Chapter 33

Environmental Sources of Ionizing Radiation and Their Health Consequences

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1. INTRODUCTION

As unstable atoms decay over time, they release radiation in the form of electromagnetic waves and subatomic particles. Some forms of radiation have sufficient energy to detach electrons (ie, ionize the atomic structure of the substances they pass through), and are thus called ionizing radiation (IR). Common types of IR include alpha particles, beta particles, neutrons, X-rays, and gamma rays (Table 33.1). The molecular, cellular, and physiological effects of IR on human beings are myriad, and depend on the source, quality, and dose of IR, the mode of exposure and the genetic background of the individual in question. The two main physical outcomes of IR exposure are stochastic effects, representing genome instability and consequent cancers (whose likelihood increases with IR dose but is not guaranteed), and deterministic effects, encompassing immediate and predictable effects with severity relating to the dose. The sources of IR exposure that are to be discussed in this chapter include, from the rarest to most commonly documented types: nuclear attack or disaster, space and aeronautical high-altitude exposure, radiotherapy, diagnostic medical imaging, and radon gas inhalation (Fig. 33.1).

2. THE MOLECULAR EFFECTS OF IR IN CELLS

IR exposure inflicts various types of damage to genomic DNA, including (but not limited to) single-strand breaks (SSBs), double-strand breaks (DSBs), base and sugar–backbone damage and DNA:DNA or DNA:protein cross-linkages. Such damage occurs either via the direct ionization of the DNA molecule or through the production of reactive oxygen species (ROS) via the ionization of intracellular water, which in turn react with the DNA (Fig. 33.2). A DSB forms when two SSBs on opposing strands of the DNA double helix occur in close enough proximity for the base pairing of intervening sequence to fail. DSBs are among the most serious of IR-induced lesions as, if unrepaired, they will lead to chromosomal fragmentation and potentially premature cell aging or death. IR can also induce intra- and interstrand DNA cross-links (ICLs), severe lesions that can distort DNA helices or block strand separation [1]. For IR to trigger the formation of an ICL, there is a requirement of three to five mismatched bases at the site of ionization [2], increasing the likelihood of these lesions in regions of non-hybridized DNA such as telomere D-loops, DNA-replication forks, and transcription bubbles, as well as in other non-β DNA structures such as slipped DNA, hairpins, and tetrahelical structures [3]. Even though ICLs will most

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TABLE 33.1 The Types of Ionizing Radiation (IR), Their Source, and Common Use

Name	Type of Ionizing Radiation (IR)	Source of IR
Gamma rays	High-energy photons with low linear energy transfer (LET) through matter and great penetrance	Cancer therapeutics optimizing gamma rays to shrink tumor size
X-rays	Charged photons with low-LET IR	Diagnostic imaging
Alpha radiation	Heavy particle with high-LET through matter and poor penetrance	Byproduct of uranium decay and its progeny
Beta radiation	Light-charged particles high-LET IR	^{90}Strontium industrial usage
Neutrons	High-LET IR particles with no charge but strong penetrance ability	Cancer therapy, for example, boron capture therapy

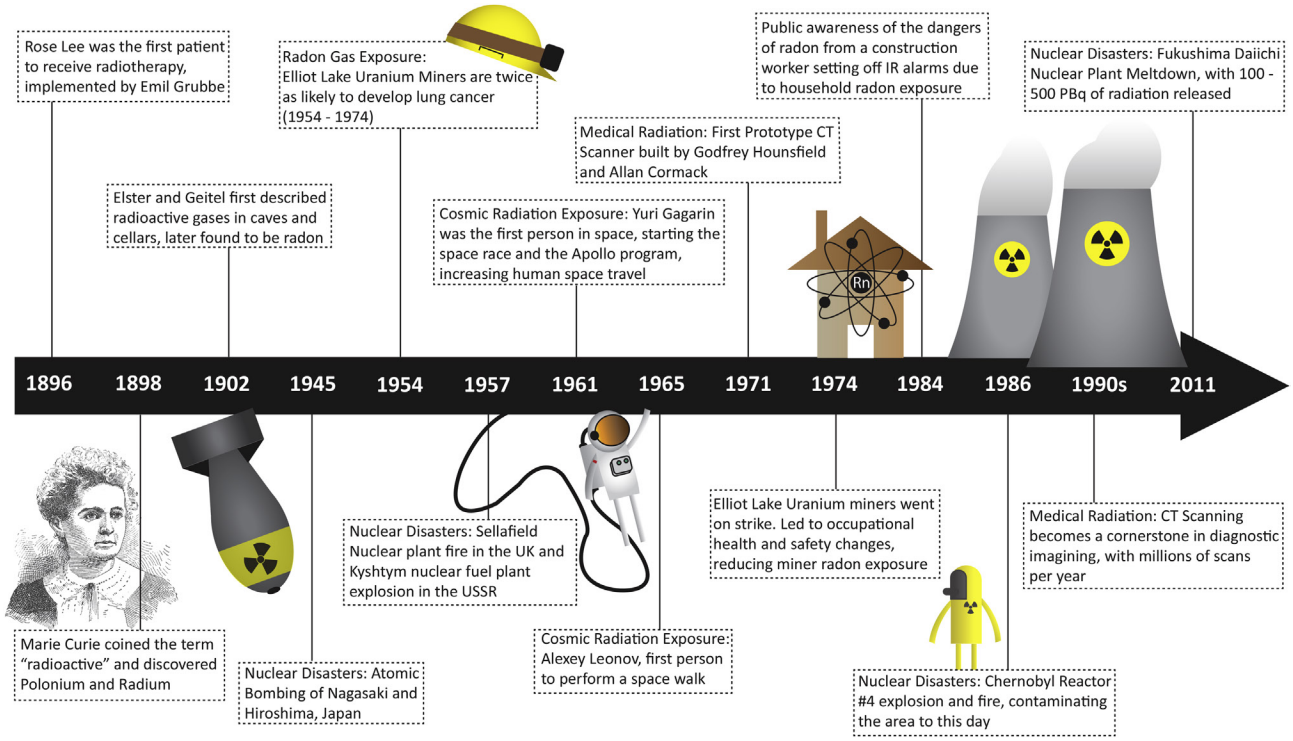

FIGURE 33.1 **A historical timeline of human exposure to sources of ionizing radiation.**

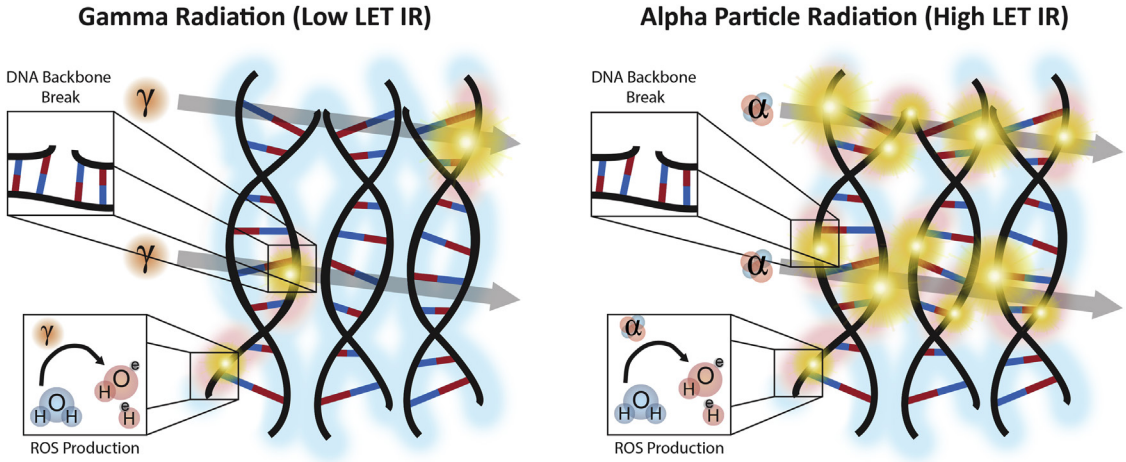

FIGURE 33.2 **The impact of high- versus low-LET ionizing radiation exposure on DNA.** Left panel: The direct effect of gamma rays, a type of low-LET IR that produces widely spaced DNA-damaged sites, both by direct ionization and indirect damage to the phosphodiester backbone by reactive oxygen species (ROS). Right panel: The direct effect of alpha particles, a form of high-LET IR whose high proximity ionization events produces clustered DNA-damage sites, defined as multiple lesions within few nanometers in a DNA molecule.

likely occur at a lower frequency than DSBs following IR, on a per lesion basis they are probably as or even more toxic due to the fact they occur commonly in regions of DNA-regulating key cellular processes [2].

In response to IR-induced DNA damage, life has evolved highly effective DNA-repair mechanisms [4]. IR induces SSBs more abundantly than any other type of lesion, although DSBs are considered to be the major factor responsible for cell death post exposure. If DSBs go unrepaired or are improperly repaired, there is a high chance of chromosomal loss, gain, or translocation events leading to a plethora of human diseases, including cancer [5]. In mammalian cells, formation of a DSB triggers a global cellular DNA-damage response (DDR) [6]. One of the earliest events to occur locally at the DSB site is phosphorylation of histone H2AX (at S139, to form "γH2AX foci"), which may be monitored by immunofluorescence microscopy and is often used as a tool to measure DSB induction and repair and diagnose radiation sensitivity [6,7]. The steady-state amount of DSBs observed by γH2AX foci enumeration will reflect a combination of IR exposure dosage and a cell's innate DSB-repair capacity, which can differ considerably between persons and tissues. DSBs are repaired generally by homologous recombination (HR) or nonhomologous end joining (NHEJ), depending on the cell-cycle stage of a cell when damage has occurred (HR, requiring an undamaged, copied sister chromatid for the repair process, is restricted to S and G2 phases). In cases where both NHEJ and HR fail or are unavailable, seen often in cancer cells, the so-called "alternative NHEJ" (alt-NHEJ) pathway can take place, although this generally produces large genomic alterations exacerbating genomic instability [8]. The choice between these pathways is a topic of intense research focus, at present, and is influenced not only by cell-cycle phase, but also the chromatin context within which the DNA damage occurs and the type of radiation from which the damage originates [8].

3. RADIATION DOSAGE AND LINEAR ENERGY TRANSFER

The emission of IR from a source is measured in becquerels (Bq), equating with one radioactive disintegration per second. The absorption of IR by a living cell is measured in gray (Gy), equating to 1 J of energy per kilogram of cells. One gray of IR is considered to produce about 20 DSBs per G0/G1 phase human cell [9], increasing (through S phase) toward 40 DSBs/Gy IR in the case of a G2 phase (which has twice as much DNA) [10]. The Sievert (Sv) is often equivalent to Gy, and represents the dose of IR absorbed by a cell/tissue/body that also has a measurable biological effect. When examining the impact of IR on cells and DNA, an important property to take into account is its linear energy transfer (LET) [11]. LET describes the rate at which energy is released by a radioactive source over a fixed distance. High-LET IR (such as alpha particles) emits more energy over the same relative distance compared to low-LET IR sources (such as gamma and X-rays) [12], and actually encompasses the majority of annual human IR exposure (see Section VI). Dose for dose, high-LET IR is much more lethal (at a cellular level) and carcinogenic than low-LET IR [13,14]. This is largely because high-LET IR produces DSBs and other lesions in very close proximity, which are both harder for the DNA-repair machinery to fix and have a greater chance of causing detrimental mutations, chromosomal translocations, cell death, or cancer [15]. Such clustered DNA damage, or multiple damaged sites (MDS), are specific types of DNA lesions generated by a single track of IR [16], including more than two individual lesions within one or two helical turns of DNA. The lesion found within clustered damage sites can be of several types: base modifications, abasic or apurinic/apyrimidinic sites, and oxidized purines or pyrimidines or SSBs in very close proximity to each other, as well as DSBs and ICLs. The complexity of IR-induced clustered damage correlates directly to ionization density; in fact, it is believed that clustered damage containing DSBs is mainly due to energy depositions of at least two to three ionization events localized within a 1–4 nm range [17]. Ninety percent of DSBs induced by high-LET IR is considered clustered, and it has been demonstrated experimentally that this is much more problematic for the cellular DDR to repair efficiently or accurately [18]. By contrast, the majority (99.9%) of DNA damage caused by low-LET IR is believed to occur indirectly via the formation of localized ROS, such as hydroxyl radical ($^{\cdot}OH$) from (relatively) isolated ionization events [19]. Consequently, they produce much more sporadic DSBs which are spread out across the nucleus and are repaired with faster kinetics compared to lesions formed by high-LET IR [9] (Fig. 33.2).

High-LET alpha particles, depositing energy at 100–150 keV/μm, produce highly linear tracks when traversing through a human cell. The microscopic pattern of energy deposition by high-LET IR represents complexity in terms of the nature of the radiation field, and the concepts of core and penumbra are important for understanding the physical characteristics of a charged particle track [20]. The core region is based on the Bohr adiabatic principle with a radius of around 0.0015 μm; within the core, excitation of all medium molecules occurs. In addition, some energy is deposited by extremely low-energy secondary electrons (δ-rays) that cannot successfully exit the core, and this defines the penumbra region. High-LET IR sources deposit their energy in two ways: 50% comes from within the core region from direct ionization and excitation of medium molecules, while δ-rays (the other 50%) are emitted from any collisions and extend for hundreds of microns outward [20]. A high-LET alpha particle passing through DNA will deposit large amounts of energy (300–500 eV) with a high probability of causing clustered lesions: about 20 DSBs per 10 μm track, with very few DSBs forming outside the track.

For high-LET IR delivered at the same dose as low-LET IR, there are also about three additional SSBs and three damaged bases produced near each DSB [20,21].

4. NUCLEAR MILITARY ATTACKS AND CIVILIAN NUCLEAR DISASTERS

While thankfully rare, nuclear attacks and disasters have provided a great deal of information on the effects of IR on human populations. These dramatic events, while undeniably tragic cases of mass, often whole-body irradiation of thousands of individuals, represent ideal scientific conditions for studying large populations with strong statistical significance. One of the largest studies of this kind is the Life Span Study (LSS) of Japanese survivors of the atomic bombing events in Hiroshima and Nagasaki towards the end of World War II [22]. The LLS examined 120,000 irradiated survivors and nonirradiated individuals, and was one of the first large studies to conclude the linkages between solid cancer incidence and IR dose. Additionally, nuclear power plant meltdowns, such as the 1986 meltdown of the Chernobyl nuclear reactor in the former USSR, provided data on initial high-dose irradiation as well as continual irradiation due to nuclear fallout. By examining the results of these studies, the initial and long-term health consequences of mass irradiation can be compared.

Irradiation from an explosive nuclear event may be broken up into two parts, the initial burst of neutrons, alpha particles, gamma- and X-rays, followed by the slower release of radioactive elements (fallout). The initial, high-dose IR bursts leads to strong deterministic effects such as acute radiation sickness (ARS). Using data obtained from the Chernobyl disaster, a correlation between the increasing severity of ARS to the increasing IR dose was observed, with the most severe ARS seen at estimated radiation doses between 6.5 and 16 Gy [23]. About 600 workers were at the Chernobyl nuclear plant immediately after the explosion, of which 237 were detectably symptomatic, 134 were officially diagnosed with ARS and 28 died [23,24]. ARS symptoms include a compromised immune system, vomiting, nausea, and diarrhea, and are associated with an overwhelming number of DNA-damaging events that kill cells outright and result in acute tissue damage [25], with proliferating cells being the most affected (particularly bone marrow and gastrointestinal cells). At exceptionally high IR doses, cerebrovascular and pulmonary dysfunction syndromes are noted, as even nonproliferating cells are affected [26,27]. Unfortunately, for those individuals close enough to the atomic event to receive massive doses, most die shortly thereafter due to bone marrow aplasia [28].

As distance from the disaster hypocenter ("ground zero") increases, estimated IR doses decrease significantly, following an inverse squared relation of dose to distance. For example, individuals within the 2 km radius of the Hiroshima/Nagasaki atomic bomb detonations received >0.5 Gy, whereas those 2–4 km from the hypocenter received acute doses of about 50 mGy [22,29]. At these doses, cases of ARS are rarer and individuals manifest stochastic effects such as cancer, with solid malignancies increasing at a rate of 26/10,000 cases per Gy IR [22], and deterministic effects such as fetal developmental abnormalities (including growth and mental retardation) [30]. Following initial high-dose irradiation, the resulting fallout of radioactive elements leads to continual low-dose irradiation over a much greater area than the initial blast radius. This generally represents the deposition of radioactive elements such as Iodine 131 and Cesium 137, which have half-lives of 8 days and 30 years, respectively, and can contaminate an area making it unsuitable for human population for decades [31]. In the case of Chernobyl, an estimated quintillion Bq (>1 EBq) of radioisotopes were released, with the initial evacuation zone being 3 km^2 but later expanded to 30 km^2 to account for spreading nuclear fallout [23], with evidence of contamination found over 100 km away from the Chernobyl hypocenter [32]. The Fukushima Daiichi Power Plant meltdown on March 11, 2011 in Japan released an estimated 100–500 PBq (1 PBq = a quadrillion Bq) of 131 Iodine and 6–20 PBq of 137 Cesium [33].

With extensive fallout, the documented incidences of thyroid, stomach, lung, liver, and blood cancers rise considerably following nuclear disaster with studies determining an inverse correlation of age at exposure to that of lifetime risk of cancer [22]. Indeed, the LSS (described earlier) demonstrated a 29% increase in the likelihood of solid cancers per decade decrease in age of exposure—meaning, the younger an individual is at the time of irradiation, the greater their likelihood of developing a tumor [22]. This fits with our understanding of IR-induced DNA damage, where genomic instability triggered by elevated DNA damage increases the chances of a mutagenic event that either ablates a tumor-suppressor gene or modifies and activates an oncogene. The longer the irradiated individual has left on their "natural life span," the more likely such mutations will occur within the same cell to trigger tumorigenesis. In addition, the highly proliferative tissue of younger humans is more susceptible to potentially cancer-causing mutations due to the vulnerability of DNA-replication processes to IR-induced DNA damage [34].

Radioactive fallout–induced cancers occur frequently in the thyroid gland due to its iodine-sequestering ability, wherein ingested Iodine 131 is progressively concentrated and increases the effective radiation dose by 1000–2000 times [24]. Lessons learned from the Chernobyl disaster have mitigated the uptake of nuclear fallout in Japan where, 6 months after the March 2011 nuclear meltdown, only 3286 of 9498 residents of the Fukushima prefecture had detectable radioisotope levels at an average of 11.4 Bq/kg, compared to Chernobyl's 49 Bq/kg still seen up to a decade afterward [35]. The Chernobyl

incident marked a 30-fold increase in childhood thyroid cancers, with 98% of these tumors derived from the papillary cells versus the 67% commonly seen in thyroid tumors in nonirradiated populations [36,37]. This bias suggested a pathology specific for IR damage, which when further investigated revealed that 50–90% of the papillary cancers had a *RET* rearrangement leading to a replacement of the RET tyrosine kinase ligand-binding domain with a coiled-coil region, stimulating uncontrolled papillary cell growth [38,39]. Interestingly, the *RET* rearrangement alone was insufficient to induce tumorigenesis, an additional point mutation was required and, the earlier the individual was exposed to radiation, the higher was the likelihood of inducing cancer [40]. Follow-up animal studies have suggested that other IR-induced thyroid cell cancers are possible, such as medullary carcinomas, indicating that IR damage does not have a specific pathology per se, only that there may yet be an influx of other thyroid cancers from nuclear fallout victims [24,41]. In addition to thyroid cancer [37,38,42], the other highest incidence form of radiation-induced malignancy is leukemia [43–45]. Indeed, data from nuclear industry workers indicate that the excess relative risk (ERR), which compares the level of risk for an exposed person to that of the risk in a nonexposed person, is 2.18/Sv for all types of leukemia (except chronic lymphocytic leukemia) [43]. Mechanistically, the mutations accrued in radiation-induced leukemias do not share as striking a homology as the papillary thyroid cancers, but show random chromosomal aberrations in hemopoietic stem cells, ultimately leading to a higher likelihood of cancer [25,28]. Indeed, these rearrangements have shown to inactivate key proteins such as p53 and ATM, whose inactivation have been linked to several cancers [46–48].

Other than cancers, nuclear disasters have been implicated in acute or systemic health conditions of the blood, heart, brain, and circulatory and respiratory systems, as well as psychological disorders [22,49,50]. Although the direct mechanism of action is unknown, evidence has indicated that cellular death, endothelial changes, or microvascular damage may contribute to the occurrence of heart disease and stroke [50]. High-dose irradiation can also leave survivors in an immune-compromised state with bone marrow ablation, T-cell apoptosis, and a host of other immune system effects, increasing their susceptibility to infections such as pneumonia and influenza [26,27,49,51]. In the case of the civilian nuclear meltdowns, the permanent physical evacuation of individuals from contaminated areas has resulted in obesity, hypertension, and polycythemia due to the psychological stress of being displaced from their lives [49,52]. Taking all these factors into consideration, the health effects of a nuclear disaster are serious but, in large population health terms, thankfully rare [53].

5. AEROSPACE TRAVEL

Removed from the full protection of Earth's atmosphere and magnetosphere, astronauts experience greater doses of high-LET radiation from high atomic number and energy (HZE) particles, and cosmic radiation [54]. Even airplane flight staff, who spend significant amounts of time closer to space versus the general population, experience significantly elevated HZE bombardment over their careers [55]. HZE ions are a component of galactic cosmic rays (GCR) and are also emitted by individual solar proton events, particle storms of massively accelerated protons that are emitted by Earth's Sun during solar flares or during coronal mass ejection shock waves. HZE particles are a significant health concern for astronauts and individuals who spend a great deal of time traveling by air [56,57]. In outer space, the effects of HZE particles are so pronounced that for the Apollo space crew members, who left Earth's protective magnetosphere between 1968 and 1972, HZE particles and proton interactions with the retina were perceived as flashes of light [58]. Not only do HZE particles induce DNA damage in a similar manner to alpha particles, more importantly, HZE particles can ionize other atoms inside the body to become sources of DNA damage, effectively multiplying their deleterious effects [59]. It is well established that HZE atoms and alpha particles have greater overall relative biological effectiveness (RBE) than either X- or gamma rays, with the complexity of induced DNA damage being directly related to the total energy of the radiation source [21]. RBE is a term referring to the ratio of biological effectiveness of one IR type in comparison to another, given the same quantity of absorbed energy. Current animal studies demonstrate that HZE nuclei have a greater carcinogenic effect compared to low-LET gamma radiation. The values of RBE measured in rodents for multiple tumors such as those of the skin and mammary gland are as high as 24–40, even with low doses of HZE ions [60].

The frequency of HZE radiation and our current inability to effectively shield astronauts from these types of radiation is what makes space travel implicitly dangerous. Space missions venturing outside Earth's protective magnetic field for significant periods of time, such as manned missions to Mars, which could last for decades, would place astronauts at significant risk. One of the most immediate health concerns is the increased susceptibility to infection [61], with HZE particle irradiation–associated decreases in B-cell and T-cell counts, and IL-2 secretion of the spleen [62]. Immune-suppression in outer space is so significant that about 50% of Apollo mission astronauts contracted either bacterial, viral, or fungal infections [61]. Even latent viral infections, such as herpes and Epstein–Barr, have been observed to reemerge in space crews [62,63]. One method to mitigate immune-suppression is to provide preemptive broad-spectrum antibiotics; however, this strategy is flawed as it enables the development of antibiotic-resistant bacteria and does not address viral

or fungal infections [61]. Of course a major risk of long-term exposure to HZE particles is cancer [56]. The likelihood of death at age 40 years due to cancer from a deep space mission (eg, Mars), calculated for lung, colon, stomach, bladder, bone marrow, breast, and ovarian malignancies, is estimated to be 4.2% for men and 5.1% for women [56]. For conventional airline pilots and cabin crew, a meta-analysis of 266,431 individuals conducted in 2015 determined crew to have about doubled rates of skin melanoma compared to the general population [64]. One likely contributing factor to all these cancers is that HZE particles have a 30-fold greater efficacy in causing interchromosomal exchanges compared to low-LET IR [56]. This suggests the HZE particles are able to elicit greater genome instability, as indicated by the presence of increased chromosomal truncations in cells exposed to HZE particles [65]. Increased cancer risk within this population would also be exacerbated by immune-suppression, as the destruction of nascent cancer cells by the immune system would be impaired [66].

Another consequence of continual exposure to low doses of high-LET radiation is reduced cognitive abilities associated with lowered neural plasticity [67–69]. Animal studies demonstrate that low IR doses alter neuronal gene regulation by suppressing five distinct genes: GNAS (a G-protein), GRIA3 (an AMPA glutamate receptor), SLC1A1 (a glutamate transporter), PRKCB1 (protein kinase C), and MEF2C (a transcription factor) [67]. These genes are also downregulated in aging and Alzheimer's disease, possibly indicative of the accelerated neuronal aging impact of irradiation. Learning, memory, and cognition capacity would certainly all be lowered, increasingly disabling spacecraft crews required to function at a high level to maintain their environment [69]. Fortunately, preliminary work has shown that antioxidants, such as α-lipoic acid reduce, albeit not completely, the effects of IR on cognition [68]. Long-term HZE particle exposure is also linked to cataracts [70–72], with several studies indicating that space and airline flight crews have a higher incidence than the general population [71–73]. The most likely causes have been associated with the production of hydroxykynurenine from the interaction of tryptophan residues with UV light, loss of antioxidant capabilities due to accelerated aging, and lenticular cell changes [71]. There also appears to be a distinction in the spatial localization of IR-induced cataracts versus age-related cataracts, with the majority of the former appearing in the posterior capsule of the lens and the latter dominating the lens nucleus [71,72]. For airline flight crews, cataracts may be mitigated through surgery; however, they pose a problem for deep space missions where optical surgery may not be possible.

6. MEDICAL RADIATION (RADIOTHERAPY AND MEDICAL IMAGING)

Each year, about 64,000 Canadian and nearly 1,000,000 American cancer patients undergo radiotherapy (RT), because this is considered one of the most effective antitumor treatments [74]. Delivered in targeted, short-spaced, very high-dose fractions, RT is very effective at killing cancer cells; however, it can also elicit tissue damage to normal cells resulting in deterministic effects (such as cataracts, heart disease, stroke, erythema, ulcers, telangiectasia, dermal atrophy, or cognitive dysfunction) or stochastic effects like secondary cancers [75–78]. As mentioned earlier, rapidly proliferating cells are particularly sensitive to the killing effects of IR, explaining the efficacy of RT as an antitumor agent and underlying the off-target side effects such as hair-loss, nausea, anemia, and delayed wound healing. Additionally, at sublethal doses, IR-induced DNA damage increases the likelihood of carcinogenesis [79]. Hence, normal cells not killed but damaged sufficiently by RT to alter their DNA can transform and become a secondary cancer years later [78]. On top of this, mild-to-severe overresponses to RT (mostly manifesting as grade 2–4 toxicity) are noted in 1–3% of adult cases (ie, >30,000 cancer patients in North America per year), likely due to undiagnosed radiosensitivity, multiplying the deleterious effects of radiation.

Children who undergo RT are thought to be especially at risk of adverse health effects due to their added life span and the elevated proliferation status of their normal tissue. Along with increased secondary cancers, it has been well documented that radiation has a profound effect on the developing cognitive abilities of children [76,80–82]. From a study of pediatric patients with acute lymphocytic leukemia (ALL) or medulloblastoma/posterior fossa primitive neural ectodermal tumor (PNET), a direct relation between cranial radiation dose and IQ lose was seen. Here, patients were given IQ tests before and after treatment and for those who received a total of 18 Gy, their scores were an average of 12.3 IQ points higher in follow-up compared to those who received 36 Gy [80]. Additionally, age was a large factor in the observed IQ decline, where patients <3 years old were predicted to lose an average of 11.9 more IQ points than for those 3–10 years old [80]. In fact, the cognitive effects are so prominent that those affected by radiation have ended up in special education or institutionalized [81]. Mechanistically, this cognitive decline results from decreased neurogenesis, where rat models have shown a 62% reduction in hippocampal neural stem/precursor cell proliferation as well as near ablation of differentiation into neurons or glia [81]. It is suggested that radiation induces mitotic stress, preventing in vitro cells from proliferating after 2–3 divisions, and the increased inflammation response alters the differentiation pathway choice [76,81]. Notably, there has been some work demonstrating reduced memory loss and increased neurogenesis with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [77].

The effects of medical radiation are exaggerated in utero, where time of exposure and dose will alter the effects of radiation in the developing fetus, causing congenital malformations, growth retardation, cancer, or death [30,83]. It is known that if doses of about 100 mGy are received during the 8–15-week gestation period, then subsequent IQ is lowered, while about 1000 mGy will cause severe mental retardation [30,83]. Indeed, the relative risk of developing cancers when exposed in utero is 1.4 times higher than nonexposed with a dose of only 10 mGy [30]. Although RT has proved effective in many cases, the side effects of treatment are numerous and have dictated the path of many treatment regimes.

The most common man-made source of IR exposure, by a large margin, is modern medical imaging with a mean effective dose estimated to be 1–3 mSv per person per year [75]. To put medical imaging into perspective, close to 100 million CT examinations are performed in Canada and the United States annually, with diagnosed and potential cancer patients representing a huge part of this population. Each whole-body CT scan represents exposure to about 10 mGy IR, a significant dose equating with one DSB for every five cells or, when considered on a whole-body level, a staggering 7.44 trillion DSBs per person [84,85]. Although widely prescribed, given these doses, it is not surprising that CT scanning is recognized as significantly increasing cancer risk, with the NCI estimating that 29,000 new US cancer cases were caused directly by the 72 million CT scans that took place in 2007 alone [86]. It should be noted that there is some dispute over the risks associated with medical imaging, as the precedence for relative risk of cancers is based upon the LSS of Hiroshima and Nagasaki. As mentioned previously, the LSS indicated a 26/10,000 increase in solid cancers per Gy of exposure; however, this trend is only seen for doses >100 mSv [22,87]. Based on this data, a linear through zero model was created where low doses also induce an observable increase in cancers, yet the evidence for this is minimal [87]. Due to the limited evidence, it has been suggested that the lower doses of radiation may not increase the likelihood of carcinogenesis [87]; however, what has not been taken into account in these suggestions is the stochastic nature of induced mutations. Although a direct correlation is difficult to draw with low-dose exposure, the fact remains that IR induces DNA damage which can lead to tumorigenesis [88]. A higher dose simply leads to a greater number of DSBs, which would increase the chances of activating an oncogene or deactivating a tumor suppressor. Given the latency period associated with IR-induced cancers (from causative event to diagnosis), and since the overwhelming majority of CT scans have taken place only since the late 1990s [89], it is possible (even likely) that most cancers resulting from CT scan usage have yet to be documented.

7. RADON GAS

The largest natural causes of IR-induced genetic damage are radioisotopes of the odorless and colorless noble gas radon, which is highly enriched within soil gases of uranium-rich geologies and can accumulate in homes via basements. In 1904, while at McGill University in Canada and based on landmark experiments conducted two years earlier by Elster and Geitel [90], Ernest Rutherford wrote [91]:

> *There can thus be little doubt that the abnormal activity observed in caves and cellars is due to a radioactive emanation, present within the earth, which gradually diffuses to the surface and collects in places where the air is not disturbed … [this activity] decays to half value in about 3.3 days, while the activity of the radium emanation decays to half value in an interval of 3.7 to 4 days. Considering the difficulty of making accurate determinations of these quantities, the rates of decay of the activity of the emanations from the earth and from radium agree within the limits of experimental error.*

Of course, Rutherford, while not fully knowing it at the time, was talking about radon gas—the "radium emanation." Radon is now recognized as second only to tobacco smoking as a direct cause of lung cancer, with over 10% of all cases worldwide attributed to its exposure [92,93]. The most common isotope of radon, ^{222}Rn, has a short half-life of 3.8 days, and will emit high-LET alpha particles before decaying rapidly to isotopes of polonium, bismuth, and lead. Radon's carcinogenic properties are attributed to the fact that every decaying atom of ^{222}Rn will emit four high-LET IR alpha particles, the first emission resulting in a transition from the gaseous state to a precipitated solid which becomes irreversibly embedded within lung tissue. These radon "daughter" radioisotopes will continue to emit alpha radiation within the lungs, with a cumulative half-life of just over 22 years before eventually decaying into solid lead. It is unsurprising, given this series of events, that radon is classified by the United Nations (UN) World Health Organization (WHO) as a Class I carcinogen in the same hazard category as benzene, mustard gas, and asbestos [94]. For most healthy individuals not involved in IR-prone occupations, radon inhalation represents the largest single source (37%) of annual radiation exposure throughout their lives [95].

Initial evidence for the significance of radon as a carcinogen came from observations of uranium mine workers who, after being exposed to high levels of radon progeny as a byproduct of ^{238}Uranium decay, developed lung cancer at substantially higher rates relative to equivalent professions [96]. Between the 1950s and 1970s, Ontario uranium miners in Canada were exposed to extraordinarily high levels of radon gas in poorly ventilated mines. By the mid-1970s miners were being diagnosed with lung cancer at twice the expected rates, such that by 1984 a total of 285 miners had already died of

lung cancer [97]. Thankfully, this eventually led to fundamental changes within the mining industry and, through adequate ventilation, such mines were rendered safe for workers [98]. In the decades that followed, radon accumulation in residential homes and workplaces was additionally recognized as a means of cancer-causing exposure and, in 2009, following several decades of research within the medical and scientific community, the UN WHO released a "Handbook on Indoor Radon," declaring radon to be "a major contributor to the ionizing radiation dose received by the general population" and "that the lung cancer risk increases proportionally with increasing radon exposure." The consolidated studies summarized by the WHO indicated that lifetime risk of lung cancer increases 16% for every 100 Bq/m^3 of radon inhaled within the domestic or workplace environment over the long term, and recommended this level as the maximum acceptable limit for human environments, with the ideal levels being as low as achievable.

Since radon is odorless, colorless, and has no immediate, detectable impact on human respiration (unlike carbon monoxide), it usually goes unnoticed and becomes a problem when it is concentrated within well-insulated homes and offices. Actual residential levels of radon will vary between buildings due to the amount of radon produced in the underlying geological substrate and factors such as the presence or absence of ventilation, insulation, or heating systems. Heating a poorly ventilated (eg, a home sealed during cold winter months) but highly insulated (eg, energy efficient) home will hyperconcentrate radon in dwellings over certain geology, as the thermal stack effect (hot air rising, creating a pressure differential) actively draws radon-laden gases up through the foundations into the structure. This may easily be countered, thankfully, through relatively straightforward and moderately inexpensive radon testing and mitigation technologies that can accurately measure ambient levels of radon gas over the long term, and prevent accumulation permanently (often via sub-slab depressurization or increased ventilation) [99]. Unsurprisingly, exposure to the high-LET IR from radon during childhood increases significantly the risk of developing lung cancer later in life. Indeed, childhood (ages 0–17 years) exposure to even moderately high radon concentrations (400 Bq/m^3) is equivalent to a lifetime exposure at 100 Bq/m^3 radon concentration; less than 2 years in a home with 4000 Bq/m^3 is sufficient to achieve the same level of risk [100]. Thus, while it is advisable for anyone to test their homes and workplaces for radon (and mitigate if a problem is detected), any homes, schools, and daycares where small children and young adults spend a great deal of time should become a priority for radon elimination.

Curiously, perhaps alarmingly, radon inhalation has been and is commercially advertised to provide beneficial health effects in some locations. For example, there are so-called "radon spas" in Austria and the United States where people pay to be exposed up to 80,000 Bq/m^3 to provide relief from chronic pain, inflammatory diseases, and dermatological conditions, ostensibly by modulating the immune system and the DNA-repair machinery [101]. While the occasional visitor to such spas might experience no significant long-term health effects (from a probably short exposure window, few days per year), permanent employees in these facilities would be expected to experience the same increase in lung cancer risk as has been documented extensively for uranium miners prior to adequate mine ventilation; hence, we would advise that these facilities should be approached with some informed caution.

Considering that radon inhalation and subsequent high-LET alpha particle irradiation of lung tissue is, overwhelmingly, the most common mode of radiation exposure encountered by humanity, we know surprisingly little about genetic risk factors for radon-induced cancer. Genetic polymorphisms of factors participating in the detoxifying (often antioxidant) process of environmental carcinogens can modulate the risk of lung cancer dramatically, but few studies have investigated the association between residential radon exposure and different cancer-susceptibility genes [102]. In 2014, studies on animals indicated that lung cancer risk from radon is higher in mice lacking genes encoding microsomal glutathione S-transferase proteins *mu* GSTM1 and *theta* GSTT1; this is likely because alpha particles, like all IR, will generate ROS that damages DNA within lung epithelia and GST proteins scavenge ROS [102]. Interestingly, studies carried out in mice exposed to high-LET IR ^{56}Fe (iron ions), showed no overall differential expression in liver-metabolizing genes; however, looking at the lung epithelium revealed a reduction in the expression of O^6-methylguanine-DNA-methyl transferase (MGMT), which is crucial in maintaining genomic instability by reversing mutagenic O^6-methylguanine back to guanine, which otherwise could trigger mismatch error and ultimately contribute to carcinogenesis [103]. Further studies exposing mice to radon gas showed differential expression of genes involved in carcinogenesis: an upregulation of E-cadherin mRNA (involved in both carcinogenesis and metastasis), downregulation of protein A1 (associated with chromosomal rearrangements), and casein kinase delta (involved in apoptosis as well as chromosomal segregation) [104].

Logically, the mutation of most factors involved in the IR-induced DNA-damage response would also be a risk factor for radon-induced lung cancer, and further work is required to confirm whether this is the case. An important consideration is that gene–environment interactions would have the greatest impact at relatively low indoor radon concentrations (50–200 Bq/m^3) most commonly observed in homes. Although some countries and agencies have started to become proactive in mitigating radon levels >300 Bq/m^3, relatively little attention has been paid to the effects of low radon concentrations <200 Bq/m^3, which is what the bulk of the population are exposed to and are responsible for the majority of radon-related deaths. Chronic, low-dose irradiation has qualitatively distinct biological consequences to acute irradiation and often fails

to trigger cell-cycle checkpoints [25]. Under these conditions, difficult-to-repair DNA damage (as would be caused by high-LET IR) would persist and be more likely to enter into DNA replication or cell division, where risks of chromosomal fragmentation or mutation would increase dramatically [92]. Any genetic polymorphisms associated with even mild DNA-repair delay would exacerbate this effect, and potentially render such individuals particularly at risk of radon-induced genetic mutation and thus cancer risk.

8. CONCLUSION

Although varied in source, features, and consequences, DNA damage underlies nearly all IR-induced human diseases. Whether from acute, high-dose exposure, chronic low-dose exposure, or IR of varying LET, it is the extent of damage and the type of cells impacted that dictates the outcome on health. At lethal doses, necrosis or apoptosis occurs and the immediate effects are seen in ARS due to tissue failure. By contrast, if a cell can survive IR-induced DNA damage, the chances of mutation are increased since repair mechanisms may erroneously repair DSBs, enabling chromosome translocations, rearrangements, and/or point mutations; however, carcinogenesis is not guaranteed. Through several studies of IR exposure survivors, a correlation for the stochastic effects of radiation has been made where the higher the IR dose at the younger the age of exposure, the more likely a cancer is to develop. This also holds true for deterministic effects of radiation, with ARS increasing in severity as the IR dose increases. Based on all of this, a simple conclusion can be drawn, radiation is a health concern whose exposure needs to be minimized and its resulting effects need to be mitigated through continued study and further understanding.

GLOSSARY

Alpha particle A helium nucleus (two protons and two neutrons).
Becquerel (Bq) One radioactive disintegration per second.
Beta particles A high-speed and energy electron or position.
Clustered damage Results from high-LET ionizing radiation, with large amounts of damage accrued over a defined distance.
Core (relating to high LET) High-LET radiation track structure consisting of energy deposited close to the high-LET particle trajectory. This arises from the excitation and collective oscillations of atoms very close to the track.
Daughter radioisotopes Radioactive elements decay to form progeny products.
Deterministic effects The immediate and predictable effects of ionizing radiation with severity relating to the dose received.
Excess relative risk This is the measure for the relative chance of developing a disorder (largely used for cancer risk assessment) for an exposed person, compared to the risk in a nonexposed person—that is, a person is 2 times as likely to develop a certain cancer per Sv of radiation received compared to a person who has not been exposed to radiation.
Fallout The radioactive elements released into an environment due to a nuclear incident.
Gamma rays Photons that have energies that can overlap with X-rays and range between 100 keV and 10 MeV, but are primarily defined as originating from atomic nuclear decay.
Gray (Gy) One Joule of ionizing radiation energy per kilogram of cells.
H2AX Histone 2A variant X (encompassing about 10% of the total histone 2A population).
γH2AX H2AX phosphorylated at serine 139 in response to DNA double-strand breaks.
Homologous recombination The error-free repair of damaged DNA double-strand breaks using template DNA (such as a sister chromatid).
LET The rate at which energy is released by a radioactive source over a fixed distance.
Neutrons Noncharged subatomic particle.
Nonhomologous end joining The error-prone repair of DNA double-strand break, not relying on template DNA.
Pneumbra (relating to high LET) Refers to high-LET radiation track structure when energy is deposited away from the trajectory of the high-LET particle—that is, scatter deposition of energy at some distance adjacent from the particle trajectory.
Relative biological effectiveness Is a term referring to the ratio of biological effectiveness of one IR type in comparison to another, given the same quantity of absorbed energy.
Sievert (Sv) Often equivalent to gray, and represents the dose of ionizing radiation absorbed by a cell/tissue/body that also has a measurable biological effect.
Stochastic effects The nonpredictable effects of ionizing radiation on health, such as genomic instability and cancer.
X-rays Photons with an energy of 100 eV–300 keV.

LIST OF ABBREVIATIONS

Alt-NHEJ Alternative NHEJ
ALL Acute lymphocytic leukemia
ARS Acute radiation sickness
ATM Ataxia telangiectasia mutated

CT Computed tomography
DDR DNA-damage response
DNA Deoxyribonucleic acid
DSBs DNA double-stranded breaks
ERR Excess relative risk
GCR Galactic cosmic rays
HR Homologous recombination
HZE High atomic number and energy
ICL Interstrand cross-link
IR Ionizing radiation
LET Linear energy transfer
LSS Life span study
MDS Multiple-damage sites
MGMT Methylguanine-DNA-methyl transferase
NHEJ Nonhomologous end joining
NSAIDs Nonsteroidal anti-inflammatory drugs
$^{\cdot}$OH Hydroxyl radical
SSBs DNA single-stranded breaks
RBE Relative biological effectiveness
ROS Reactive oxygen species
RT Radiotherapy
UN United Nations
UV Ultraviolet
WHO World Health Organization

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