

# **Radiation Induced Carcinogenesis; Epidemiology and Mechanisms: *A Review***

By Stuart Anderson

## **Abstract:**

Exposure to ionizing radiation has been proven to cause cancer and initiate mutagenesis in human and animal cells. This paper reviews some of the epidemiological data collected over the past 60 years and literature describing the current search for a genetic link to radiation induced carcinogenesis. Increased incidences of Leukemia, Breast Cancer, Lung Cancer, Skin Cancer and Bone Cancer in a broad spectrum of study groups. These groups include workers engaged in the mining and milling of Uranium, recipients of and workers in nuclear medicine, survivors of atomic blasts and accidents. Ionizing radiation has been found to induce serious damage at the molecular level to nucleotide sequences on chromosomal DNA. Mutational events at these key points such as proto-oncogene or tumor suppressor gene loci provide a probable mechanism for radiation induced malignant transformation.

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# **Radiation Induced Carcinogenesis, Epidemiology and Mechanisms: A Review**

*By Stuart C. Anderson*

## **Radiation and Carcinogenesis**

### **Introduction**

In the years following the discovery of radioactive phenomena, a strong correlation has been observed between exposure to ionizing radiation and the development of cancer. The principal points of reference for these studies have been on workers in and recipients of Nuclear Medicine, workers in Uranium mines and mills, survivors of the Hiroshima and Nagasaki Atomic bombs and survivors of nuclear reactor accidents such as Chernobyl. The characteristics of exposure for each of these groups are quite different:

Workers and patients in Nuclear medicine tend to be exposed to fractionated high doses of low LET radiation over days, weeks or years. Survivors of the Atomic Bombs in contrast, tend to be exposed to massive external doses of both high and low LET radiation over a matter of seconds with significant secondary fallout effects. Survivors of large scale nuclear accidents such as Chernobyl are exposed to lower doses of radiation over long periods of time, with the exposure involving the whole organism due to the intake of contaminated air, water and food. The final study group comprises workers in the Uranium Industry, primarily miners and mill workers who are exposed for protracted intervals to alpha emitters such as Radon 222 and its radioactive decay products.

Induction of sarcomas in laboratory animals was first demonstrated in 1910 (Marie et al 1910, 1912). This evidence was then used to explain the spiraling incidence of bone cancer among women employed to paint clock and watch dials with fluorescent Radium based paints (Martland 1931). Skin cancers on the hands of Radiologists were found to develop at around 20-30 years post exposure to x-ray radiation, but in some cases as early as 7 years. Also associated with this exposure were leukemias which typically manifested at around the 20-30y mark also (Upton 1975).

It is now accepted that ionizing radiation can cause cancer in any organ which cancer occurs naturally. Organs vary significantly in their susceptibility to cancer and in their latent period before the onset of malignant transformation. Age and sex are also significant variables.

### **Epidemiological Evidence linking Cancer with Radiation Exposure**

**Leukemia:** Studies of the Hiroshima and Nagasaki survivors revealed that there was a peak in the incidence of leukemia 7-8 years post bombing, with the rate of new incidences falling slowly over time, the incidence is however still greatly elevated. Amongst this group it was found that 39% of deaths could be attributed to Leukemia and 10% to other cancers among survivors that received a 10cGy dose or greater (Finch 1984). This observation is due to the extreme sensitivity of rapidly dividing haemopoietic stem cells in bone marrow to ionizing radiation. In the diagnosis of the various leukemia subtypes increased incidences of Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), but no increase in Chronic Lymphocytic Leukemia (CLL) was observed (Ichimaru et al 1945). Studies of recipients of X-ray Therapy for Ankylosing Spondylitis, a chronic progressive arthritis showed recipients of this therapy to be at a significantly increased risk of contracting Leukemia (Darby et al 1987). Analysis of the now abandoned practice of diagnostic use of x-rays in-utero revealed the incidence of Leukemia and other childhood cancers was heightened. Further studies of twin pregnancies irradiated in-utero reported a twofold increase in risk among the twins irradiated (Stewart 1956).

**Breast Cancer:** Like leukemia the incidence of breast cancer was found to be elevated amongst bomb survivors (Preston et al 1986), patients treated with X-rays for post partum mastitis (Shore et al 1956) and among patients who had multiple fluoroscopies for Tuberculosis (Baral et al 1977, Howe 1984). Among the survivors of atomic blasts an increased risk was noticed between 5-9 years after initial exposure. Risk was also shown to increase in a linear fashion with dose and at the same rate per unit dose in all study groups (Boice et al 1979).

**Lung Cancer:** An elevated risk of lung Cancer has been demonstrated in a variety of study groups exposed to ionizing radiation. Of these groups the best data has come from studies of uranium miners, especially those engaged in underground mining and other workers in the uranium industry. The Australian Atomic Energy Commission states that "A clear relationship has been established between lung cancer incidence and exposure to radon, and its radioactive daughter products in mine air". Underground miners who's bronchial mucosa was

exposed to Radon gas was reviewed by the IARC in 1988, which concluded that it was occupational exposure to Radon 222 gas and its decay products that caused the observed increased incidence of lung cancer. Further to this, the risk of lung cancer was also shown to increase with age, in proportion to the risk to unexposed individuals (Waxweiler et al 1981). Studies in the 1930s of miners in central Europe revealed that Lung Cancer accounted for between 40% to 50% of deaths among them. In a more recent study of the same group of miners 205 deaths from lung cancer were observed compared the expected number of 40. The number of deaths observed when compared to the expected number has been increasing consistent with the long latent period for respiratory carcinomas (Wagoner 1979). The causative agent was shown to be alpha particle (high LET) radiation emitted by Radon 222 gas emanating from Uranium and Radium deposits in the orebodies. Estimation of this risk proved to be complicated due to difficulties assessing dose, the long latency period to onset of carcinogenesis (>20y) and the evidence that cigarette smoking among workers significantly increases the risk. Smoking has been studied as a magnifier of risk among survivors of the atomic blasts, in which the relationship was found to be additive (Prentice et al 1983). Further studies of underground miners in Colorado were more consistent with a multiplicative effect (Whittemore & McMillan 1983). Closer to home, studies have been done on workers formerly employed at the Radium Hill Uranium mine in South Australia for periods exceeding one year. Of those miners that have consequently died, 40% died of lung cancer (Hansard 1979)

**Skin Cancer:** The frequency of skin Cancer was found to be elevated among Radiologists exposed to high levels of low LET radiation at the start of the century (Matanoski 1984). These results were mirrored among study groups consisting of children treated with x-rays for ringworm (Shore et al 1976) and amongst Uranium miners (International Commission for Radiological Protection 1987).

**Bone Cancer:** The bulk of information known about bone cancer has been collected from studies of Czechoslovakian women employed as clock and watch dial painters. Licking the brush by workers using the Radium 226 and 228 based paint resulted in absorption of these long lived isotopes. Radium like Calcium is a group II metal which is preferentially laid down in bone tissue. This resulted in the occurrence of bone sarcomas some 60 years post exposure (Rowland et al 1978). Another large US study found 60 cases of bone sarcoma and 32 cases of mastoid and paranasal sinus carcinoma in a study group of 2000 female workers similarly employed. The expected incidence for both conditions in a normal population should have been 1! Bone cancers were also found among patients receiving Radium 224 which has a half life of a few days. The latency period was found to be closer to that of Leukemia (7-8 years) with this risk strongly dependent of the number of doses given.

### Mechanisms of Radiation Carcinogenesis:

Radiation is termed "ionizing" when it has the capacity to accelerate electrons in atomic orbitals in matter. When this matter happens to be the double helical molecule of Deoxyribonucleic Acid (DNA) that constitutes the genetic material of our chromosomes, ionizing radiation becomes a mechanism for mutagenesis. Mutations in the genome of somatic body cells form a point of initiation of carcinogenesis. Mutations can be of three broad kinds, Point Mutations, Dimerisations and Direct Physical Changes.

**Point mutations** are those changes that affects single nucleotides, changing the nucleotide sequence and interfering with base pairing. The biochemical mechanisms are not well understood, but one such pathway is as follows:

Thymine (T)		<i>mutation</i>	5-Bromouracil (BU)
Base Pairs	A—T	<i>mutation</i>	A—BU
BU		<i>enolisation</i>	BU*

BU\* behaves as Cytosine (C) instead of Thymine (T) in original nucleotide forming the base pair arrangement BU—G if possible, or a localized area of unpaired bases as shown below:

A C T G C T A C	A C BU G C T A C
T G A C G A T G	T G C G A T G
	A

The above mechanism is substitution event, point mutations also include insertions and deletions. Insertions consist of base or base pair additions to the nucleotide sequence, whilst deletions are removal of bases or base pairs. Point mutations change either the nucleotide sequence in the case of substitutions or the reading frame of the DNA sequence in the case of insertions and deletions, all of which flow on to mRNA transcription and protein biosynthesis by translation.

**Dimerisation** can occur between adjacent bases on a DNA strand preventing accurate copying.

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A C G G T A      A C G=G T A
T G C C A T      T G   A T
                  C C
    
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**Physical changes** include the breakage or loss of part of a DNA strand or translocational rearrangement. These changes tend to occur on a chromosomal level. When cellular DNA is irradiated and results in chromosomal breakage a number of things can happen. In the majority of cases the strands will rejoin to the identical chromosome and return to the original undamaged state. If however there are many chromosomal breaks, then the broken ends of two different chromosomes may occur to form an abnormal chromosome, this process is an exchange type aberration. In some cases a broken fragment can be totally lost leaving an incomplete fragment known as a acentric fragment or terminal deletion.

Among radiation induced chromosome aberrations the frequency of terminal deletions increases in a linear fashion with increasing radiation dose. In the case of exchange type aberrations two breaks can be caused by one ionizing particle (one hit event) and similarly their frequency increases linearly with increasing radiation dose. If however the breaks are caused by different particles (two hit event) then the frequency of aberrations increases proportional to the square of the radiation dose. The frequency of aberration varies with the type of ionizing radiation.

Exposure to low linear energy transfer (LET) radiation such as X-rays and Gamma Rays increases the frequency of aberration proportional to the square of the radiation dose. In the case of highly ionizing high LET radiation such as neutrons the frequency of aberration is linear.

Studies of survivors from the Hiroshima and Nagasaki atomic blasts ( Awa et al 1978) revealed that the frequency of chromosomal aberrations in peripheral blood lymphocytes increased with radiation dose in both cities. The relationship being a linear one for Hiroshima, whilst at Nagasaki the relationship was curved proportional to the square of the radiation dose.

Studies of bone marrow samples from survivors of the Hiroshima bombing found an increased incidence of the Philadelphia Chromosome (abnormal chromosome 22) characteristic of **Chronic Myeloid Leukemia** and carrying the mutant oncogene bcr-abl. ( Kamada, Tsuchimoto and Uchino 1970). Further studies revealed the incidence of chromosomal aberrations to be 7 in 9 cases of those people exposed within 0.5km of the hypocentre(78%); 7 in 17 cases of people exposed between 0.5 and 1 km (Oguma et al 1975).

### **Quantitative and Qualitative Aspects of Radiation Exposure:**

In order to understand the damage done by ionizing radiation to living cells it is important to understand the interactions radiation has with matter at a molecular level over time. Radiation deposits its energy in discrete packages as either waves or particles. Densely ionizing high LET alpha radiation, protons and neutrons lose energy over short distances as streams of particles. This contrasts with low LET radiations like X-rays and Gamma rays which although highly penetrating transfer their energy as waves with lower ionization capacity. Biological damage is hence significantly higher for high LET radiation.

Radiation interacts with matter in three main phases according to the duration of exposure, these are the Physical phase, Physico-chemical/ Chemical phase and Cellular Tissue Damage phase.

#### **The Physical Phase:**

10 <sup>-18</sup> - 10 <sup>-17</sup> sec	fast particle traverses small atom or molecule
10 <sup>-16</sup> sec	ionisation H <sub>2</sub> O® H <sub>2</sub> O <sup>+</sup> + e <sup>-</sup>
10 <sup>-15</sup> sec	electronic excitation H <sub>2</sub> O <sup>+</sup> ® H <sub>2</sub> O <sup>*</sup>
10 <sup>-13</sup> sec	molecular vibrations and dissociations
10 <sup>-12</sup> sec	rotational relaxation e <sup>-</sup> ® e <sup>-</sup> <sub>(aq)</sub>

#### **The Physicochemical and Chemical Phase:**

10 <sup>-10</sup> - 10 <sup>-7</sup> sec	reactions of e <sup>-</sup> <sub>(aq)</sub> with other free radicals
10 <sup>-7</sup> sec	homologous distribution of free radicals
10 <sup>-3</sup> sec	free radical reactions largely complete
sec/min/hrs	biochemical changes to vital enzyme reactions

#### **The Cellular and Tissue Damage Phase:**

hrs	cell division inhibited in microorganisms and mamillian cells, reproductive death
days	damage to gastrointestinal tract and central nervous system
months	haemopoietic death, acute damage to skin and other organs
years	carcingenesis and expression of genetic damage in offspring

Cells undergoing frequent mitotic cell divisions are the most sensitive to the damaging effects of radiation. For example Zygotes, gastrointestinal epithelium and haemopoietic stem cells in bone marrow are more sensitive than lung and basal skin tissues which are in turn more sensitive than parenchyma cells of the liver. Sensitivity of cells to radiation correlates well with a cells inability to initiate enzyme mediated DNA repair. Studies of cell lines derived from the autosomal human genetic disorder Ataxia Telanglectasa (AT) reveal a sensitivity to radiation which is linked to faulty DNA repair mechanisms. This then explains te suceptability of AT sufferers to T-cell neoplasias.( Cox et al 1986). The probability of a cell undergoing malignant transformation increases with increasing dose, up to a peak point where there the dose is sufficient to kill enough cells and limit the cell population within which malignant transformation can occur. A radiation dose of 1 Gy causes approximately 200, 000 ionisations within the mammalian cell, of these around 1% occur in genomic DNA. Of the 1000 or so DNA strand breakages most are mended by spontaneou rejoining and enzyme mediated strand repair. Even among the 40% of those cells that sustain significant biological damage ability for growth and regeneration is retained in the majority of cases. Carcinogenesis is hence initiated in a relatively small number of cells where critical biochemical sites are damaged by a local ised high energy deposition. Critical sites may include proto-oncogene/ oncogene locii that are distinct to many cancers and tumour suppressor genes.

### A Precise Genetic Link:

Oncogenic transformation has been demonstrated in many studies to date to be an integral stage in carcinogenesis. Oncogenes are produced by mutational changes in proto-oncogenes present in the normal genomic DNA of cells. Exposure to mutagenic agents including ionizing radiation and especially high LET radiation can result in changes in the nucleotide sequence at these key points. Proto-oncogene nucleotide sequences encode for essential cellular proteins and enzymes, however once the sequence is changed by a mutational event so too is the encoded protein. An aberrant enzyme or protein can have profound effects on cell metabolism and can be a key factor in malignant transformation. In the case of Chronic Myeloid Leukemia (CML) a translocation of the chromosome 11 and chromosome 22 produces the Philadelphia chromosome which in turn results in the c-abl proto-oncogene fusing with the bcr gene forming the hybrid bcr-abl protooncogene. The c-abl proto-oncogene encodes for the vital cellular enzyme tyrosine kinase, but when it is transformed to a the bcr-abl oncogene and abnormal p210 Tyrosine Kinase results. The bcr-abl oncogene is a key diagnostic feature of many CMLs, affected white blood cells as a result show abnormally high growth rates and fail to differentiate to mature white blood cells.

### There are many oncogenes including:

<u>Oncogene</u>	<u>Tumor of Origin</u>	<u>Human Chromosome</u>
<i>hst</i>	stomach tumor	11q13
<i>N-myc</i>	Neuroblastoma	2p23-p24
<i>L-myc</i>	Lung Carcinoma	1p23
<i>met</i>	Osteo sarcoma*	7p11-p14
<i>bcr-abl</i>	Chronic Myeloid Leukemia	22q11
<i>bcl-1</i>	B cell Leukemia	11q13
<i>n-ras</i>	Neuroblastoma	1cen-p21

Inhalation of Radon gas presents a very real risk to human health, and has been directly implicated in the development of lung Cancer in both Uranium miners and the general public. Radon 222, an alpha emitter has been shown to induce 13x more cytogenetic damage than a similar dose of Cobalt 60 (Jostes 1996). A study of 19 US uranium miners found no mutations in the Ki-ras proto oncogene. However when the p53 tumor suppressor gene was studied 9 mutations were found including 2 deletions by direct DNA sequencing after PCR amplification (Vahakangas et al 1992). A further study of miners exposed to alpha emitting alpha radiation showed 31% of squamous cell and large cell lung carcinomas contained p53 mutations at codon 249 (AAG Arg è ATG Met). This finding was confirmed by in-vitro studies of normal human bronchial epithelial (NHBE) cells. NHBE cells exposed to 4Gy doses of ionizing radiation, equivalent to 1460 level working months in Uranium mining showed induced mutations at codon 249 AGGè AAG and 250 CCC è ACC transversions at a mutational frequency of 3.6x10<sup>-7</sup> and 3.8x10<sup>-7</sup> respectively (Hussain et al 1997)

### Conclusions:

Epidemiological evidence has consistently linked exposure to ionizing radiation with increased rates of carcinogenesis in any organ in which cancer can occur. Exposure to alpha particle emitting radiation and other high LET radiation sources, particularly Radon 222 and its radioactive breakdown products is especially damaging to living cells. Occupational exposure to Radon 222 has been proven time and time again to directly cause lung

cancer via inhalation of the gas and its decay products. The epidemiological data is well supported by genetic studies which demonstrate a clear correlation between radiation exposure and mutations in the p53 tumor suppressor gene in bronchial epithelium. Cellular damage in at the molecular level is initiated after even one millionth of a seconds exposure. There is hence no safe level of radiation exposure, no safe way to mine, process or handle radiation nor dispose of the associated wastes. Governments worldwide need to take heed of the well documented link between radiation and Cancer as a global health problem, stop the proliferation of all uranium mining before we create another Hiroshima, Nagasaki, Chernobyl or Radium Hill.

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