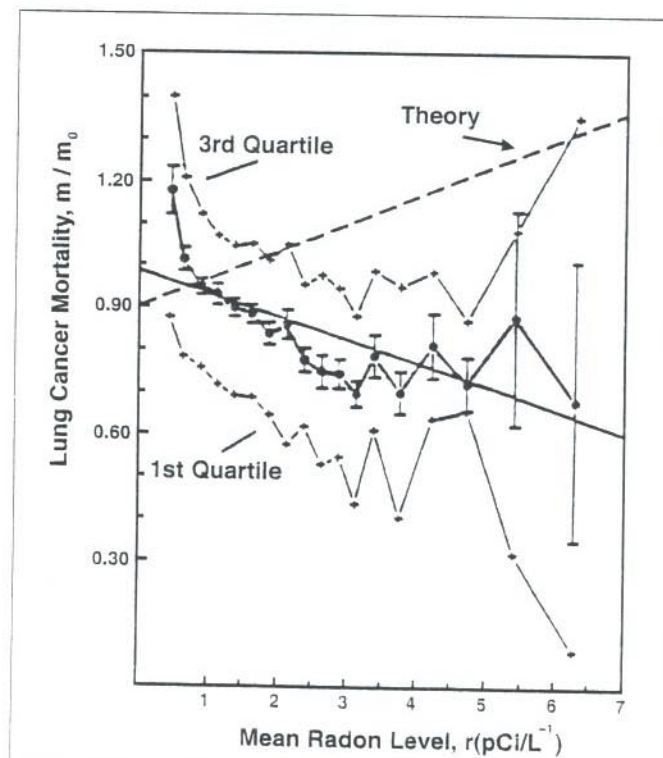
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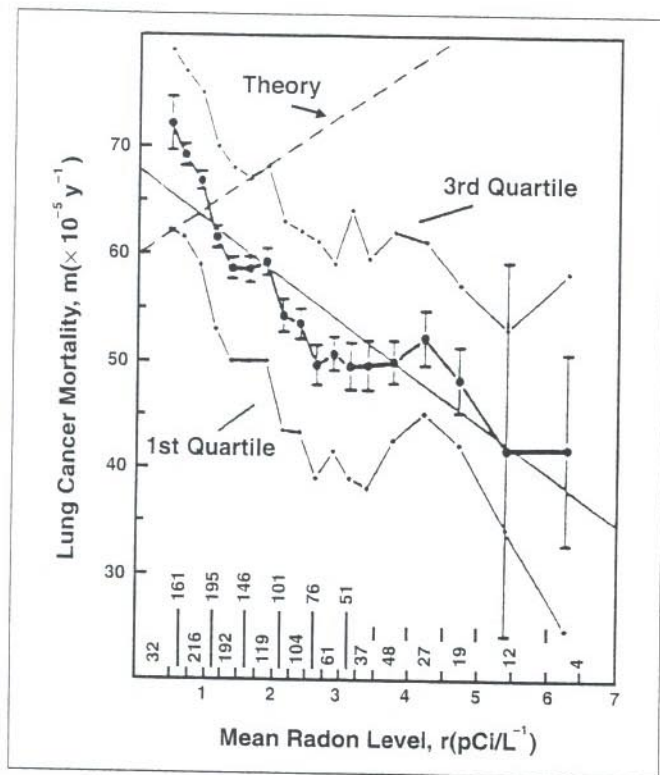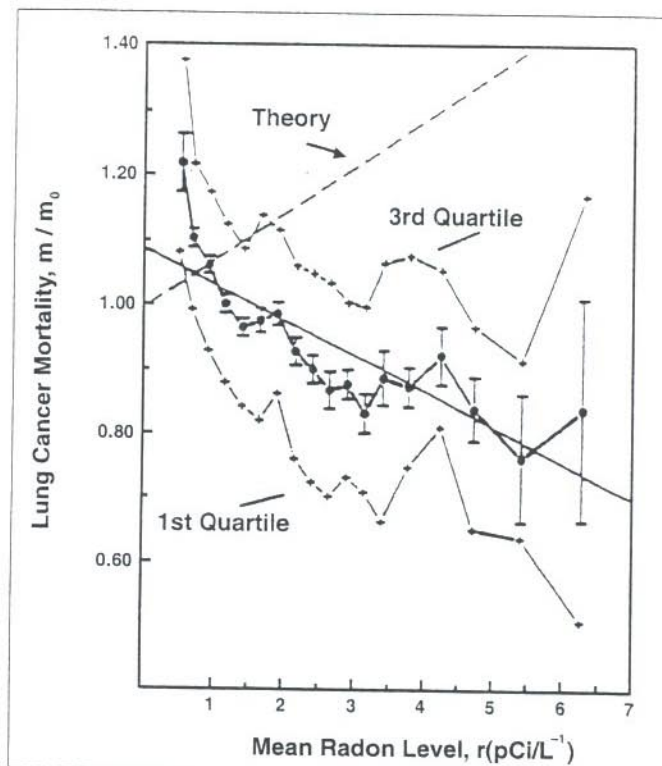
Fig. 5.—Lung cancer mortality rates (m) in the United States. Plot data are drawn from [37].
A, Plot shows lung cancer mortality rates (age-adjusted) for males versus average radon level (r) in homes in 1729 counties (90% of nation's population), y = year.
B, Plot shows lung cancer mortality rates for males from **A,** corrected for smoking prevalence.
C, Plot shows lung cancer mortality rates (age-adjusted) for females versus average radon level (r) in homes in 1729 counties (90% of nation's population), y = year.
D, Plot shows lung cancer mortality rates for females from **C,** corrected for smoking prevalence.

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