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□ The current radiation safety paradigm using the linear no-threshold (LNT) model is based on the premise that even the smallest amount of radiation may cause mutations increasing the risk of cancer. Autopsy studies have shown that the presence of cancer cells is not a decisive factor in the occurrence of clinical cancer. On the other hand, suppression of immune system more than doubles the cancer risk in organ transplant patients, indicating its key role in keeping occult cancers in check. Low dose radiation (LDR) elevates immune response, and so it may reduce rather than increase the risk of cancer. LNT model pays exclusive attention to DNA damage, which is not a decisive factor, and completely ignores immune system response, which is an important factor, and so is not scientifically justifiable. By not recognizing the importance of the immune system in cancer, and not exploring exercise intervention, the current paradigm may have missed an opportunity to reduce cancer deaths among atomic bomb survivors. Increased antioxidants from LDR may reduce aging-related non-cancer diseases since oxidative damage is implicated in these. A paradigm shift is warranted to reduce further casualties, reduce fear of LDR, and enable investigation of potential beneficial applications of LDR.

Keywords: Radiation safety, Low dose radiation, LNT model, Immune system, Antioxidant stimulation, Aging-related diseases

INTRODUCTION

Whereas the carcinogenic nature of high dose radiation is well established, the health effects of low dose radiation are still being debated. The current radiation safety paradigm is based on the linear no-threshold (LNT) premise that even the smallest amount of radiation may cause DNA damage and mutations increasing the risk of cancer. An analysis of the historical foundation of the LNT model shows that the no-threshold model was adopted in the 1950s due to carcinogenic concerns following the observation of excess leukemias in atomic bomb survivors, but without much supporting data at low doses since most of the radiobiological data available at the time was for high doses, e.g. observed increase in leukemias in atomic bomb survivors and observed increase in mutations in drosophila subjected to radiation (Calabrese, 2009). The decision to adopt the LNT model may also have been influenced by the political movements of that time period to stop the development of nuclear weapons (Jaworowski, 2010b). Recent measurements have shown a U-shaped dose response curve for X-ray induced mutations in drosophila

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(Ogura *et al.*, 2009; Koana and Tsujimura, 2010) invalidating one of the original justifications for adopting the LNT model.

The use of a no-threshold model results in efforts and expenditures that generally do not reduce cancer incidence significantly, but may increase it. Cancer incidence is known to be affected by many factors, with some factors that increase the risk, e.g. smoking (Hymowitz, 2011), obesity (Basen-Engquist and Chang, 2011), alcohol (Testino *et al.*, 2011), and infection (Sell, 2011), and other factors that decrease the risk, e.g. physical activity (Alberts *et al.*, 2008) and vaccination (Frazer *et al.*, 2011). The effect of such factors on cancers can be quite significant. An estimate of the fraction of cancers that can be attributed to sub-optimal past exposures of 14 lifestyle and environmental risk factors indicates 42.7% of cancers in the UK in 2010 may be attributed to these factors (Parkin *et al.*, 2011). Such analysis can enable us to design an optimum allocation of available resources among the different risk factors in order to maximize the overall reduction of cancers. The use of a no-threshold model for one of the factors can result in a lopsided allocation of resources to remedy that factor to an extreme level, resulting in a large deviation from this optimum allocation of resources and hence leading to a sub-optimal reduction in cancers. Thus, using a no-threshold model for remedying a carcinogenic factor is in general not a conservative approach.

Though these general arguments invalidate the use of a no-threshold model for low dose radiation (and other carcinogens), the LNT model has become firmly established in radiation protection policies around the world. Recent reports from advisory bodies such as International Commission on Radiological Protection (ICRP, 2007), National Research Council (NRC, 2006) and National Council on Radiation Protection & Measurements (NCRP, 2001) have re-affirmed the use of the LNT model. There is continuing support for the use of the LNT model in publications (Nussbaum, 1998; Kellerer, 2000; Preston, 2003; Martin, 2005; Brenner and Sachs, 2006; Little *et al.*, 2009). The government regulatory agencies continue to use the LNT model for regulatory purposes, generally following the guidelines set by the above advisory bodies.

The support for the use of the LNT model is however not universal. The validity and wisdom of using the LNT model has been questioned by many scientists over the years, because of radiobiological data that is inconsistent with the LNT model, e.g. (Luckey, 1980; Hickey *et al.*, 1983; Luckey, 1991; Thomas, 1994; Jaworowski, 1997; Cohen, 2002; Feinendegen, 2005; Cook and Calabrese, 2006; Cohen, 2007; Mitchel, 2007; Jaworowski, 2008; Scott, 2008; Averbeck, 2009; Cuttler and Pollycove, 2009; Tubiana *et al.*, 2009; Jaworowski, 2010a; Sanders, 2010; Calabrese, 2011; Scott, 2011). The French Academy of Sciences has recommended that the possibility of beneficial effects of low dose radiation should be investigated (Tubiana, 2005). A re-evaluation of the current

approach to radiation safety has been recommended (Mitchel, 2007) and an alternative radiation safety approach has been proposed that raises recommended dose limits considerably from the present values (Allison, 2011). Some scientists have even suggested utilizing the hormetic effects (e.g. cancer preventive effects) of low dose radiation, taking a stand completely opposite to that of the current radiation safety paradigm (Hickey *et al.*, 1983; Luckey, 1991; Cook and Calabrese, 2006). Reduction of many diseases and conditions has been reported from the use of low dose radiation in controlled animal studies, e.g. chemical induced brain damage (Kojima *et al.*, 1999), metastasis (Hashimoto *et al.*, 1999), autoimmune diseases (Tanaka *et al.*, 2005), thymic lymphoma (Ina *et al.*, 2005), diabetes (Nomura and Sakai, 2006), atopic dermatitis and tumor metastasis (Takahashi and Kojima, 2006), collagen-induced arthritis (Nakatsukasa *et al.*, 2008), tumor growth (Hayase *et al.*, 2008), diabetes related nephropathy (Nomura *et al.*, 2011), diabetes related cardiac damage (Zhang *et al.*, 2011), prion infection in brain (Plews *et al.*, 2010), and atherosclerosis (Mitchel *et al.*, 2011). Human studies have also shown reduction of some diseases using low dose radiation, e.g. hypertension, diabetes, and pain (Yamaoka and Komoto, 1996), bronchial asthma (Mitsunobu *et al.*, 2003), degenerative joint and spine diseases (Becker, 2004), and rheumatic diseases (Falkenbach *et al.*, 2005). The current vast difference of opinion in the scientific community on the health effects of low dose radiation in humans may be resolved by performing prospective studies. Considering the current radiation safety regulations based on the LNT model, and the fear of low dose radiation among the general public, such studies in humans are not feasible. If the reported beneficial effects of low dose radiation are true, the current paradigm may be causing considerable harm to human health by preventing the study of these effects. Thus, it is important to evaluate the validity of the current radiation safety paradigm.

In this paper, arguments will be presented to justify a paradigm shift in radiation safety by showing that the present radiation safety paradigm has fundamental flaws and so is not scientifically justifiable, has likely led to missed opportunities in reducing cancer deaths among atomic bomb survivors, has prevented the study of beneficial effects of low dose radiation, and has likely prevented progress in reducing aging-related diseases including cancer.

FUNDAMENTAL FLAWS OF THE CURRENT RADIATION SAFETY PARADIGM

Exclusive attention to mutations as the cause of cancer.

The basic premise of the current radiation safety paradigm and the consequent LNT model is that even a single ray of ionizing radiation can result in a base change leading to a mutation that could cause cancer (Hall and Giaccia, 2006). How important are mutations in the pathogen-

esis of clinical cancer?

Figure 1A shows the percentage of patients having cancer cells (mutations indicative of cancer) as determined from full body autopsies in a geriatric hospital in Japan during 1982-1994 (Imaida *et al.*, 1997). It is seen that the percentage of patients having cancer cells is ~40% and is relatively unchanged for the age ranges covering 48 to 94 years. The cancer mortality rate for a similar age range in Japan has on the other hand increased by a factor of ~10 (see Fig. 1B) (WHO, 2011), indicating that the presence of cancer cells is not a decisive factor in the occurrence of clinical cancer.

A similar pattern is seen in an autopsy study of Hungarian men (Soos *et al.*, 2005), where the percentage of patients having prostate cancer cells has increased by a factor of ~2 between the ages of ~50 and ~70 whereas the prostate cancer mortality rate has increased by a factor of ~38 between these ages (WHO, 2011). A third example is that in a recent review, the presence of occult cancer is reported to be quite high for cancers of the prostate (30-70%), thyroid (36-100%), and breast (7-39%) for specified age groups, whereas the lifetime risk of death or metastatic disease from these cancers is quite low at 4%, 0.1%, and 4% respectively (Welch and Black, 2010). These examples show that mutations, though essential, are not the determinant factors in clinical cancer.

Ignoring the influence of immune system response in carcinogenesis

A second feature of the current radiation safety paradigm is that it completely ignores the effects of the different bodily defense mechanisms in estimating the cancer risk from low dose radiation. Let us consider the importance of immune system response (which is just one of the body's defense mechanisms) in the occurrence of clinical cancer. The incidence of cancers in kidney disease patients has been estimated at various stages of their disease treatment (Vajdic and van Leeuwen, 2009a). The cancer incidence for kidney transplant patients (in whom the immune system was suppressed) was observed to be higher by a factor of ~2.4 in comparison to kidney dialysis patients, indicative of the importance of the immune system in keeping the occult cancers in check. This increase included not only cancers known to be caused by viruses, but also cancers not viral in origin. The immune system can play a key role in maintaining cancers in an equilibrium state preventing occult cancers from becoming clinical cancers (Koebel *et al.*, 2007). If the immune system were suppressed in the general population, and resulted in an increase in cancer similar to kidney transplant patients (i.e. by a factor of ~2.4), essentially the whole population would face clinical cancer, since the lifetime risk of cancer incidence is ~40%. What appears to separate those who have cancer from those who do not is not the presence of cancer cells (or carcinogenic viruses) but the immune system response. The increased risk of

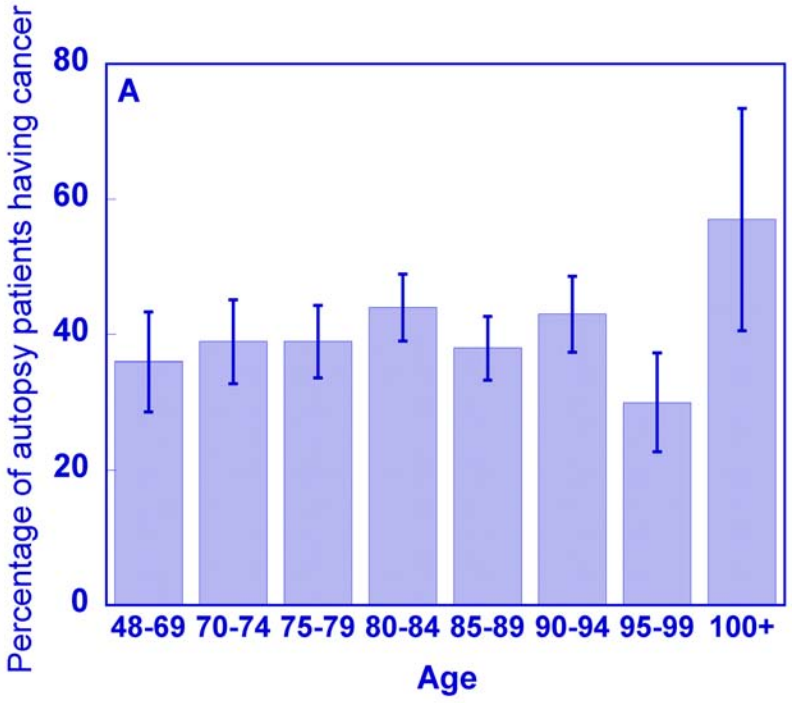

FIGURE 1A. Percentage of patients from a geriatric hospital in Japan who had cancer as determined by autopsy during 1982-1994, as a function of age. Data from (Imaida *et al.*, 1997).

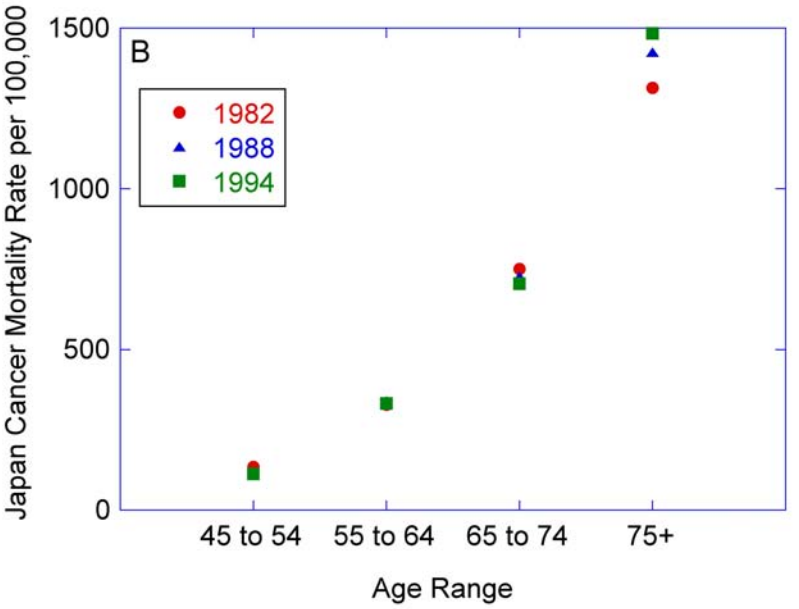

FIGURE 1B. Cancer mortality rate per 100,000 in Japan as a function of age (WHO, 2011).

cancer from immune suppression in organ transplant patients was reported more than forty years ago (Allison, 1970).

A considerable amount of additional evidence is available indicative of the importance of the immune system response in modulating the carcinogenic process. AIDS patients, whose immune system is suppressed, also have higher levels of cancer incidence in a manner similar to kidney transplant patients (Vajdic and van Leeuwen, 2009b). The age-related decline in immune system (Weinberger *et al.*, 2008) may be mainly responsible for the age-related increase in cancer incidence rather than the mutations (Jones, 2011). Increase in lung cancer and other cancers among smokers is attributed to the adverse effect of cigarette smoke on the immune system (Stampfli and Anderson, 2009). The lower immune response may also be responsible for the higher recurrence rate of prostate cancer and poorer survival among smokers (Kenfield *et al.*, 2011a).

Since suppression of the immune system has been observed to correlate with increased cancers, it would be logical to infer that improving the immune system response may reduce the cancer incidence. Moderate exercise is known to stimulate the immune system (Martin *et al.*, 2009) and is known to reduce the incidence of many types of cancers (Warburton *et al.*, 2006; John *et al.*, 2010). Higher immune response is correlated with longer survival in pancreatic cancer patients (Hamanaka *et al.*, 2003). An overactive immune system as indicated by allergies has been associated with reduced incidence of some types of cancers and overall cancer rates (Wang and Diepgen, 2005). Increased immune response was indicative of lower ovarian cancer risk in a prospective study (Pinheiro *et al.*, 2010). Success has been reported in treating cancers with immunotherapy, e.g. with Ipilimumab, which improves the immune response by overcoming T-cell suppression (Weber, 2007).

All these data point to an extremely important role played by deficiencies in the immune system in the pathogenesis of clinical cancer, with oncogenic mutations in the cancer cells playing an essential but not the decisive role. The immune system is however not a perfect defense against cancer, and cancer can develop in spite of the fully functioning immune system (Dunn *et al.*, 2004). The LNT model completely ignores the immune system response in its estimation of cancer risk.

Since the immune system is so crucial in modulating the carcinogenic process, let us consider how radiation affects the immune system. Low dose radiation has been observed to stimulate the immune system (Hashimoto *et al.*, 1999; Yu *et al.*, 2004; Ina *et al.*, 2005; Liu, 2007). Low dose radiation also stimulates other aspects of the bodily defense mechanisms, e.g. it increases antioxidant levels reducing the endogenous DNA damage, increases DNA repair capacity, and increases apoptosis of damaged cells (Feinendegen, 2005). High dose radiation, on the other hand,

suppresses the immune capacity (Kennedy, 1965; Anderson and Lefkovits, 1979; Celer, 1990; Liu, 2003; Kusunoki and Hayashi, 2008).

An analogy with exercise may be helpful in understanding the biphasic dose response of the immune system to radiation. Whereas moderate exercise is known to stimulate the immune system, extreme exercise has an immune suppressive effect (Nieman, 2003; Radak *et al.*, 2008; Martin *et al.*, 2009). The benefits of moderate exercise in reducing the incidence of many diseases including cancer have been well documented (Warburton *et al.*, 2006). For patients diagnosed with breast cancer and prostate cancer, vigorous physical activity has been linked to decreased mortality from the diseases (Holick *et al.*, 2008; Kenfield *et al.*, 2011b). On the other hand, extreme exercise such as marathon or ultra-marathon running is associated with increased upper respiratory tract infections indicative of the suppression of the immune system (Peters and Bateman, 1983), and increased intensity of training is associated with an increased number of melanoma markers in marathon runners (Richtig *et al.*, 2008).

Ignoring the large variation in cancer rates in specifying no threshold.

A third aspect of the current radiation safety paradigm and the consequent LNT model is that even the smallest dose of radiation is claimed to increase the risk of cancer, as there is no threshold. Meaningful measurement of the small predicted increase in cancer from the low dose radiation would be possible only if the cancer rates are stable, and have small measurement errors. It is well known that cancer incidence rates are highly variable as they depend on a large number of factors including age, tobacco use, ionizing radiation, chemicals, infections, alcohol, diet, exercise, etc. Separating the effect of one factor such as radiation in the presence of all the other variables would be subject to large errors and uncertainties. The measured cancer incidence rate is also affected by the sensitivity of the technologies used for screening for different types of cancers, and the extent of the screening. Over short periods of time most of these variables may be expected to have changed by a smaller amount. Hence, we may be able to obtain an indication of the stability of the cancer rates and uncertainties in their measurements by studying differences in cancer rates between successive years.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute collects and publishes cancer incidence data from population-based cancer registries covering a large segment of the population in the USA (Altekruse *et al.*, 2010). A large variation (much higher than standard errors) has been observed in the SEER age-adjusted cancer incidence rates between successive years, ranging from -3.4% to +4.5% (See Fig. 2). This variation is indicative of the effect of the multiple factors that can change the cancer rates between successive years. When calculating the lifetime risk of cancer for any cohorts, these

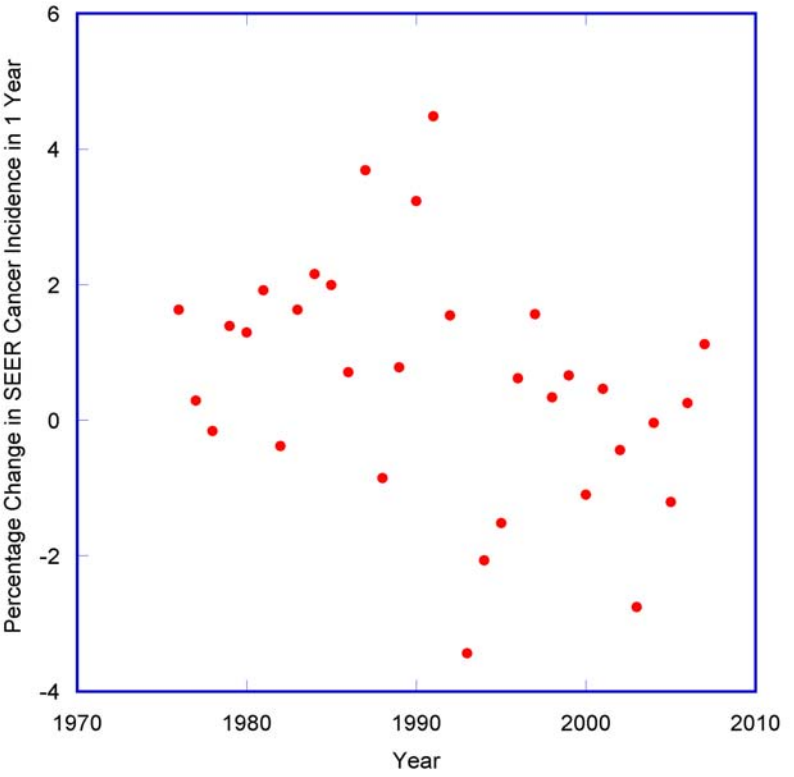

FIGURE 2. Percentage change in SEER age-adjusted cancer incidence rates in 1 year.

variations can compound and become substantial. Hence there can be large uncertainties in estimating low dose cancer risk factors from carcinogens like radiation using long term studies. Indeed, the 95% confidence interval (C.I.) of cancer risk factor for low dose radiation spans a wide range of 400 to 1600 excess solid cancers per 100 mSv per 100,000 (for males), in the recent BEIR VII report (NRC, 2006). The uncertainty in the recommended risk factor has actually worsened when compared to the range of 420 to 1040 given in the BEIR V report (for 90% C.I.) 16 years earlier (NRC, 1990). Such a large and increasing uncertainty in the basic parameter of the LNT model after more than fifty years of study indicates the relationship between low dose radiation and cancer is very tenuous indeed, and low dose radiation may not be a relevant factor in carcinogenesis.

In the above analysis, I have described three fundamental flaws of the current radiation safety paradigm:

1. The paradigm pays exclusive attention to DNA damage and mutations which are not decisive factors in clinical cancer.

2. The paradigm completely ignores the effect of the immune system response which is an extremely important factor modulating the occurrence of clinical cancer. The effect of radiation on immune system response is not linear, as low dose radiation stimulates the immune system, and high dose radiation suppresses it.
3. The paradigm and the consequent LNT model ignore the large variability in cancer rates in specifying no threshold. The lifetime risk measurements are likely to have large errors arising from the variability in the confounding factors and cancer rates from year to year. In view of this, specifying no threshold and implying that the smallest calculated increment in cancer rate is significant, is not credible.

Notwithstanding these fundamental flaws, we have been using the current radiation safety paradigm during the past five decades to guide us in our use of radiation. Were there any adverse health consequences from following this flawed paradigm?

FAILURE OF THE CURRENT RADIATION SAFETY PARADIGM

Our current radiation safety paradigm (exclusive attention to mutations, and ignoring the importance of bodily defense mechanisms including the immune system, as signified by the adoption of the LNT extrapolation model) may have led to missed opportunities in reducing cancer deaths in populations exposed to high doses of radiation such as the atomic bomb survivors in Japan. The importance of the immune system in holding cancers in check was noted as early as the 1970s, from the observed dramatic increase in cancers in organ transplant patients whose immune systems were suppressed, e.g. (Allison, 1970; Hoover and Fraumeni, 1973). The effect of exercise on enhancing different aspects of the immune system has been known for more than a century (Gleeson, 2000). Increased exercise had been correlated with decreased growth of tumors in animal models (Rusch and Kiline, 1944; Rashkis, 1952; Newton, 1965). Improved immune response (leukocytosis) from exercise had been observed in atomic bomb survivors (Belsky *et al.*, 1972). Therefore, data was available in the 1970s to infer the beneficial effects of exercise in improving the immune system response and in reducing cancer. However, during this period, radiation-induced mutations became the primary focus in the carcinogenic process as signified by the dominance of the LNT model in radiation safety policies. The possibility of reducing cancers in the atomic bomb survivors through lifestyle modification (by educating them on the importance of the immune system and encouraging more physical exercise) was missed. A recent prospective study of the effects of lifestyle on cancer among atomic bomb survivors has shown that the group that exercised had between 15% and 35% less cancer mortality with 95% confidence compared to the group that did

not exercise, indicating the effectiveness of exercise in reducing cancers in this population group (Mine *et al.*, 2011). If we had conducted a study such as this in the 1970s, demonstrated the importance and effectiveness of exercise in reducing cancers, and initiated an education and support program for the atomic bomb survivors to exercise regularly, it may have resulted in significantly decreased cancer incidence and mortality in the radiated population. Instead, the LNT model has led us to a fatalistic and pessimistic approach towards population groups subjected to high doses of radiation, where we monitor their health closely, but take little action to reduce their risk of developing clinical cancer, for example by boosting their immune system with exercise. It is ironic that lack of action due to our radiation safety paradigm may have resulted in increased cancer deaths in the most radiated population group, whom the radiation safety paradigm should have protected. The radiation safety paradigm may have failed in its primary responsibility of protecting the health of the radiated population. It is imperative we consider a shift in the current radiation safety paradigm to include consideration of biological defense mechanisms in order to reduce further casualties in population groups that have been subjected to high dose radiation. Exercise intervention should be prescribed to the atomic bomb survivors and other radiated population groups (e.g. Chernobyl liquidators) to reduce their cancer risk in a pilot study, and if the intervention is found to be beneficial, should be expanded to the whole group. A shift in the present radiation safety paradigm can also enable study of the many reported beneficial effects of low dose radiation.

POTENTIAL BENEFICIAL EFFECTS OF LOW DOSE RADIATION

The biological effects of low dose radiation have been found to be similar to that of moderate exercise in animal studies, in that they stimulate the production of antioxidants (Yamaoka *et al.*, 1991; Kojima *et al.*, 1999; Khassaf *et al.*, 2001; Ji, 2002), have a similar effect on cancer-initiation related parameters such as DNA damage, double-strand breaks, and apoptosis, (De Lisio *et al.*, 2011; Phan, 2011), and enhance the immune system response (Nieman, 2003; Farooque *et al.*, 2011). Several different classes of beneficial health effects of low dose radiation may be envisioned based on these observed biological effects.

The first class of potential beneficial effects of low dose radiation is its cancer preventive or therapeutic effect, since low dose radiation stimulates the bodily defense mechanisms including the immune system (Feinendegen, 2005). Low dose radiation has been observed to have a cancer preventive effect in controlled animal studies (Ullrich and Storer, 1979; Ito *et al.*, 2007; Nowosielska *et al.*, 2010; Phan, 2011). Low dose radiation has been shown to be an effective method of treating cancer by boosting the immune system in animal and human studies with little

adverse side effects (Sakamoto, 2004; Farooque *et al.*, 2011). Several retrospective human studies have shown a reduced cancer incidence from low dose radiation, however such studies are subject to many confounding factors, and so they are not discussed here. Prospective cancer prevention studies have been suggested (Cameron, 2002) but would require subjecting an asymptomatic population group to low dose radiation to measure the change in cancer rates. Considering the present radiation safety regulations and the widespread fear of radiation, such a prospective study is neither feasible nor advisable.

A second class of beneficial effects of low dose radiation may be in the control of aging-related non-cancer diseases. Oxidative damage has been implicated in the pathogenesis of many of these aging-related diseases and conditions, e.g. Alzheimer's disease (Martins *et al.*, 1986; Bonda *et al.*, 2010), arthritis (Vasanthi *et al.*, 2009), cataract (Spector, 1995), diabetes (Henriksen *et al.*, 2011), heart disease (Heitzer *et al.*, 2001), osteoporosis (Baek *et al.*, 2010), Parkinson's disease (Zhang *et al.*, 1999), and stroke (Nanetti *et al.*, 2011). Elevating antioxidant levels in the relevant organs may be helpful in reducing the oxidative damage and the impact of such diseases. In animal models, increased amount of antioxidants has led to a reduction of some of the non-cancer diseases, e.g. (Jung *et al.*, 2001; Redout *et al.*, 2010). Application of this idea in humans has however been problematic. Antioxidant therapies have failed to reduce diabetes (Sheikh-Ali *et al.*, 2011), cardiovascular disease (Kris-Etherton *et al.*, 2004) and stroke (Schurks *et al.*, 2010) in controlled clinical trials, though oxidative damage has been identified as playing a key role in these. Bioavailability of the antioxidants in the relevant organs may be a factor, as the administered antioxidants are distributed throughout the body. Increased administration of antioxidants may be considered for improving bioavailability. However, excessive levels of antioxidants can interfere with essential cellular signaling mechanisms and so may be harmful (Halliwell, 2011). Use of antioxidants more than seven times per week has been associated with a doubling of prostate cancer risk when compared to the population not using any antioxidant supplements in a large study (Lawson *et al.*, 2007). Antioxidant supplements have been observed to prevent the health-promoting effects of exercise (Ristow *et al.*, 2009). A compilation of a large number of randomized clinical trials on the effects of antioxidant supplements has shown a slight increase in mortality in the groups using antioxidant supplements (Bjelakovic *et al.*, 2007). Whereas externally administered antioxidants have been observed to not be beneficial and potentially harmful, endogenous production of antioxidants, such as from moderate exercise, has been found to be beneficial (Briones and Touyz, 2009).

Low dose radiation is known to elevate the antioxidant levels in many organs in animal studies, e.g. (Yamaoka *et al.*, 1991; Kojima *et al.*, 1999;

Pathak *et al.*, 2007), and so may play a role in reducing the impact of the diseases and conditions caused by oxidative damage. Animal studies have shown low dose radiation reduces several non-cancer diseases, e.g. diabetes and diabetes related complications (Nomura and Sakai, 2006; Wang *et al.*, 2008; Nomura *et al.*, 2011), autoimmune diseases (Tanaka *et al.*, 2005), arthritis (Nakatsukasa *et al.*, 2008), brain injury from chemical induced oxidative damage (Kojima *et al.*, 1999) and prion infection in the brain (Plews *et al.*, 2010). Human studies with low dose radiation have also shown a reduction in some non-cancer diseases, e.g. asthma (Mitsunobu *et al.*, 2003), and rheumatic diseases (Falkenbach *et al.*, 2005). Reduced non-cancer mortality has been reported in atomic bomb survivors exposed to low dose radiation for the period 1950-67 (but not in a later period) indicative of a non-cancer disease preventive effect of low dose radiation in the near term (Preston *et al.*, 2003; Luckey, 2008). In a study of fluorspar miners exposed to high dose radiation to the lungs from radon, the miners had higher mortality from lung cancer as expected, but the standardized mortality ratio for non-cancer diseases was 0.74 (95% CI: 0.70-0.77) (Villeneuve *et al.*, 2007). Thus, there is suggestive evidence in epidemiological studies for the beneficial effect of low dose radiation for non-cancer diseases. Considering that currently there is no method of preventing, curing or controlling some of these diseases (e.g. Alzheimer's), the effect of low dose radiation on the non-cancer diseases should be studied systematically, to determine if low dose radiation has a beneficial effect for any of these diseases. The beneficial effects may become evident in a short period of time in terms of reduced sickness and mortality. By not studying the health effects of low dose radiation systematically because of the LNT model based fear, we may have missed an opportunity to reduce non-cancer diseases.

A third class of beneficial effects of low dose radiation may be the reduction of adverse side effects of standard cancer therapies. Radiation-induced free radicals and the oxidative damage they cause are predominantly responsible for the biological damage and adverse side effects from the high-dose radiation used in radiotherapy (Lawenda *et al.*, 2008). Likewise, for many chemotherapy agents, oxidative damage to normal tissues is responsible for the adverse effects (Chen *et al.*, 2007). Elevating the level of antioxidants in the normal tissues prior to the cancer therapies may be helpful in reducing the damage and the side effects. However, systemic administration of antioxidants may reduce the effectiveness of the therapies, and so is not recommended (Lawenda *et al.*, 2008). The advantage of low dose radiation is that it can be applied selectively to normal tissues while minimally exposing the tumors, thus limiting the primary adaptive response to normal tissue only. For example, prior low dose radiation of normal cells surrounding the tumor volume has been tested in a canine model to demonstrate reduction of skin and

mucous membrane side effects of radiation therapy by inducing an adaptive response in the normal cells (Blankenbecler, 2010). Another advantage of using low-dose radiation is that it has been shown to stimulate the immune system leading to improved tumor control in animal studies (Wu *et al.*, 2008). It may also lead to increased apoptosis of pre-cancerous cells through inter-cellular communication (Portess *et al.*, 2007). Thus pretreatment of normal tissues with low dose radiation may reduce the adverse side effects from cancer therapies, without reducing the effectiveness of the therapies, and may even enhance their effectiveness.

A fourth class of beneficial effects of low dose radiation may be to impart the beneficial effects of exercise to persons with disabilities, painful conditions or weakness that prevent or discourage them from exercising. Though the benefits of appropriate exercise for such populations have been well documented, compliance with exercise programs due to pain is a considerable problem as there are high dropout rates (Richards and Scott, 2002).

The use of low dose radiation contrasts sharply with traditional approaches for these illnesses and conditions. Many of the standard drugs and treatments are effective in controlling the symptoms of the diseases, e.g. coronary plaque formation, hormonal imbalance, hypertension, tumors, etc. without addressing the underlying causes of the aging-related diseases which appear to be oxidative stress and/or deficiencies in the immune system. Thus the diseases and the symptoms tend to recur, e.g. blockage of arteries, second cancers, etc. Since the administered drugs are distributed throughout the body and act on normal tissues and organs in addition to the targeted organs, many of the drugs have serious side effects. Standard cancer therapies also have immediate and long lasting adverse side effects (Cukier, 2005). Even targeted therapies can have serious side effects when continued over a long period of time (Appleby *et al.*, 2011). On the other hand, low dose radiation has beneficial biological effects similar to moderate exercise, as it elevates antioxidant levels and addresses the underlying cause of the diseases and conditions, and it can be applied to any organ or tissue locally minimizing the effects on other organs and tissues, if so desired. Low dose radiation may be useful in reducing the recurrence of the diseases by reducing oxidative damage after the symptoms have been addressed through traditional means.

DISCUSSION

It is clear from the discussions above that there is no justification for continuing the use of the current radiation safety paradigm, as it was established based on premises that have turned out to be false, is fundamentally flawed, has no scientific foundation, has likely led to missed opportunities in reducing cancer deaths among atomic bomb survivors, has led to an irrational fear of low dose radiation, has prevented the study of poten-

tially beneficial applications of low dose radiation, and has likely prevented progress in reducing aging-related diseases, side effects of cancer therapies, and diseases in the infirm. We need to shift to a paradigm that recognizes adaptive response and the potential for beneficial effects of low dose radiation. Making this change is not going to be easy, as the new paradigm is contrary to the recommendations of most advisory bodies, present government regulations, and the public perception of the effects of low dose radiation. Any attempts to rescind the current regulations may be viewed with suspicion by the public because of the widespread belief in the LNT model. A sustained educational campaign should be initiated to correct the current misconceptions in the scientific community and the public about the pathogenesis of clinical cancer and the health effects of low dose radiation. Demonstration of beneficial health effects of low dose radiation through pilot clinical trials may be helpful in reducing the fear of low dose radiation, and enabling the paradigm shift.

To guide us in this change, the scientific community should form new advisory bodies that use experimental evidence (including the observed beneficial effects of low dose radiation) in recommending radiation safety policies rather than the unproven LNT extrapolation hypothesis advocated by most of the present advisory bodies. Such advisory bodies can also guide us in studying and implementing the beneficial applications of low dose radiation.

The last paradigm shift in radiation safety occurred in the 1950s. Prior to this period, the main concern with radiation use was skin erythema (Sinclair, 1981), and it was considered as appropriate to treat many diseases and conditions with radiation, including for children, e.g. (Mottram and Hill, 1949). In the 1950s, following the observation of increased leukemias in atomic bomb survivors, genetic effects became the dominant concern leading to the adoption of the current radiation safety paradigm, as the advisory bodies such as NCRP and ICRP reduced the radiation dose limits. This was not because of any observed harm from low dose radiation but because of general public concerns (Sinclair, 1981). Realization that the current paradigm may have led to missed opportunities in preventing cancer deaths among atomic bomb survivors may again raise public concerns and scrutiny by the media, and facilitate another paradigm shift in radiation safety in the near future.

SUMMARY AND CONCLUSIONS

The current radiation safety paradigm using the LNT model was introduced following the observation of linear dose dependence of leukemias in atomic bomb survivors for high dose radiation, observation of linear dose dependence of mutations in drosophila for high dose radiation, linking the two, and extrapolating linearly to low doses since cancer is such a feared disease. The LNT model pays exclusive attention to

DNA damage, which is not a decisive factor in clinical cancer as observed in autopsy studies, while ignoring the immune system response, which plays a major role in keeping occult cancers in check, as indicated by the huge increase in cancers in organ transplant and AIDS patients. The large temporal and regional variations in cancer rates have been ignored in setting a zero threshold in the LNT model, implying the smallest changes in projected cancer rates are significant. The large expenditures for dose reduction based on the LNT model may not result in any measurable reduction in cancers. In view of the large number of factors that have measurable effects on cancer rates, an optimum allocation of available resources between the different risk factors can result in maximizing the reduction in cancers. The lopsided allocation of resources based on the LNT model deviates from this optimum allocation and so would result in a sub-optimal reduction in cancers. Thus, the use of a no-threshold model is not a conservative approach to radiation safety.

Our misunderstanding of the pathogenesis of clinical cancer and the resultant radiation safety paradigm paying exclusive attention to mutations may have resulted in missed opportunities in preventing cancer deaths in atomic bomb survivors and in other radiated populations. The importance of the immune system in preventing cancers was known in the 1970s from the increased cancers in organ transplant patients in whom the immune system had been suppressed. The increase in immune response from exercise has been known for more than a century. A recent prospective study of the effect of lifestyle on cancers has shown the effectiveness of exercise in reducing cancers in atomic bomb survivors. An exercise intervention study in the 1970s could have resulted in reduced cancer deaths among atomic bomb survivors. However, the focus of the radiation safety paradigm in that time period was on reducing mutations as the cause of cancer, and so missed the opportunity to reduce cancers in this population group. The current radiation safety paradigm has likely failed in its primary responsibility of reducing radiogenic cancers. A paradigm shift is warranted to reduce further casualties.

The biological effects of low dose radiation are similar to that of moderate exercise in that they both lead to slightly increased production of free radicals stimulating the body's defensive mechanisms such as increased antioxidant capacity and the immune system. Thus, low dose radiation may be expected to reduce rather than increase cancers, since the immune system plays an extremely important role in preventing cancers. This has been observed in many controlled animal studies. The increased antioxidants may also help to reduce aging-related diseases since oxidative damage has been implicated in many of these diseases. External administration of antioxidants has failed to reduce diseases in clinical trials, possibly because there may not have been sufficient bioavailability of the antioxidants in the relevant organs to reduce the

oxidative damage. Administration of large doses of antioxidants can interfere with important cellular signaling mechanisms, resulting in worsening of health and so is not recommended. Thus we are at an impasse in dealing with the underlying cause of aging-related diseases. Low dose radiation may provide a solution to this impasse by endogenous production of antioxidants in the relevant organs. Controlled animal studies have shown reduction of many of these diseases using low dose radiation, and some human studies have also shown promising results. Low dose radiation can be used to supplement traditional treatments which address the symptoms of the diseases, in order to reduce the recurrence of the diseases. The increased antioxidants from low dose radiation may also reduce the adverse side effects of cancer therapies, since many of these are caused by oxidative damage also. Another potential application of low dose radiation may be in providing the benefits of exercise to the infirm that are unable to exercise.

The current situation with respect to these different diseases and conditions is far from satisfactory, as there is no effective way to prevent the cancers, aging-related diseases such as Alzheimer's, adverse side effects of cancer therapies, and inactivity related diseases in the infirm. Pilot clinical trials should be conducted to study the effects of low dose radiation for these diseases and conditions to identify the beneficial ones for potential use. The current radiation safety paradigm and regulations, and the consequent fear of low dose radiation have discouraged such studies, preventing progress in dealing with these unsolved problems in human health.

A paradigm shift is warranted to reduce further casualties and improve human health. Since the proposed changes are completely contrary to the recommendations of most of the current advisory bodies, it may be preferable to form new advisory bodies with a fresh perspective to guide us in these changes. Realization by the media and the public that the present paradigm, by its inaction, may have missed opportunities in reducing cancer deaths among radiated populations may lead to increased public concerns and closer scrutiny, and hasten the process of dismantling the current radiation safety paradigm in the near future.

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