PREVENTION OF CIGARETTE SMOKE INDUCED LUNG CANCER BY LOW LET IONIZING RADIATION

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Lung cancer is the most prevalent global cancer, ~90% of which is caused by cigarette smoking. The LNT hypothesis has been inappropriately applied to estimate lung cancer risk due to ionizing radiation. A threshold of ~1 Gy for lung cancer has been observed in never smokers. Lung cancer risk among nuclear workers, radiologists and diagnostically exposed patients was typically reduced by ~40% following exposure to <100 mSv low LET radiation. The consistency and magnitude of reduced lung cancer in nuclear workers and occurrence of reduced lung cancer in exposed non-worker populations could not be explained by the HWE. Ecologic studies of indoor radon showed highly significant reductions in lung cancer risk. A similar reduction in lung cancer was seen in a recent well designed case-control study of indoor radon, indicating that exposure to radon at the EPA action level is associated with a decrease of ~60% in lung cancer. A cumulative whole-body dose of ~1 Gy gamma rays is associated with a marked decrease in smoking-induced lung cancer in plutonium workers. Low dose, low LET radiation appears to increase apoptosis mediated removal of α -particle and cigarette smoke transformed pulmonary cells before they can develop into lung cancer.

KEYWORDS : Radistion Hormesis, Lung Cancer, Cigarette Smoke

1. INTRODUCTION

There are about 1.5 million new cases of lung cancer diagnosed in the world each year. Lung cancer is the most prevalent cause of cancer mortality in the U.S., accounting for approximately 30% of all cancer deaths [1]. Lung cancer accounted for 1.2 million deaths worldwide in 2002, representing 18% of global cancer deaths [3]. About 90% of lung cancer mortality is due to cigarette smoking [2].

With the LNT (Linear No Threshold) hypothesis, any dose of radiation is expected to increase the risk of lung cancer. In using the LNT hypothesis, BEIR VII, ICRP, EPA, and NCRP assume that cancer risk is directly proportional to radiation dose, that biological mechanisms of cancer causation are the same at low and high doses, and that there is no threshold. Although admitting that simple extrapolation from high doses to low doses may not be justified, they do so anyway [6]. In contrast, the 2005 French Academy of Sciences (Paris) and National Academy of Medicine report [7] concluded that the LNT hypothesis should not be used for low-LET doses < 100 mGy for assessing carcinogenic risks [8]. The French Academies found abundant evidence for the radioadaptive response and radiation hormesis (benefit) and believed

that this data should be implemented in establishing radiation protection guidelines [7]. The same position was also taken by the Australasian Radiation Protection Society [177] and by participants in the 15th Pacific Basin Nuclear Conference [31]

The radiation hormesis response, whereby low doses of ionizing radiation stimulate protective mechanisms in the cell, leading to a reduction in naturally occurring cancer, has been extensively studied. Low dose, low LET radiation activates a system of transient protective processes that includes antioxidants, high efficiency DNA repair, immunosurveillance and apoptosis preventing, repairing or removing genomically unstable (transformed) cells from developing into cancer. The adaptive response is associated with increased lifespan, and decreased mutations, chromosome aberrations, neoplastic transformations, congenital malformations, and cancer [9-13]. The protective processes are transient over time intervals of hours to weeks [179]. The selective removal of transformed cells by apoptosis is thought to involve intracellular signaling due to interactions with oxygen and nitrogen species and cytokines [22,175-176]. Apoptosis of chemical or radiation induced transformed cells is activated by low-dose, low-LET gamma or x-radiations, preventing expression of cancer [14-16].

2. LUNG CANCER IN SMOKERS

Cigarette smoke is a complex mixture of more than 6000 chemicals, separated into a vapor phase and a particulate phase. Numerous carcinogenic compounds have been identified in primary and side-stream tobacco smoke. Hundreds of chemicals in tobacco smoke, including ^{212}Pb and ^{210}Po , react covalently with DNA to form adducts or produce free radicals causing oxidative damage. More than 40 chemicals in smoke are known to cause cancer in humans and/or animals [23]. Cigarette smoke exhibits very significant synergistic interactions with ethanol to induce oral/pharyngeal cancers [24] and with asbestos to induce lung cancer [25].

The lung cancer incidence in Dresden, Germany increased about a hundred-fold from 0.06% in 1852 that was associated with cigarette production beginning in 1862 [26]. The Relative Risk (RR) for lung cancer in heavy smokers living in the U.S. and European countries can be >100 [27-28]. Typical RR values for lung cancer mortality associated with ever-smoking, as compared to never-smoking, ranges from 15 to 30 [29,182]. The risk of lung cancer is highly dependant upon the number of cigarettes smoked per day, the length of time smoking, and time since quitting for ex-smokers [30]. The RR for lung cancer in France was 15.6 for current smokers, 9.2 for ex-smokers who stopped within the previous ten years and 2.9 for ex-smokers who stopped at least 10 years [31]. Survival from lung cancer is poor with only $\sim 10\%$ of patients living longer than one year after diagnosis [32].

The cancer burden from tobacco use is enormous, confounding the usually much smaller lung cancer risks associated with ionizing radiation. The interaction of smoking and radiation makes lung cancer risk estimation more difficult [31]. The large variability among epidemiological studies of lung cancer and radiation dose is due to this powerful confounding influence of cigarette smoking [36-39]. Cigarette smoking so confounds studies of lung cancer formation in irradiated populations that it is difficult to determine if ionizing radiation exerts a significant effect on lung cancer formation in smokers unless they exhibit a $\text{RR} > 2.0$ [40,46].

Eighty percent of male A-bomb survivors reported that they were smokers [47]. Of the about 600 lung cancer cases in Japanese A-bomb survivors, about 50 were related to radiation [48-49]. These few "excess" lung tumors could be mostly explained by the uncertainty of smoking habits [50-51]. Insufficient smoking data are commonly given in most published papers of lung cancer risk in irradiated populations [52-54]. Cohorts of nuclear workers in 15 countries were evaluated in a large meta-analysis of cancer risk. The authors admit that the study was not well controlled for smoking [55].

3. LUNG CANCER IN IRRADIATED NEVER SMOKERS

Over 100 epidemiological studies have failed to demonstrate a significant radiation risk of lung cancer in never smokers at doses $< 1\text{-}2\text{ Gy}$ [31,33-35]. A meta-analysis study indicated that doses $< 2\text{ Gy}$ did not cause lung cancer in never smokers "but, in fact, indicate a reduction of the natural incidence" [33]. Other meta-analyses failed to show a significant association of indoor radon with lung cancer in never smokers [41-44,139-140]. The radon database in the IARC (International Agency for Research on Cancer) was reviewed without finding a single study of occupational risk for lung cancer in never smokers [44-45]. The lowest dose for which lung cancer was found in non-smoking U.S. uranium miners was >100 Working Level Months (WLM) [34]. Average lung doses among Chernobyl liquidators were as high as 0.6 Gy due largely to inhalation of radionuclides [56]. No increase in the incidence of lung cancer was found in any group associated with the Chernobyl accident [57-58]. An increase in lung cancer in never smokers was not detected in A-bomb survivors [50].

4. LUNG CANCER AND LOW LET RADIATION

"No one has been identifiably injured by radiation while working within the numerical standards set first by the NCRP and then the ICRP in 1934" [63]. The 1934 ICRP standard was $\sim 500\text{ mSv yr}^{-1}$ [64]. The approximate human cumulative threshold dose for lung cancer induction for low LET, near continuous exposures is $\sim 15\text{ Sv}$ [65].

A significant part of the heterogeneity in carcinogenicity following low LET exposures may be due to dose-rate effects [59-60]. Plotting data from several epidemiological studies, as a daily dose instead of total cumulative dose, removed much of the heterogeneity, with a threshold of $\sim 100\text{ mSv d}^{-1}$ for excess relative risk of all solid cancers [61]. A dose-rate of $1\text{-}10\text{ mGy d}^{-1}$ was associated with radiation hormesis [62].

Evidence for reduction in lung cancer risk from low dose radiation exposures has been found in a large number of epidemiological studies including airline flight personnel, inhabitants of high radiation backgrounds, shipyard workers, nuclear site workers, nuclear power utility 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, radiologists and radiological technicians and radiological diagnostic and therapeutic patients [12,23,31].

Annual determinations of cancer mortality from 1946 to 1997 have consistently shown evidence of hormesis in UKAEA nuclear workers [67] and in Chernobyl liquidators [68]. At three UK nuclear facilities, the Standardized Mortality Ratio (SMR) for lung cancer in workers with the highest cumulative whole-body dose (400+ mSv) was 0.59 for monitored workers and 0.97 for unmonitored

workers [69]. The RR for lung cancer at the UK Chapelcross nuclear plant was 0.57 ($p < 0.0001$) based on Scottish rates and 0.65 when based on rates for England and Wales [70].

In a cohort of 45,468 Canadian nuclear power industry workers (1957-1994) the RR for lung cancer was 0.81 in males and 0.40 in females [71]. Nearly 200,000 participants in the National Dose Registry of Canada from 1951 to 1988 were examined for cancer mortality. The Standardized Incidence Ratio (SIR) for lung cancer was 0.64 in males and 0.79 in females [72]. Mortality was examined in 176,000 Japanese nuclear industry workers from 1986-1997. The RR for lung cancer was 0.43 and 0.72 at cumulative doses of 50-100 mSv and >100 mSv, respectively [73]. The RR for lung cancer was 0.59 in a study of US workers employed at 15 nuclear power plants between 1979 and 1997 [74].

British radiologists who joined UK radiological societies between 1897 and 1997 were divided into four groups depending on when they joined: 1897-1920, 1921-1935, 1936-1954, and 1955-1979. Exposure limits during 1936-1954 were 2 mSv day⁻¹ or 500 mSv year⁻¹, and 50 mSv y⁻¹ from 1955-1979. SMR comparisons were made with UK male non-radiology physicians. The RR for lung cancer was 0.74 in the 1936-1954 cohort with no lung cancers for the 1955-1979 cohort (6.5 cases were expected). For all cohorts post 1920 the RR for lung cancer was 0.70 [66]. The RR for lung cancer in Japanese technologists was 0.62 for those who worked from 1897 to 1933 and 0.45 for those who worked from 1934 to 1950 [77]. The RR values for lung cancer in U.S. technologists who worked from 1926-1939, 1940-1949, 1950-1959, 1960-1982 were 0.72, 0.76, 0.83 and 0.61, respectively [78].

Fig. 1. Relative Risk of Lung Cancer in Patients Given Repeated Fluoroscopic Examinations During Therapy for Tuberculosis [79-80], and in Contralateral Lung Lobe Receiving Radiation from Radiotherapy for Breast Cancer [181]. The Figure is Redrawn from Rossi and Zaider [33]

Evidence of radiation hormesis was found for lung cancer in fluoroscopy patients being treated for tuberculosis (Figure 1) [79-80]. The RR for lung cancer in the contralateral lung at ten or more years after diagnosis of breast cancer in those receiving fractionated radiotherapy was 0.50 at a lung dose of 1.4 Gy [181].

5. EVIDENCE NEGATING THE HEALTHY WORKER EFFECT

The current peer review system for many journals with respect to hormesis is 'institutionally' influenced by a type of toxicological political 'correctness' in applying the LNT hypothesis to epidemiological studies of radiation risk [82]. The use of the Healthy Worker Effect (HWE) as a mantra-like explanation for potential benefit from low dose radiation is actually censoring-like behavior that has become routine in many publications without adequate scientific explanation or evidence. Proponents of the LNT hypothesis attribute mortality reductions in nuclear workers to the HWE [83]. The HWE is a "catch-all" term that is used irrespective of the extent or degree of benefit obtained within the workplace, to avoid invoking the other obvious scientific conclusion, that there is a benefit to be had from exposure to low dose ionizing radiation.

The HWE has been attributed to pre-employment medical screening examinations, better working and socioeconomic conditions, annual medical physicals, and superior medical care for nuclear workers than national populations. No reduction in cancer mortality was found in men who received annual medical physicals compared to men who did not [84-85]. Medical screening decades ago had no capacity to detect those who might later develop cancer.

Epidemiological studies of occupational nuclear workers exhibit an all cause mortality rate that is typically 15% less than the general population [87-88]. Yet decreases in all cause and all cancer mortality are often much larger than 15% [89]. Epidemiological studies designed to compare exposed and unexposed cohorts in the same company or workplace, where medical procedures for employment and employee health are the same, should best delineate the HWE from radiation hormesis. In addition, the HWE-like response has been seen in many epidemiological studies not involving employee screening or medical care, such as for high environmental exposures, medical exposures and the Taiwan residential study [86].

The HWE usually lasts for only the first few years of employment and not for the decades seen in nuclear workers [91]. The 'apparent' HWE effect should increase with duration of employment if low dose ionizing radiation is beneficial. A pooled 15-country study of cancer risk in 154 nuclear facilities, with a mean cumulative dose of about 20 mSv, failed to show a decrease in the HWE with increasing years of employment. In fact, a decrease

in mortality was observed with increasing duration of employment [89].

A large radiation hormesis effect was seen in French nuclear EDF workers. Mortality was less than half what was expected. The EDF workers and referent were all under the same selection procedures at hiring, under the same medical surveillance procedures with the same medical care and vacation regime. A longer duration of employment was associated with markedly less all cause and all cancer mortality. SMRs for all cause and all cancer were 0.55 and 0.81, respectively, at <5 y duration of employment, decreasing to 0.47 and 0.57, respectively, at 10+ y duration of employment [92]. Similar large benefits from cancer formation continued throughout employment for nuclear workers in Germany [94] and at the Pantex weapons plant [95]. Another group of French nuclear workers had less all cancer mortality than managers of the same nuclear power facilities; RR for all cancer mortality was 0.45 for nuclear workers and 1.05 for managers [93].

The thirteen year US Nuclear Shipyard Workers Study (NSWS) evaluated workers health at eight shipyards, finding significantly reduced all cause and all cancer mortality [76,90]. The study was carried out by Johns Hopkins Department of Epidemiology and a final report written in 1997 [76]. 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 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. The SMR for all malignant tumors at the highest dose cohort was significantly less ($p < 0.05$) than controls [90].

Wilkinson studied the causes of mortality for women working in twelve U.S. nuclear weapons facilities. The study covered a total of 67,976 women who worked at these sites before 1980. [75]. Mortality data was compared for female nuclear workers who wore badges to monitor radiation exposure with mortality in female workers who did not wear badges. There were 25% more deaths from all causes and 17% more deaths from cancer in unbadged workers than in badged workers. A strong radiation hormesis effect was seen in all facilities for all cancers. The relative risk for lung cancer mortality in unbadged women who were not monitored was 49% higher than in badged workers [75]. Both the NSWS and Wilkinson studies used internal controls as referents for entrance into employment and medical care once employed, and both demonstrated clear evidence of radiation hormesis for lung cancer [75-76].

UKAEA nuclear workers from 1946-1997 were compared to UKAEA non-nuclear workers with respect to mortality. The RR for lung cancer in radiation workers

was 0.89 compared to non-radiation workers [67]. All cause mortality and mortality from smoking-related diseases were decreased at three UK nuclear facilities with non-nuclear workers acting as referent [70,96-97]. The SMR for lung cancer in workers with the highest cumulative whole-body dose was 0.59 for radiation-monitored workers and 0.97 for unmonitored workers [69]. All tumor mortality was decreased in monitored nuclear workers employed at Hanford [98] and at Rocketdyne [99] compared to non-monitored workers used as referent. A study of nuclear workers at the Idaho National Engineering and Environmental Laboratory (INEEL) compared SMR for all cancer mortality in badged workers who received zero dose with those workers who received a positive occupational dose. All cancer mortality was significantly less in badged workers with a positive dose than in those with zero dose [100].

Early Soviet nuclear workers at Mayak lived and worked in a dirty, poorly lighted and toxic chemical and radiation environment, always under the watchful eye of intelligence agents, as a result of Stalin's determined effort to develop nuclear weapons in as short a period of time as possible. A case-control study of all morphologically verifiable lung cancer cases from 1966-1991 found significantly less lung cancer among Mayak nuclear workers [101]. The HWE was even claimed as the reason for substantial decrease in cancer mortality compared to the general Russian population for over a decade after the Chernobyl accident, even though the workers were not recruited on the basis of health and their mean stay as cleanup workers was only about 70 days [102].

6. RADON

The greatest exposure to environmental radiation is from radon and radon daughters which involves both high-LET and low-LET radiations. The gamma ray component of radon and radon daughters are thought to stimulate hormetic effects. The average, annual, background radiation exposure in the U.S. is ~ 2.0 mSv y^{-1} . However, parts of the world exceed this background value by more than ten times [81]. More than half of the U.S. natural background radiation is associated with exposure to ^{222}Rn and its daughter radionuclides, including low LET radiations. The annual, external, gamma radiation dose from thorium and uranium series radionuclides is ~ 0.20 mSv in Greek homes [105]. Most homes in the U.S. have a radon concentration of about 2 pCi L^{-1} [132-133]. The lifetime, cumulative, residential radon exposure ranges from 14 to 20 WLM [21].

The beneficial effects of inhaled and radon-laden water are evident in Russian and European spa hospitals where 100,000s of patients are annually treated for a variety of inflammatory, immune and hormonal disorders at radon concentrations up to a 1000 times that of the

Table 1. Comparison of Annual Cancer Mortality (Per 10⁵ Persons) in the Southeastern and Mountain U.S. States. * (Louisiana, Mississippi, Alabama); ** (Idaho, Colorado, New Mexico) [111]

States	All Cancer Mortality	Lung Cancer Mortality	Radon Level (pCi L ⁻¹)
Mountain**	147	47	2.6
Southeastern*	185	68	0.5
Ratio (mountain/southeastern)	0.79	0.69	5.2

Environmental Protection Agency (EPA) residential radon limit [26,106-107]. Protracted low-dose irradiation with radon enhances cell-mediated immunity and reduces pulmonary metastasis of melanoma in mice [108]. Radon balneology (therapeutic effects of baths) has been shown to be effective in randomized double-blind studies [109]. One study found an optimum therapeutic dose for radon of 2 mSv given over a two-week period [110].

The BEIR VI committee using the LNT hypothesis estimated that 10-15% of the annual 160,000 lung cancer deaths in the United States are attributed to indoor radon, based upon an analysis of lung cancer risk in eleven studies of underground miners. The mean cumulative exposure among miners was about 30-fold higher than that found in an average home [4]. The EPA action level for residential radon is 4 pCi L⁻¹ [5]. The EPA estimates an excess of 29 lung cancers in 1000 persons exposed lifetime to 4 pCi L⁻¹ in cigarette smokers and 2 cases in never smokers. In contrast, a recent well designed case control study of indoor radon indicated a 60% reduction in RR for lung cancer at 4 pCi L⁻¹ [21]. This section examines the evidence for this astonishing statement.

6.1 Environmental Radon

A negative cancer risk has been found in regions of high background radiation [114-117]. The relative rates of cancer in native populations of Iran, India and China exposed to high levels of background radiation were decreased [81,113]. Several reports have shown a negative relationship between environmental radon levels and lung cancer rates [119-121]; the lung cancer mortality rate for 43 U.S. urban populations was -0.51 ($p < 0.001$) [179]. Residents near Yangjiang in Guangdong province, China, receive an annual background dose of 6.4 mSv. The RR for lung cancer was 0.81, while the Excess Relative Risk (ERR) per Sv was -0.68 [118].

Americans living in Rocky Mountain states receive radon exposures that are five times greater than those living in Southeastern states; the lung cancer rate was much less in the Rocky Mountain states (Table 1) [111]. Colorado radon levels average 7.3 pCi/L. The EPA estimates the average indoor radon level nationwide is 1.3 pCi/L. For the period 1993-1997, the Colorado cancer

death rate per 100,000 population was 48.2 among males and 25.6 among females. These rates are well below the national averages of 69.4 for males and 34.0 for females. Relative to other states, Colorado has the third lowest lung cancer death rate in the nation [112].

Cohen found a powerful protective effect against lung cancer from residential radon exposures (Figure 2) [122-123]. The trend of county lung cancer mortality in males and females was strikingly negative with increasing radon exposure, even after adjusting for smoking and over 50 other categorizations. The study encompassed 300,000 radon measurements in 1,601 counties representing 90% of US residents [122]. For lung cancer in males the negative slope for lung cancer and radon exposure was -7.3 %/pCiL⁻¹ for 1970 – 1979 and -7.7 %/pCiL⁻¹ for 1979 – 1994 periods [124]. Equally strong negative correlations with radon exposure were also found for oral, laryngeal and esophageal cancers, also associated with smoking [125].

Cohen's data points have very small error bars which

Fig. 2. Lung Cancer Mortality Rates Compared with Mean Home Radon Levels by U.S. County and Compared with the Linear Model by BEIR IV (RR = Ratio of Lung Cancer Mortality Rate for Residential Radon Levels to that of Average Residential Level, 1.7 pCi) [122]

are given in small increments of dose [122]. At higher lung doses (>10 pCi L⁻¹) the radiation hormesis effect disappears and the lung cancer risk exceeds the expected spontaneous incidence. This ecologic study of lung cancer and radon has much greater statistical significance and a sample size that is greater than all other published radon ecologic studies combined [126]. There was a huge discrepancy of 25 standard deviations between Cohen's results and the predictions of the LNT hypothesis by BEIR VI (Figure 2) [127]. The trend of county lung cancer mortality was strikingly negative even after adjusting for smoking and 500 other confounding factors [122,127-129]. A statistically significant negative association between radon concentration and lung cancer was also found in 55 counties of England and Wales [131].

6.2 Indoor Radon

The results of most published case-control, indoor radon studies and lung cancer are ambiguous, highly variable and uncertain [134]. The 95% confidence intervals in some studies are so wide that published plotted ascending lines with an inconsistent dose-response are actually more compatible with a descending line [135-137]. The combined carcinogenic effect of indoor radon and smoking has not been clarified in most case-control studies [44,138].

Ubiquitous false positive claims are more likely in epidemiological studies when the effect size is very small ($RR < 2.0$). Meta-analysis findings, with pooling of low power single studies, often prove to be false. These problems are most often seen in biomedical research [146-148]. Some journals, such as the New England Journal of Medicine, do not accept epidemiological studies for publication unless the RR values are <0.5 or >3.0 [149].

Pooling several indoor radon case-control studies has not been successful in removing heterogeneity [41,139,141-142]. Pooled analyses from indoor radon studies are unable to rule out the existence of a threshold [143]. A meta-analysis of eight case-control studies of indoor radon and lung cancer was carried out [42]; five of the studies showed evidence of hormesis [144]. A meta-analysis of 17 case-control studies found that "no definitive conclusions could be drawn on the role of radon residential exposure on the risk of lung cancer" [142]. No multiple dose bin data was published for each reported study in several meta-analysis studies, making it impossible to evaluate the presence or absence of hormesis [41,139,141]. A meta-analysis of 21 case-control studies of indoor radon found negative ERR values for lung cancer for 1950-1954, 1978-1987 and 1988-1997 cohorts [145].

A very well designed (nine categories of smoking, continuous radon monitoring, controls individually matched to cases), case-control study of indoor radon showed a significant reduction in lung cancer risk (Figure 3). AORs (Adjusted Odds Ratio) for lung cancer

Fig. 3. Case-Control Study of Lung Cancer Risk from Residential Radon Exposure in Worcester County, Massachusetts; Data is for Adjusted Odds Ratio with 95% CI [21]

at 25, 50, 75, 150 and 250 Bq m⁻³ were 0.53, 0.31, 0.47, 0.22 and 2.50, respectively [21]. According to the authors, *this result was entirely unexpected*. This case-control study [21] gave results similar to the ecologic epidemiological studies of Cohen [124].

BEIR VI has inappropriately extrapolated radon-related lung cancer risk from high dose, high dose-rate occupational (underground mines) exposures to low dose, low dose-rate indoor radon exposures [150-152]. Estimates of excess lung cancer risk using the LNT hypothesis at exposures less than threshold values, such as ~800 WLM in German miners [153], are not credible. The LNT hypothesis clearly does not present the true dose-response relationship of epidemiological data in either individual or pooled studies of indoor radon.

6.3 Underground Uranium Miners

Underground miners were heavily exposed to radon, often at high exposure levels in the early years of mining, which resulted in high lung cancer risks. For example, the RR for lung cancer was ~25 in uranium miners with cumulative exposures of $>1,450$ WLM compared to those exposed to <80 WLM [82,155]. The lowest dose for which lung cancer in non-smoking U.S. uranium miners was found ranged between ~200 WLM [155] and 465 WLM [156]. A very large fraction of uranium miners were smokers [153,157]. Good smoking data are lacking in most studies of uranium miners.

Exposure to uranium ore dust and γ -rays may contribute 25-75% of the 'effective' dose to the lung in uranium mines. Applying this observation decreases the risk estimates of lung cancer from radon by a factor of 2-3, increasing the likelihood of thresholds [154]. The threshold for lung cancer in combined U.S. uranium miners was

>80 WLM [82], >40 WLM in Australian uranium miners [158], >600 WLM in Chinese tin miners [159], and >800 WLM in German uranium miners [153]. Interestingly, the RR for all non-lung cancers in uranium miners was less than expected, ranging from 0.73-0.89 [160].

7. INTERNAL HIGH LET ALPHA RADIATION

Substantial alpha-dose thresholds for bone and liver tumors have been found: 10 Gy to skeleton for bone tumors from radium [163] and 2 Gy to liver for liver tumors from thorotrast [164-165] and plutonium [166]. Observation of thresholds have also been made for lung tumors following inhalation of plutonium. Statistically significant increased risk of lung cancer was found in Rocky Flats plutonium workers only at cumulative lung doses >400 mSv [161]. An increased risk of lung cancer was found in Mayak Pu workers only at a lung dose >1800 mSv, which were statistically significant only at a dose >7000 mSv [162].

A case-control study of all morphologically verifiable lung cancer cases from 1966-1991 among Mayak nuclear workers found a threshold of 0.80 Gy for incorporated ^{239}Pu . The RR for lung cancer at lung doses <0.8 Gy was significantly less ($p < 0.05$) than national rates (RR values of 0.56, 0.59, and 0.83 at average ^{239}Pu body burdens of 0.34 kBq, 1.2 kBq, and 4.2 kBq, respectively) [101]. The plutonium workers also received a whole body dose of ~1 Gy from ^{60}Co [166, 168-169]. Manhattan plutonium workers had a median lung dose of 1.25 Sv and a RR for lung cancer of 0.68 [170]. The RR for lung cancer among Russian radiochemical workers from chronic gamma irradiation was 0.39 at a lung dose of 0.1-12 mGy and 0.53 for a dose of 12.1-50 mGy [167].

8. MECHANISM

Two nearly identical lifespan studies were carried out in the same laboratory with 70-day old female Wistar rats exposed to submicron-sized, insoluble aerosols of high-fired $^{239}\text{PuO}_2$ particles. The first study [171] was with 936 rats exposed to $^{239}\text{PuO}_2$ and the second study was with 3142 rats exposed to $^{169}\text{Yb}_2\text{O}_3$ - $^{239}\text{PuO}_2$ [172-173]. The only difference between the two studies is that rats in the second study received 1-2 mSv γ -ray doses from the ^{169}Yb tag used to determine plutonium lung depositions. The lung tumor, threshold α -particle dose for $^{239}\text{PuO}_2$ was 0.05 Gy for the $^{239}\text{PuO}_2$ -only in the first study, while the lung tumor, threshold α -dose from $^{169}\text{Yb}_2\text{O}_3$ - $^{239}\text{PuO}_2$ was 1.5 Gy in the second study (Figure 4). Mixed LET radiation exposures from ^{239}Pu and ^{60}Co in Mayak plutonium workers is associated with a ~80% decrease in lung cancer below that expected from alpha irradiation alone, which is similar to the decrease in lung cancer seen

Fig. 4. Frequency of Lung Tumors in Female Wistar Rats Following Inhalation of $^{239}\text{PuO}_2$ or $^{169}\text{YbO}_3$ - $^{239}\text{PuO}_2$ [171,173]

Fig. 5. Relative Risk of Lung Cancer in Mayak Nuclear Workers Exposed to ^{239}Pu α -Particles and ^{60}Co γ -Rays. Data Obtained from a Model Developed by Scott [180]

in rats exposed to ^{239}Pu and ^{169}Yb [178,180] (Figure 5).

Low dose, low LET radiation enhances normal apoptosis and activated Protective Apoptosis-Mediated (PAM) process that selectively removes precancerous cells [174-175], including cells transformed by chemical carcinogens [14,16]. A protracted gamma ray dose of 1-2 mSv from ^{169}Yb to the lung of rats or from chronic ^{60}Co in Mayak plutonium workers may have induced apoptosis of pulmonary cells genomically damaged by high LET α -radiation and/or cigarette smoke [15,17-19,101]. The low-LET radiation component of mixed LET exposures associated with radon and radon daughters and plutonium and ^{60}Co may trigger the hormetic response and protect

against the carcinogenic effects of cigarette smoke and alpha radiation. Low dose, low LET radiation appears to not only protect against spontaneous lung cancer but also against lung cancers associated with exposure to chronic alpha radiation and to cigarette smoking.

REFERENCES

- [1] Jemal A, A Thomas, T Murray and M Thun. Cancer statistics. *CA Cancer J Clin* **52**:23-47 (2002).
- [2] Chyou PH, AM Nomura and GN Stemmermann. A prospective study of the attributable risk of cancer due to cigarette smoking. *Amer. J. Public Health* **82**:37-40 (1992).
- [3] Field AW, D Krewski, JH Lubin, et al. An overview of the North American residential radon and lung cancer case-control studies. *J Toxicol Environ Hlth Part A* **69**:599-631 (2006).
- [4] National Research Council. Committee on Health Risks of Exposure to Radon, "Health Effects of Exposure to Radon" (BEIR VI), National Academy Press, Washington, DC (1999).
- [5] U.S. Environmental Protection Agency (EPA). "Air toxics risk assessment reference library". Volume 1, Technical Resource Manual, Office of Air Quality Planning Standards, Emissions Standards Division (2004).
- [6] Sanders CL. Hormesis as a Confounding Factor in Epidemiological Studies of Radiation Carcinogenesis. *Korean Assoc Radiat Prot* **31**:69-89 (2006).
- [7] Aurengo A, D Averbeck, A Bonnin, et al. "Dose-Effect Relationships and Estimation of the Carcinogenic Effects of Low Doses of Ionizing Radiation". Executive Summary. French Academy of Sciences, French National Academy of Medicine (2005).
- [8] Tubiana M and A Aurengo. 2005. Dose-Effect Relationship and Estimation of the Carcinogenic Effect of Low Doses of Ionizing Radiation. *Int J Low Radiation* **2**:134-151 (2005).
- [9] Leonard BE. Adaptive response and human benefit: Part I. A microdosimetry dose-dependent model. *Intern J Radiat Biol* **83**:115-131 (2007).
- [10] Luckey TD. Radiation Hormesis. CRC Press, Boca Raton, FL (1991).
- [11] Luckey TD. A Rosetta stone for ionizing radiation. *ROS Magazine* **8**:22-30 (2003).
- [12] Tubiana M, A Aurengo, D Averbeck, et al. "Dose-effect relationships and the estimation of the carcinogenic effects of low doses of ionizing radiation". Joint Report of the French National Academies of Science and of Medicine, Edition Nucleon, Paris (2005).
- [13] Tubiana M, A Aurengo, D Averbeck, et al. The debate on the use of linear no threshold for assessing the effects of low doses. *J Radiol Prot* **26**:317-324 (2006).
- [14] Mitchel REJ, NJ Gragtmans and DP Morrison. Beta-radiation-induced resistance to MNNG initiation of papilloma but not carcinoma formation in mouse skin. *Radiat Res* **121**:180-186 (1999).
- [15] Monchaux G, JP Morlier, M Morin, et al. Carcinogenic and cocarcinogenesis effects of radon and radon daughters in rats. *Environ Health Perspect* **102**:64-73 (1994).
- [16] Sakai K, Y Hoshi, T Nomura T, et al. Suppression of carcinogenic processes in mice by chronic low dose rat gamma-irradiation. *Int J Low Radiat* **1**:142-146 (2003).
- [17] Sanders CL and BR Scott. Smoking and Hormesis as Confounding Factors in Radiation Pulmonary Carcinogenesis. *Dose-Response* **6**:53-79 (2008).
- [18] Thompson HJ, R Strange and PJ Schedin. Apoptosis in the genesis and prevention of cancer. *Cancer Epidemiol Biomarkers Prev* **1**:597-602 (1992).
- [19] Stephens LC, K Kang, TE Schultheiss, et al. Apoptosis in irradiated murine tumors. *Radiat Res* **127**:308-316 (1991).
- [20] Thomas DC, KG McNeill and C Dougherty. Estimates of lifetime lung-cancer risks resulting from Rn progeny exposures. *Health Phys* **49**:825-846 (1985).
- [21] Thompson RE, DF Nelson, JH Popkin and Z Popkin. Case-control study of lung cancer risk from residential radon exposure in Worcester County, Massachusetts. *Health Phys* **94**:228-241 (2008).
- [22] Scott BR, SA Belinsky, S Leng, et al. Radiation-stimulated epigenetic reprogramming of adaptive-response genes in the lung—an evolutionary gift for mounting adaptive protection against lung cancer. (submitted for publication) (2008).
- [23] Sanders CL. Prevention and Therapy of Cancer and Other Common Diseases: Alternative and Traditional Approaches. Infomedix, Richland, WA, 3000 pp (1996).
- [24] Blot WJ. Alcohol and cancer. *Cancer Res.* (suppl) **52**:2119s-2123s (1992).
- [25] Hammond EC, IJ Selikoff and H Seidman. Asbestos exposure, cigarette smoking and death rates. *Ann. NY Acad. Sci.* **330**:473-491 (1979).
- [26] Deetjen P and A Falkenbach (eds). "Radon und Gesundheit", P. Land, Frankfurt, Germany (1999).
- [27] Kreienbrock L, M Kreuzer, M Gerken, et al. Case-control study on lung cancer and residential radon in western Germany. *Am J Epidemiol* **153**:42-52 (2001).
- [28] Wichmann H-E, A Schaffrath Rosario, IM Heid, et al. Increased lung cancer risk due to residential radon in a pooled and extended analysis of studies in Germany. *Health Phys* **88**:71-79 (2005).
- [29] Crispo A, P Brennan, KH Jockel, et al. The cumulative risk of lung cancer among current, ex- and never-smokers in European men. *Br J Cancer* **91**:1280-1286 (2004).
- [30] U.S. Public Health Service. "The health consequences of smoking: Cancer". A report of the Surgeon General. U. S. Public Health Service, DHHS Publication no. (PHS) 82-50179 (1982).
- [31] Higson DJ, DR Boreham, AL Brooks and Y-C Luan. Effects of low doses of radiation: Joint statement from the following participants at the 15th Pacific Basin Nuclear Conference, October 2006. *Dose-Response* **5**:259-262 (2007).
- [32] Sethi T. Science, medicine, and the future: lung cancer. *Brit. J. Med.* **314**:652-660 (1997).
- [33] Rossi HH and M Zaider. Radiogenic lung cancer: The effects of low doses of low linear energy transfer (LET) radiation. *Radiat. Environ. Biophys.* **36**:85-88 (1997).
- [34] Hornung RW and TJ Meinhardt. Quantitative risk assessment of lung cancer in U. S. uranium miners. *Health Phys.* **52**:417-430 (1987).
- [35] Enflo A. Lung cancer risks from residential radon among smokers and non-smokers. *J Radiol Prot* **22**:A95-A99 (2002).
- [36] Gustavsson P, R Jakobsson, F Nyberg, et al. Occupational exposure and lung cancer risk: a population-based case-

- referent study in Sweden. *Am J Epidemiol* **152**:32-40 (2000).
- [37] IARC (International Agency for Research on Cancer). "Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42". (IARC monographs on the evaluation of carcinogenic risks to humans, supplement no. 7). Lyon, France: IARC, pp. 1-440 (1987).
- [38] Toth E, I Lazar, D Selmeczi, et. al. Lower cancer risk in medium high radon. *Pathol. Oncol. Res.* **4**:125-9 (1998).
- [39] Villeneuve PJ, HI Morrison and R Lane. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health Phys* **92**:157-169 (2007).
- [40] Doll R. The lessons of life: keynote address to the nutrition and cancer conference. *Cancer Res* **52**:2024s-2029s (1992).
- [41] Darby S, D Hill, A Auvinen, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *Br Med J* **330**:223-228 (2005).
- [42] Lubin JH and JD Boice. Lung cancer risk from residential radon: meta-analysis of eight epidemiological studies. *J Natl Cancer Inst* **89**:49-57 (1997).
- [43] Lubin JH, ZY Wang, JD Boice, et al. Risk of lung cancer and residential radon in China: Pooled results of two studies. *Int J Cancer* **109**:132-137 (2004).
- [44] Neuberger JS. and TF Gesell. Residential radon exposure and lung cancer: Risk in nonsmokers. *Health Phys* **83**:1-18 (2002).
- [45] Neuberger JS and RW Field. Occupation and lung cancer in nonsmokers. *Rev Environ Health* **18**:251-267 (2003).
- [46] Schull WJ and KM Weiss. Radiation carcinogenesis in humans. *Adv Radiat Biol* **16**:215-258 (1992).
- [47] Pierce DA, GB Sharp and K Mabuchi. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat. Res.* **159**:511-520 (2003).
- [48] Pierce DA, Y Shimizu, DL Preston, et al. Studies of the mortality of atomic bomb survivors. Report 12. 1. Cancer: 1950-1990. *Radiat. Res.* **146**:1-27 (1996).
- [49] Kopecky KJ, E Nakashima, T Yamamoto, et al. Lung cancer, radiation, and smoking among A-bomb survivors, Hiroshima and Nagasaki: TR-13-86. Radiation Effects Research Foundation, Hiroshima (1986).
- [50] Little MP. Comparisons of lung tumour mortality risk in the Japanese A-bomb survivors and in the Colorado Plateau uranium miners: Support for the ICRP lung model. *Intern. J. Radiat. Biol.* **78**:145-163 (2002).
- [51] Heidenreich WF, EG Luebeck, WD Hazelton, et al. Multistage Models and the Incidence of Cancer in the Cohort of Atomic Bomb Survivors. *Radiat. Res.* **158**:607-614 (2002).
- [52] Gilbert ES, NA Koshurnikova, ME Sokolnikov, et al. Lung cancer in Mayak workers. *Radiat. Res.* **162**:505-516 (2004).
- [53] Kreishermer M, NA Koshurnikova, E Nekolla, et al. Lung Cancer Mortality Among Male Nuclear Workers of the Mayak Facilities in the Former Soviet Union. *Radiat. Res.* **154**:3-11 (2000).
- [54] Shilnikova NS, DL Preston, E Ron, et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat. Res.* **159**:787-798 (2003).
- [55] Cardis E, M Vrijheid, M Blettner, et al. Risk of cancer after low doses of ionizing radiation: Retrospective cohort study in 15 countries. *Brit. Med. J.* **331**:77-80 (2005).
- [56] Baverstock K and D Williams. Chernobyl: An overlooked aspect? *Letters, Science* **299**:44 (2002).
- [57] Chernobyl Forum (IAEA, WHO, UNDP, UNEP, UN-OCHA, UNSCEAR, World Bank). "Chernobyl's Legacy: Health, Environmental and Socio-Economic Impacts". The work is in three volumes and 600 pages by more than 100 scientists (2005).
- [58] Hatch M, E Ron, A Bouville, et al. The Chernobyl disaster: Cancer following the accident at the Chernobyl nuclear power plant. *Epidemiol. Reviews* **27**:56-66 (2005).
- [59] Thompson, R.C. and Mahaffey, J.A. "Life-Span Radiation Effects Studies in Animals: What Can They Tell Us?" Proceedings of the 22nd Hanford Life Science Symposium, Richland, WA (1986).
- [60] Stannard, JN. "Radioactivity and Health: A History". Baalman RW (editor), Pacific Northwest Laboratory, Richland, WA (1988).
- [61] Gregoire O and MR Cleland. Novel approach to analyzing the carcinogenic effect of ionizing radiations. *Int J Radiat Biol* **82**:13-19 (2006).
- [62] Okamoto K. Critical values of linear energy transfer, dose rates and doses for radiation hormesis. *Health Phys* **52**:671-674 (1987).
- [63] Taylor LS. Some non-scientific influences on radiation protection standards and practice. *Health Phys* **32**:851-874 (1980).
- [64] Cameron JR. Correspondence: Radiation increased the longevity of British radiologists. *Br J Radiol* **75**:637-639 (2002).
- [65] Keirim-Markus IB. Radiation exposure normalization taking account of specific effects at low doses and dose rates. *Atomic Energy* **93**:836-844 (2004).
- [66] Berrington A, SC Darby, HA Weiss, et al. 100 years of observation on British radiologists: mortality from cancer and other causes 1987-1997. *Br J Radiol* **74**:507-519 (2001).
- [67] Atkinson WD, DV Law, KJ Bromley, et al. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-97. *Occup Environ Med* **61**:577-585 (2004).
- [68] Ivanov V, L Iiyin, A Gorski, et al. Radiation and epidemiological analysis for solid cancer incidence among nuclear workers who participated in recovery operations following the accident at the Chernobyl NPP. *J Radiat Res (Tokyo)* **45**:41-44 (2004).
- [69] Carpenter LM, V Beral and PG Smith. Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. *Br J Cancer* **78**:1224-1232 (1998).
- [70] McGeoghegan D and K Binks. The mortality and cancer morbidity experience of employees at the Chapelcross plant of British Nuclear Fuels, 1955-95. *J Radiol Prot* **21**:221-250 (2001).
- [71] Zablotska LB, JP Ashmore and GR Howe. Analysis of mortality among Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat. Res.* **161**:633-641 (2004).
- [72] Sont WN, JM Zielinski, AP Ashmore, et al. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Amer. J. Epidemiol.* **153**:309-318 (2001).
- [73] Iwasaki T, M Murata, S Ohshima, et al. Second analysis of nuclear industry workers in Japan, 1986-1997. *Radiat.*

- Res. **159**:228-238 (2003).
- [74] Howe GR, LB Zablotska, JJ Fix, et al. Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat. Res.* **162**:517-526 (2004).
- [75] Wilkinson GS, N Trieff, R Graham, et al. "Final Report. Study of Mortality Among Female Nuclear Weapons Workers". Grant Numbers: 1R01 OHO3274, R01/CCR214546, R01/CCR61 2934-01, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (2000).
- [76] Matanoski GM. "Health effects of low-level radiation in shipyard workers. Final Report". Report No. DOE DE-AC02-79EV10095. US Department of Energy, Washington, D.C (1991).
- [77] Yoshinaga S, T Aoyama, Y Yoshimoto, et al. Cancer mortality among radiological technologists in Japan: updated analysis of follow-up data from 1969 to 1993. *J. Epidemiol.* **9**:61-72 (1999).
- [78] Doody MM, JS Mandel, JH Lubin, et al. Mortality among USA radiologic technologists 1926-1990. *Cancer Causes Control* **9**:67-75 (1998).
- [79] Howe GR. Lung Cancer Mortality Between 1950 and 1987 after Exposure to Fractionated Moderate-Dose-Rate Ionizing Radiation in the Canadian Fluoroscopy Cohort Study and a Comparison with Lung Cancer Mortality in the Atomic Bomb Survivors Study. *Radiat. Res.* **142**:295-304 (1995).
- [80] I Davis FG, JD Boice, C Hrubec, et. al. Lung cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res.* **49**:6130-6136 (1989).
- [81] Luxin WEI, T Sugahara and Z Tao. High level of natural radiation 1966: Radiation dose and health effects". Amsterdam, Elsevier (1997).
- [82] Calabrese EJ. Historical blunders: How toxicology got the dose-response relationship half right. *Cell Molec Biol* **51**:643-654 (2005).
- [83] Howe GR, AM Chiarelli and JP Lindsay. Components and modifiers of the healthy worker effect: evidence from three occupational cohorts and implications for industrial compensation. *Am J Epidemiol* **128**:1364-1375 (1988).
- [84] Franks P, MR Gol and CM Clancy. Use of care and subsequent mortality: the importance of gender. *Health Serv Res* **31**:347-363 (1996).
- [85] Friedman GD, MF Collen and BH Fireman. Multiphasic health checkup evaluation: a 16-year follow-up. *J Chronic Dis* **39**:453-463 (1986).
- [86] Chen WL, YC Luan, MC Shieh, et al. Is chronic radiation an effective prophylaxis against cancer? *J. Amer. Physicians and Surgeons* **9**:6-10 (2004).
- [87] Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. 2007. "Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2". National Academies Press, Washington, D.C (2007).
- [88] Monson RR. "Occupational Epidemiology". CRC Press, Boca Raton, FL (1990).
- [89] Vrijheid M, E Cardis, M Blettner, et al. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: design, epidemiological methods and descriptive results. *Radiat Res* **167**:361-379 (2007).
- [90] Spousler R and JR Cameron. Nuclear shipyard worker study (1980-1988): A large cohort exposed to low-dose-rate gamma radiation. *Int. J. Low Radiation* **1**:463-478 (2005).
- [91] Skelcher B. Healthy worker effect. *J Radiol Prot* **21**:71-72 (2001).
- [92] Rogel A, N Carre, E Amoros, et al. Mortality of workers exposed to ionizing radiation at the French National Electricity Company. *Am J Indust Med* **47**:72-82 (2005).
- [93] Gros H, A Chevalier, et al. Epidemiological surveillance at Electricite de France-Gaz de France: health assessment of nuclear power plant employees between 1993 and 1998. *Occup Med* **52**:35-44 (2002).
- [94] Hammer GP, F Fehring, et al. Exposure and mortality in a cohort of German nuclear power workers. *Radiat Environ Biophys* **47**:95-99 (2008).
- [95] Acquavella JF, LD Wiggs, RJ Waxweiler, et al. Mortality among workers at the Pantex weapons facility. *Health Phys* **48**:735-746 (1985).
- [96] McGeoghegan D and K Binks. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946-95. *J Radiol Prot* **20**:111-137 (2000).
- [97] McGeoghegan D and K Binks. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946-95. *J Radiol Prot* **20**:381-401 (2000).
- [98] Gilbert ES, E Omohundro, JA Buchanan, et al. Mortality of workers at the Hanford site: 1945-1986. *Health Phys* **64**:577-590 (1993).
- [99] Boice JD, SS Cohen, MT Mumma, et al. Mortality among radiation workers at Rocketdyne (Atomics International), 1948-1999. *Radiat Res* **166**:98-115 (2006).
- [100] Schubauer-Berigan MK, GV Macievic, DF Utterback, et al. "An epidemiologic study of mortality and radiation-related risk among workers at the Idaho Engineering and Environmental Laboratory", a U.S. Department of energy facility. HHS (NIOSH) Publication No. 2005-131, Cincinnati, OH (2005).
- [101] Tokarskaya ZB, ND Okladnikova, ZD Belyaeva, et al. Multifactorial analysis of lung cancer dose-response relationships for workers at the Mayak nuclear enterprise. *Health Phys* **73**:899-905 (1997).
- [102] Ivanov VK, AI Gorski, MA Maksioutov, et al. Mortality among the Chernobyl emergency workers: estimation of radiation risks (preliminary analysis). *Health Phys* **81**:514-521 (2001).
- [103] Daunt N. Decreased cancer mortality of British radiologists. *Br J Radiol* **75**:639 (2002).
- [104] Smith PG and R Doll. Mortality from cancer and all causes among British radiologists. *Brit. J Radiol.* **54**:187-194 (1981).
- [105] Clouvas A, S Xanthos and M Antonopoulos-Domis. Simultaneous measurements of indoor radon, radon-thoron progeny and high-resolution gamma spectrometry in Greek dwellings. *Radiat Pro Dosim.* **118**:482-490 (2006).
- [106] Mitsunobu F, K Yamaoka, K Hanamoto, et al. Elevation of antioxidant enzymes in the clinical effects of radon and thermal therapy for bronchial asthma. *J. Radiat. Res. (Tokyo)* **44**:95-99 (2003).
- [107] Yamaoka K, C Sugie, S Futatsugawa, et al. Basic Study of Biologic Effects of Thoron Hot Spring on Hypertension. Proceedings of the Forty-Eighth Annual Meeting of the

- Japan Radiation Research Society/ the First Asian Congress of Radiation Research, Research Institute for Radiation Biology and Medicine, Hiroshima University, Japan, Abstract P-A-108, p. 139 (2005).
- [108] Takahashi M and S Kojima. Suppression of atopic dermatitis and tumor metastasis in mice by small amounts of radon. *Radiat. Res.* **165**:337-342 (2006).
- [109] Franke A, L Reiner, Pratzel, et. al. Long-term efficacy of radon spa therapy in rheumatoid arthritis - a randomized, sham-controlled study and follow-up. *Rheumatology* **39**: 894-902 (2000).
- [110] Bogoljubov WM. Clinical aspects of radon therapy in the USSR. *Z. Phys. Med. Balneol. Med. Klimatol.* **17**:58-63 (1988).
- [111] Jagger J. Natural background radiation and cancer death in Rocky Mountain states and Gulf Coast states. *Health Phys* **75**:428-430 (1998).
- [112] City of Fort Collins, CO. Air Quality Department, <http://www.ci.fort-collins.co.us/airquality/radon-health> (2005).
- [113] National Council on Radiation Protection and Measurements. "Evaluation of the Linear-Nonthreshold Model for Ionizing Radiation". NCRP Report 136, Bethesda, MD: National Council on Radiation Protection and Measurements, p. 6 (2001).
- [114] Frigerio NA and RS Stowe. "Carcinogenic and genetic hazards from background radiation" (Vol. 2), pp. 385-393, IAEA, Vienna (1976).
- [115] Nambi, KSV and SD Soman. Environmental radiation and cancer in India. *Health Phys* **52**:653-657 (1987).
- [116] Sun Q, ZS Akiba, Z Tao, et al. Excess risk of solid cancer mortality after prolonged exposure to naturally occurring high background radiation in Yangjiang, China. *J Radiat Res (Tokyo)* **41**:43-52 (2000).
- [117] Tao T, Y Zha, S Akiba, et al. Cancer mortality in the high background radiation areas of Yangjiang, China during the period between 1979 and 1995. *J Radiat Res (Tokyo)* **41**:31-41 (2000).
- [118] Wei L and T Sugahara. An introductory overview of the epidemiological study on the population at the high background radiation areas in Yangjiang, China. *J Radiat Res (Tokyo)* **41**:1-7 (2000).
- [119] Neuberger JS. Residential radon exposure and lung cancer: an overview of ongoing studies. *Health Phys* **63**:503-509 (1992).
- [120] Wang Z, JH Lubin, L Wang, et al. Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. *Am J Epidemiol* **155**:554-564 (2002).
- [121] Bowie C and SHU Bowie. Radon and health. *Lancet* **337**:409-413 (1991).
- [122] Cohen BL. Test of the linear no-threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys* **68**:157-174 (1995).
- [123] Cohen BL. A test of the linear no-threshold theory of radiation carcinogenesis. *Environ Res* **53**:193-220 (1990).
- [124] Cohen BL. Radon exposure and the risk of lung cancer. *J Radiat Prot* **21**:64-66 (2001).
- [125] Puskin JS. Smoking as a confounder in ecologic correlations of cancer mortality rates with average county radon levels. *Health Phys* **84**:526-532 (2003).
- [126] Stidley CA. and JM Samet. A review of ecologic studies of lung cancer and indoor radon. *Health Phys* **65**:234-251 (1993).
- [127] Cohen BL. Response to "residential radon exposures and lung cancer risk: Commentary on Cohen's county-based study". *Health Phys* **87**:656-658 (2004).
- [128] Cohen BL. Updates and extensions to tests of the linear no-threshold theory. *Technology* **7**:657-672 (2000).
- [129] Heath CW, PD Bond, DG Hoel and CB Meinhold. Residential radon exposure and lung cancer risk: Commentary on Cohen's county-based study. *Health Phys* **87**:647-655 (2004).
- [130] Auvénin A, I Maekeläinen, M Hakama, et al. Indoor radon exposure and risk of lung cancer: a nested case-control study in Finland. *J Natl Cancer Inst* **88**:966-972 (1996).
- [131] Haynes RM. The distribution of domestic radon concentrations and lung cancer mortality in England and Wales. *Radiat Prot Dosim* **25**:93-96 (1988).
- [132] Lubin JH. Invited commentary: lung cancer and exposure to residential radon. *Am J Epidemiol* **140**:323-332 (1994).
- [133] NCRP (National Council on Radiation Protection and Measurements). "Exposure of the population in the United States and Canada from natural background radiation". NCRP Report No. 94, Bethesda, MD (1987).
- [134] Lubin JH., JD Boice, C Edling, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst* **87**:817-827 (1995).
- [135] Lachet B. 2005. Indoor radon and lung cancer. Letters to the Editor. *Epidemiol* **17**:121.
- [136] Cothorn CR. Indoor air radon. *Environ Geochem Health* **21**:83-90 (1999).
- [137] Lin CY, A Gelman, PN Price, et al. Analysis of local decisions using hierarchical modeling, applied to home radon radon measurement and remediation. *Statistical Science* **14**:305-337 (1999).
- [138] Price P. "Assessing uncertainties in the relationship between inhaled particle concentrations, internal deposition, and health effects". In: Ruzer, LS (editor), *Aerosol Handbook: Measurement, Dosimetry and Health Effects*, pp. 157-188. CRC-Taylor & Francis (2004).
- [139] Lubin JH, L Tomasek, C Edling, et al. Estimating lung cancer mortality from residential radon using data for low exposures of miners. *Radiat Res* **147**:126-134 (1997).
- [140] Krewski D, SN Rai, JM Zielinski, et al. Characterization of uncertainty and variability in residential radon cancer risks. *Ann. N.Y. Acad. Sci.* **895**:245-272 (1999).
- [141] Krewski D, JH Lubin, JM Zielinski, et al. Residential radon and risk of lung cancer. A combined analysis of 7 North American case-control studies. *Epidemiol* **16**:137-145 (2005).
- [141] Pavia M, A Bianco, C Pileggi and Angelillo, I.F. Meta-analysis of residential exposure to radon gas and lung cancer. *Bull World Health Organization* **81**:732-738 (2003).
- [142] Tracy BL, D Krewski, J Chen, et al. Assessment and management of residential radon health risks: a report from the Health Canada radon workshop. *J Toxicol Environ Health A* **69**:735-758 (2006).
- [144] Kauffman JM. Radiation hormesis: Demonstrated, deconstructed, denied, dismissed, and some implications for public policy. *J. Scientific Exploration* **17**:389-407 (2003).
- [145] Yarmoshenko I, I Kirdin and Zhukovsky, M. Uncertainty analysis of relative biological effectiveness of alpha-radiation for human lung exposure. *J Toxicol Environ Health Part A* **69**:665-679 (2006).

- [146] Ioannidis JP, AB Haidich and J Lau. Any casualties in the clash of randomized and observational evidence? *Brit Med J* **322**:879-880 (2001).
- [147] Ioannidis JP. Why most published research findings are false. *PLOS Medicine* **2**(8): (http://medicine.plosjournals.org/perlserv?request=get_document&doi=10.1371/journal.pm) (2005).
- [148] Vandenbroucke JP. When are observational studies as credible as randomized trials? *Lancet* **363**:1728-1731 (2004).
- [149] Taubes G. Epidemiology faces its limits. *Science* **269**:164-169 (1995).
- [150] Cavallo A, A Hutter and P Shebel. Radon progeny unattached fraction in an atmosphere far from radioactive equilibrium. *Health Phys* **76**:532-536 (1999).
- [151] James AC, A Birchall and GH Akabani. Comparative dosimetry of BEIR VI revisited. *Radiat Prot Dosim* **108**:3-26 (2002).
- [152] Puskin JS and AC James. Radon exposure assessment and dosimetry applied to epidemiology and risk estimation. *Radiat Res* **166**:193-208 (2006).
- [153] Bruske-Hohfeld I, AS Rosario, G Wolke, et al. Lung cancer risk among former uranium miners of the Wismut Company in Germany. *Health Phys* **90**:208-216 (2006).
- [154] Duport P. (2002). Is the radon risk overestimated? Neglected doses in the estimation of the risk of lung cancer in uranium underground miners. *Radiat Prot Dosim* **98**:329-338 (2002).
- [155] Gilliland FD, WC Hunt, VE Archer, et al. Radon progeny exposure and lung cancer risk among non-smoking uranium miners. *Health Phys* **79**:365-372 (2000).
- [156] Roscoe RJ, K Steenland and WE Halperin. Lung cancer mortality among nonsmoking uranium miners exposed to radon daughters. *J Am Med Assoc* **262**:629-633 (1989).
- [157] Saccomano G, C Yale, W Dixon, et al. An epidemiological analysis of the relationship between exposure to Rn progeny, smoking and bronchogenic carcinoma in the U-mining population of the Colorado plateau-1960-1980. *Health Phys* **50**:605-618 (1986).
- [158] Woodward A, D Roder, AJ McMichael, et al. Radon daughter exposures at the Radium Hill uranium mine and lung cancer rates among former workers, 1952-87. *Cancer Causes Control* **2**:213-220 (1991).
- [159] Xiang-Zhen X, JH Lubin, L Jun-Yao, et al. A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health Phys* **64**:120-131 (1993).
- [160] Darby SC, E Whitley, GR Howe, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J Natl Cancer Inst* **87**:378-384 (1995).
- [161] Brown SC, MF Schonbeck, D McClure, et al. Lung cancer and internal lung doses among plutonium workers at the Rocky Flats plant: a case-control study. *Am J Epidemiol* **160**:163-172 (2004).
- [162] Koshurnikova NA, MG Bolotnikova, LA Iyin, et al. Lung cancer risk due to exposure to incorporated plutonium. *Radiat Res* **149**:366-371 (1998).
- [163] Rowlands RE, AF Stheney and HF Lucas. Dose-response relationships for radium-induced bone sarcomas. *Health Phys* **44**(S1):15-31 (1983).
- [164] Andersson M. and HH Strom. Cancer incidence among Danish thorotrast patients. *J Natl Cancer Inst* **4**:1318-1325 (1992).
- [165] Van Kaick G, H Wesch, H Luhrs, et al. Neoplastic diseases induced by chronic alpha irradiation. Epidemiological, biophysical and clinical results by the German Thoratrast study. *J Radiat Res* **32**:20-33 (1991).
- [166] Tokarskaya ZB, GV Zhuntova, BR Scott, et al. Influence of alpha and gamma radiations and non-radiation risk factors on the incidence of malignant liver tumors among Mayak workers. *Health Phys* **91**:296-310 (2006).
- [167] Khokhriakov VF and SA Romanov. Estimation of the temporal distribution and dose dependency of lung cancer among workers of nuclear fuel reprocessing plant. *Health Phys* **71**:83-85 (1996).
- [168] Khokryakov V and S Romanov. Lung cancer in radiochemical industry workers. *The Science of the Total Environment* **142**:25-28 (1994).
- [169] Tokarskaya ZB, BR Scott, GV Zhuntova, et al. Interaction of radiation and smoking in lung cancer induction among workers at the Mayak nuclear enterprise. *Health Phys* **83**:833-846 (2002).
- [170] Voelz GL, JNP Lawrence and ER Johnson. Fifty Years of Plutonium Exposure to the Manhattan Project Plutonium Workers: An Update. *Health Physics* **73**:611-619 (1997).
- [171] Sanders CL, GE Dagle, WC Cannon, et al. Inhalation carcinogenesis of high-fired $^{239}\text{PuO}_2$ in rats. *Radiation Research* **68**:340-360 (1976).
- [172] Sanders CL, KE Lauhala, KE McDonald and GA Sanders. Lifespan studies in rats exposed to $^{239}\text{PuO}_2$ aerosol. I. Dosimetry. *Health Physics* **64**:509-521 (1993).
- [173] Sanders CL, KE Lauhala and KE McDonald. Lifespan studies in rats exposed to $^{239}\text{PuO}_2$ aerosol. III. Survival and lung tumors. *Intern J Radiat Biol* **64**: 417-430 (1993).
- [174] Redpath JL, SC Short, M Woodcock, et al. Low-dose reduction in transformation frequency compared to unirradiated controls: The role of hyper-radiosensitivity to cell death. *Radiat Res* **159**:433-436 (2003).
- [175] Scott BR. A biologically-based model that links genomic instability, bystander effects, and adaptive response. *Mutat Res* **568**:129-143 (2004).
- [176] Scott BR, CL Sanders, REJ Mitchel and DR Boreham. CT scans may reduce rather than increase the risk of cancer. *J Am Physicians and Surg* **13**:8-11 (2008).
- [177] Higson D. The Australasian Radiation Society's position statement on risks from low levels of ionizing radiation. *Dose-Response* **5**:299-307 (2007).
- [178] Scott BR and J Di Palma. Sparsely ionizing diagnostic and natural background radiations are likely preventing cancer and other genomic-instability-associated diseases. *Dose-Response* **5**:230-255 (2006).
- [179] Hickey RJ, EJ Bowers, DE Spence, et al. Low level ionizing radiation and human mortality: multi-regional epidemiological studies. *Health Phys* **40**:625-641 (1981).
- [180] Scott BR. Low-dose-radiation stimulated natural chemical and biological protection against lung cancer. *Dose-Response* **6**:299-318 (2008).
- [181] Neugut AI, E Robinson, WC Lee, et al. Lung cancer after radiation therapy for breast cancer. *Cancer* **71**:3054-3057 (1993).
- [182] Vineis P, M Alavanja, P Buffler, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst* **96**:99-106 (2004).