Review Articles

Low-dose Radiation Exposure and Carcinogenesis

Keiji Suzuki and Shunichi Yamashita

1Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki and 2Fukushima Medical University, Fukushima, Japan

For reprints and all correspondence: Shunichi Yamashita, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan. E-mail: shun@nagasaki-u.ac.jp

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Absorption of energy from ionizing radiation by the genetic material in the cell leads to damage to DNA, which in turn leads to cell death, chromosome aberrations and gene mutations. While early or deterministic effects result from organ and tissue damage caused by cell killing, latter two are considered to be involved in the initial events that lead to the development of cancer. Epidemiological studies have demonstrated the dose–response relationships for cancer induction and quantitative evaluations of cancer risk following exposure to moderate to high doses of low-linear energy transfer radiation. A linear, no-threshold model has been applied to assessment of the risks resulting from exposure to moderate and high doses of ionizing radiation; however, a statistically significant increase has hardly been described for radiation doses below 100 mSv. This review summarizes our current knowledge of the physical and biological features of low-dose radiation and discusses the possibilities of induction of cancer by low-dose radiation.

Key words: ionizing radiation – low-dose – epidemiology – thyroid cancer – A-bomb survivors – Chernobyl accident

INTRODUCTION

After Röntgen discovered X-rays in 1895, it was recognized that radiation exposure causes acute tissue damage. Later, it was found out that cancer, particularly leukemia, is induced by exposure to radiation. By the early 1970s, accumulated evidences demonstrated that radiation is capable of inducing cancer in many types of tissues. It became possible to estimate the risk of leukemia and solid cancer primarily on the basis of the data collected from the survivors of the 1945 atomic bombings in Hiroshima and Nagasaki (1). During the 1980s, the data from the follow-up of A-bomb survivors provided revision of the earlier risk estimates (2,3). However, since the risk estimates have been obtained from epidemiological studies of A-bomb survivors, they are appropriate for populations at high doses. Thus, a reducing factor of 2, which is called a dose and dose-rate effectiveness factor (DDREF), has been proposed for exposure at low doses or at low dose rate (4), while another report proposed a DDREF value of 1.5 (5). Further information from a number of epidemiological studies of cancer induction by exposure to external and internally incorporated radioactive nuclides has indicated that caution is needed in interpreting the dose–response relationships obtained by direct extrapolation from epidemiological studies conducted in A-bomb survivors, particularly at lower doses of <100 mSv of low-linear energy transfer (LET) radiation (6). In the following sections, every aspect with the emphasis on low-dose radiation effects will be taken into consideration. Particularly, much attention has been paid to the dose–response relationship between radiation doses to the thyroid gland and thyroid cancer incidence. Specific genetic alterations found in papillary-type childhood thyroid cancers after Chernobyl accident and their possible relation to radiation signature will also be discussed.

PHYSICAL EFFECTS OF LOW-DOSE RADIATION

DEFINITION OF LOW-DOSE RADIATION

Based upon the dose–response for mortality from solid cancers among A-bomb survivors, United Nations Scientific
Committee on the Effects of Atomic Radiation (UNSCEAR) 1993 report considered that a low dose could be <200 mGy (7). Lately, it was reported that statistically significant risk elevation is not observed at doses of 100 mSv or less (8), so that a low dose could be 100 mSv or less. The Biological Effects of Ionizing Radiation (BEIR) VII report of the US National Academy of Sciences defined low dose as doses up to ~100 mSv (5). In this review, low doses are defined as those <100 mSv.

UNITS OF RADIATION EXPOSURE

The quantity used to refer to the amount of ionizing radiation is absorbed dose, which is defined as the energy absorbed per unit mass. The unit of absorbed dose is gray (Gy), and 1 Gy equals 1 joule of energy absorbed per kilogram of matter. As different types of radiation produce different biological effects, equivalent dose, which is the product of absorbed dose and radiation-weighting factor, is introduced. The unit of equivalent dose is sievert (Sv). Finally, effective dose is used to limit health risks involved in radiation exposure. Effective dose is the sum of all of the weighted equivalent doses in all the tissues and organs exposed. Since different tissues have different radiation sensitivities, tissue-weighting factors are used to calculate weighted equivalent doses. Thus, if the effective dose is used for radiation exposure, radiation health effects are the same between external and internal exposure. The unit of effective dose is also sievert (Sv).

DIRECT AND INDIRECT EFFECTS

Absorption of radiation energy to DNA directly induces structural alterations of DNA, which is called a direct effect. Alternatively, interaction of radiation with water molecules in the cell produces water-derived free radicals that indirectly cause DNA damage. This action is called an indirect effect. It is estimated that low-LET radiation with 100 mGy causes at least 100 instances of oxidative DNA damage, ~100 DNA single-strand breaks (SSBs) and ~4 DNA double-strand breaks (DSBs) (9). For low-LET radiation, 60–70% of such DNA damage is estimated to result from indirect effects, while 30–40% of the damage is caused by the direct effect (10). Although free radicals are created along the radiation track, radiation is not the only source to generate them.

It is well known that endogenous (intracellular) free radicals, which are collectively called reactive oxygen species (ROS), arise from mitochondrial oxidative metabolism and other reactions in cells (11). The estimated average generation rate is ~10^6 ROS per cell per day (12), which results in 10^6 oxidative DNA damage, 10^5 SSBs and 0.1 DSBs per cell per day (11). The rate is much higher than those estimated in cells receiving 100 mGy per year, which is ~0.01 DSBs per cell per day. Although it was not described more in detail, such low-dose rate exposure should be treated as totally different from high-dose rate or acute exposure. For example, acute 100 mGy of radiation induces four DSBs per cell at once, while 100 mGy per year creates approximately one DSB in a cell out of 2400 cells/h.

CELLULAR EFFECTS OF LOW-DOSE RADIATION

DNA DAMAGE AND REPAIR

Both direct and indirect absorption of radiation energy to genetic materials results in structural alterations of DNA. A variety of changes—so-called DNA damage—have been identified. Those include base damage, apyrimidinic/apurinic (AP) sites, SSBs, DSBs and cross-links (13–15). The yield of DSBs has been calculated as described earlier, and ~40 DSBs could be induced per gray (9). Theoretical numbers of DSBs have been confirmed experimentally by counting the foci formation of DNA damage checkpoint factors, and ~40 foci are reported to be induced by 1 Gy of low-LET radiation (16–18).

Induction of DNA damage by low-dose radiation has been quantified by foci formation, and over a few mGy to 1000 mGy dose range, the induction shows a linear dose–response (16,17). In vivo formation of DSBs was also examined in lymphocytes obtained from individuals undergoing computed tomography examinations. It was found that the number of DSBs increased linearly depending on the dose—length product (19).

The ability to repair DNA damage is inherited through evolution. Most of the repair systems found in prokaryotes exist in mammalian cells (20). Thus, oxidative DNA damage, such as base damage, AP sites and SSBs, is efficiently repaired through the base excision repair and SSB repair pathways (21–24). The first step in base excision repair is the excision of modified base, which is catalyzed by DNA glycosylase. The resultant AP sites are cleaved by AP endonuclease, which result in SSBs. Nucleotides gaps are filled with DNA polymerases, and DNA termini are rejoined by DNA ligases. Oxidative base damage, such as 8-oxoguanine, causes mismatch base pairing during DNA replication and eventually induces mutation (25). AP sites as well as SSBs have also been considered pre-mutagenic lesions (26).

DNA DSBs result in disruption of the higher-order structure of chromatin, which manifests itself as chromosomal aberrations. Multiple DNA repair pathways are involved in repairing DSBs (27–29). Non-homologous end joining (NHEJ) is the major repair pathway for DSBs through the cell cycle. Classical NHEJ does not use any sequence homology; therefore, it does not need DNA end processing. However, alternative-NHEJ and homologous recombination (HR) are dependent on DNA end resection. HR is functional only after the sister chromatid is provided through DNA replication. In principle, HR is an error-free pathway, whereas NHEJ, particularly alternative-NHEJ, is error prone (30,31).

Since DSBs are spontaneously generated during DNA replication, or produced by specific nucleases during V(D)J...
recombination, class switch recombination and meiotic recombination, in addition to those induced by endogenous ROS, repair of DNA DSBs has been an efficient process, and repairable DSBs are generally eliminated within 24 h of radiation exposure. In fact, it has been shown that DSBs induced by X-ray doses of up to 200 mGy are completely repaired in proliferating human cells after 24 h (16). Thus, while the initial induction of DSBs shows a linear dose–response relationship, DNA damage caused by low-dose radiation has little chance to persist in cells. This is in sharp contrast to those induced by high-dose radiation, which often result in residual DSBs (16,17).

Repair DSBs were also examined during chronic low-dose-rate irradiation. In vitro experiments have shown that normal human diploid fibroblasts exposed to γ-rays at a dose rate of 18 mGy/h do not accumulate DSBs nor phosphorylation of p53 (32). According to a previous report, endogenous DSBs are formed from single-strand DNA lesions, including SSBS, AP sites and oxidative base damage, in replicating cells at a rate equivalent to that of DSBs induced by radiation at a dose rate of 282 mGy/h (33). Therefore, around this dose rate, human cells are expected to repair DSBs efficiently and faithfully. This assumption is in good agreement with the data showing that DSBs induced at a dose rate of 238 mGy/h are repaired with no error (34). Although increased levels of residual DSBs were observed with 102 mGy/h in confluent non-dividing cells (35), a similar paper has reported that DSBs induced in quiescent normal human fibroblasts by very low-dose radiation, such as 1 mGy of X-rays, remains unrepaired for many days, but it is rapidly repaired if the cells are allowed to proliferate (16). Thus, it is obvious that low-level DSBs are efficiently repaired with high fidelity especially in proliferating human cells.

DNA DAMAGE RESPONSE

While DNA repair pathways amend DSBs efficiently, a certain fraction of the initial breaks possibly remains unrepaired. Such lesions could be complex lesions or clustered damage, or DSBs induced in heterochromatic regions (36,37). If cells with residual DSBs are replicated, the stability of the genome is threatened. Thus, cells have evolved a system called DNA damage checkpoint, by which the integrity of the genome is maintained (27,29). The central players of DNA damage checkpoint pathway are ataxia-telangiectasia mutated (ATM) and p53 proteins. Once DSBs were sensed by ATM, it is activated as a protein kinase and catalyzes phosphorylation of downstream factors, including p53. The p53 protein is a well-known tumor suppressor and regulates transcription of various genes, whose products regulate cell death or irreversible growth arrest (27,29).

Recently, it has been shown that DNA damage signal is amplified through formation of a multiple protein complex (38). ATM-dependent phosphorylation of a histone H2AX, a member of histone H2A, initiates sequential protein interactions, and phosphorylation of histone H2AX expands for over several megabase chromatin regions surrounding the initial DSB site (39). Thus, these protein complexes come to be visualized as discrete foci under a fluorescence microscope. Moreover, the number of foci is well correlated with the actual number of DSBs, so that the foci are now widely used as sensitive surrogate markers for DSBs (39). Amplification of DNA damage signal plays a crucial role when the number of instances of DNA damage is small. It is essential for execution of cell cycle arrest, particularly G1 arrest, as AT cells defective in ATM function fail to initiate G1 arrest (38). Although a recent study reported that the G1 checkpoint was inefficiently maintained (40), it should be mentioned that cells with DNA damage terminate cell proliferation at the G1 phase within a next few cell cycles (41). Thus, cells have evolved a sophisticated system by which they can respond to very limited number of DSBs induced by low-dose radiation.

LOW-DOSE RADIATION AND CARCINOGENESIS

EPIDEMIOLOGICAL STUDY

A-BOMB SURVIVORS

The most informative epidemiological study of the survivors of the atomic bombings at Hiroshima and Nagasaki has been conducted by the Radiation Effects Research Foundation (RERF). The Life Span Study (LSS) is based upon large numbers of persons with various whole-body doses (42). Excess relative risk (ERR), which is a measure of the size of the increase in cancer risk in the study population due to the radiation at given doses, has been used to examine the relationship between radiation doses and the risk of cancer induction. The latest report on LSS mortality from RERF demonstrated that the dose–response relationship at low doses below 1 Gy might be described by both a linear and a curvilinear function (43). The ERR estimate for solid cancers was 0.47/Gy. In the dose range 0–150 mSv, the excess risk of solid cancer seems to be linear; however, there is no statistically significant elevation in risk at doses below 100 mSv. The strong link between radiation exposure and thyroid cancer was also provided by studies of A-bomb survivors (44). The dose–response relationship appeared to be linear, and the gender-averaged ERR estimate was 0.57/Gy (43). Age at exposure is the most important modifier of thyroid cancer risk, and elevated risk is no longer detectable among survivors exposed after the age of 30.

The A-bomb survivors received higher external doses over a short period, which is in contrast to the other populations receiving low-dose radiation over long periods. However, as the most-esteemed epidemiological study of radiation-exposed human populations, the LSS cohort has played a critical role in obtaining the basic coefficients of risk.
estimation. Also, the data obtained from the LSS cohort have enabled evaluation of the scientific validity of the linear, no-threshold (LNT) model. So far, the dose–response relationship supported the LNT model in principle; however, the dose–response relationship below 100 mGy tends to fluctuate, which limits statistical significance in the increase in the incidence of cancer at lower doses. While the LNT model has been used for evaluating the cancer risk from radiation exposure, even the most-celebrated epidemiological study could not uncover the uncertainties of the radiation effects below 100 mSv, which requires understanding of the molecular mechanisms of radiation-induced carcinogenesis.

**Chernobyl Accident and Childhood Thyroid Cancer**

The accident at the Chernobyl nuclear power plant on 26 April 1986 released a large amount of radioactive materials that resulted in radiation exposure in the populations of the affected regions (45–47). In particular, fallout of radioactive iodines resulted in exposure of local residents through ingestion of contaminated foodstuffs and inhalation, which caused childhood thyroid cancer as one of the main health effects of the accident (48). Among children and adolescents under 18 years in 1986, 6848 cases of thyroid cancer were reported between 1991 and 2005 (46). A large case–control study of Belarusian and Russian children showed a very strong dose–response relationship, and the risk appeared to increase linearly with doses up to 1.5–2 Gy, whereas a statistically significant increase in risk was not observed below 200 mGy (49). The estimated ERR of thyroid cancer among children younger than 15 years at the time of the accident was 5.6/Gy. A recent analysis of thyroid cancer prevalence in the Belarus cohort showed a linear dose–response below 5 Gy with an excess risk of 2.15/Gy (50). The result of an analysis in the Ukrainian cohort also reported a linear dose–response relationship below 5 Gy, and the ERR was 1.91/Gy (51). In both the cases, no statistically significant increase in risk was observed below 100 mGy. Several ecological studies have also been conducted (52–54), and one study in Belarus and Russia reported statistically significant elevation of thyroid cancer risk in the settlements with an average thyroid dose of 50 mGy (52). It has been applied for the projected dose that needs to provide iodine thyroid blocking in recent International Atomic Energy Agency (IAEA) publication (55).

While childhood exposure of thyroid to radiation from $^{131}$I is a well-established risk factor for thyroid cancer, recent studies have identified genetic determinants that modify individual predisposition to childhood thyroid cancer (56–59). Particularly, a genome-wide association study in Belarusian cases aged 0–18 years at the time of the accident pointed out that a single nucleotide polymorphism (SNP) marker, Rs965513 located in the FOXE1 locus, showed a strong association with radiation-related thyroid cancer (59). Thus, genetic predisposition to thyroid cancer needs more attention in order to estimate individual risks from radiation exposure especially at lower doses.

**Thyroid Cancer Risk by Medical Exposure**

Although the association between thyroid cancer and medical exposure was implicated in the early 1950s, systemic epidemiological studies were limited during the 1980s (60). A pooled analysis of seven studies with organ doses to individual subjects was conducted in 1995 (61). It included five cohort studies (atomic bomb survivors, children treated for tinea capitis, children irradiated for enlarged tonsils and infants irradiated for an enlarged thymus gland) and two case–control studies (patients with cervical cancer and childhood cancer). To estimate a dose-dependent increase in the thyroid cancer risk for exposure before age 15, the data from five studies were pooled. A linear dose–response relationship was observed, and the ERR was estimated to be 7.7/Gy. An elevated risk of thyroid cancer was observed at doses as small as 100 mGy; however, it was no longer statistically significant below this level.

Data on thyroid cancer risk after the diagnostic use of $^{131}$I in Germany, Sweden and the USA were compiled (62). Since thyroid cancer risk is greatly influenced by age at exposure, subjects under age 18 and 20 years old when administrated $^{131}$I were evaluated in German and Swedish studies, respectively (63,64). The estimated doses to the thyroid on average were 1 Gy for German subjects and 0.94 Gy for Swedish ones. In both the studies, no increased risk of thyroid cancer was observed. A US study, in which the median age at $^{131}$I administration was 11 years and the mean thyroid dose was 0.8–1.0 Gy, also failed to show an increase in thyroid cancer risk (65).

**Thyroid Cancer Risk Posed by Environmental Exposure**

Radioactive iodine, particularly $^{131}$I, released from the Hanford nuclear weapons site in the USA between 1944 and 1957 has been a matter of concern to the public. A descriptive epidemiological study of thyroid cancer incidence among residents of counties near the Hanford nuclear facility site was conducted. People born between 1940 and 1946 were identified, and a comprehensive dosimetry program estimated that the mean thyroid dose is 170 mGy. There was no association between thyroid cancer and estimated radiation doses in children (62).

**Conclusion**

While epidemiological studies have demonstrated the dose–response relationships for cancer induction following exposure to moderate-to-high doses of low-LET radiation, a statistically significant increase has hardly been described with radiation doses below 100 mSv. An LNT model has been applied to assessment of the risks resulting from exposure to ionizing radiation; however, epidemiological
studies are insufficient to elucidate the shape of the dose–response relationship at low doses. Therefore, a clear understanding of the mechanisms of radiation carcinogenesis is essential to gain further insights into the health effects of low-dose radiation (66). Furthermore, current models for radiation carcinogenesis have paid much attention to the stochastic process of energy deposition in cells, but accumulating evidences have shown that the nature of the target cells, i.e. tissue stem cells and progenitor cells, needs to be taken into consideration (67). Such information should improve our assessment of the likely form of the dose–response at exposure below 100 mSv.

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Conflict of interest statement

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