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Hormesis as a Confounding Factor in Epidemiological Studies of Radiation Carcinogenesis

Charles L. Sanders
Visiting Professor, Department of Nuclear & Quantum Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea

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Abstract - Biological mechanisms for ionizing radiation effects are different at low doses than at high doses. Radiation hormesis involves low-dose-induced protection and high-dose-induced harm. The protective component is associated with a reduction in the incidence of cancer below the spontaneous frequency, brought about by activation of defensive and repair processes. The Linear No-Threshold (LNT) hypothesis advocated by the International Commission on Radiological Protection (ICRP) and the Biological Effects of Ionizing Radiation (BEIR) Report VII for cancer risk estimations ignores hormesis and the presence of a threshold. Cancer incidences significantly less than expected have been found in a large number of epidemiological studies including, airline flight personnel, inhabitants of high radiation backgrounds, shipyard workers, nuclear site workers in scores of locations throughout the world, nuclear power utility workers, plutonium workers, military nuclear test site participants, Japanese A-bomb survivors, residents contaminated by major nuclear accidents, residents of Taiwan living in ^{60}Co contaminated buildings, fluoroscopy and mammography patients, radium dial painters, and those exposed to indoor radon. Significantly increased cancer was not found at doses <200 mSv*. Evidence for radiation hormesis was seen in both sexes for acute or chronic exposures, low or high LET radiations, external whole- or partial body exposures, and for internal radionuclides. The ubiquitous nature of the Healthy Worker Effect (HWE)-like responses in cellular, animal and epidemiological studies negates the HWE as an explanation for radiation hormesis. The LNT hypothesis is wrong and does not represent the true nature of the dose-response relationship, since low doses or dose-rates commonly result in thresholds and reduce cancer incidences below the spontaneous rate. Radiation protection organizations should seriously consider the cost and health implications of radiation hormesis.
Key words : Hormesis, LNT hypothesis, epidemiological study

INTRODUCTION

Hormesis is a dose-response phenomenon characterized by a low dose stimulation and a high dose inhibition. Hormesis has been demonstrated with a wide variety of chemical and physical agents for many diseases, including cardiovascular disease, diabetes and cancer[1-4]. The radiation hormesis hypothesis states that low-level ionizing radiation is stimulatory at cellular, molecular and organismal levels, decreasing the incidences of cancer (and other diseases) below the spontaneous frequency. This radioadaptive response to low-dose radiation, including enhancement of antioxidant defenses, enzymatic repair of DNA, removal of DNA lesions, apoptosis, and immunologic stimulation, is well established in the scientific literature [1,5-11] (Figure 1). The benefits are inducible and transient. The effectiveness of hormesis-related defense mechanisms varies with dose and dose-rate. Defenses stimulated at low doses

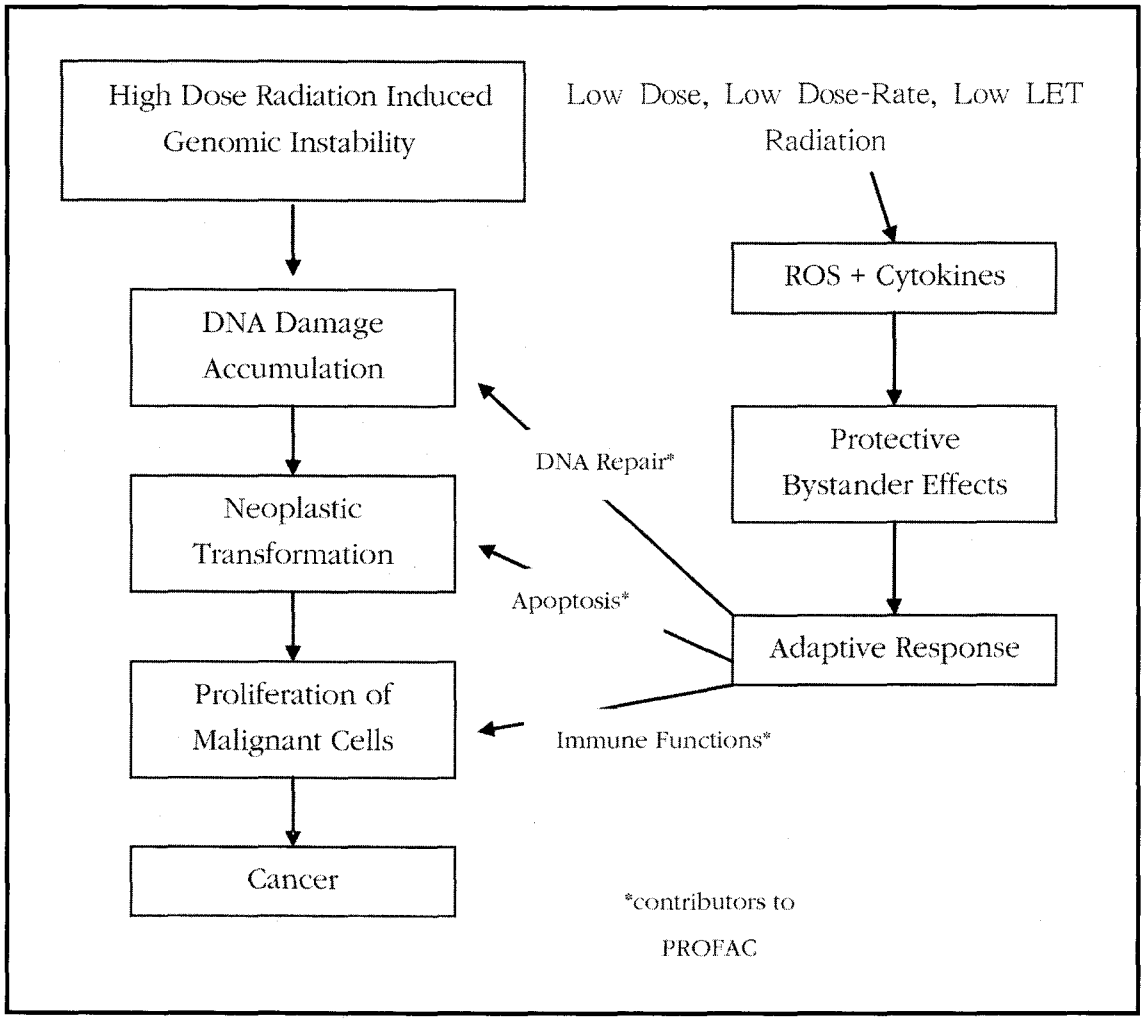

Fig. 1. Sequence of molecular and cellular events that leads to smoking-related lung cancer formation and radiation hormesis-related decrease in expected lung tumor formation.

and high doses cause un-repaired and misrepaired damage. Thus, the carcinogenic response to irradiation is suppressed at low doses and increased from a threshold dose in a stochastic manner at higher doses, leading to a curvilinear or U-shaped dose-response curve [3,12].

In his book, *Radiation Hormesis*[7], Luckey describes evidences of radiation hormesis in workers at nuclear facilities, A-bomb survivors and many other groups exposed to low doses of radiation. Luckey predicted that about one-third of all cancer deaths are preventable by low-dose ionizing radiation[5-8]. The hormesis response was associated with decreased mutations, chromosome aberrations, neoplastic transformations, congenital malformations, cancer, and increased lifespan[13-18]. The benefits of small acute or chronic doses are observed soon after exposure, while the stochastic effects of higher doses are typically seen after a long latency period.

The Linear No-Threshold (LNT) hypothesis does not consider the role of biological defense mechanisms, but assumes that cancer risk proceeds in a proportionate linear fashion without a threshold to a point of zero dose through the origin. The LNT hypothesis with a low dose and dose rate effectiveness factor (DDREF) guarantees that any radiation dose, no

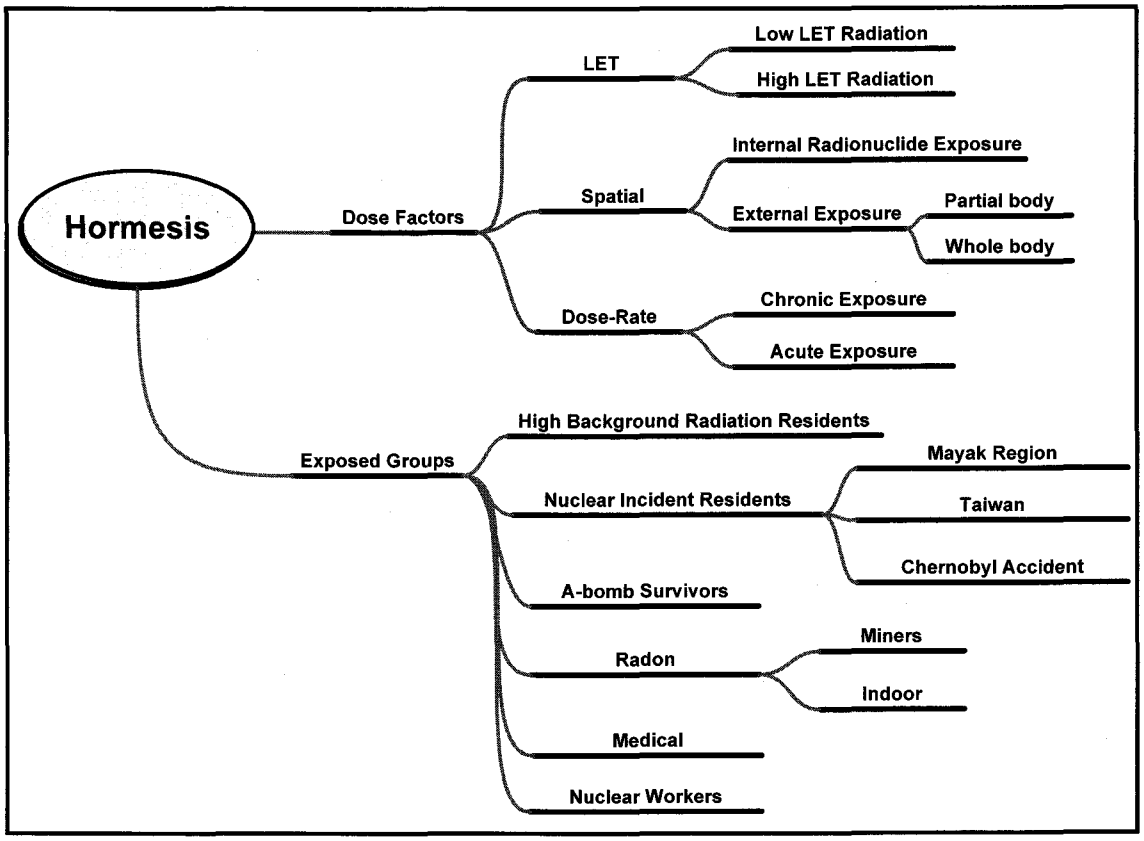

Fig. 2. Dose factors and population groups associated with epidemiological studies that demonstrate radiation hormesis.

matter how small, increases the risk of cancer. In 1951, Lewis determined the number of leukemia cases in the US which could be attributed to background radiation using the LNT hypothesis[20]. Current radiological protection methods are based upon the recommendations of the International Commission on Radiological Protection (ICRP), who utilized collective dose and the LNT hypothesis[152].

The LNT hypothesis is now widely accepted and applied, even though it has not beenvalidated by scientific study and is not consistent with radiobiological data[2,12,25]. BEIR VII, ICRP, Environmental Protection Agency(EPA) and National Council on Radiation Protection and Measurements (NCRP) support the LNT hypothesis for estimation of cancer risk from exposure to ionizing radiation [22,28-30]. Little thought has been given by radiation protection groups, such as BEIR VII and ICRP[22,23], to radiation hormesis associated adaptive and inducible repair processes and thresholds at low doses and low dose-rates[26,27].

EPIDEMIOLOGICAL STUDIES

Many epidemiological studies have been published that demonstrate radiation hormesis for low LET, low dose and low dose-rate exposures to ionizing radiation (Figure 2, Table 1).

There was no increase in cancer among airline crews and attendants who received annual doses during flight of 1.5 to 6.0 mSv [40,41]. The Standardized Mortality Ratio (*SMR*) for all cancers in women cabin attendants in Germany was 0.79, while among men it was

Table 1. Evidence of radiation hormesis from epidemiological studies of populations exposed to low dose, low dose-rate, low LET ionizing radiation.

Exposure Group	SMR for All Malignant Cancer	Reference
US DOE Nuclear Sites	0.75	138
US Shipyard	0.85	141
US Nuclear Power	0.65*	52
Canadian Nuclear Power	0.74	53
UKAEA	0.89	174
Canadian Dose Registry	0.79**	87
US Radiological Techs	0.73-0.86	94
Japanese Radiological Techs	0.81	171
Canadian Radiological Techs	0.56-0.66	172
German Aircrews	0.71-0.79	42
Chernobyl Cleanup	0.73-0.85	162
USSR Waste Tank Explosion	0.61-0.73	73
Taiwan Residents	0.03	85

* all solid cancer
** SIR

0.71. The *SMR* did not change with duration of employment[42]. Among Air Canada pilots there was a statistically significant decreased mortality from all cancers (*SMR* = 0.61)[170].

Studies of several million nuclear workers in nine studies failed to demonstrate any increased cancer risk[8]. Cancer mortality in nuclear workers at several DOE sites within the US showed either no increase in overall cancer incidence[43] or less than expected cancer incidences attributable to the Healthy Worker Effect (HWE)[44-48] (or radiation hormesis). The Relative Risk (*RR*, observed/expected) for all cancers averaged about 0.80. A study of 26,389 employees of Hanford (Richland, WA) who were hired between 1944 and 1978 found evidence of hormesis, particularly for lung cancer mortality[49,50]. An analysis of cancer mortality was carried out in 106,020 persons employed at Oak Ridge, Tennessee between 1943 and 1984. The *SMR* was 0.80 for all deaths and 0.87 for all cancers. The excess risk for leukemia was negative[51].

Mortality was examined in workers employed in 15 nuclear power utilities in the US between 1979 and 1997. No significant associations were seen for leukemia. Thislarge cohort displayed a very substantial radiation hormesis response with a *SMR* for all solid cancers of 0.65 and 0.59 for lung cancer[52]. In a cohort of 45,468 Canadian nuclear power industry workers (1957-1994) the *SMR* for all cancers was 0.74 for combined genders. The *SMR* for leukemia in males was 0.68. The *SMR* for lung cancer was 0.81 in males and 0.40 in females[53]. The cancer mortality in China of nuclear plant workers showed a radiation hormesis effect[173]. Mortality was examined in 176,000 Japanese nuclear industry workers from 1986-1997. The *SMR* for malignant tumors at all sites was 0.94 and 0.97 for lung cancer. No dose-response trend was noted[54,157].

No positive relationship between cumulative radiation dose and mortality for solid cancers or leukemia was found in 50,000 UKAEA workers[55]. However, the SMR for all

malignant tumors was 0.90 in UKAEA radiation workers compared to non-radiation workers, with substantially lower SMR values for all causes and all cancers during the early years (1946-1953) of employment with the UKAEA [174]. In a combined study of nuclear workers from the US, UK and Canada, it was claimed that leukemia was significantly associated with cumulative external radiation dose. This claim was based on only eight cases of leukemia spread among four dose groups[55]. The data showed radiation hormesis at 20-40 mSv (*RR*= 0.73) and an increased risk only at doses >40 mSv[56]. The *SMR* for all cancers at the UK Chapelcross nuclear plant was 0.73; the *SMR* for lung cancer was only 0.53[57]. At three UK nuclear facilities, the *SMR* for lung cancer in workers with the highest cumulative whole-body dose (400+ mSv) was 0.59 for radiation-monitored workers and 0.97 for unmonitored workers[58].

Cohorts of nuclear workers in 15 countries were evaluated in a pooled data analysis of cancer risk. Only excess relative risk numbers were given as determined by the LNT hypothesis. Risk by dose level was not given. Even so, at least two of the country studies exhibited a negative excess relative risk for all cancers, excluding leukemia. The authors admit that their data may be confounded by smoking[59].

A total of 123,661 person-years follow-up was evaluated in Korean nuclear workers. There was no dose-response relationship between cancer incidence and radiation dose. A radiation hormesis response for total cancer incidence was observed at doses <50 mSv (*RR* = 0.51) and >50 mSv (*RR* = 0.44)[60].

The *SMR* for Department of Atomic Energy (DAE) radiation workers in India, aged 20-59 years, was 108 (95% CI, 80-138) as compared to a *SMR* of 113 (95% CI, 84-149) for DAE employees who were not radiation workers[61].

The cancer incidence for nuclear workers in Obninsk, Russia hired before 1981 was compared with the general population of Russia during 1991-1997. The Standardized Incidence Ratio (*SIR*) in males for all cancers was 0.93 (95% CI: 0.76, 1.12)[62]. Other Russian studies described a decreased incidence of lung cancer in nuclear radiochemical workers[14,63].

About 30,000 people lived along the Techa River during the early years (1949-1956) of the Mayak nuclear weapons facility operation in the Southern Urals. Radiation exposures involved both external and internal sources from contaminated river sediments ad ingested food. External exposure involved ^{137}Cs gamma rays, and internal beta exposure involved with ^{90}Sr and other radionuclides. Radiation dose estimates were difficult to accurately determine. Significant leukemia risk occurred only for doses >0.2 Gy to bone marrow. The *RR* for solid cancers was 0.60 in males[65].

Evacuees and others living close to the exclusion zone around Chernobyl received whole body doses in the range of 0.1 to 0.5 Gy. Average lung doses were as high as 0.6 Gy due largely to inhalation of radionuclides[66]. About 1,000 workers were heavily exposed on the first day of the accident, 200,000 recovery workers were exposed during 1986-87 and about five million people living in Belarus, Russia and Ukraine were exposed as a result of radionuclide fallout. Twenty years after the nuclear disaster at Chernobyl, a three-volume report listed health effects associated with the accident[68]. Fewer than 50 deaths have been directly attributed to radiation, almost all being highly exposed rescue workers, most of whom died within a few months. Excess leukemia or other cancers was not found in 5000 cleanup workers from Estonia. Only mortality from suicide was statistically increased[169]. From 17-25% of contaminated residents in Ukraine and Belarus accumulated thyroid doses >1 Gy[67]. Several thousand cases of thyroid cancer, mainly in those who were exposed as children and adolescents, have been found in the populations; only nine children have died of thyroid cancer. No evidence of an increase in the incidence of leukemia or solid cancers has been found[67,68]. In fact, the mortality rate was statistically lower for clean-up staff than for the

general public[163]. A study of 8600 workers involved in the early cleanup of the accident site, who received external doses > 50 mSv, showed a cancer incidence that was 12% less than expected[69]. Analysis of a cohort of 65,905 emergency workers from 1991-1998, who received an external dose of 0.005-0.3 Sv showed annual *SMR*s for malignant neoplasms that ranged from 0.73 to 0.85[162].

From 1949 to 1989, the former USSR conducted more than 450 nuclear explosion tests at the Semipalatinsk nuclear test site. Dolon village in the Semipalatinsk region was 110 km down-wind from the weapon test site. The mean radiation dose to residents of Dolon from nuclear fallout was about 0.5 Gy[71,72,154]. No dose-response trend was seen for total solid cancers at doses up to 750 mSv. Cancer mortality, including leukemia, was less than expected among military participants at US nuclear test sites[70].

Athermo-chemical explosion at a nuclear waste tank in 1957 contaminated 22 villages in the Eastern Urals of the USSR. Cancer mortality was significantly reduced in 7,852 inhabitants by 28%, 39% and 27% for mean dose-cohorts of 49 cGy, 12 cGy and 4.0 cGy, respectively[73].

Twenty-three Japanese fishermen were given whole-body exposures to 200-670 cGy gamma radiation from an American H-bomb test in 1954. All experienced evidence of the acute radiation syndrome and one died within eight months. None of the remaining twenty-two fishermen has died of cancer by 25 years after exposure[74].

There were 86,572 Japanese A-bomb survivors forty years after the bomb detonations. About 80% of the Japanese study population had doses < 200 mSv and 65% had doses <100 mSv. However, 80% of the 'excess cancer deaths' were in the 20% receiving > 200 mSv. Of the total, 8% received > 2 Sv, 23% received 1-2 Sv and 26% received 0.5-1 Sv[12,146]. Estimates of cancer risk were extrapolated from high dose/dose-rate data using the LNT hypothesis. A U-shaped lifespan pattern was found in A-bomb survivors, with increased lifespan at low doses[76-78]. Only 334 excess solid cancer deaths and 28 excess leukemia deaths were recorded in this group. A significant increase in the incidence of all cancers at all ages and genders in A-bomb survivors was not found below 200 mSv for adults or 100 mSv for children[12]. Recent results show not a linear but a curvilinear response for cancer[80,81]. The solid cancer incidence was not significantly increased, while the leukemia incidence was significantly increased using the LNT hypothesis. Evidence of a threshold and radiation hormesis was seen for leukemia at < 20 cSv[65,82]. Leukemia incidence in Nagasaki A-bomb survivors decreased as doses increased from 2 cGy to 50 cGy (zero at 39 cGy)[86]. Morphological malformations were significantly reduced in children born of A-bomb surviving mothers who received <20 cGy[83].

Recycled steel contaminated with cobalt-60 was used in the construction of about 180 buildings in Taiwan, housing 10,000 persons for 9 to 20 years. The average whole-body gamma-ray dose was 0.4 Sv given at an average dose-rate of 50 mSv/y. About 1,100 persons received cumulative doses of 4 Sv from 1983 to 2003. The average dose received by the Taiwan residents was higher than the average doses received by Japanese A-bomb survivors and emergency workers in the Chernobyl accident, but similar to those residing in high radiation background regions of the world[84]. Only seven cases of fatal cancer were found in Taiwan building residents from 1983 to 2003. The cancer mortality rate of residents was 3.5 per 100,000 person-years, while the expected spontaneous cancer mortality rate was 116 persons per 100,000 person-years. Only three children were born with congenital malformations. The *RR*for residents was only 0.030 for fatal cancer and 0.065 for congenital malformations[85].

Nearly 200,000 participants in the National Dose Registry of Canada from 1951 to 1988 were examined for cancer mortality. The

combined *SIR* for all cancers in both sexes was 0.79. For lung cancer, the *SIR* was 0.69, and for leukemia, it was 0.72[87].

The Canadian fluoroscopy study involved 31,710 women being treated for tuberculosis from 1930 to 1952[88]. The *RR* of breast cancer was 0.66 at 15 cGy and 0.85 at 25 cGy. This study predicted 7,000 fewer breast cancer deaths in a million women receiving 15 cGy. The paper was revised to include only one dose-cohort of 1-49 cGy, removing this highly significant inverse relationship[89]. Five Swedish mammography studies, where women received an average of 0.12 Gy to the breast showed an overall *RR* of 0.79 for breast cancer mortality[92]. A threshold of at least 1 Sv was found for lung cancer in Canadian and American fluoroscopy patients with lung cancer mortality being about 15% less than expected[90,91].

No evidence of increased cancer risk was found in radiologists and radiologic technicians employed after 1950 in Japan[75]. Medical diagnostic radiation did not increase the incidence of leukemia at cumulative doses <200 mSv[24,93]. Radiologists and radiological technicians did not exhibit significantly increased cancer rates at annual doses of 10-50 mSv or at cumulative doses of <200 mSv [94,95,155,156,158]. The *RR* for leukemia among Calvert Cliffs Nuclear Power Plant workers was 0.5; the mean cumulative occupational dose was 21 mSv with a maximum dose of 470 mSv[170]. The *SMR* for cancer mortality in British radiologists working from 1955 to 1979 was 0.71 relative to that of male physicians in England and Wales[156] (Table 2). The *SMR* for all cancers among US technologists was 0.86 (female) and 0.73 (male)[94]. For Japanese technologists the *SMR* for all cancers was 0.81[171], while for Canadian radiation workers the *SMR* was 0.66 (female) and 0.56 (male)[172].

From 1940 through 1970 about one million children and 8,000 military personnel were treated with nasopharyngeal radium irradiation for swollen adenoids, tonsils, hearing lose and chronic ear infections. Local doses were about 20 Gy mostly from beta irradiation to local tissues, while other tissues of the head and neck were exposed to much lower doses of gamma irradiation. No increase in cancer of the head and neck was found in these two populations treated with radium[164,165].

The Hanford Thyroid Disease Study showed a negative slope for thyroid cancer risk versus dose to the thyroid[96]. About 35,000 Swedish patients who received a thyroid dose of 0.5 Gy from ^{131}I for diagnostic purposes experienced a 38% reduction in expected thyroid cancers[97].

Several studies show a significantly decreased cancer death rate in areas of high background radiation[31]. The age-adjusted cancer mortality rate for the US population (1950-1967) decreased with increasing background radiation [32]. A 20% lower cancer mortality rate was found in Idaho, Colorado and New Mexico than in Louisiana, Mississippi and Alabama with background radiation levels that were over three times for those living in the southeast[32]. The incidence of leukemia and lymphoma was 19% less in males and 6% less in females for those living in the US at an altitude of 2000-5300 feet

Table 2. Cancer in British Radiologists working from 1897 to 1979[156].

Years Joined	Tolerance or Exposure Limits	SMR (compared to UK male non-radiologist physicians)	
		All Cancers	Lung Cancer
1897-1920	> 1 Sv $year^{-1}$	1.75	2.46
1921-1935	< 1 Sv $year^{-1}$	1.24	1.06
1936-1954	2 mSv day^{-1} or 500 mSv	1.12	0.74
1955-1979	50 mSv $year^{-1}$	0.71	0

as compared to those living at an altitude of <500 feet[34]. Decreased cancer levels were found in inhabitants of Yangjiang, China[35], Kerala, India[36,37] and Ramsar, Iran[38,39] living in high natural radiation areas (7.5-500+ mGy^{-1}).

The Mayak plutonium workers had mean lung doses that ranged from 1-2 Gy. Lung cancer cases were primarily due to smoking, and most of the remaining cases to interaction of smoking and internal alpha-radiation[98-100,159]. A case-control study of all morphologically verifiable lung cancer cases from 1966 to 1991 among the Mayak nuclear workers found a threshold of 3.7 kBq or 0.80 Gy for incorporated plutonium-239 which could be described by linear-quadratic or quadratic models. The incidence of lung cancer at lung doses <0.8 Gy was below control levels[100]. The *RR* for lung cancer in Russian nuclear fuel reprocessing plant workers was 0.39 at 0.1-12 mGy and 0.53 at 12-50 mGy[14,160].

In a study of solid cancers, all Mayak nuclear workers with doses <0.5 Gy were lumped together[102]. No clear dose response relationship was noted with *RR*values of 1.15, 1.21, 1.85, 1.81 and 2.20 at dose groupings of <0.5 Gy, -1 Gy, -3 Gy, -5 Gy and >5 Gy from external whole-body gamma radiation, respectively. Excess mortality was seen only in workers with plutonium-239 burdens exceeding 7.4 kBq[102]. Data at low doses for bone and liver cancers were not provided in two other Mayak cancer studies[103,104].

Twenty-six male workers employed at Los Alamos from 1944-45 received a median effective dose of 1.25 Sv (range 0.1 to 7.2 Sv). Only seven have died as compared to an expected sixteen (*SMR* = 0.43)[105]. Seventeen 'terminally ill' patients received IV injections of 95-400 nCi ^{239}Pu between 1945 and 1947. None who lived longer than a year died of cancer. Four lived from 30 to 44 years free from cancer[106].

A study of Rocky Flats Plant employees employed from 1951 and 1989 showed a threshold for lung cancer of 400 mSv. An inconsistent dose-response was found at higher doses. A statistically significant radiation hormesis effect was also found[107]. The *SMR* for all cancer deaths for plutonium nuclear workers was 0.70; for lung cancer the *SMR* was only 0.14[108]. The *SMR* for cancer mortality was 0.54 and the *SMR*for lung cancer mortality was 0.20 in a later study[109].

No association between ^{210}Po dose and cancer mortality was seen in a cohort of 4,402 workers at Mound Facility who had been exposed from 1944 to 1972. No dose-response trend was observed. The relative risk for lung cancer attwo of the dose groups was 0.34 and 0.54[110].

The National Research Council (BEIR VI) estimated that 10-15% of the annual 160,000 lung cancer deaths in the United States may be attributed to indoor radon at levels >37 Bq/m^3, with an uncertainty of 3,300 to 32,000 deaths[21,93,105]. Protracted exposures to radon were found to be more hazardous[113,114]. The possibility of a threshold was not ruled out by BEIR VI. BEIR VI felt that it is especially difficult to estimate radon risks for nonsmokers in homes using high dose data from uranium miners[161], and that the assumption of linearity of lung cancer risk down to the lowest exposures could not be validated against observational data[21].

A meta-analysis of eight case-control studies of indoor radon and lung cancer showed significant differences in the dose-response relationships. Five of the studies showed evidence of radiation hormesis[101,107]. A study of lung cancer and indoor radon in China showed evidence for hormesis at 200-249 Bq/m^3 (*RR* = 0.75) in the Shenyang study[111]. A meta-analysis of 20 case-control studies, including seven in North America, failed to provide *RR* data for dose-exposure groups in each study, giving only the excess odds ratio obtained by regression using the LNT hypothesis[115]. A meta-analysis of indoor radon and lung cancer from 13 European case-control studies did not provide stratified dose-cancer data from each study[116]. No

significant risk of lung cancer was found in never smokers in either meta-analysis.

Several reports have shown a negative relationship between environmental radon levels and lung cancer rates[39,79,117-120]. One study showed a threshold at about 1,000 Bq/m^3 [121]. The relative risk of lung cancer in female non-smokers in four counties of Saxony in East Germany was 0.60, where the average indoor radon levels exceeded the country average by 3-10 fold[122]. Overall, the *RR* for lung cancer in females in the Free State of Saxony was 0.98[123]. Less than expected lung cancers were found in a high radon region in the Hungarian village of Matraderecske[140].

Cohen[39,117,124-126] found a non-linear, negative dose-response for lung cancer from environmental radon using ecologic epidemiological studies. Cohen's study encompassed about 300,000 radon measurements in 1,601 counties of the United States, representing about 90% of residents living in the U.S[126]. The trend of county lung cancer mortality was strikingly negative even after adjusting for smoking and 54 other socioeconomic factors. Using 1 pCi/L (37 Bq/m^3) as the baseline risk, or 1.0, Cohen showed that lung cancer risk increased at 0.5 pCi/L to 1.2, and then decreased in a linear manner to about 0.80 at 5 pCi/L. At higher doses the radiation hormesis effect began to disappear[127]. Cohen's data points have very small error bars which are given in small increments of dose. Cohen later evaluated over 500 methodological and confounding issues, none of which explained the large negative correlation of lung cancer with increasing radon exposure.

Similar inverse relationships between environmental radon levels and lung cancer rates have been shown in other studies [118,124,125]. A case-control study of lung cancer and radon in Finland fit the Cohen curve well[128]. The relative risk of cancer in the lung, stomach, breast and for leukemia were significantly less in a high radon Japanese spa area than in a control area of much lower radon[129]. Haynes[130] evaluated 55 counties in England and Wales and found a statistically significant negative association between radon concentration and lung cancer.

SMR values of 0.52 for cancer of the tongue and mouth, 0.35 for cancer of the pharynx and 0.69 for cancer of the nose were found in a combined analysis of 11 studies of underground miners[166]. SMR values for all non-lung tumors in three underground mines were 0.89, 0.73 and 0.76 at average final cumulative exposures of 30, 11 and 164 WLM, respectively [161,167,168]. There was no evidence for an association between indoor radon and childhood leukemia[123,131].

Among the US radium dial painters of the 1920s, there were 65 cases of bone cancers in those receiving bone doses >10 Gy and no cases in dial painters with bone doses <10Gy[132-134]. A clear threshold for bone cancer was also seen in dogs injected with radium and other alpha-emitters[135]. A threshold of about 1 Gy was found for bone tumors in 900 German patients injected with radium-244 for therapy of ankylosing spondylitis or bone tuberculosis[64]. Female dial painters received average bone marrow doses of 4 cGy/y. The *SMR* for leukemia in 1,285 US dial painters was only 0.22[137]. No leukemia deaths were found in female British dial painters. The British dial painters also had a non-significant increased lifespan[136].

Wilkinson studied the causes of mortality in women working in twelve U.S. nuclear weapons facilities (Table 3). The study covered a total of 67,976 women who worked at these sites before 1980. A strong radiation hormesis response was seen in all facilities for all causes of death and most cancers. Ten of twelve facilities showed decreased lung cancer and eleven of twelve showed decreased breast cancer[138]. Wilkinson compared mortality data for female nuclear workers who wore badges to monitor radiation exposure with mortality in female workers who did not wear badges. He showed that there were 25% more deaths from all causes and 17% more deaths from cancer in unbadged workers than in badged workers. The relative risk for

Table 3. Specific Standardized Mortality Ratios (Observed/Expected) Among White Females at DOE Weapons Facilities. Data is from Wilkinson[138].

Nuclear Facility	Cause of Death			
	All Causes	All Cancers	Respiratory Track Cancer	Breast Cancer
Fernald	0.70	0.77	0.65	0.69
Hanford	0.75	0.78	0.87	0.85
K-25	0.81	0.77	0.80	0.71
Linde	0.97	0.92	1.07	0.98
Los Alamos	0.67	0.70	0.72	0.80
Mound	0.73	0.89	0.76	1.28
Pantex	0.65	0.59	1.19	0.25
Rocky Flats	0.54	0.60	0.70	0.68
Savannah Rv	0.79	0.73	0.53	0.50
X-10	0.71	0.75	0.80	0.82
Y-12	0.76	0.76	0.95	0.73
Zia	0.74	0.71	0.93	0.70

lung cancer mortality in unbadged women who were not monitored was 49% higher than in badged workers[138].

The thirteen year US Nuclear Shipyard Workers Study (NSWS) evaluated workers health at eight shipyards. The study was carried out by Johns Hopkins Department of Epidemiology and a final report written in 1997[139]. Workers were primarily exposed to ^{60}Co gamma rays. The average shipyard dose was 7.6 $mSvy^{-1}$. The study was designed to avoid the HWE in comparing age-matched and job-matched nuclear workers and unexposed controls. A high-dose cohort (>5 mSv) of 27,872, low-dose cohort (<5 mSv) of 10,348 and a control cohort of 32,510 unexposed shipyard workers were examined. The high-dose workers demonstrated significantly lower cancer and all-cause mortality than did unexposed workers. The results showed a statistically significant decrease ($p<0.001$) for nuclear workers (*SMR* = 0.76) from all cause mortality as compared to non-nuclear workers (*SMR* = 1.02) at the same shipyard[141]. For all malignant tumors the *SMR* values were 1.12 (controls), 0.96 (low dose cohort) and 0.95 (high-dose cohort); the *SMR* for the highest dose cohort was significantly less ($p<0.05$) than controls. The *SMR* for leukemia and hematopoietic cancers was 1.06 (controls), 0.51 (low-dose cohort) and 0.79 (high-dose cohort) [141].

DISCUSSION

The HWE is the name given to the observation of employee cohorts that showed a reduced mortality from all causes and/or cancer when compared to the general population[7,143]. The HWE is commonly observed in many industries. However, the effect usually lasts for only the first few years of employment and not for the decades seen in nuclear workers[142]. HWE has been attributed to pre-employment and routine medical screening for workers employed for long periods of time at the same site[75,77]. This assumes that those who work

at a nuclear site exhibit better medical care than those who live in the same area.

The HWE-like response is seen in many epidemiological studies not involving employee screening or medical care. No reduction in mortality from all cancers was found in men who received annual medical physicals compared to men who did not[144,145]. The HWE does not explain radiation hormesis responses found in epidemiological studies that do not include workers. Epidemiological studies that compare exposed and unexposed cohorts in the same company or workplace, where medical procedures for employment and employee health are similar, should best delineate the HWE from hormesis[7]. The large size of the NSWS and Wilkerson multi-facility studies for exposed and control cohorts provided powerful statistically significant evidence for radiation hormesis [138,141]. These and other studies, which had appropriate internal controls for entrance into employment and medical care once employed, demonstrated clear evidence of radiation hormesis (Table 4).

Radioadaptive and HWE-like responses are seen in a large number of experimental animal studies. Evidence for radiation hormesis is found in both sexes over a wide range of spatial-temporal dose-distribution patterns, for varying dose-rates (acute to continuous), LET values, external whole-body or partial-body exposures or internal exposures in selected organs (thyroid gland, lung or skeleton). The Taiwan study[85] provides the most compelling evidence for radiation hormesis with its low dose-rate, low-LET continuous external exposures. The rather ubiquitous nature of HWE-like radiation hormesis responses in cellular, animal, and epidemiological studies would negate the HWE as an explanation for the radiation hormesis phenomenon in human population studies.

BEIR committees apply the LNT hypothesis using a DDREF, converting risk estimates at high dose rates to corresponding risks at low dose-rates down to natural background radiation. This approach guarantees that any amount of radiation is harmful. BEIR VII emphasizes the excess relative risks of solid cancer for the Japanese A-bomb survivors as representing the appropriateness of the LNT hypothesis, but ignores a massive literature to the contrary, as being "phenomenological data with little mechanistic information…in some cases appear to be restricted to special experimental circumstances"[22]. The ICRP committee on health risks concluded that "the concept of adaptive responses to radiation lacks adequate biological support and the available data fail to provide good evidence of robust protective effects for cancer…the possibility that there might be a threshold dose, below which there would be no radiation-related cancer risk, has been ignored"[151]. Only one page of BEIR

Table 4. Epidemiological studies with internal controls that negate the HWE.
In each study, the SMR (RR) for all cancer in radiation-exposed cohorts was compared with non-radiation cohorts in the same workplace or environment to reduce the biases resulting in the HWE.

Worker Comparison	SMR All Cancer	Reference
Badged/Unbadged DOE Female Workers	0.83	138
High-Dose/Control Shipyard Workers	0.85	141
Radiation/Non-Radiation Chapelcross UK Nuclear Workers	0.73	57
Radiation/Non-Radiation UKAEA Workers	0.89	174

VII's 700+ pages discusses radiation hormesis [19,22]. In using the LNT hypothesis, BEIR VII, ICRP, and EPA ignore the possible presence of any threshold[22,28-30,152,153]. Although admitting that simple extrapolation from high doses may not be justified, they feel that it is scientifically justified to do so[23,150].

Data in favor of radiation hormesis are exceedingly robust. Not presenting this data in the evaluations by ICRP and BEIR VII is difficult to understand. Their prize study to demonstrate the accuracy of the LNT hypothesis is the Japanese A-bomb survivors. This is a high dose and very high dose-rate study that exhibits evidence of a threshold, increased lifespan and radiation hormesis at low doses. There is no evidence of an increased cancer rate in A-bomb survivors at doses <200 mSv[149]. However, there is evidence that A-bomb survivors are living longer[78]. If dose-rate is taken into consideration, the threshold level may be as high as 500 mSv. The concept of collective dose can be ignored when using a threshold and/or radiation hormesis in assessing the stochastic cancer risk in large populations exposed to low doses[163].

The Health Physics Society and the American Nuclear Society position statements are that "there is insufficient scientific evidence to support the use of the LNT in the projection of health effects of low-level radiation". Raymond Orbach of the US DOE in his letter to the president of the National Academies expressed his disappointment with the BEIR VII's shortcomings[147]. Russian scientists find the LNT hypothesis to be "highly questionable" [163]. Participants of the "Wingspread Conference" (1997) felt that an increase in cancer has not been found at doses <10 rem[19]. NCRP-136 said "It is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased, and in most cases the rates have appeared to be decreased"[30].

The 2005 French Academie des Sciences (Paris) & the Academie Nationale de Medecine report[12] is in stark contrasted with the BEIR VII report. The French Academies concluded that the LNT hypothesis should not be used for assessing the carcinogenic risks of low or very low doses[148]. They found that the dose-effect relationship for solid tumors in the Japanese A-bomb survivors is not linear but curvilinear between 0 and 2 Sv[12]. The French Academy found abundant evidence for radiation hormesis and believed that this data should be implemented in making radiation protection guidelines.

Most epidemiological data describes radiological environments of relatively high dose exposures. The relevance of high dose data to estimations of risk at low doses is being question by more investigators. Pooled data analyses or individual epidemiological publications should provide the cancer risks for all dose categories, including the lowest doses for each study, and not just a single excess relative risk estimate of cancer obtained by the LNT hypothesis. The practice of grouping several low dose categories into one dose group to remove evidence of radiation hormesis should be abandoned. The current biased practice by some of reporting epidemiological results is misleading.

CONCLUSIONS

The LNT hypothesis is not justified for assessing cancer risks at low doses. Robust significant evidence of radiation hormesis was found in epidemiological studies of radiation exposed human populations at doses <200 mSv. The ubiquitous nature of the hormetic responses in cellular, animal and epidemiological studies negates the HWE as an explanation for radiation hormesis. Because the LNT hypothesis is very well established and because many strong radiation protection organizations are in place, scientists and government officials are reluctant to seriously consider the implications of the radiation hormesis phenomenon, which has very important public health consequences.

The cost in lives and money in implementing current radiation guidelines is enormous, while the benefit to our health may be negative with not less but more cancer.

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