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Cancer risk at low-dose ionizing radiation has been the subject of great scientific controversy in the past century. The clear majority of national and international radiation protection regulators adopt the linear no-threshold (LNT) model based on the atomic-bomb survivors Life Span Study (LSS) for solid cancer risk assessment. The LNT model assumes a linear relationship between radiation dose and cancer risk including interpolation of high dose values down to zero dose with no 'safe' threshold. New scientific evidence in the fields of molecular biology and epidemiology challenge the validity of the LNT model suggesting beneficial effects at low doses of ionizing radiation in a process better known as 'hormesis'. This paper investigates current evidence for radiation hormesis with respect to solid cancer risks in adults and proposes a modest study design to test the hormesis hypothesis in humans with the potential of using low dose ionizing radiation to reduce solid cancer incidence in a population, if hormesis is proven. Current evidence confirms that hormesis does occur at low dose and low dose rates of low LET ionizing radiation. Every effort should be made from scientists in related fields in order to make the best use of the hormesis phenomenon with the aim of benefiting and protecting the public as the main objectives.

Low-Dose Ionizing Radiation Solid Cancer Risk in Adults: Radiation Hormesis Study Design.

by
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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

Abdulaziz S. Alhussan, Author

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I dedicate this thesis to my parents; my mother, Diaa Albarjas; and my father, Salah Alhussan, I would not be here today if it was not for them.

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1. INTRODUCTION & BACKGROUND

Ionizing radiation — radiation that has enough energy to free electrons from molecules — is proven to be damaging to living organisms at high doses (Hall & Giaccia, 2012). The health effects of being exposed to ionizing radiation can be categorized as stochastic effects (the probability of incidence increases with dose while the severity is independent of dose) such as cancer and heritable diseases; and deterministic effects (the probability is zero at small doses, but increases above a threshold dose, and so does the severity) such as tissue reactions, skin burn, sterility, and radiation sickness (Hall & Giaccia, 2012). Though, since deterministic effects are seen at doses of several Gray with a threshold, what is of most concern to people is radiation induction of cancer with an unknown latent period of up to decades after exposure. Despite our understanding of high dose radiation carcinogenesis, the effects of low doses of ionizing radiation has remained controversial for decades. Due to ethical constrains the scientific community is yet to conduct a large experiment on humans to purposely assess solid cancer risks associated with exposure to low doses of ionizing radiation (Doss, 2013; Luckey, 2008; Sanders, 2010; Tubiana, Feinendegen, Yang, & Kaminski, 2009; Vaiserman, 2010b).

Nowadays, regulators and most scientific organizations from all over the world assume that any amount of radiation no matter how small carries cancer risk to living organisms by extrapolating high dose data down to zero dose (Figure 1.1). This assumption has favored the use of the Linear no-threshold (LNT) model as a measure of radiation dose response for risk estimates. According to the LNT model, an increase in radiation dose increases the probability that a single cell will develop into a cancer even at very low doses, with no ‘safe’ dose.

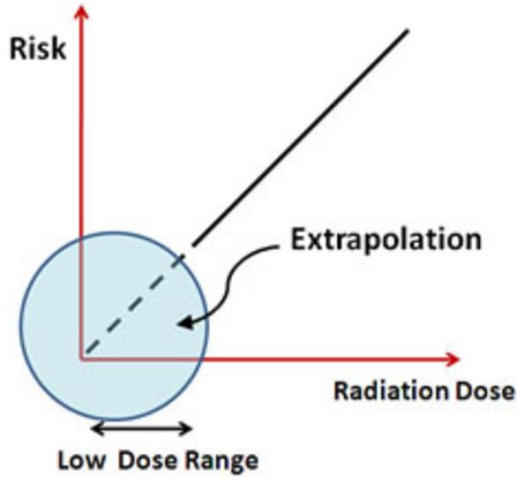

Figure 1.1. The Linear No-Threshold Model (GNE Trading, 2011).

The controversy on whether a threshold exists or not goes back to the early days of discovering ionizing radiation. During the late 1920s to 1940s, Hermann Muller and his colleague Curt Stern along with other scientists, focused their studies on irradiating fruit flies with X-rays. Challenged by an extensive study from Ernst Caspari in favor of the existence of a threshold, Muller acknowledged the need for empirical data for validating the extrapolation down to zero dose resulting from his experiments since only high doses and dose rates were used (Siegel & Pennington, 2015; Calabrese 2013). However, Muller overlooked Caspari's data and went to earn the 1946 Nobel Prize in Physiology or Medicine, birthing the concept of the Linear no-threshold of radiation (Calabrese, 2013; Sutou, 2016). Then, important findings in 1948 by Spencer and Stern, and later in 1949 by Uphoff and Stern, showed a strong dose rate effect supporting Caspari's data (Siegel & Pennington, 2015). Yet again, the new information was disregarded, "this was the start of fabrication of LNT" (Sutou, 2016). Siegel & Pennington (2015) explain their distrust and disappointment in the scientific community of the time, stating:

> These extremely important findings were either discounted or missed by the investigators and scientific community of the day; if they had been appreciated, as

> they should have been by 1949, it is highly likely that the LNT would not have survived its birth, as it was a linear threshold, not a linear no-threshold, dose-response relationship that was demonstrated. To be clear, this is not a matter of opinion; rather, the conclusions here are firmly rooted in the researchers' own cited publications and are, thus, irrefutable from a scientific perspective. (p. 47)

Soon after, in 1957, the work of Edward Lewis, using very early data from both the Hiroshima and Nagasaki atomic bomb reports, backed up the LNT hypothesis which proved extremely controversial (Siegel & Pennington, 2015).

The U.S. National Academies concerning radiation health effects committee, better known as the Biological Effects of Ionizing Radiation (BEIR), clearly supported the linear no-threshold (LNT) model for solid cancer risk estimates in humans in their seventh publication report, BEIR VII (2006). The committee accepts a linear relationship between low-LET doses and chromosomal mutations (2006). It is argued that error-prone repair of DNA double-strand breaks (DSBs), induced by a single ionizing cluster, is the initiation to neoplastic transformations growing into cancers (2006). They reasoned that risk estimates can then be enhanced using a multiplicative adjustment known as dose and dose-rate effectiveness factor (DDREF) (2006). Though, whether the modified LNT model or the adopted linear quadratic model was used they both are built on the assumption that being exposed to any amount of radiation can cause cancer.

The idea behind this assumption is that a single radiation track, regardless of its ionization density, can cause DSBs, and that each DSB will then induce a cell transformation regardless of the number of DSBs existing in the cell, and that each transformation will have the same probability of growing into cancer, although this can never be proven (Hall & Giaccia, 2012; Sanders, 2010). It is argued that this hypothesis can only be true if the organism has no biological defense mechanisms against radiation (Sutou, 2016). It is very well known that all living organisms are continuously being bombarded by natural background ionizing radiation since the beginning

of life. This led to the development of a set of defense mechanisms through millions of years of evolution against reactive oxygen species improving DNA repair mechanisms and the removal of damaged cells (Scott et al., 2009; Sutou, 2016; Vaiserman, 2010b).

More recently, after the Fukushima incident of 2011, the Japanese government set the safe limit dose as low as 1 mSv for the public (Sutou, 2016) which was even lower than the average worldwide background radiation of 2.4 mSv/year (National Research Council [NRC], 2006). To put things into the context of radiation doses, a single screening mammogram delivers a dose of around 3 mSv (Figure 1.2). Overprotective governments' actions have led people to virtually believe that any amount of radiation exposure is lethal, thus reawakening the understandable, yet excessive fear of radiation among the general public. This triggered a damaging effect on the mental health of people caused by what the media calls 'radiophobia' followed by enormous human and economic losses. Ironically, this unproven belief gave birth to the LNT concept some 70 years ago, and today is adopted by radiation regulators worldwide. (Cuttler, 2007; Jolly & Meyer, 2009; Marcus, 2016; Miller, 2016; Sanders, 2010; Sutou, 2016).

Some societally relevant exposures	**Dose (mSv)**
Round-trip flight, New York to London	0.1
Single screening mammogram (breast dose)	3
Background dose due to natural radiation exposure	3/yr
Dose (over a 70-year period) to 0.5 million individuals in rural Ukraine in the vicinity of the Chernobyl accident	14
Dose range over 20-block radius from hypothetical nuclear terrorism incident [FASEB scenario 1: medical gauge containing cesium (6)]	3–30
Pediatric CT scan (stomach dose from abdominal scan)	25
Radiation worker exposure limit (1)	20/yr
Exposure on international space station	170/yr
Some low-dose epidemiological studies	
A-bomb survivors [mean dose in LSS cohort (2)]	200
Medical x-rays [breast dose in scoliosis study (4)]	100
Nuclear workers [mean dose from major studies (5)]	20
Individuals diagnostically exposed *in utero* (3)	10

Figure 1.2. Approximate Mean Individual Doses from Different Exposures. (Brenner et al., 2003).

Furthermore, some scientists have suggested that not only the LNT is scientifically unproven, for low doses (<100 mSv) and low dose rates (<200 mSv/year), but also that exposure to low level of radiation may improve immune response and DNA repair processes (Luckey, 1991; Mattson & Calabrese, 2010; Sanders, 2010; Vaiserman, 2014). This has led three experts in the field, Dr. Mohan Doss, Dr. Carol Marcus and Mark Miller, to prompt filing of three petitions for rulemaking (PRMs) to the U.S. Nuclear Regulatory Commission (NRC) in 2015 on this issue. The petitions requested standards calling for the end of using this model in support of the radiation hormesis model (Figure 1.3), that indicates radiation-induced benefit at low doses (Nuclear Regulatory Commission, 2015).

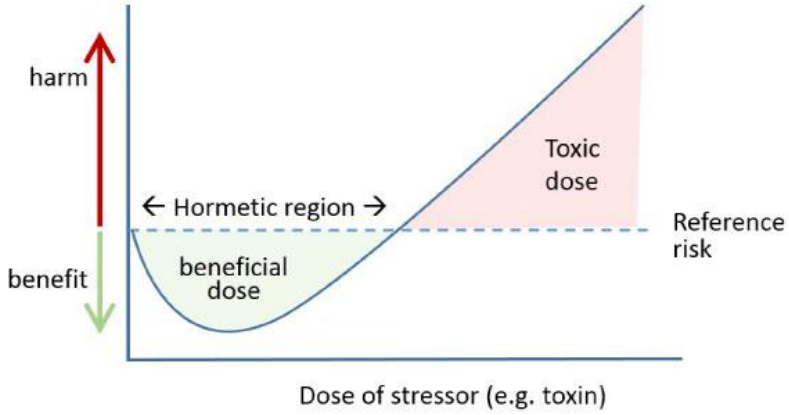

Figure 1.3. The Hormesis Model (Mangan, 2017).

In simple terms, hormesis is the phenomenon that describes the net positive effects of being exposed to a small stimulating dose of a stressor or toxic substance, in this case, ionizing radiation. It is a very well documented phenomenon in toxicology (Calabrese, 2009). The model is represented by a J or U-shaped dose response curve with a threshold (Figure 1.3). Beneficial effects to an organism are seen in the hormetic region, i.e., below a specific threshold, and harmful effects are seen in doses above the specific threshold, in which the threshold is determined by the strength

of the defense capability of the organism (Sanders, 2010). The hormetic effects range from being tolerant to higher doses of ionizing radiation to increasing the life span of the organism and improving its overall health (Luckey, 1991). It is proposed that low doses and dose-rates of low LET ionizing radiation (X-ray and γ-radiation), awaken several hormetic defense mechanisms at cellular, molecular, and organismic levels against initiation, proliferation, and buildup of damage cells in tissues that may develop into cancer, hence, reducing the total number of cancer incidences and decreasing the occurrences of other harmful health effects in a population (Luckey, 1991; Mattson & Calabrese, 2010; Sanders, 2010; Sutou, 2016; Vaiserman, 2014).

Over the past decades, the scientific community has built a strong foundation for the rebirth of the radiation hormesis concept. A decent number of scientists show indications of hormetic response, in humans exposed to low doses of radiation, including: survivors of the Atomic bomb, survivors of nuclear accidents, workers in the nuclear industry, and people living in areas with high levels of background radiation (E. Calabrese et al., 2013; Cuttler, 2007; Doss, 2013; Luckey, 1991; Luckey & Lawrence, 2006; Mattson & Calabrese, 2010; Sanders, 2010; Sutou, 2016). Nevertheless, there has been no actual experiment that tests radiation hormesis on people mainly due to radiophobia. BEIR VII addressed some evidence related to radiation hormesis in its appendix concluding that:

> Although examples of apparent stimulatory or protective effects can be found in cellular and animal biology, the preponderance of available experimental information does not support the contention that low levels of ionizing radiation have a beneficial effect. The mechanism of any such possible effect remains obscure. At this time, the assumption that any stimulatory hormetic effects from low doses of ionizing radiation will have a significant health benefit to humans that exceeds potential detrimental effects from radiation exposure at the same dose is unwarranted. (p. 335)

Undoubtedly, BEIR VII committee does not consider radiation to hold a net hormetic beneficial effect at low doses. This is mainly due to the proclaimed lack of experimental data supporting the hormesis hypothesis. The committee also added that more research is needed to explain the molecular defense mechanisms of hormesis; "Definitive experiments that identify molecular mechanisms are necessary to establish whether hormetic effects exist for radiation-induced carcinogenesis" (NRC, 2006, p. 315).

Till this day, the scientific community has favored the no-safe dose model for risk estimates with a growing number of voices calling for the use of the hormesis model instead. Both groups of advocates are doing their best to reach a scientific-based conclusion on this issue, with a top priority of protecting the public, despite the growing public, political and financial pressures. If radiation hormesis does exist and is proven, countless number of lives would be saved from getting cancer by receiving an immunizing radiation dose that stimulates the body defense mechanism against tumor development. Likewise, numerous unnecessary radiophobia deaths from suicide, abortion, forced evacuation and fear of diagnostic radiation would be prevented. Though, the real question is not whether there is enough scientific evidence to support the hormesis hypothesis, but whether we are ready to accept it or not. BEIR VII was published in 2006, roughly ten years ago, meaning that we have a full decade worth of new information on this sensitive topic. Thus, giving more weight to studies from the last decade, the next chapter will be an extensive literature review on the question of *Radiation Hormesis: fact or fiction?* Followed by a chapter proposing an experiment to test the radiation hormesis hypothesis at low doses with respect to solid cancer risk in adults due to the fact that solid cancers are much more common than other cancer types (Cooper, 2000).

2. LITERATURE REVIEW

The first section of this chapter will discuss current problems with the LNT model followed by a section on what we currently know about cancer and radiation carcinogenesis. The third section will cover the molecular biology aspect of how the human body reacts to low doses and low dose rates of ionizing radiation. The fourth and fifth sections will cover the bulk of available epidemiological data of people exposed to low doses of ionizing radiation and current attempts to model radiation hormesis, respectively. The last section of this chapter is a brief summary of the previous sections, ending with what research needs to be conducted. The main source of material was the *PubMed* service of the US National Library of Medicine which comprises more than 27 million citations for biomedical literature.

2.1 The LNT Model Dilemma

The Linear No-Threshold model (LNT) is a radiation protection model used to estimate the stochastic biological damage (cancer) caused by ionizing radiation. It assumes a linear relationship between the received dose and the incidence of cancer in humans at ALL dose levels. In other words, it assumes that an increase in dose causes an increase in cancer risk for humans meaning that there is no amount of ionizing radiation no matter how small that is harmless. The linear relationship is extrapolated down to zero dose with no scientific evidence to prove it at low doses (Figure 1.1). According to Tubiana et al. (2009):

> This approach is based on one set of data and two hypotheses: (a) The relationship between dose and DNA damage *in vivo* seems linear from 1 mGy to 100 Gy...(b) each DSB is hypothesized to have the same probability of inducing cell transformation, irrespective of the quantity of DSBs present simultaneously in the cell; and (c) each transformed cell is hypothesized to have the same probability of developing into an invasive cancer, irrespective of the dose delivered to the tissue.

Under the LNT model, if a dose equal to 1 Gy gives a cancer risk *X*, the risk from a dose of 0.1 Gy is *X*/10, and so on. For example, a worker who receives 50 mSv annually incurs 10 times as much risk of getting cancer as another worker who receives only 5 mSv. For over 70 years, the vast majority of regulatory agencies worldwide have adopted the Linear No-Threshold model (LNT) for solid cancer risk assessment, including the international and the national Commission on Radiation Protection ICRP and NCRP respectively (Sanders, 2010). Although, the concept itself might make sense on first thought and many scientific data suggest that cancer risks increase proportionally with dose at high doses, current scientific data does not support the LNT assumption in the region of low doses (Aleta, 2009; Averbeck, 2009; Hoffmann & Stempsey, 2008; Miller, 2016; Ricci & MacDonald, 2010; Sanders, 2010; Siegel, Pennington, Sacks, & Welsh, 2015; Socol & Dobrzynski, 2015; Socol et al., 2014; Sutou, 2016; Tubiana et al., 2009).

The Life Span Study (LSS) of the Hiroshima and Nagasaki atomic bomb survivors has provided the primary data to support the LNT hypothesis, even though they involved high doses of high-energy gamma radiation and neutrons delivered over a very short period of time, not to mention the massive electromagnetic pulse following dropping the atomic bomb and the ruthless conditions following six years of war (Raabe, n.d.; Siegel & Pennington, 2015; Sutou, 2016). However, numerous scientists from all over the world highly question the strength and the bias of the data; the inconsistency of the assumptions and 'opinions' made; the failure in considering some confounding factors such as smoking, electromagnetic pulse and black rain; and the uncertainties of dosimetry and cancer risks estimations of the LSS; consequently, disapproving of how the data were used to fit the unverified LNT model at low doses of around 100 mSv (Aleta, 2009; Doss, 2012; Sanders, 2010; Siegel & Pennington, 2015; Socol & Dobrzynski, 2015; Socol et al., 2014; Sutou, 2016; Tubiana et al., 2009). In spite of all of that, a J-shaped dose-response model s clearly

seen at low and mid doses when adjusting the atomic-bomb survivors' data for the year-to-year age and location baseline cancer mortality rates (Doss, 2013).

Large numbers of experimental and epidemiological studies challenge the validity of the LNT model (Sanders 2010; Tubiana et al., 2009). Many scientists even dispute the ethicality of using the LNT model believing that it was fabricated a long time ago and that it is used due to pressures from certain parties (Calabrese, 2013; Marcus, 2016; Siegel & Pennington, 2015; Sutou, 2016). Others indicated some tricks used in epidemiological data that favor the LNT hypothesis, for instance: dose lagging (removing dose), averaging of odds over wide dose intervals and making the dose-response curve to have a positive slope (Scott, 2008). In the case of a lack of decisively verified scientific basis at low doses, LNT supporters extrapolate the verified higher doses results to lower doses for 'simplicity', assuming a positive response for the sake of 'protecting the public' and being conservative (US NRC Regulatory Guide 8.29, 1996). Currently, in the US, the radiation protection ideology is based on three principles:

- Justification; which requires a net positive benefit to the person receiving the dose.
- Optimization; all exposures shall be kept as low as reasonably achievable (ALARA). Economic and social factors are to be considered.
- Limitation; the dose equivalent to individuals shall not exceed the limits recommended by the International Commission on Radiation Protection (ICRP) of 1 mSv/year to the general public and 20 mSv/year the occupational radiation worker (ICRP, 2007).

Though is the LNT assumption truly protecting the public? In the case of radiation protection at low doses, being too conservative has shown to be problematic. Many scientists have

expressed their anger with the LNT hypothesis for many reasons, mainly the contradicting scientific data at low doses, social problems (radiophobia), and unnecessary economic and life loses, all leading to harming people instead of protecting them; examples of these effects are summarized below (Luckey & Lawrence, 2006, Doss et al., 2015; Rockwell, 2004; Socol et al., 2014; Sutou, 2016; Tubiana et al., 2009):

- Traumatic evacuation: More than 1000 deaths in Fukushima area from the urgent evacuation following the 2011 nuclear power plant accident and about 200,000 traumatic evacuations of individuals in Chernobyl 1986.
- Displacement of people: More than 100,000 people in the Fukushima area were displaced, due to radiophobia.
- Abolishing nuclear energy to produce electricity (Germany and Kuwait): Despite it being the safest in terms of number of fatalities per amount of energy produced.
- Suppression of research on cancer: "10% of the current deaths from cancer can be prevented using low-dose radiation…. considering the annual worldwide cancer death toll of 7.6 million, the LNT model is probably responsible for causing over 2,000 preventable cancer deaths every day worldwide" (Doss et al., 2015).
- Suppression of low dose rate research: Many recent studies suggest that hormesis is not observed in leukemia and solid cancer cells unlike in normal cell lines. In fact, hypersensitivity is seen in cancer cells following low doses/ low dose rates of low LET irradiation (Liang et al., 2016). However, less number of studies showed hormesis in some cancer cells, suggesting that there

might be an ‘optimal dose rate’ that stimulates hormesis in normal cells and stimulates hypersensitivity in cancer cells, to be used for cancer treatment (Cui et al., 2017).

- Incorrect disease diagnoses: Due to radiophobia, many patients refuse having CT scans.
- Economic Loss: Billions of dollars per year are wasted by the nuclear industry and the public on attaining ALARA with no health benefits.
- Abortions: More than 100,000 abortions of pregnancies following Chernobyl.
- Suicide: An increase in suicides due to radiophobia among Fukushima evacuees following the 2011 accident and an estimated 1250 suicides from the 1986 Chernobyl accident.
- Radiological terrorism: Radiophobia caused by the unproven LNT hypothesis may inspire radiological terrorism causing huge economic and psychological consequences.

A good way to test the LNT hypothesis, is to calculate the number of people that will die from exposure to background and natural radiation levels which are in the region of low doses and dose rates. Theodore Rockwell, a member of the Manhattan Project, estimated that number, using the LNT assumption, to be 650,000 per year as well as 100,000 additional deaths annually because of routine medical use of x-rays, which is not the case (Rockwell, 1998). Furthermore, Dr. Michael O’Connor of Mayo Clinic has shown a huge overestimation of the number of all cancer incidences and deaths from medical radiation studies that are predicted using the LNT model of BEIR VII. He questioned the high estimated number of people that will die as a result of living in places with naturally higher levels of radiation if the LNT assumption was correct (O’Connor, 2012). In his

book on Radiation Hormesis, T.D. Luckey estimated that one-third of all cancer deaths are avoidable by low-dose ionizing radiation (Sanders, 2010).

One of the main issues debunking the LNT hypothesis is the fact that the LNT does not consider the biological defense mechanism which plays an important role in preventing cancer growth in the human body (Aleta, 2009; Sutou, 2016). An increasing number of biological studies are showing that different defense mechanisms for DNA damage repair are trigged at low doses and low dose rates which are easily overwhelmed at higher doses/dose rates; this is contradictory to the LNT hypothesis (Aleta, 2009; Sanders, 2010; Socol et al., 2014; Sutou, 2016; Tubiana et al., 2009). In other words, the body react differently to different doses and dose rates of ionizing radiation, making extrapolation of risks several orders of magnitude from high doses down to zero, without data to prove it, very imprecise (Miller, 2016). Tubiana et al.'s (2009) study concluded that:

> The advances during the past 2 decades in radiation biology, the understanding of carcinogenesis, and the discovery of defenses against carcinogenesis challenge the LNT model, which appears obsolete…The French Academies report (10) concluded that the LNT model and its use for assessing the risks associated with low doses are not based on scientific evidence.

2.2 Ionizing Radiation Carcinogenesis

Carcinogenesis or oncogenesis or tumorigenesis is the initiation or formation of cancer. Cancer is a disease that involves an abnormal cell division without control and has the potential to invade or spread to other parts of the body. Most cancers are grouped into one of three groups: carcinomas (malignancies of epithelial cells; most common ~ 90%), sarcomas (rare; solid tumors of connective tissues, such as muscle, bone, fat and cartilage), and leukemias (blood-forming cells) or lymphomas (immune system cells) (Cooper, 2000). It is known in cancer biology that tumors are formed from cells with different regeneration capacities and functional heterogeneity. The two

acceptable models attempting to describe how tumors grow are: the cancer stem cell (CSC) model and stochastic model. The CSC model proposes that only a tumorigenic minority of cells, i.e. cancer stem cells (CSC), in the cancer population of cells, drives the progression of cancer. Those cells can self-renew and differentiate into non-tumorigenic offspring of cells that contributes to the growth of the tumor. On the other hand, the stochastic model suggests that any cell in the body could become tumorigenic if it underwent a significant number of alterations to its DNA sequence. Once these cells become tumorigenic, they possess the ability to self-renew and differentiate, leading to tumor heterogeneity. Some of these tumorigenic cells differentiate into non-CSCs leading to a diversity of cell types in the cancer cell populations (Rich, 2016). Note that there is no current enough evidence to support one model over the other (Rich, 2016). So, how does ionizing radiation cause cancer?

Ionizing radiation can be divided based on the rate of energy transfer, better known as linear energy transfer (LET). Neutrons products such as protons, α-particles and heavy charged particles, are high LET particles meaning that are densely ionizing since they transfer more energy per unit length along their path. In contrast, X- and γ-rays radiation produce low LET electrons that are sparsely ionizing because they deposit less energy per unit length along their tracks. Both low LET and high LET radiation can interact 'directly' with the DNA (the critical target) in the cell nucleus causing damage, or 'indirectly' by interacting with other molecules (mostly water since 80% of cell is water) which produce free radicals or reactive oxygen species (ROS) —an atom or molecule with an unpaired electron such as the highly reactive hydroxyl radical OH·— that can then damage the DNA. Indirect action through free radicals is dominant for low LET radiation and can be chemically modified by free radicals' scavengers, whereas high LET radiations produce most biological damage by direct action which cannot be chemically modified.

The DNA damage of most concern is the double-strand break (DSB) which can be formed by single tracks of ionizing radiation, in a single nucleus, in a single cell, and may result in mutations and carcinogenesis (Hall & Giaccia, 2012).

DNA damage can be recognized by enzymes; DSBs are repaired mainly by homologous recombination (HR) and non-homologous end joining (NHEJ) which are error-prone (Kourtis & Tavernarakis, 2011). Sometimes this damage cannot be repaired or is misrepaired which may cause cell death or may facilitate the production of gene mutations or chromosomal aberrations such as chromosomal translocations, deletions, inversions, amplifications, or a simple point mutation. These same aberrations may also be caused by natural background radiation or by radiation from within the own body mainly from potassium-40. It is worthwhile to mention that in humans, at doses <100 mSv no induction of chromosomal inversions and deletions have been observed; at doses <20 mSv no increase of chromosomal aberrations was seen either; and no genetic instability was seen at doses <250 mSv of low-LET ionizing radiation (Tubiana et al., 2009).An accumulation of gene mutations, particularly in genes that control proliferation, apoptosis, immortalization, and genetic stability, is thought to cause tumor development (Hall & Giaccia, 2012).

These genes fall into one of three main groups: proto-oncogenes, tumor suppressor genes and DNA stability genes. Examples of mutations that affect the function of these genes are: gain-of-function mutations to proto-oncogenes that activate oncogenes (growth stimulators), loss-of-function mutations that inactivate tumor suppressor genes (growth inhibitors and apoptosis promoters), and loss of activity of genome stability genes (repairers, e.g. DNA repair genes and Mismatch repair genes) that increases the probability for genomic instability (Hall & Giaccia, 2012). It is thought that carcinogenesis is likely to start from a mutation in one of the genome stability gene families, which then may lead to an increase in genetic mutation rates possibly in

both oncogenes and tumor suppressor genes, which then leads to a sequence of events such as cell immortalization and transformation, ending with the growth of an invasive (attacking surrounding normal tissues), metastatic (spreading throughout the body via blood or lymph system) cancer (Hall & Giaccia, 2012). This whole multistep process, from the moment ionizing radiation deposit its energy in the cell nucleus to the progression of the neoplasm from normal tissue to malignant tumor to metastasis cancer, may take up to decades (Figure 2.1). Most mutations that lead to cancer are somatic mutations as opposed to the rare germline (heritable) mutations (Hall & Giaccia, 2012). Some studies have shown that the number of mutagenic effect per unit dose reaches a minimum at doses of 1–10 mGy/min, which corresponds to the rate of DNA damage induced by ROS during oxidative stress (Tubiana et al., 2009).

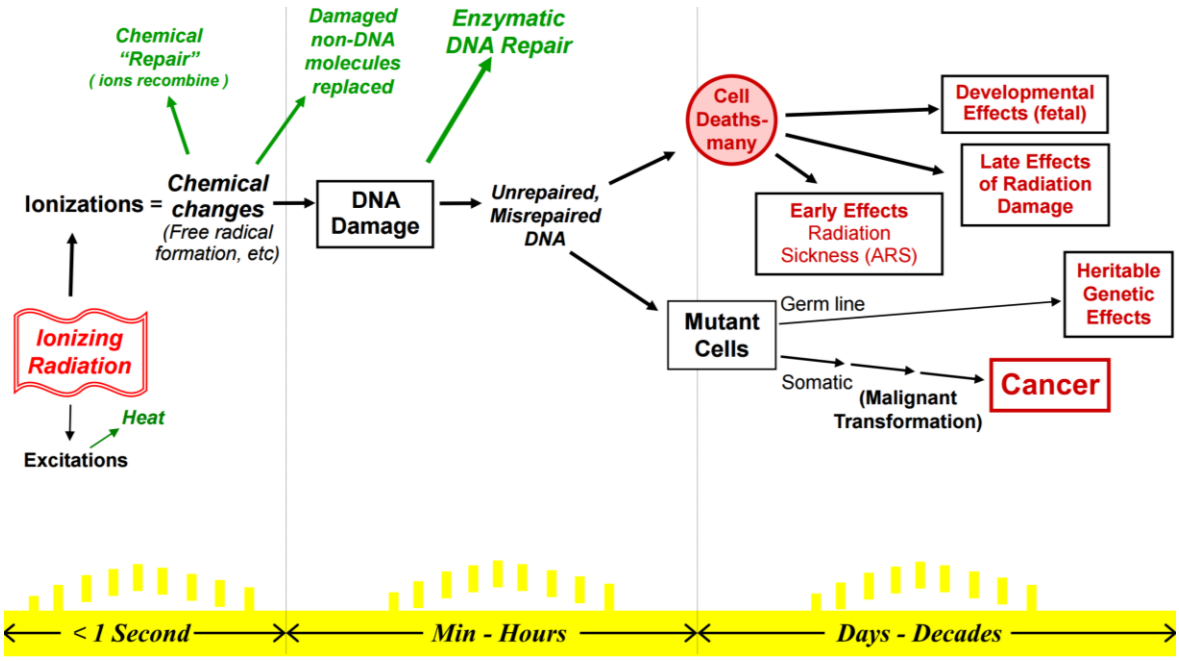

Figure 2.1. Classic Paradigm of Ionizing Radiation Injury (Metting, 2011).

Note that the previously described process is not the definite answer on how a tumor grows. In fact, many questions about how cancer progresses remain unanswered (Hanahan & Weinberg, 2011). The main debate comes down to the question of how neoplasms come into existence and develop into cancer. The leading theory trying to answer this question is the somatic mutation theory (SMT). The SMT suggests that cancer is a cell-based disease and is triggered by mutations in genes that control proliferation and the cell cycle as described earlier. It arises from a single somatic cell with multiple DNA mutations by a single hit of radiation and that the default state of cell is quiescence as opposed to proliferation. Proliferation is the base of an alternative theory of carcinogenesis known as the tissue organization field theory also known as the TOFT (Soto & Sonnenschein, 2011). The TOFT proposes that cancer is a tissue-based disease, with stroma (parts of tissue or organ that has a connective and role and do not conduct the specific functions of the organ) being the primary target, and that exposure to a carcinogen causes communication errors between cells in the parenchyma (the cells that perform the function of the tissue or organ) and stroma of an organ leading to the development of cancer. TOFT also suggests that carcinogenesis is a reversible process, meaning that a normal tissue may be able to normalize a neoplastic tissue if they are in contact (Soto & Sonnenschein, 2011). This might explain why a large threshold of 2-10 Gy for liver and bone cancer are seen in thorotrast patients and radium dial painters, respectively (Sanders, 2010). Furthermore, some studies invalidate the somatic mutation theory showing an absence of cancer development when cancerous epithelial cells are transplanted into tissues with normal stroma (Soto & Sonnenschein, 2011).

> Despite decades of research, however, the carcinogenic properties of radiation at low doses -the dose range within which most radiation exposure takes place- remain a matter of scientific controversy. The reason for the controversy is clear: To date, there are no generally accepted data in that dose range to indicate that radiation causes cancer (Brock & Sherbini, 2012).

2.3 Defense Mechanisms

In spite of the different theories and models of cancer formation and development, if we took the worst-case scenario which is that every single track of radiation has the ability to cause cancer, and knowing that we are being bombarded every second by 15,000 nuclear particles or rays, how did organisms survive living in a sea of ionizing radiation (Rockwell, 1998)? The answer lies in how our bodies deal with low levels of ionizing radiation as explained by Tubiana et al. (2009):

> Life developed in a bath of ionizing radiation and solar ultraviolet radiation and created aerobic organisms requiring (a)defenses against the metabolically induced reactive oxygen species, (b) DNA repair, and (c) elimination of damaged cells. Several sets of data show the efficacy of these defenses to be much higher at low than at high doses and for fractionated or protracted irradiation than for acute irradiation.

To put things into perspective, the average human body consists of roughly 37.2 trillion cells with 100 to 200 billion cells produced every day (Bianconi et al., 2013). The normal body metabolism creates billions of free radicals per day in each cell, only a million of them are close enough to cause damage to the DNA. The total number of damage to the DNA in each cell per day is ~ 0.2 million with less than 0.2 DSB per cell per day. A background annual dose of 2 mSv creates ~ 0.011 total DNA damage in each cell per day, with less than 0.0003 DSB per cell per day (Sanders, 2010). Thus, the DSBs in each cell per day caused by a 2 mSv annual dose is less than 0.15% of that of our body natural metabolism. The error during the repair of DSBs decreases as the distance and time between two DSBs increases. Naturally occurring intracellular ROS may cause up to about 8 DSBs per cell per day, equivalent to that induced by 200 mGy or 0.14 mGy/min (Tubiana et al., 2009).

The mechanism in which intracellular and intercellular signaling pathways are stimulated by low doses of ionizing radiation leading to net beneficial effects to the organism or reduction in the damaging effects of an ionizing radiation dose is known as hormesis (Luckey & Lawrence, 2006). In the last few decades, both hormesis and the adaptive response (body developing temporary protective responses against a challenging dose of ionizing radiation that was preceded by a small inducing dose) to low dose and low dose rate ionizing radiation has been extensively studied (Sutou, 2016). In his book, *Radiation Hormesis,* Dr. T.D. Luckey, a pioneer in the field of radiation hormesis, referenced over a 1000 study, showing the effects of hormesis in workers at nuclear facilities, LSS survivors, and many other groups, but most of the studies came from experimental animals (Luckey, 1991). More recently, a wide range of hormetic effects has been observed in hundreds of studies, both *in vitro* and *in vivo*. These effects include: an increase in the average lifespan of the organism, activation of membrane receptors, improvement of free radical scavenging and antioxidants activities, production of stress proteins, increases enzymatic DNA repair and apoptosis, enhancement of immunologic stimulation and cell cycle arrest, secretion of growth factors and cytokines, and a reduction not only in the frequency of genomic instability, such as mutations, chromosome aberrations and neoplastic transformation, but also a decrease in inherited defects below spontaneous levels (for reviews refer to Luckey & Lawrence, 2006; Sanders & Scott, 2008; Sanders, 2010; Sutou, 2016; Tubiana et al., 2009; Vaiserman, 2010).

Epidemiological data also shows a decrease in noncancer diseases, as well as a reduction in cancer incidence, suggesting that stimulating doses of low and mixed LET protect against high dose and other carcinogenic agents and improve the immune system defense capabilities (Miller, 2016; Sanders, 2010; Scott, 2011b; Sutou, 2016). Scott et al. (2009) described in their paper that exposure to chronic low dose rates improves immune system by increasing the activity of cytotoxic

lymphocytes and upregulating nuclear factor (NF) κB which is a protein complex that controls DNA transcription, cytokine production and cell survival. Another study by Scott et al. shows that exposure to 1–2 mGy of γ-ray provided protection against lung cancer, induced by α-particle dose of up to 600 mGy, for more than 1 year (2008). Elmore et al. also showed a suppression in neoplastic transformation *in vitro* and cancer incidence *in vivo* in cells exposed to very low dose rates of a few mGy/day and low total doses of around a hundred mGy (2008).

Sanders & Scott, (2008) explained that low dose and low dose rate of low-LET radiation activates the immune system and can eliminate cigarette-induced transformed pulmonary cells, by apoptosis or by activating high fidelity DNA repair mechanism, thus, suppressing the effect of different carcinogens, leading to reduction in lung cancer incidences. They suggested that "Cell regulators, such as growth factors, cytokines, and hormones, are involved with the activation and repression of genes associated with apoptosis" (Sanders & Scott, 2008). Two different types of apoptosis that are activated by low dose rates were described in the paper; a normal apoptosis that depends on the tumor suppressor protein p53, and a protective apoptosis-mediated or PAM that is independent of p53 (PAM is a bystander effect that involves cross-talk between genomically compromised cells and non-genomically compromised cells). It is thought that normal apoptosis removes severely damaged cells, whereas, PAM removes cells that have DNA damage that was misrepaired/not repaired, any cell that neoplastically transformed or is genomically instable. This might explain why a huge suppression of two different chemical carcinogens, 20-methylcholanthrene and methyl-nitro-nitroso guanidine, was observed in mice irradiated prior to treatment with the chemical carcinogen (Sanders & Scott, 2008). Several other studies also show a protection against DNA damage, a better repair of DNA DSBs, a reduction in mutations, chromosomal aberrations and neoplastic transformations, and a lifespan increase, following an

exposure to a priming dose of around 100 mGy that precede a challenging dose a challenging dose (Feinendegen, Paratzke & Neumann, 2007; Ina & Sakai, 2005; Mitchel, 2006; Portess, Bauer, Hill & O'Neill, 2007; Wang et al., 2004).

Another study by Zhao et al. showed an increase in the p53 protein, which plays a role in regulating radiation-induced DSBs, following a challenging dose to fibroblasts (2015). They suggested that a dosage of the range 200-500 mGy could trigger hypersensitivity by leading to biological effects to unirradiated cells through the bystander effect (effects seen in cells that receive no direct radiation exposure but receive signals from irradiated neighboring cells), including "…DNA damage, chromosomal aberration, gene mutation, malignant transformation and tumor formation." They concluded that low dose ionizing radiation may have various effects on organisms, depending on LET, dose and dose rate (Zhao et al. 2015). However, there is currently not enough evidence to support that the bystander effect promotes carcinogenesis in humans at low doses (Blyth & Sykes, 2011). On the contrary, Sanders (2010) suggested that bystander effect may be a protective response in which irradiated cells send signals to neighboring unirradiated cells to activate their defenses, thus, allowing for the selective elimination of nonhit genomically instable cells by bystander-induced apoptosis. Some studies have also shown that low LET radiation doses < 250 mSv do not cause genetic instability (Okada et al., 2007).

In his book, *Radiation Hormesis and the Linear-No-Threshold Assumption* (2010), Sanders, supported by over a hundred studies (for review see, chapter 2 of Sanders, 2010), described the main defense systems stimulated by low dose/dose rate of ionizing radiation as (Figure 2.2): (1) Prevention: increasing antioxidant, e.g. glutathione, and detoxifying enzymes, e.g. catalase and superoxide dismutase, to protect against ROS and free radicals; (2) Repair: increasing DSBs DNA repair; and (3) Removal: of neoplastic transformed and genomically

damaged/malignant cells by cancer immunosurveillance and apoptosis (especially at the radiosensitive G2/M phases of the cell cycle). Following an exposure, these defense mechanisms are expected to last for a few hours against ROS, a few days for DSBs repair, and for up to several months for immune enhancement (Figure 2.3) decreasing cell damage below spontaneous levels. Studies show that low-LET doses of 10 to 500 mGy and dose rates of 10 to 1000 mGy/min can activate these defense mechanisms, peaking at doses <100 mGy and starting to disappear at doses >200 mGy (Sanders, 2010). These effects have also been observed in peripheral blood lymphocytes in several human studies following high-background environmental exposures, LSS survivors, the Chernobyl accident, and occupational exposures in medical and nuclear workers (Sanders, 2010). Whole-body exposure to low doses of ionizing radiation stimulated the immune system in animals, both *in vivo* and *in vitro*, and in humans by inducing the mobilization of hematopoietic progenitor cells into the peripheral blood and increasing the production of cytokines which have direct and indirect antitumor effect (Sanders, 2010).

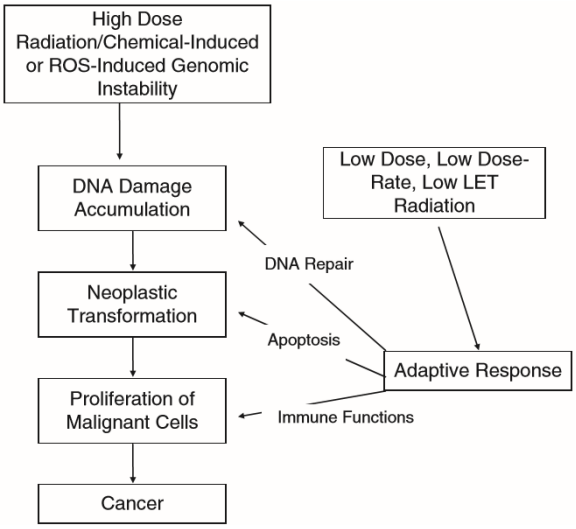

Figure 2.2. Low Doses Activation of Body Defense Mechanisms (Sanders, 2010).

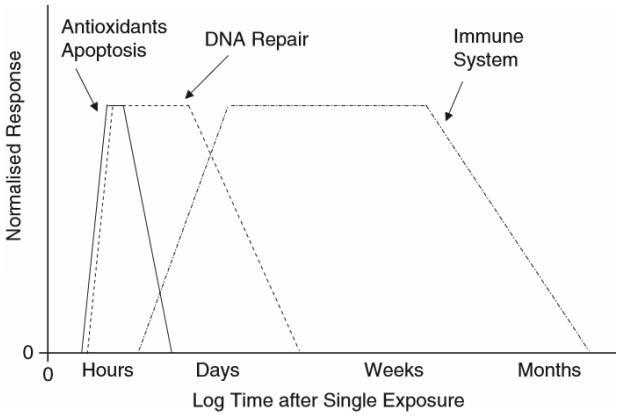

Figure 2.3. Adaptive Response Following Low Doses (Sanders, 2010).

Tubiana et al. summarized over 150 references, most of them from the 2000's, that show adaptive response/hormesis in organisms (2009). Tubiana et al. (2009) also described the defense mechanism of mammalian cells against doses of 1-500 mSv of low LET ionizing radiation as a dose dependent process (Figure 2.4). Regardless of the cause of the DNA damage, irradiated cells protect themselves by two different processes: (1) an immediate defense, consisting of: (a) Defenses against reactive oxygen species by scavengers and antioxidants (b) DNA damage repair and removal by the activation of signaling factors. (c) Elimination of damaged cells by apoptosis or proliferation arrest; and (2) a delayed defense: protection against renewed DNA damage (Tubiana et al., 2009). Checkpoints throughout the cell cycle are believed to help with DNA repair and apoptosis, consequently, decreasing the number of aberrations and genomic damages in a dose dependent manner. DNA damage caused by doses of < 3 mSv whether at high or low dose rates result in mitotic cell death with no signaling since DNA repair is not activated. At doses of 3–50 mSv the DNA damage is error-free repaired, and any aberrant cells are removed by apoptosis or mitotic death. At slightly higher doses of 50-100 mSv, the DNA damage could be repaired error-free or it could be misrepaired, this depends on the damage, dose, dose rate and cell type. A

misrepair is seen more frequently in cells that received doses > 100 mSv; most of these aberrant cells are removed by different cellular death pathways. The ones that are not removed may grow into pre-neoplastic cells and then into neoplastic cells, and these are eliminated or suppressed by immune defenses, by the micro-environment and tissues, or become senescent (Tubiana et al., 2009).

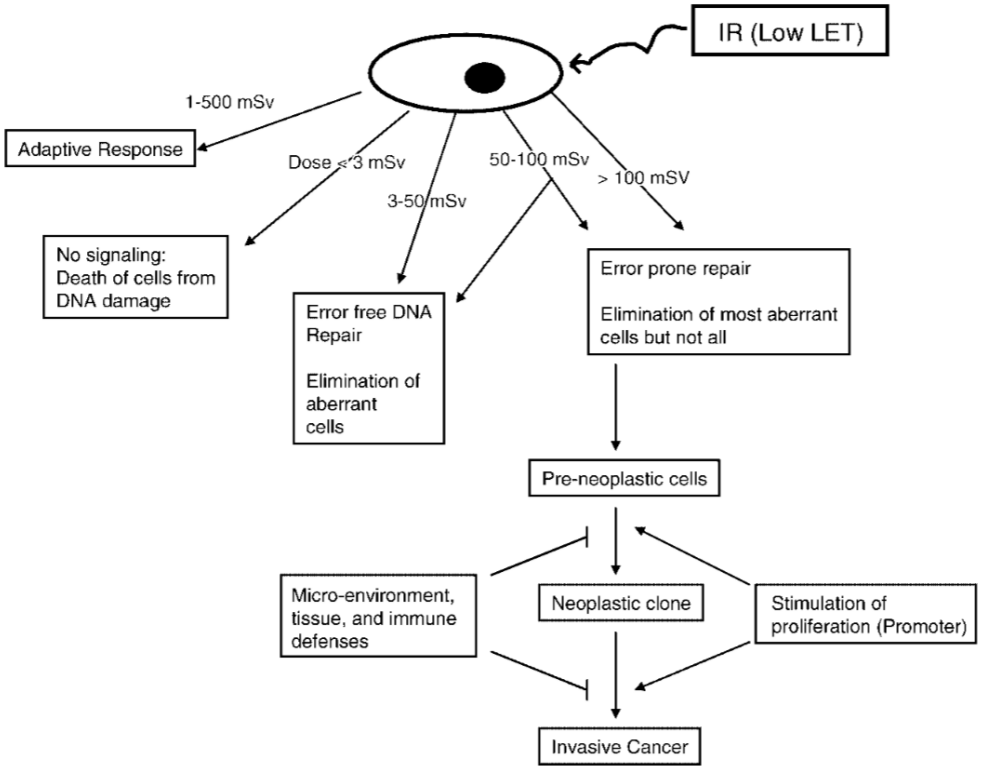

Figure 2.4. Effects of Low LET Ionizing Radiation on Mammalian cells (Tubiana et al., 2009).

Contrary to popular belief, adaptive response and hormesis are well established in the scientific literature. At low doses of < 100 mSv and dose rates of < 200 mSv/year of low or mixed LET ionizing radiation, the cell defense mechanisms are more effective than at high doses and high dose rates. Thus, the carcinogenic response resulting from the encounter between DNA damage, which increases linearly with dose, and the protection system, is not linear and a threshold

or hormetic effect exists. Figure 2.5 shows a summary of organisms' defense mechanisms stimulated by low doses of ionizing radiation. Chemical changes in the form of free radicals caused by ionizing radiation are dealt with by free—radical scavengers and antioxidant molecules. If free radicals were able to cause DNA damage, the damage is spotted by DNA repair enzymes and is repaired. Any misrepaired/unrepaired damage may cause a mutant cell which is eliminated by apoptosis before it can transform into a malignant cell. Finally, any cancerous cell that beat all these security checkpoints, is faced by immune suppression before it can transform into cancer. These cell defense mechanisms depend on dose, dose rate, and the total damage in neighboring cells. In summary, current molecular biology data, both *in vivo* and *in vitro*, suggest the presence of a threshold for carcinogenesis, below which, hormesis or adaptive response is observed. Though, can radiation hormesis be observed in epidimiological human data?

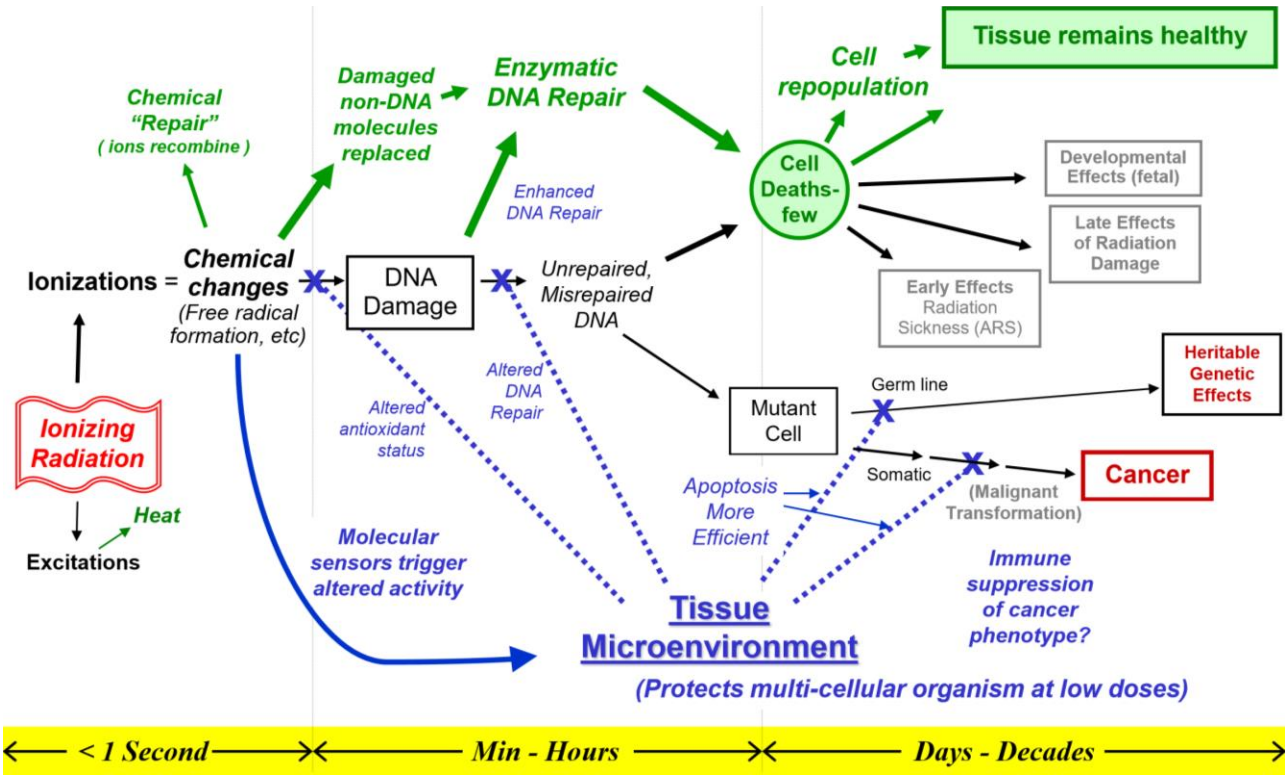

Figure 2.5. Alternative Pathways at Low Doses (Metting, 2011).

2.4 Epidemiological Data

During the second half of the past century thousands of unethical human irradiation experiments, mostly on helpless and poor people and without their knowledge, were conducted in the US and elsewhere to determine the effects of different doses of ionizing radiation on humans (Loue, 2002). Access to these data is very restricted and most of the information about these experiments is kept secret. However, many epidemiological studies that discuss the relationship between solid cancer risk and dose are available. The association is usually given in terms of a standardized incidence ratio (*SIR*) or a standardized mortality ratio (*SMR*). Exposure can be classified based on the type of LET delivered to the people exposed. Some people receive higher percentage of high LET radiation, primarily from: radon exposure or occupational exposure to alpha emitting radionuclides. Though more people are exposed to higher percentage of low LET radiation, either occupationally, e.g., nuclear and medical workers, or environmentally/accidently, e.g., from background radiation and from some nuclear accidents. Low dose rates appear to provide the clearest evidence for radiation hormesis (*Section 2.3*). Therefore, this section will mainly focus on large epidemiological studies, of humans exposed to chronic low dose rates of low/mixed LET ionizing radiation. Accordingly, acute doses and high dose rates received from radiotherapy and some accidental exposures such as the LSS data will not be discussed.

2.4.1. High LET Exposure

Almost 85% of high LET background radiation exposure is due to radon inhalation (NRC, 2006). Radon, a chemically inert gas, and its alpha-emitting progeny, is associated with an increased rate of lung cancer among people who are exposed to high amounts of this gas > 20 mSv/year (Lehrer & Rosenzweig, 2015). It can easily move through the soil and accumulate in

confined places such as home basements and underground tunnels delivering about 1.2 mSv to the lungs annually (NRC, 2006). Thus, radon exposure is very common residentially in many households and occupationally among underground miners. Currently, the LNT model is used to extrapolate the underground miners' data to estimate lung cancer risk for residential radon exposure (Scott, 2011b). However, some studies have shown that the mean exposure experienced residentially is at least one order of magnitude lower than that of the underground miners (Thompson, 2011). Nonetheless, using the LNT assumption, two large meta-analysis studies in Europe by Darby et al. (2004) and North America by Krewski et al. (2006) have observed an excess in lung cancer risk with an increase in indoor radon exposure [Darby et al.: lung cancer risk increased by 8.4% with 95% CI, 3.0%-15.8% per 100 Bq/m^3 increase in radon]. It is worthwhile to mention that no significant risk of lung cancer was found in never-smokers in these two studies (Darby et al., 2004; Krewski et al., 2006). A large study by Turner et al. (2011) of ~ 1.2 million individuals, also showed a positive association between lung cancer mortality and residential radon exposure [15% lung cancer mortality [95% CI, 1–31] per 100 Bq/m^3 increase in radon].

On the other hand, two independent studies with great statistical significance and very large sample sizes, by Bogen and Cohen respectively, showed that low dose radon home exposure has a strong negative association with lung cancer (Bogen, 1998; Cohen, 1997). A recent case-control study conducted in Worcester County, MA, found a statistically significant decrease in lung cancer risks at low to intermediate radon concentrations of < 157 Bq/m^3, with a maximum hormetic effect at 70 Bq/m^3 in J-shaped dose-response curve equivalent to ~3.5 mSv/year (Thompson, 2011). Thompson speculated that the hormetic dip seen in his data and in some other similar case-control studies is the result of an adaptive response mechanism but did not disregard the possibility of random variation (2011). Sanders (2010), also provided tens of different types of studies, from

case-controls studies to environmental and ecological studies, with strong statistical significance showing lower lung cancer risks for groups expose to high radon concentrations, as well as a negative association between radon exposure and cancers related to smoking. This suggests that radon exposure might be activating the body defense mechanisms against smoking carcinogens.

Scott (2011b) investigated the data of Turner et al. (2011) and other similar indoor radon exposure case-control studies, shedding light on the fact that, in most of these studies, both the cases and controls are exposed to radon progeny, i.e., there is no true unexposed group. He concluded that the reference group might be in the hormetic zone already and that the increase in lung cancer incidence or mortality might be because of the loss of radon activated natural protection (ANP) against lung cancer induction by smoking or other risk factors especially at radon concentration of 150 Bq m^{-3} where ANP beneficial effects start to decrease (Scott, 2011b).

Other alpha-emitter exposures, such as plutonium exposure, is also common in some nuclear facilities. One great example is the Mayak Production Association of the Soviet Union which operated under unsafe conditions. It contained radiochemical plants and plutonium production reactors, exposing many workers to prolonged internal and external radiation by plutonium and gamma/neutron, respectively, as well as many chemical agents (Sokolnikov, Preston, Gilbert, Schonfeld, & Koshurnikova, 2015). Plutonium is mainly deposited in lung, liver and the skeleton via internal exposure due to the nature of its chemical compounds (ICRP 30 Part 1, 1979; Tokarskaya et al., 2006). Several cohort studies on Mayak workers have been conducted in the last decades showing results that are less than expected by the LNT model predictions at low doses with $p < 0.05$ (Sanders, 2010).

Gilbert et al. (2013), found an excess relative risk (*ERR*) per Gy increase of 1.3 [95% CI, <0–9.4, p> 0.5] in lung cancer for over 90,000 individuals receiving doses < 100 mGy. Though,

despite acknowledging that error in bioassay measurements and other sources might have caused an uncertainty and a bias in the results in a way that is difficult to predict, they debatably concluded that the data support the LNT model (Gilbert et at., 2013). In another study, by V. Jacob, P. Jacob, Meckbach, Romanov, & Vasilenko, 2005, estimated lung cancer ERR/Sv to be 0.11 [95% CI, 0.08-0.17] with most of lung cancer deaths being due to smoking. Bone cancer mortality has only been observed in workers with doses over 10 Gy (Wilson, Mohr, Frey, Lackland, & Hoel, 2010). Tokarskaya et al. (2006), showed no excess liver cancer risk for alpha doses < 2.2 Gy to the liver and no liver cancer incidences are associated with chronic low doses of gamma rays. These findings might support the TOFT of cancer.

Mortality from solid cancers other than lung, liver, and bone for Mayak workers were presented in a study by Sokolnikov et al. (2015). Aside from esophagial cancer, the rest of the 13 site-specific solid cancer locations show ERR/Gy raging from <0 to 0.29 with *p*-values ranging from 0.16 to >0.5 for a mean external gamma dose of 354 mGy and internal alpha dose to the liver of 266 mGy (Sokolnikov et al., 2015). Smoking was accounted for to some degree in the previous data, however, chemical agents and alcohol consumption were not (Sokolnikov et al., 2015). Sanders (2010), provided several plutonium workers' studies showing solid cancer SMR of less than 1, indicating lower cancer deaths in the exposed group compared to the non-exposed group. It is worthwhile to note that most of the previously mentioned studies showed concerns regarding the uncertainty in dosimetry.

In conclusion, it appears that the low dose indoor radon exposure studies provide no strong positive nor negative dose-dependent association between lung cancer and radon exposure at low dose rates. Similarly, plutonium workers' data does not seem to have a significant association between risk of cancer and radiation dose. Nonetheless, current radon and plutonium exposure

data is indicating the possibility of a threshold below which hormesis might be observable. Better designed studies that account for potential confounding variables (smoking, chemical agents, dosimetry uncertainties…etc) will most likely provide more solid results for high LET radiation.

2.4.2. Accidental Exposure

There have been multiple accidental exposures in the past century exposing large numbers of people to different chronic dose rates of ionizing radiation. The most prevalent epidemiological studies of those accidents are on people living along the contaminated Techa river (following the release of waste into the river by the Mayak Plant), on populations living close to Chernobyl, as well as residents of the Taiwanese contaminated buildings.

The Techa river cohort is a great example of the few epidemiological studies of chronic low dose rate radiation exposure (100 mGy) on a large, unbiased population. Schonfeld et al. (2013) analyzed the Techa river data and concluded that the data were consistent with the LNT model, however, they acknowledged that risks of solid cancer are less than that predicted by LNT model. Several factors were taken into account in their analysis, yet, chemical exposure from the radiochemical plant's waste and other factors such as smoking and medical exposure were not adjusted for (Schonfeld et al., 2013). On the other hand, data analysis of residents of the city of Ozyorsk (a closed city built around the Mayak plant) and the workers of Mayak, showed a much lower cancer mortality ratio for the workers compared to the city residents, and a lower cancer mortality ratio for both groups compared to that of other Russian cities; these results were attributed to the healthy worker effect (Deltour, Tretyakov, Tsareva, Azizova, & Schüz, 2015).

The Chernobyl accident of 1986 caused a massive release of radioactive materials to many areas across Europe. Due to the release of Iodine-131, thyroid cancer rates had increased in areas

surrounding Chernobyl especially in children (Cardis & Hatch, 2011). Though studies on the liquidators, the nuclear workers who participated in recovery operations of the Chernobyl incident, who received an average dose of 50-100 mSv, showed an SIR for solid cancers lower than that of the general population (Balonov, 2007; Ivanov, Ilyin, Gorski, Tukov, & Naumenko, 2004). Furthermore, studies conducted on people of northern Ukraine cities, receiving doses of ~ 10 mGy, showed a significant decrease in cancer incidences, other than thyroid (Hatch et al., 2015).

Another interesting case, is that of the residents of contaminated apartments in Taiwan. The buildings were accidently made of steel contaminated with cobalt-60 ($T_{1/2}$= 5.3 years), exposing about 10,000 people to gamma radiation for 9 to 22 years. The average whole-body dose in the first year for 1,100 residents was ~ 525 mSv and for the rest of the residents was <60 mSv. Over their length of stay, the 1,100 residents received a total individual dose of 4000 mSv, with the rest of the residents receiving < 420 mSv each (Chen et al., 2007). A huge reduction in cancer mortality and incidence rates in the contaminated apartments residents compared to that of the spontaneous cancer mortality and incidence in Taiwan was observed (Chen et al., 2007).

In summary, although such accidents might have had much worse consequences depending on the amount of dose delivered to people, accidental exposure data might be of some help in better understanding the effects of low doses of radiation. Aside from the clear increase in thyroid cancer following the Chernobyl accident, the decrease in solid cancer incidences cannot be explained by the LNT hypothesis. The LNT model, once again, failed to provide reliable predictions.

2.4.3. High Natural Background Radiation Areas

The average worldwide natural background radiation is ~2.4 mSv/year (NRC, 2006). However, there are places on earth with much higher background radiation such as in Ramsar,

Iran; Kerala, India; Guarapari, Brazil; and Yangjiang, China; delivering external and internal doses to people, ranging from 7 mSv/year up to over 200 mSv annually in some locations (Hendry et al., 2009). A few epidemiological studies have been conducted during the last three decades to assess the health effects of exposure to high natural background radiation. Hendry et al. (2009) and Sanders (2010) analyzed multiple epidemiological studies independently, showing that the Brazilian cities with high background radiation level data revealed both slight increase and decrease in cancer mortality. Similarly, no increase in solid cancer incidences or mortalities has been found in populations of Yangjiang, Kerala and Ramsar (Hendry et al., 2009; Sanders, 2010). In conclusion, solid cancer risk was not found to be higher for people living in places of high natural background radiation. Because of the small number of high natural background radiation studies and their limitations, it is best not to rush to conclusions from these data.

2.4.4. Occupational Exposure

The bulk of epidemiological data available on low dose rate chronic exposure is from occupational exposure. In the last few decades, tens of studies have been conducted on nuclear and medical workers from all over the world to study the association between radiation dose and cancer mortality. According to Sanders (2010) “Eight major studies of medical radiation workers have been carried out: U.S. radiologists, UK radiologists, U.S. technologists, U.S. Army technologists, Chinese X-ray worker, Danish radiation therapy workers, Japanese technologists, and Canadian radiation workers.” Post 1940s, doses to radiologists and technicians did not exceed 150 mSv/year [1940s: 100 mSv/year; 1950s: 50–150 mSv/year; 1957: 50 mSv/year; 1990 20 mSv/year] (Sanders, 2010). In 2004, Yoshinaga, Mabuchi, Sigurdson, Doody, & Ron, reviewed these 8 cohorts, finding that several types of solid cancer mortalities were of little consistency, and that

current levels of radiation dose in medical radiation workers does not show an increase in cancer risk.

Two retrospective cohort studies of mortality amongst US and UK radiologists, show: an *SMR* of 0.71, for all cancer mortality for UK radiologists entering the profession between 1955–79; and an *SMR* of 1.15, for all cancer mortality for US radiologists entering profession between 1940–69, relative to all physicians (Brenner & Hall, 2003). Observed deaths in the entire cohort of 146,022 radiologic technologists showed *SMRs* significantly < 1 for almost all cancer types for both males and females compared to the general population of the United States (Mohan et al., 2003). A 29-year follow up for cause of death of US army technologists compared with medical, laboratory, or pharmacy technologists indicated no statistically significant differences between these groups for cancer risk mortality (Jablon & Miller, 1978). A slight increase in solid cancer incidence among Chinese medical diagnostic X-ray workers for the period of 1950–1995, with an ERR/Gy of 0.87 [95% CI: 0.48-1.45] was observed (Sun et al., 2016). Similarly, a very small increase in cancer risk among staff at two radiotherapy Danish departments during 1954–1982, with an *SIR* of 1.07 was seen (Andersson, Engholm, Ennow, Jessen, & Storm, 1991). An updated analysis of follow-up data among Japanese radiological technologists from 1969 to 1993, shows a decrease in solid cancer mortality with an *SMR* of 0.77 (Yoshinaga, Aoyama, Yoshimoto, & Sugahara, 1999). Last but not least, the Canadian radiation workers' data reveals a clear reduction in all cancer *SMR* and *SIR* for both males [*SMR*: 0.56, *SIR*: 0.64] and females [*SMR*: 0.66, *SIR*:0.86] (Yoshinaga et al., 2004).

On the other hand, data of workers in the nuclear industry might be of most interest to researchers due to the large population size of millions of workers who have been exposed to mostly external whole-body chronic low doses and dose rates of low LET radiation, mainly <100

mSv, and were monitored and followed up for many years (Sanders, 2010). Luckey (1991), was one of the first to analyze numerous epidemiological papers of nuclear workers, presenting the hormesis effects in many of these data. Likewise, Sanders (2010) examined hundreds of similar data, also coming to the same conclusion of clear hormetic effects at low-dose-rates. In fact, they both believe that radiation hormesis is so obvious that "most radiation protection agencies deliberately ignore and dismiss radiation hormesis" (Sanders, 2010), and that by denying these data "…advisory committees and government practices have caused, and are now causing, premature cancer deaths for millions of people" (Luckey, 2008) by underexposing people to useful radiation doses.

A review of the data of most epidemiological studies presented by Sanders (2010) provides clear signs of reduction of solid cancer mortality in nuclear workers from all over the world exposed to low doses. The vast majority of these studies show SMR of <1 for most solid cancers types compared to non-radiation workers or the general public (Atkinson, Law, Bromley & Inskip, 2004; Cardis et al., 1995; Frome et al., 1997; Howe, Zablotska, Fix, Egel & Buchanan, 2004; Iwasaki et al., 2003; McGeoghegan & Binks, 2001; Muirhead, O'Hagan, Haylock, Phillipson, Willcock, Berridge & Zhang, 2009; Rogel et al., 2005; Sponsler & Cameron, 2005; Sun, Li & Yuan, 1996; Vrijheid et al., 2007; Zablotska, Ashmore & Howe, 2004). A summary of large studies of nuclear industry workers is presented in Table 2.1. Tens of additional similar epidemiological studies with 95% CI, *p*-values close to 0.05 and a *RR(SMR)* of <1 can be found in Tables 6.6 & 6.7 in Sanders (2010).

Table 2.1. All Solid Cancer RR (SMR) vs Mean Cumulative Equivalent Dose (mSv) of Large Studies of Nuclear Industry Workers.

Reference	**Population Size**	**Mean Cumulative Equivalent Dose (mSv)**	**RR (SMR)**	***p*-value**
Zablotska, Ashmore & Howe, 2004.	45,468	13.5	0.76	-
Cardis et al., 1995	95,673	40	0.99	0.08
Muirhead, O'Hagan, Haylock, Phillipson, Willcock, Berridge & Zhang, 2009.	174, 541	25	0.82	-
Atkinson, Law, Bromley & Inskip, 2004.	51,367	19	0.76	-
Rogel et al., 2005.	22,395	19	0.58	-
Howe, Zablotska, Fix, Egel & Buchanan, 2004.	53,698	26	0.65	-
Sun, Li & Yuan, 1996.	40,122	57	<1	-
Iwasaki et al., 2003.	120,000	Mostly < 100	0.94	0.002
Frome et al., 1997.	106,020	< 650	0.87	-
Sponsler & Cameron, 2005.	27,872	>5	0.95	< 0.01
Vrijheid et al., 2007.	407,391	19.4	0.74	0.007

In summary, exposure of large medical worker populations, from radiologists to radiological technologists, to low doses of ionizing radiation, results in less mortality from solid cancer. Likewise, a decrease in solid cancer mortalities for millions of nuclear workers is clearly seen in

tens of different epidemiological studies from across the world. Although leukemia is not the topic of this paper, it is worthwhile to mention that there was no evidence for increased or decreased leukemia mortality risk was for doses <100 mSv (Sanders, 2010). The question remains though, is this decrease in solid cancer mortalities a result of a strong healthy worker effect? or is it just statistical variations? or is it due to defense mechanisms and adaptive response stimulated by low doses of ionizing radiation? Regardless of the answer, most data do indicate a hormesis or a J-shape dose-response.

2.5 Hormesis Models

Most of the literature on hormesis modeling is on chemical hormesis rather than radiation hormesis. However, the availability of the previously discussed epidemiological studies backed with the huge leap in molecular biology, improving our understanding of how body defense mechanisms work, inspired some scientists to attempt to build a radiation hormesis dose-response model that better predicts cancer incidences.

Dr. Mohan Doss of the Fox Chase Cancer Center, built a case for radiation hormesis by noticing that the current cancer risk *ERR* has a systematic bias in the measured baseline cancer mortality rate (Doss, 2012; Doss, 2013). This bias is the result of the variability in the year-to-year age-adjusted cancer incidences/mortalities, thus, causing error in estimating the lifetime cancer risk of a population. After adjusting for this systematic bias and recalculating for the *ERR*, Doss was able to show a J-shaped hormesis dose-response in the atomic bomb survivor data (Doss, 2012; Doss, 2013). On the other hand, Kant (2009), approached the situation differently, by modifying the linear plus quadratic model to account for repair mechanisms when estimating cancer risk. His equation, produces a U-shaped dose-response curve in which at low doses, the

beneficial effects are dominate, and as dose increases, the harmful effects overcome the beneficial effects. The equation was tested against data from an epidemiological study of higher radon concentrations that showed a negative correlation with lung cancer (Kant, 2009).

However, most of the work that has been done on modeling hormesis was conducted by Dr. Bobby R. Scott of the Lovelace Respiratory Research Institute. Over the past 15 years, Scott published a couple dozen publications introducing new concepts and new factors regarding modeling radiation hormesis. Figure 2.6, shows Scott's notable biologically-based hormetic relative risk (HRR) model for cancer induction by low/mixed LET radiation doses. The HRR model contains several thresholds for triggering and inhibiting adaptive protection and hormetic effects. In the hormetic zone, where the *RR* is < 1, with the lower end including natural background radiation, a system of protective mechanisms is maximally stimulated. The model consists of four main dose zones: Transition Zone A, Zone of Maximal Protection, Transition Zone B, and Linear Zone (Scott, 2007a; Scott, 2011b). The phantom risk represents the extrapolation of the LNT hypothesis from high doses down to zero and *b* is the natural background radiation excluding residential radon.

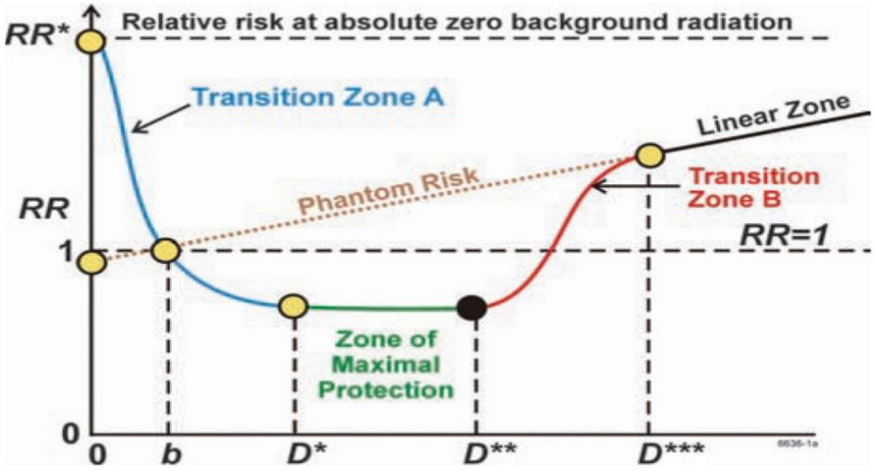

Figure 2.6. Hormetic Relative Risk Model: Cancer Relative Risk (*RR*) at Low Doses of Ionizing Radiation (Sanders, 2010).

Transition zone A includes doses less than *b* and doses slightly larger than *b*. Super low-doses are presumed to have *RR*>1 due to its inability to activate protective systems, reaching a maximum *RR* at absolute zero dose. As dose increases from *b* to D^*, the stochastic thresholds occur and the protective processes start to be stimulated and relative risk is given by: $RR(d) = 1 - PROFAC \bullet B(d)$. The protection factor (*PROFAC*) represents the fraction of spontaneous cancer incidences/mortalities that are avoided due to the presence of radiation hormesis. *PROFAC* relates only to low-LET radiation such as x-rays, gamma rays, and beta radiation. It is assumed to depend on individual genetics/epigenetics, dose rate history, radiation physical characteristics, and cancer type (Sanders & Scott, 2008; Scott et al., 2009; Scott, 2011b). *B(d)* is the benefit function, which represents the adaptive protection probability, *d* represents dose in excess of natural background (Scott, 2011b). *RR* = 1, for *d* =0, as *d* increases over the transition zone A, *B(d)* increases causing *RR(d)* to decrease gradually.

In the zone of maximal protection, between doses of D^* and D^{**}, the stochastic individual-specific thresholds for all adaptive responses are exceeded and the radiation benefits are maximized, i.e., $B(d) = 1$ and $RR = 1 - PROFAC$, independent of the dose, however, the width of this zone is dose-rate dependent, decreasing dose rates increase the range of the maximal protection zone (Scott, 2011b). As dose increases beyond D^{**}, stochastic thresholds for adaptive-response genes inhibition occur and *B(d)* decreases from 1 to 0 as *d* increases over the transition zone B, leading to loss of protection processes progressively. Any additional increase in dose causes stochastic thresholds for adaptive-response genes inhibition to be completely exceeded enabling cancer incidences in a, more or less, linear fashion (Scott, 2011b). In a population, D^{**} is the minimum tolerable absorbed dose for a specific tissue from a specific radiation type and it depends on the radiation type and energy, dose rates, the population at risk, and the tissue of interest, thus,

it is determined by the most sensitive member of the population (Scott, 2008). Scott et al. (2009) demonstrated that about 80% of alpha-radiation-induced rat lung cancers were prevented by chronic, low-rate gamma-ray ANP.

Other notable works of Scott are the biological-based NEOTRANS3 and MULTISIG1 models (Scott, 2004; Scott, 2011a). The dose–response NEOTRANS3 model relates stochastic effects (genomic instability, mutations, neoplastic transformation, bystander effects, and adaptive response) in mammalian cell communities associated with short exposure to low doses of ionizing radiation, with probability of neoplastic transformation given cell survival is the primary goal of the model (Scott, 2004). It assumes that the main line of defense, protective apoptosis-mediated, (PAM) has a stochastic low-LET threshold to be activated, has a larger stochastic low-LET threshold to be inactivated, still active at 24 hours after exposure, is activated by prolonged low dose rate low-LET exposure, and is genetic-dependent (Scott, 2004). A set of 14 different parameters are associated with the NEOTRANS3 model. Values of some of these parameters were estimated experimentally while others were estimated mathematically (Scott, 2004). Using NEOTRANS3, a reduction in transformation frequency below the spontaneous frequency was found for gamma doses < 200 mGy in HeLa × skin fibroblast human hybrid cells (Scott, 2004).

In a different paper, Scott (2007b) was able to link the *RR* relationships for neoplastic transformation induced by mixed and single type LET to *RR* relationships for cancer induction in humans. In 2011, Scott introduced the multicellular signaling model (MULTISIG1) which simulates the kinetics of DNA DSBs repair in non-dividing cells by a very low to moderate radiation dose (Scott, 2011a). MULTISIG1 assumes that DSB repair initiation require a threshold number of cells with DSBs connecting with each other via an intercellular stress-response

signaling. MULTISIG1 also accounts for cells with different susceptibility, different repair capacity, and different epigenetically regulated apoptosis capacity.

2.6 Summary & Needed Research

The LNT model might have been a realistic starting point when it first came out some 70 years ago, but with its contradictions to current epidemiological data, its repeated overpredictions and its inability to explain data at low doses, it, undoubtedly, can no longer serve its purpose of protecting people. In addition to the huge human and economic losses due to the LNT model-induced radiophobia, the LNT model appears to cause many unnecessary losses of lives by underexposing people to confirmed useful small doses of ionizing radiation that can simulate the human body defense mechanisms against DNA damage and cancer development as shown in the previous sections. Despite the great progress in our understanding of carcinogenesis in the past decades, many concepts on the initiation and the development of cancer remain uncertain. However, with our current understanding of cancer biology, and the availability of tons of experimental and epidemiological data, developing a model that can better estimate cancer-incidence risk vs dose/dose rate is very achievable. The works of Scott over the last two decades serve as great examples. Nevertheless, no actual study to test the radiation hormesis hypothesis in humans has been found in the literature. Thus, the next chapter will propose an experiment to test radiation hormesis in the low dose region with respect to solid cancer risk and find the optimal dose and dose rates.

3. THE RADIATION HORMESIS HYPOTHESIS: A STUDY DESIGN

The first section of this chapter will discuss the healthy worker effect and existing problems in designing an experiment that tests the hormesis hypothesis in relation to solid cancer incidences in humans. The second section will propose a study design to test the radiation hormesis hypothesis in adults vs solid cancer risks and two alternative approaches.

3.1 The Experiment Dilemma

The literature has hundreds of papers on radiation hormesis, from molecular biology data to large epidemiological studies as seen in *chapter 2*, however, no experiment that purposely tests radiation hormesis in humans was found. Yet, the recommendation of investigating the radiation hormesis hypothesis is not a new idea. Luckey did propose conducting such a study almost four decades ago with the aim of possibly using low doses of ionizing radiation to prevent and reduce cancer occurrences in humans if the hypothesis was proven (Doss 2013). However, due to radiophobia initiated by adopting the LNT hypothesis, no such study ever took place (Doss 2013). Additionally, ionizing radiation is tied with horrific events in the public consciousness; the two atomic bombs in the second world war, the 1986 Chernobyl accident and the recent Fukushima incident of 2011, all cementing the idea that any ionizing radiation is deadly. On an ethical level, the consequence of testing the radiation hormesis hypothesis is either good by reducing cancer incidence, if the hypothesis is proven, or bad by increasing cancer incidence, if it is disproven. Since a stronger priority is given to avoiding harm, experimenting the radiation hormesis hypothesis on humans is a true dilemma (Hoffmann & Stempsey, 2008).

Most epidemiological studies attributed the clear reduction in cancer *SMR* and *SIR* of nuclear workers in over 100 facilities from all over the world compared to the general public to

the healthy worker effect or HWE (Atkinson et al., 2004; Brown et al., 2004; Cardis et al., 2007; Deltour et al., 2015; Frome et al., 1997; Hammer et al., 2008; Howe et al., 2004; Iwasaki et al., 2003; Ivanov et al., 2004; McGeoghegan & Binks, 2001; Muirhead et al., 2009; Samson et al., 2011; Sanders & Scott, 2008; Sponsler & Cameron, 2005; Vaiserman, 2010b; Wing & Richardson, 2005; Yoshinaga et al., 1999; Yoshinaga et al., 2004; Zablotska, Ashmore & Howe, 2004; Zielinski, Shilnikova & Krewski, 2008). HWE indicates that individuals who are employable in the workforce are relatively healthier than those who are not. It is attributed to better medical care and socioeconomic conditions for workers compared to the general population (Sanders, 2010). Accordingly, disease incidence and mortality rates are expected to be lower for workers than for the public (NRC, 2012). Due to the strong influence of applying the LNT assumption to epidemiological studies no other explanations to cancer risk reduction were provided; the hormesis phenomenon has always been overlooked (E. Calabrese, Iavicoli, & V. Calabrese, 2013; Sanders, 2010). BEIR VII addressed some evidence related to the reduction in *SIR* and *SMR* seen in nuclear industry workers concluding that:

> In most cases, rates for all causes and all cancer mortality in the workers were substantially lower than in the reference populations. Possible explanations include the healthy worker effect and unknown differences between nuclear industry workers and the general population. (p.194)

BEIR VII estimates that the HWE is responsible for a reduction of 15% in all-cause mortality (NRC, 2006). However, many occupational epidemiological studies of nuclear workers show a reduction in all-cause mortality closer to 30–50% (Sanders, 2010). The large decrease in mortality and incidence rates has been demonstrated in numerous human and animal studies (*Chapter 2*) and it is inconsistent with the current estimations of BEIR VII, thus, it cannot be merely attributed to the HWE (E. Calabrese, Iavicoli, & V. Calabrese, 2013; Sanders, 2010). One

could also argue that higher level of healthcare in the workforce facilities could result in increased diagnosis and registration of cancers, thus increasing workers *SIR* compared to that of the general population (Ivanov et al., 2001). Better study design should compare between incidence and mortality rates of exposed workers to those of unexposed workers in equivalent jobs in the same company, where healthcare and socioeconomic conditions are similar for all employees, rather than comparing them to the general public, to diminish the HWE.

Another big problem facing scientists is that the spontaneous cancer risk in humans is already very high. It is proposed by Dr. Robert A. Weinberg of MIT that if humans live long enough everyone will eventually develop cancer (Johnson, 2010). The current human lifetime, from birth to death, risk in the US of developing cancer is about 40% or 2 in 5, and the risk of dying from it is about 21% or 1 in 5. Males are slightly more vulnerable to develop and die from cancers compared to females (Siegel, Miller, & Jemal, 2016). The current estimates of risk of cancer death due to radiation exposure is ~ 5% per Sv (Brock & Sherbini, 2012). To put things into perspective, if every person in a population of 1 million people received a dose of 100 mSv, i.e. in the low dose region, then the number of fatalities from cancer is expected to be about 5,000 individuals. This number is so small and very hard to measure compared with the spontaneous deaths from cancer not related to radiation exposure in that same population which is about 200,000 individuals (Brock & Sherbini, 2012). Ionizing radiation is considered to be a weak carcinogen; hence, the small number of radiation-induced cancers can easily be lost within the variations from population to another (Sanders, 2010). Thus, the size of the population required to detect changes in cancer incidences with strong statistical power needs to be very large (Hendry et al., 2009).

The variations in cancer incidences from one population to another is dependent on many risk factors, in addition to ionizing radiation, that can easily influence cancer risks. Some of these factors can be avoided—such as lifestyle factors (smoking, dietary, alcohol use, physical activity rate…etc.), while others—such as family cancer history, age, gender, hormone levels, exposure to chemical/toxic substances or pollutants, and infectious agents —cannot (National Research Council [NRC], 2012). There are also other factors that can change the degree of association between ionizing radiation and cancer mortality and incidence rates in a population, for example: age at exposure, environment oxygen levels, previous radiation exposures (background radiation levels, radon levels, medical diagnosis, occupational exposure, and cosmic radiation from frequent air travel), and socioeconomic factors (income, job/workplace, access to healthcare…etc.) (NRC, 2012). These risk factors have the potential to overwhelm the actual risk attributed to ionizing radiation. The magnitude of the risk from these factors might not even be measurable and it is extremely hard to account for or eliminate all of them (NRC, 2012).

While a solid cancer 10-year minimum latency period (time between exposure and the development of the disease), that extends for the rest of the individual lifetime, is typical for people exposed to a carcinogen, such long latency periods are a disadvantage in epidemiological studies. Latency period is not very well understood and it varies by cancer type, age at exposure, and follow-up length (NRC, 2012). Thus, solid cancers occurring earlier than the latency period are most probably not attributed to the exposure in question. Conducting a follow-up of a huge number of people during their life time, will require lots of finances, time, resources, and most importantly keeping track of any of their activities that might lead to cancer (Hendry et al., 2009).

Another dilemma to add to the pile is not only that we do not have such a huge controlled irradiated population followed over their life time, but also that we cannot know if that specific

cancer is radiation-induced or was developed because of other factors. In other words, the process of cancer development is essentially indistinguishable regardless of the agent that caused it (Hall and Giaccia, 2012; NRC, 2006). Some types of chromosomal aberrations, e.g. dicentric aberrations, are increased by exposure to ionizing radiation but they are not unique to it (Hall & Giaccia, 2012). Even when it comes to ionizing radiation and the human body itself, there many factors to consider that could affect cancer incidence rates, such as: dose factors (LET type, amount of dose, dose rate…etc.) and biological factors (hyper-radiosensitive people, radiosensitivity of tissue/organ exposed, cell-cycle phase at exposure…etc.) (Hall & Giaccia, 2012). Not to mention uncertainties in the dosimetry system that estimates radiation doses (NRC, 2012).

Additionally, in all radiation-related epidemiological studies there is no control group with an actual zero dose. In these situations, the group with the lowest exposure is used as a reference group. Though, the reference group might be in the hormetic zone already, thus, depending on the magnitude of the hormetic effect for the reference group, a hormetic dip may not be seen in the dose-response curve. So, in studies where a positive association between cancer risk and ionizing radiation exposure is apparent, the hormetic effect for the reference group is larger than that for higher dose groups, hence, the dose-response curve appears to increase linearly. Accordingly, in studies where a negative association between cancer risk and exposure is seen, the hormetic effect for the reference group is smaller than for higher dose groups, thus, a hormetic curve will be apparent (Scott, 2011b).

In conclusion, the negative association between solid cancer mortalities and dose in populations exposed to ionizing radiation was attributed to ‘strong’ healthy worker effect. Most papers did not even discuss the possibility of hormetic effects or other plausible scientific explanations of the results. Unfortunately, no proper scientific approach to perform a study that

tests the predictions of the LNT hypothesis or the hormesis hypothesis on humans has been undertaken to this day (Doss, 2012). Radiophobia is just one of many problems preventing scientists from properly examining the hormesis hypothesis in humans. Risk factors, dose factors and biological factors all play a crucial role in affecting the relationship between cancer incidences and low dose ionizing radiation.

3.2 Radiation Hormesis Study Design

A study design to test the hormesis hypothesis and find the optimal dose for low LET radiation in the low dose region of ≤ 100 mSv in association with solid cancer incidences in adults not susceptible to cancer or radiation will be proposed in this section. Two additional alternative approaches will also be discussed. The goal of each approach is to eliminate as many confounding factors as possible and attempt to solve the difficulties that have been faced by scientists in the past.

3.2.1. Novel Approach

3.2.1.1. Type of Study

The first step towards designing a study to test a hypothesis is to choose the best type of study for the propose of achieving the study goal. The two main approaches to assessing the relationship between an exposure and a disease of interest are observational and experimental. Observational (non-experimental) studies can be classified as: Cohort, Case–control and Routine-data-based, whereas the main type of experimental or interventional studies is Field trials (Silva & IARC, 1999).

In cohort studies, a population of exposed and unexposed individuals is chosen and is followed up over time. Cancer rates are then compared between the exposed and unexposed individuals in relation to the radiation dose received. Radiation cohort studies can be prospective (cancer incidences in the population are expected to occur in the future) or retrospective (cancer incidences have already occurred in the population and accurate data are available by the beginning of the study) (NRC, 2012). Although, current radiation cohort studies might be of large population size and have good individual dose estimations, e.g. nuclear workers data, thus increasing their statistical power, they are still subject to some disadvantages that make them not the ideal candidate to test the hormesis hypothesis. Examples of these disadvantages in retrospective cohort studies are: data on confounding factors (past exposure, lifestyle, radiosensitivity...etc.) are either absent or of poor quality; no control over the exposed group regarding dose and other factors; no comparison group of similar factors; no comparison group in the ultra-low dose region (doses close to zero); and some data are lost in the follow up process.

On the other hand, in spite of the high cost of following up a large population for their life time, prospective cohort studies are of better strength if efforts are made to avoid the disadvantages mentioned above. Individual data history should be made for every person exposed with respect to all confounders from cancer family history to past exposure and lifestyle choices to socioeconomic status. From the exposed group, individuals can then be grouped based on their confounding factors history and dose received. Comparison groups are then chosen with individuals of similar factors to the exposed ones except dose. However, there is currently no actual zero dose group that could be used for this cohort study; more on that will be covered in later sections. The main problem with a prospective cohort is that the exposed and unexposed groups are not under full control regarding their characteristics (who should be exposed and who should

not be exposed) and amount/type of dose received. Thus, the size of the exposed population will be very uneven and very small at doses close to the higher end of 100 mSv. Also, individuals in comparison groups in different occupations may differ in many confounding factors not only in exposure to radiation.

In case–control studies individuals with cancer (cases) are compared to individuals without cancer (controls) with respect to their past exposure to radiation. Since cancer incidences have already occurred at the beginning of such studies, long latency periods are avoided and much smaller numbers of cases are need which make case-control studies less costly. The main problems though with case-control studies are that controls selection is subject to bias and the amount of dose received by the cases is extremely hard to determine (Silva & IARC, 1999). In routine data-based studies, such as in ecologic studies, routine data-collection systems are used to collect data on exposure and cancer (Silva & IARC, 1999). Those studies are of limited use in testing the hormesis hypothesis due to the very limited information on dose and the unavailability of adequate comparison groups.

As for intervention studies, such as field trials, an agent is tested to whether it reduces the risk of developing a disease among individuals who are disease-free, in this case ionizing radiation and cancer (Silva & IARC, 1999). Accordingly, a large number of individuals followed up for a long period of time will be needed. Because of the full control of many factors, intervention trials are the ideal candidate to test a hypothesis (Silva & IARC, 1999). Though, due to 'ethical restraints' driven by radiophobia and the LNT model, low-dose ionizing radiation field trials are restricted. However, in situations of uncertainty where there is actual doubt about the risks and benefits, it might be possible to conduct such trial experiments, though evidence of the benefits should be provided (Silva & IARC, 1999). This is exactly the case with radiation hormesis, where

evidence in the molecular-level and observational epidemiological studies do support the hypothesis (*Chapter 2*). The case with hormesis is even stronger because if it is proven true, it means that implementing ALARA, which is inspired by the partially false LNT hypothesis, is underexposing people to useful levels of ionizing radiation, thus increasing their cancer risk. Therefore, to test the hormesis hypothesis with high precision interventional trials should be used.

3.2.1.2. Study Population

The population under study is an extremely important factor to know whether the association between the exposure and the disease is real or simply due to bias (systematic error) or confounding factors (Silva & IARC, 1999). Thus, several considerations should be taken into account when choosing the study population to avoid bias and minimize the effects of confounding factors on the factor under investigation.

Since the goal of this interventional study is to investigate the association between ionizing radiation and solid cancer rates in adults, with the expectation that low doses of low LET radiation are able to simulate the body defense mechanisms against the formation of cancer, the target population is all adults in general. However, there are some people with certain diseases, e.g. ataxia-telangiectasia, and/or have mutations in certain genes, e.g. BRCA1 and BRCA2, that make them radiosensitive to ionizing radiation and more vulnerable to cancer (Elahimanesh et al., 2013). To eliminate subjects with greater risk of developing cancer, people with these type of diseases and gene mutations should be excluded from the study population. Also, it is important to conduct a thorough investigation on potential participants prior to the study to exclude individuals with heritable family cancer syndromes or who actually have cancer, but are yet to discover it, to avoid bias. Last but not least, subjects with deadly viruses or diseases (e.g. HIV) or physical or mental

disabilities and pregnant women should not be eligible to participate in the study due to their health conditions. Therefore, the study population for this trial is physically and mentally capable adults who are not susceptible to ionizing radiation or cancer and who are known to be cancer free prior to the beginning of the study.

It would be ideal to eliminate all confounding factors to have only dose vs cancer risk. However, this is far from being possible. The choice of the trial population, though, should be intended to minimize the effects of confounding factors. This could be done by eliminating the confounding factor, or taking it into account by assigning a risk value to it, or having a comparison group with the same exact confounding factor conditions. Eliminating the confounding factor is extremely important when possible because there is yet a way to know what specific external factor initiated the cancer in question, i.e., the mechanism of radiation-induced cancers is indistinguishable from other-factors-initiated cancers mechanism (Hall and Giaccia, 2012; NRC, 2006). Therefore, persons who are smokers, alcoholics or are known to consume/be exposed to a carcinogen (e.g. chemical exposures, radiation therapy…etc.) are to be excluded from the study because it is very hard to assign a specific value on such variable risk factors in association with cancer. There are other factors, however, that can be eliminated using similar comparison groups. For example, comparison groups should be as similar as possible to the control groups with respect to geographical factors (diet, background radiation…etc.), socioeconomic factors, age group, gender, physical activity level and such similar factors.

It is also important to have a high level of compliance throughout the study especially with respect to confounding factors, thus, having monitored volunteers who meet the eligibility requirements is sought. All current evidence for the hormesis hypothesis, as well as the expected risks/benefits and all other aspects of the study, should be clearly presented to eligible volunteers.

Also, to avoid selection bias and bias due to placebo effect, volunteers should be randomly and evenly assigned to either the intervention group or the comparison group without knowing which group they have been assigned to until the end of the study. Once eligible volunteers know all their rights and responsibilities, they should be given enough time to consider whether they are willing to participate or not. Noncompliance, loss of follow-up or withdrawal from the study may create bias and unbalanced groups. Special measures, such as using the intention-to-treat analysis (a comparison of treatment groups that includes all subjects as allocated after randomization), should be used to reduce the effects of such biases and provide unbiased comparison among the groups (Silva & IARC, 1999). Volunteers participating in this study should then be individually tracked with regard to all factors that might affect either ionizing radiation dose or cancer risk.

3.2.1.3. Dose Factors

The current limits for dose equivalent are 1 mSv/year for a number of the public and 20 mSv/year for occupational radiation workers (ICRP, 2007). The amount of dose under uncertainty with respect to cancer risk is ~ ≤ 100 mSv. In this study, at least 5 main interventional groups are needed. The first group is the zero-dose group which will receive as low dose as achievable. The second group is the reference group which will receive no doses other than the background dose which is on average of 2.4 mSv/year worldwide (NRC, 2006). The third and fourth groups are intermediate groups; which are necessary to determine the optimal hormetic dose region. Individuals in these two groups will receive doses above background but below the upper limit. Luckey (2008) and Sander (2010) suggest doses of ~ 50 mSv/year and 60 mSv/year to be the optimal dose, respectively. The fifth group is the upper-limit group which will receive a total of 100 mSv. Within these main groups, smaller subgroups are constructed based on socioeconomic

factor, geographical factors, sex…etc. Subgroups from each main group are to be compared with their peers in the other main groups in which the only difference between them is dose. Therefore, allocation of volunteers should be evenly distributed among all subgroups to achieve the optimal 1:1 comparison ratio as closely as possible (Silva & IARC, 1999).

Natural background radiation exposes people to about 60% high LET radiation (mostly internally exposed) and 40% low LET radiation (mostly externally exposed) (NRC, 2006). Molecular and epidemiological data support the radiation hypothesis in the low dose region for whole body external low LET radiation, while it does not disprove it for mixed LET and high LET radiation (*Chapter 2*). Although it does not mimic the environment that life evolved in, volunteers are to be exposed to whole body external low LET radiation only. It would also be wise to have hourly, daily, weekly, monthly and yearly limits in correspondence to the repair of the DNA DSBs not to overwhelm the repair mechanisms. In other words, the radiation process should also depend on dose rates not only dose. For example, the dose limit of the 100 mSv group, could be reached by irradiating the group members to ~ 0.0083 mSv/min for 1 hour/day, 5 days/week, 40 weeks/year. The same limit could also be reached with an acute dose of ~1 mSv/day, 3 days/week, 34 weeks/year. It is suggested that low LET dose rates of 0.5 to 10 mSv/day could prevent cancer, which could be used as guidance (Sanders, 2010). Though current biological and epidemiological data do not clearly specify exact limits for humans. Varying dose rates should depend on their abilities to stimulate the defense mechanisms and give the DNA enough time for DSB repair. Cell samples from patients should be taken and evaluated for DNA DSBs repair using, for example, the 53BP1 or γH2AX proteins focus assays (Hall & Giaccia, 2012). Nevertheless, dose rate consistency for all main groups should be considered regardless of their total dose limit. To help

verify the optimal dose rate in the hormetic zone, subgroups with different dose rates, but the same total yearly limit, are to be compared with each other.

While irradiating people to a certain amount of dose is relatively easy and measurable, eliminating dose to zero mSv is extremely challenging if even possible. There is no place on earth with background radiation close to zero mSv. However, there are two available ways to reach such ultra-low radiation levels; 1- in a radiation protected man-made facility, 2- in submarine deep under the ocean. The former option does actually exit in the ultra-low level radiation biology laboratory some 650 meters underground at the Waste Isolation Pilot Plant in Carlsbad, New Mexico. Efforts are even made to eliminate traces of the naturally occurring radioactive potassium-40 in food and the facility walls. Radiation levels in this facility are about 0.01 mSv/year, i.e., equivalent to less than 1% of the natural radiation background levels (Orion international technologies, 2006). The main challenge, though, will be keeping people in such a facility for the whole trial period, which is not plausible. Also, current experimental data on bacterial systems suggest that ultra-low doses of ionizing radiation are likely to be harmful, having such a zero-dose human group is unethical (Castillo & Smith, 2017; Castillo et al., 2015; Lampe et al., 2016). Thus, instead of using a human zero-dose group, two groups of mice, a background dose group and a zero-dose group, should be used in conjunction with the interventional study to verify the proposition of higher cancer rates in the zero-dose group compared to the background dose group.

3.2.1.4. Trial Time

Since the clinical endpoint of this study is cancer incidence, and solid cancers have a 10-year minimum latency period that could extend to a lifetime, a lifetime trial duration would provide the most accurate results. Latency period is crucial because, for example, a cancer that is incident

a month after the trial started is extremely unlikely to be due to the exposure in the trial. However, since special considerations will be made with respect to how free of cancer the volunteers are prior to the study, and since comparison groups are cherry-picked to match the reference groups with respect to all factors but dose, the effect of the pre-latency period cancer incidence in all groups is expected to be the same.

It is suggested that to shorten the trial time people who are more vulnerable to develop the disease should be chosen (Silva & IARC, 1999). However, using those people for this trial will probably mess up the effects of confounding factors since a third factor, which is the susceptibility of people developing cancer which will differ from a person to person, will be created. A better way though to shorten the duration of the trial is to use surrogate endpoints, instead of the clinical endpoint, that lie on the causal pathway to cancer to help diagnose early stage of cancer (Silva & IARC, 1999). Cancer biomarkers found in the volunteers' blood or body tissues could be used as surrogate endpoints. These biomarkers are typically different for different cancer types and have different accuracies since they do not necessarily indicate that people who have that cancer biomarker are going to get that specific cancer 100% of the time (Ramsey et al., 2015). Thus, it would be wiser to use both early and intermediate surrogate endpoints routinely while the study is taking place and the clinical endpoint, i.e. malignancy incidence, as the looked-for outcome at the end of the trial duration. The surrogate endpoint, in this case, would be used as an indicator of if the experiment is going well or if it has to be stopped immediately. For example, if an extraordinary increase in number of cancer biomarkers was found in the volunteers' cells, then it is an indication of a potential increase in solid cancer incidence in the whole population at the end of the trial duration. This defies the goal of the study of decreasing solid cancer incidence in humans, accordingly, the study would be halted.

3.2.1.5. Statistical Power & Sample Size

Power calculations are desired to determine the sample size needed to detect the magnitude of the sought *RR*. Typically, a study power of 80% and above is satisfactory (Silva & IARC, 1999). The stronger the power of the study the more the probability of getting an estimate whose confidence interval does not include the null hypothesis value. Sample size could also be determined using one of the sample size formulas (Loue, 2002). Based on the epidemiological studies of Table 2.1., and Luckey's prediction of a one-third reduction in all cancer deaths by low LET radiation (Sanders, 2010), a sample size that could detect a 20% difference in *RR* would be a reasonable statistical choice.

Both the value and the stability of the *RR* determines if the observed number of cases is statistically significant or merely due to chance. The confidence level of the confidence interval (CI) and its width assess the stability of the *RR*. A 95% CI (level of statistical significance $\alpha = 0.05$) indicates that we are 95% confident that the true *RR* value for the population is within the upper and lower limits of the CI. The narrower the confidence interval limits the more stable the result. A 95% CI range that does not include the value 1, indicates a strong statistical significance with less than 5% chance that the observed difference is due to chance or statistical fluctuations. Whereas, if the range of the CI does include the value 1, then it cannot be determined with statistical significance that the observed difference is not due to chance or statistical fluctuation since the true RR value could be 1 (Massachusetts Department of Public Health, 1998). We also seek a small *p*-value of 0.05 or less, since the smaller the *p*-value the smaller the probability that the hypothesis of no association will be rejected by mistake when it is true (Loue, 2002).

Since people will be voluntarily participating in this study, the minimum sample size needed for this experiment might not be within control. It is estimated (Figure 3.1) that a sample

size of 50,000 would be needed to detect such a significant association between dose and cancer risk assuming lifetime follow-up for a 100 mSv dose, and a sample size of roughly 5 million for a 10 mSv dose. Thus, a very large sample size will be needed for this study to maintain statistical precision and power.

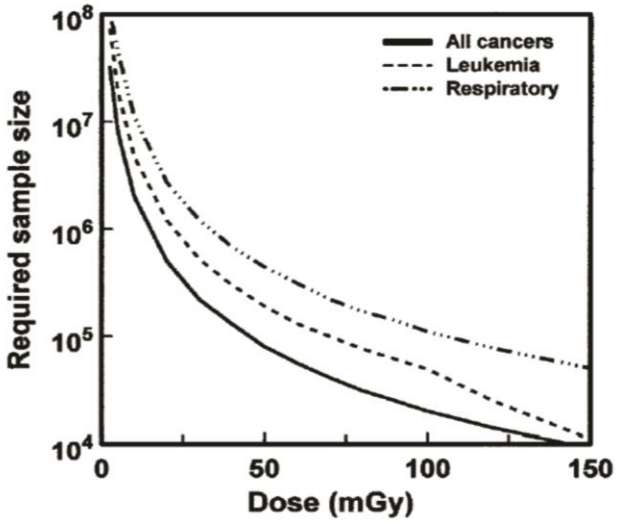

Figure 3.1. Dose vs Sample Size Required to Detect a Significant Increase in Cancer Risk for a Population Followed for Their Lifetime (Brenner et al., 2003).

A sample size calculator knows as Sampsize (Glaziou, 2003) was used to estimate the minimum sample size for a single subgroup and the total sample size in all groups for different control-to-case ratios with specific assumptions (Table 3.1). The assumptions made were: odds ratio of 0.8 (the odds of disease in the exposed to the odds of disease in the unexposed), since a decrease in cancer incidences in the exposed groups is expected based on current available epidemiological and molecular biology data; a CI of 95% thus an α value of 0.05; a power of 0.8 since it is often the minimum acceptable power value; a 10% loss of follow up at the end of the study; and 5 total subgroups in each of the four main group.

Table 3.1. Sample Size for Multiple Control-to-Case Scenarios, assuming: Odds Ratio = 0.8, α= 0.05, Power= 0.8, Loss of Follow Up= 10%, 5 total subgroups in each group.

Control -to-Case Ratio	Single Subgroup Sample Size				Total Sample Size (persons)
	Background Radiation Group (persons)	Intermediate Group 1 (persons)	Intermediate Group 2 (persons)	Upper Limit Group (persons)	
1:1	388,900	388,900	388,900	388,900	**7,778,000**
2:1	592,000	296,000	296,000	296,000	**7,396,000**
3:1	794,400	265,000	265,000	265,000	**7,947,000**
4:1	997,000	249,250	249,250	249,250	**8,724,000**

One way to try to increase the sample size and decrease the error is to have volunteers from different countries each irradiated at their locations, only if they have identical factors (geographical factors, socioeconomic factors…etc.) to the volunteers they are compared to. It is also important to measure the baseline cancer incidence in the new population under study. This will affect the size of the sample needed to detect the desired *RR* change. Withdrawal, losses to follow-up and deaths should all be taken into consideration when determining the sample size needed for a certain degree of power of the study (Silva & IARC, 1999).

3.2.1.6. Expected Outcome

Since efforts will be made to compare groups that match with respect to all confounding factors except dose, comparing cancer incidence in these groups should provide the most direct association between dose and solid cancer risk. The reference group is the background dose

radiation group which will have a *RR* value of 1. A *RR* value > 1 indicates an increase in cancer incidence in that specific group relative to the reference group. Likewise, a *RR* value < 1 indicates a decrease in cancer incidence relative to the reference group. A *RR* value = 1 indicates no observed difference in cancer incidence relative to the reference group. The expected outcome of the study if hormesis is occurring, is that the zero-dose group, if applicable, will have a *RR* value > 1; the two intermediate groups will have a *RR* < 1; the upper limit group will have a *RR* value higher than the intermediate groups, but might as well still be < 1. In other words, a hormetic dip is expected to be observable between the upper limit and the reference background radiation dose with a RR of ~ 0.7 close to the optimal dose (Sanders, 2010) (Figure 2.6). The expected *p*-values for the four-different control-to-case scenarios were calculated using a two-tailed z-score test calculator developed by Jeremy Stangroom (2017) (Table 3.2).

Table 3.2. Expected *p*-values for the sample sizes of Table 3.1, assuming cancer incidence rate of: 40% in background group, 0.8×40% in intermediate group 1, 0.7×40% in intermediate group 2, and 0.9×40% in upper the limit group.

Control -to- Case Ratio	***p*-values**		
	Background Group to Intermediate Group 1	**Background Group to Intermediate Group 2**	**Background Group to Upper Limit Group**
1:1	0.021	0.00038	0.24
2:1	0.021	0.00044	0.26
3:1	0.020	0.00042	0.28
4:1	0.020	0.00046	0.25

It was assumed that cancer incidence rate for: the background group is 40% of its total population; intermediate group 1 is 0.8×40% of its total population; intermediate group 2 is 0.7×40% of its total population; and the upper limit group is 0.9×40% of its total population. The *p*-value varies very little with different control-to-case ratios; however, it gets smaller as the rate of cancer incidence decreases, thus, indicating a strong association between cancer reduction and radiation dose.

3.2.1.7. Strengths & Weaknesses

While this study design might have one or more disadvantages that are common in most human study designs such as: cost, duration, large initial sample size, mixed level of compliance and loss of follow up, it has at least one problem of its own…ethical constrains. A well-designed, individual-level interventional trial will without a doubt provide the most accurate relationship between solid cancer incidence and low radiation dose! The main advantages of this study are its elimination of most confounding factors and its partial degree of freedom of dose, thus, increasing the accuracy of the outcome. Many of the disadvantages in this study design could be avoided in animal studies which will be discussed in the next section.

3.2.2. Alternative Approach: Animal Experimentation

Animal experimentation is one way of avoiding doing an interventional study on humans. In general, shorter trial time and large sample size are readily achieved in animal studies due to shorter latency period, lesser lifespan, and the ability to breed animals. Also, there is much less ethical constrains with animal irradiation compared to humans', this allows for a greater degree of freedom with respect to dose and dose rate. Another advantage of animal studies is the less variations in confounding factors among the species of choice; no socioeconomic or lifestyle

factors or weak level of compliance. Prior to conducting such a study animal who have certain diseases that could make them sensitive to radiation or to developing cancer could be dismissed from the experiment. One big advantage of using animals for this experiment is the ability to have and maintain the zero-dose group for the whole trial time. It is also easier to have a 1:1 comparison ratio due to no withdrawal or loss of follow-up; although losses due to early deaths among the study population is possible.

Despite these advantages, several problems do arise in animal studies that could affect the true relationship between dose and solid cancer risk for humans. The first problem is to find an ideal animal that could mimic the cancer mechanisms and the radiation sensitivity of humans (Mak, Evaniew & Ghert, 2014). Genetically engineered mice, a.k.a. GEMs, are often use as animal models of human diseases in cancer research (Shanks, Greek, & Greek, 2009). It is important to know that animals are not affected by the same carcinogens as humans (Shanks, Greek, & Greek, 2009). This should be taken into consideration when eliminating all confounding factors. Though, the main challenge in such studies is extrapolating data from mice to humans which has its limitations (Mak, Evaniew & Ghert, 2014; Mitrofanova et al., 2015; Shanks, Greek, & Greek, 2009). For example, stress factor, especially in caged animals, could affect the translation of data from animals to humans (Mak, Evaniew & Ghert, 2014). Many of these experiments and animal models fail to predict the actual human responses especially when it comes to cancer drugs (Mak, Evaniew & Ghert, 2014; Shanks, Greek, & Greek, 2009). The most important disadvantage in animal experimentation is the fact that animals have different radiation tolerance compared to humans. Consequently, animal experimentation is a good alternative to test the hormesis hypothesis but not to determine the optimal dose and optimal dose rates for humans.

3.2.3. Improved Approach: Current Epidemiological Data

If current available data of people exposed to ionizing radiation, such as nuclear and medical workers who meet the criteria mentioned in the novel approach, were to be used as an alternative approach to conducting an interventional study, very special considerations should be taken into account to reduce any bias presented in most of these radiation-related epidemiological studies (Luckey, 2008; Sanders, 2010; Scott 2011):

- Avoid dose lagging which shifts the dose-response curve to the left masking the hormesis dip and makes small doses appear more dangerous than they actually are.
- Evade averaging over wide dose range which could remove non-linearity and might indicate higher dose values to individual than what they actually got.
- Avoid using high acute doses data and forcing linear extrapolation to low doses.
- Adjust for confounding factors as possible.
- Defense mechanisms should not be wrongly attributed to HWE.
- Cancer incidence should be selected as the clinical outcome instead of cancer mortalities since some people could die from other causes while still having cancer that is not registered.
- Choose comparison groups with similar factors to eliminate HWE.
- Only high statistical power data should be used.
- Low dose data in the hormetic zone should not be simply ignored.

Most of epidemiolocal studies available display total accumulated doses vs ERR regardless of the dose rate. A novel approach to analyzing the carcinogenic effect of ionizing radiations by Gregoire & Cleland (2006) demonstrates negative ERR values as a function of daily and biweekly doses in multiple epidemiological studies for dose rate < 100 mSv/day and $\sim \leq 100$ mSv/2weeks.

They suggested that daily dose limits should replace the total accumulated dose concept in radiation protection regulations (Gregoire & Cleland, 2006). This new approach might better demonstrate hormesis in epidemiological studies than accumulated doses.

Although, such a modified approach would save time and money by making a better use of available data of large populations with some information on dose and other factors accessible, it will still lack accuracy compared to conducting an interventional study. This is mainly due to the inability to track many important confounding factors that could alter the true relationship between dose and solid cancer risk such as family cancer history, lifestyle factors and past chemical and radiation exposures. Thus, using epidemiological data of nuclear and medical workers might be of some importance if prospective cohort studies are used instead, and if efforts are made to eliminate the disadvantages of current available epidemiological data as mentioned in more details in *section 3.2.1.1*. However, both approaches are not ideal compared to conducting an interventional study.

4. CONCLUSION & FUTURE WORK

The controversy over the effects of low doses and low dose rates of ionizing radiation with respect to cancer risk has led the scientific community to be divided between being in favor of the LNT hypothesis and advocating for the hormesis or the threshold hypothesis. Current radiation protection bodies worldwide questionably adopt the opinion-based, unprotective, flawed, outdated, and scientifically unproven LNT model. On the other hand, the hormesis model is based on massive evidence reported in hundreds of published scientific papers of humans' and animals' data. With increasing biological and epidemiological evidence reinforcing the hormesis model and exposing the flaws in the LNT model, conducting a study on humans to test either hypothesis is inevitable. The biggest challenge that will face scientists in carrying out such an experiment on humans is the huge sample size needed to detect a practical relative risk difference with high precision. The study design presented in this paper is to serve as an initial humble step for a necessary much bigger collaborative effort from experts in the fields of: oncology, cancer epidemiology, molecular biology, medical physics, health physics, statistics, and related fields, to make the best use out of the hormesis phenomenon. The goal is to make this experiment as efficient as possible in terms of sample size, accuracy, cost, maximizing benefits and minimizing risks. Experimenting with low doses and low dose rates of ionizing radiation might also open more doors in science such as expanding human space explorations if it could be proven to make humans more adaptable to higher level of ionizing radiation environments.

Based on the results of such a study, an exclusive general hormesis model in the low dose region could be built. This model could then be expanded to include children and people with radiation sensitivities. More extensive risk models for site-specific solid cancers and leukemia vs high and mixed LET radiation should be investigated. Mathematical equations for cancer risk vs

dose and dose rate that include cancer risk factors and defense mechanisms need to be created. Efforts should also be made to make the best use of Fukushima disaster data in the near future. It would be interesting to consider developing a phone application (or even develop a smartphone that works as a dosimeter) that can estimate a person's radiation dose and cancer risk based on daily activities, age, sex, lifestyle, geographical location, type of job…etc., and send it to an online data collection to try to build a relationship between the two.

It is not a matter of if hormesis is *fact* or *fiction* anymore, it is a matter of finding the optimal dose and dose rate that can prevent as much cancer in a population as possible. Until optimal doses and dose rates are specified, a scientifically-based threshold model should replace the LNT model. Cancer is a nightmare on humanity and is claiming the lives of millions of people every year worldwide. A growing body of evidence is confirming that low dose and low dose rates of low LET ionizing radiation has the potential to reduce cancer incidence. Scientists who are deliberately ignoring and denying this evidence for some personal interests; and who are planting the seed of radiophobia in the public consciousness causing billions of dollars of loses, and deaths from suicide, premature cancers, abortions, fear of having diagnostic radiation, and traumatic evacuations; are a disgrace to humanity. Radiation protection regulations should be science and facts-based and not faith and opinions-based with the goal of protecting the public as the main priority.

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