Low-dose radiation exposure and carcinogenesis

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ABSTRACT

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

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

INTRODUCTION

Since Röntgen discovered X-rays in 1895, it had been recognized that radiation exposure caused acute tissue damage. Later, it was known that cancer, particularly leukemia, is induced by radiation exposure. By the early 1970s accumulated evidences demonstrated that radiation is capable of inducing cancer in many of the tissues. It became possible to estimate the risk of leukemia and solid cancer based primarily on the survivors of the atomic bombings in Hiroshima and Nagasaki in 1945 (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 exposures at low doses or at low dose rate (4), while the other report proposed a DDREF value of 1.5 (5). Further information from a number of epidemiological studies on 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 in A-bomb survivors, particularly at lower doses less than 100 mSv of low-LET radiation (6). In the following sections, every aspects 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 its 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 less than 200 mGy (7). Lately, it was reported that statistically significant risk elevation was 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 about 100 mSv (5). In this review, low doses are defined as those less than 100 mSv.

Units of radiation exposure

The quantity used to determine the amount of ionizing radiation is the absorbed dose, which is defined as the energy absorbed per unit mass. The unit of absorbed dose is the gray (Gy), and 1 Gy equals to 1 joule of energy absorbed per kilogram of matter. As different types of radiation produce different biological effects, the equivalent dose, which is the product of absorbed dose and radiation weighting factor, is introduced. The unit of equivalent dose is the sievert (Sv). Finally, effective dose is used to limit health risks from radiation exposure. Effective dose is the sum of all of the weighted equivalent doses in all tissues and organs exposed. Since different tissues vary in their

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 again the sievert (Sv).

Direct and indirect effects

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

It is well known that endogenous (intracellular) free radicals, which collectively called reactive oxygen species (ROS), arise from mitochondrial oxidative metabolism and other reactions in cells (11). The estimated average generation rate is approximately 10^9 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 that those estimated in cells receiving 100 mGy per year, which is approximately 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 4 DSBs per cell at once, while 100 mGy per year creates approximately one DSB in a cell out of 2400 cells per hour.

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, single strand breaks, double strand breaks and crosslinks (13-15). The yield of DSBs has been calculated as described above, and approximately 40 double strand breaks could be induced per Gy (9). Theoretical number of DSBs has been confirmed experimentally by counting the foci formation of DNA damage checkpoint factors, and approximately 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 linear dose-response (16,17). In vivo formation of DSBs was also examined in lymphocytes obtained from individuals undergoing computed tomography (CT) examinations. It was found that the number of DSBs increased linearly dependent on the dose-length product (DLP)(19).

Ability to repair DNA damage is inherited through evolution. Most of the repair

systems found in prokaryotes are existed 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 single-strand break 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 mis-match base pairing during DNA replication and eventually induces mutation (25). AP sites as well as SSBs have also been considered as pre-mutagenic lesions (26).

DNA double strand breaks result in disruption of higher-order structure of chromatin, which manifest as chromosomal aberrations. Multiple DNA repair pathways are involved in repairing DSBs (27-29). Nonhomologous 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 double strand breaks has been an efficient process, and reparable DSBs are generally

eliminated within 24 hours after radiation exposure. In fact, it has been shown that DSBs induced by X-ray doses up to 200 mGy were completely repaired in proliferating human cells after 24 hours (16). Thus, while the initial induction of DSBs shows 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 was also examined during chronic low-dose-rate irradiation. In vitro experiments showed that normal human diploid fibroblasts exposed to γ-rays at a dose rate of 18 mGy/hr did not accumulate DSBs nor phosphorylation of p53 (32). According to the previous estimation, 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/hr (33). Therefore, at 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/hr were repaired with no error (34). Although increased levels of residual DSBs were observed with 102 mGy/hr in confluent non-dividing cells (35), there was a similar paper reporting that DSBs induced in quiescent normal human fibroblasts by very low dose radiation, such as 1 mGy of X-rays, remained unrepaired for many days, but it was rapidly repaired if the cells were 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 efficiently amend DSBs, 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. 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 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 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 DNA damage is small. It is essential for executing cell cycle arrest, particularly G1 arrest, as AT cells defective in ATM function

fail to initiate G1 arrest (38). Although recent study reported that the G1 checkpoint was inefficiently maintained (40), it should be mentioned that cells with DNA damage terminate cell proliferation at G1 phase within a next few cell cycle (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 the 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 per 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 the A-bomb survivors (44). The dose-response relationship

appeared to be linear, and gender-averaged ERR estimate was 0.57 per Gy (43). Age at exposure is the most important modifier of thyroid cancer risk, and elevated risk is no loner detectable among survivors exposed after the age of 30.

The A-bomb survivors received higher external doses over short period, which is in contrast to the other populations receiving low dose radiation over long periods. However, as the most esteemed epidemiological study for radiation-exposed human populations, the LSS cohort has played a critical role in obtaining the basic coefficients of the risk estimation. Also, the data obtained from the LSS cohort have been provided the chance to evaluate the scientific validity of the LNT model. So far, the dose-response relationship supported the LNT model in principle, however, the dose-response relationship below 100 mGy tend to fluctuate, which limits statistical significance in the increase 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 understandings of the molecular mechanisms of radiation-induced carcinogenesis.

Chernobyl accident and childhood thyroid cancer

The accident at the Chernobyl nuclear power plant on April 26, 1986 released large amount of radioactive materials that resulted in radiation exposures 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 causes childhood thyroid cancer as one the of 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 dose up to 1.5 to 2 Gy, whereas statistically significant increase in risk was not observed below 200 mGy (49). The estimated excess relative risk of thyroid cancer among children younger than 15 years at the time of the accident was 5.6 per Gy. 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 per Gy (50). The result of an analysis in the Ukrainian cohort also reported a linear dose-response relationship below 5 Gy, and the excess relative risk was 1.91 per Gy (51). In both cases, no statistically significant increase in risk was observed below 100 mGy. Several ecological studies have also been performed (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 employing Belarusian cases aged 0 - 18 years at the time of the accident pointed out that a SNP marker, Rs965513 located in the FOXE1

locus, showed 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 exposures

Although the association between thyroid cancer and medical exposure was implicated in early 1950's, systemic epidemiological studies were limited during 1980's (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 captis, 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 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 excess relative risk was estimated to be 7.7 per 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.

Thyroid cancer risk after diagnostic use of ^{131}I in Germany, Sweden, and the United states was 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 studies, no increased risk of thyroid cancer was observed. A US study, in which the

median age at ^{131}I administration was 11 years old 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 by environmental exposures

Radioactive iodine, particularly ^{131}I, released from the Hanford nuclear weapons site in the United States between 1944 and 1957 has been a 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 comprehensive dosimetry program estimated that the mean thyroid dose was 170 mGy. There was no association between thyroid cancer and estimated radiation doses to the thyroid of 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, statistically significant increase is hardly described with radiation doses below 100 mSv. A linear no-threshold model has been applied for assessing the risks resulting from exposures to ionizing radiation, however, epidemiological studies are insufficient to elucidate the shape of the dose-response relationship at low doses. Thus, understandings of the mechanisms of radiation carcinogenesis are essential for further insights into 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 implicated 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 exposures below 100 mSv.

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