Review

Medical Radiation Exposure and Human Carcinogenesis-Genetic and Epigenetic Mechanisms

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Ionizing radiation (IR) is a potential carcinogen. Evidence for the carcinogenic effect of IR radiation has been shown after long-term animal investigations and observations on survivors of the atom bombs in Hiroshima and Nagasaki. However, IR has been widely used in a controlled manner in the medical imaging for diagnosis and monitoring of various diseases and also in cancer therapy. The collective radiation dose from medical imagings has increased six times in the last two decades, and grow continuously day to day. A large number of evidence has revealed the increased cancer risk in the people who had frequently exposed to x-rays, especially in childhood. It has also been shown that secondary malignancy may develop within the five years in cancer survivors who have received radiotherapy, because of IR-mediated damage to healthy cells. In this article, we review the current knowledge about the role of medical x-ray exposure in cancer development in humans, and recently recognized epigenetic mechanisms in IR-induced carcinogenesis.

CARCINOGENESIS

Cell proliferation is tightly regulated under physiological conditions. Cancer is a disease that arises from uncontrolled growth of a transformed cell. Control of cellular growth is lost in cancer. Cancer development is a multi-stage process characterized by the cumulative effects of cellular processes such as increased replication rate, suppressed apoptosis, enhanced angiogenesis and metastasis. Various alterations occur in the expression of the genes associated with many critical cellular processes during the carcinogenesis. Primary target genes in carcinogenesis are proto-oncogenes, tumor suppressor genes, DNA repair genes, apoptosis-related genes and the genes regulating cell cycle. Alterations in these genes involve 1) gene mutations, DNA deletions or DNA rearrangements which result in the conversion of proto-oncogenes to oncogenes and/or loss of the function of tumor suppressor genes; 2) epigenetic changes that effect expression of the target genes[1-3]. Only a small fraction of cancers are associated with inheritance, the majority of the various forms of cancer are caused by environmental factors which are able to cause genetic and epigenetic changes. The role of environmental factors in carcinogenesis has been revealed by epidemiological data and experimental animal studies. Cumulated genetic alterations because of carcinogenic exposures during the lifetime may result in malignancy if apoptosis is inhibited and the immune system can not eliminate the transformed cells. The environmental factors leading cancer development are classified as physical, chemical and biological carcinogens. The major physical agents causing cancer are IR and UV.

CELLULAR EFFECTS OF IONIZING RADIATION

IR is a kind of radiation which has sufficient energy to break chemical bonds and displace electrons from atoms and molecules. IR consists of electromagnetic radiation, such as x-rays or gamma rays (γ-rays), or of subatomic particles, such as protons, neutrons, and α-particles. When organisms exposed to IR, radiation energy is transferred to the cellular atoms and molecules, and biomolecules are ionized or excited. By this way IR can cause breaks in chemical bonds, production of free radicals, crosslinking between biomolecules, and finally damage in all cellular macromolecules. Radiobiological studies have suggested the DNA as the main target for biologic effects of IR that can be categorized in three groups: genetic effects, epigenetic effects and bystander effects. In addition, IR effects on expression of small non-coding RNAs has been introduced.

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Genetic Effects of IR

The damaging effects of IR on DNA occur through direct or indirect manner, and initiate a series of molecular signaling events that may result in permanent physiological changes or cell death. Radiation-induced DNA lesions can cause cell death, mutation, chromosome aberration, cell transformation and carcinogenesis.

Direct action IR has a potential to directly interact with DNA molecules. It initiates the chain of events that lead to biological changes, and causes a broad spectrum of DNA lesions. Transfer of radiation energy in DNA results in formation of strand breaks. Formed strand breaks either triggers apoptosis or stimulates DNA repair. Strand breaks temporarily formed during the repair process increases the cell death. The most important biological effects of IR in humans arises through double-strand breaks (DSB). Single-strand breaks (SSB) are usually repaired properly. However, DSB can be repaired by an error prone mechanism. DNA strands may rejoin itself incorrectly and this triggers cell death. Alternatively, strands may rejoin as a symmetrical translocation which may lead to oncogene expression during cell division.

Indirect Action Indirect effect of IR arises via oxidative stress. When cells exposed to radiation, most of the energy is absorbed primarily by intracellular water. Excited water molecule undergoes cleavage and then reactive oxygen species (ROS) are produced rapidly.

$H_2O^{\bullet} + H_2O \rightarrow H_3O^{+} + OH^{\bullet}$

$H_2O^{*} \rightarrow H^{\bullet} + OH^{\bullet}$

ROS have unpaired electrons in separate orbitals in theirs outer shell and exhibit a high reactivity. They cause structural and functional defects in nucleic acids, proteins and lipids by interacting with these molecules. Hydroxyl radicals ($OH^{\bullet}$) are the most reactive radical species and they interact with pyrimidines, purines and chromatin proteins. $OH^{\bullet}$ attacks to DNA results in formation of strand breaks, base modifications and genomic instability. These lesions are largely repaired by DNA repair systems. However, damages that have missed by repair activity and become permanent may effect the structure of genome. Intracellular accumulation of ROS leads tumor development by increasing the mutational rate[4]. 8-hydroxydeoxyguanosine (8-OHdG) is the most abundant and most mutagenic lesion formed as the result of interaction of ROS with DNA. 8-OHdG is able to pair with cytosine instead of adenine during the replication and causes GC-TA mutation. Depending on the altered DNA sequences gene amplification, proto-oncogene activation and tumor suppressor gene repression may develop[5]. Increased 8-OHdG adducts have been reported at all stages of carcinogenesis, and in many tumor types. However, oxidized bases has been thought to have a minor role in IR-induced mutagenesis. Oxidized bases can be repaired through the base excision repair pathway. Investigations on radiation damages have shown that SSB are also not very important since they can be repaired via DNA ligation with high fidelity. It has been determined that DSB is responsible for IR-induced carcinogenesis. Repair of DSB is more complex than repair of SSB. In mammalian cells, DSB are repaired by non-homologous end joining (NHEJ) which is an error-prone pathway. In this process, the two ends of DSB rejoins without the requirement of sequence homology between the two ends, but a few nucleotides may be lost or may be added during this process. Misrepaired DSB cause to deterioration of genomic structure[6].

The predominant molecular-structural alterations associated with IR are deletions, chromosomal rearrangements or recombinational processes. Ras and p53 are the most investigated target genes in carcinogenesis. Many investigators have reported IR-associated ras and p53 mutations[5,7]. The data obtained from subjects investigated in late period of radiation accidents have shown that the mutations in areas of codons 246-250 exon 7 of p53 gene and codon 12 of N-ras gene are more frequent in survivors of radiation accidents than those in control group[7]. It has been thought for a long time that the initiating event in radiation carcinogenesis would be more likely to involve inactivation of a tumor suppressor gene by loss of heterozygocity rather than the activation of a proto-oncogene[1,8-9]. One specific example supporting this idea is the *RB* tumor suppressor gene. It has been suggested that hypersensitivity of retinoblastoma patients to the development of secondary cancers, primarily osteosarcomas in the irradiated area following radiotherapy, is probably derived from radiation-induced loose of heterozygocity of the *RB* gene[9].

ROS-mediated oxidative damage in mitochondrial DNA (mtDNA) also plays an important role in the carcinogenesis. In general, mtDNA is more susceptible to oxidative damage than nuclear DNA. Because mtDNA is not protected by histones and its

repair capacity is limited. In addition, mtDNA is located in close proximity to the respiratory chain and is readily exposed to ROS. A significant increase in ROS production in the mitochondria, the oxidation of mitochondrial DNA and mitochondrial dysfunction have been observed in cells after gamma-irradiation[10]. Large mtDNA deletions in mouse brain and spleen cells exposed to X-radiation at doses of 2 and 5 Gy have been shown[11]. IR-induced mtDNA deletions have also been shown in human lymphocytes[12].

It has been thought that oxidative modifications arised from IR occurs not only in the irradiated cells but also in their progeny[13-16]. The persistence of such oxidative stress in progeny cells has profound implications for development of a secondary malignancy following radiotherapy in cancer patients[17-20].

Epigenetic Effects

Today, it is known that epigenetic events play an important role in carcinogenesis and low-dose IR can induce epigenetic events in cells. Reversible events that change the gene expression without any change in the base sequence of DNA are termed as epigenetic. The most frequently studied epigenetic changes in living organisms are DNA methylation and histone modifications. DNA methylation of CpG islands in the promoter regions of genes prevents the binding of transcription factors and leads to suppression of gene expression, and demethylation allows for the re-expression of the gene[21]. Another key mechanism in epigenetic pathways is histone modifications. Some covalent modifications (methylation, phosphorylation, acetylation, sumoylation, ubiquitination) occur on specific amino acids of histone tails in response to various external and internal stimulatory signals. Acetylation/ deacetylation is the most recognized modification of histone tails. Acetylation decreases the affinity of histones to DNA and leads an open chromatin conformation to allow gene transcription, and histone deacetylation causes to closed chromatin. Histone acetyltransferases and histone deacetyltransferases balance the acetylation of histone tails. A large number of studies have shown epigenetically activated oncogenes, silenced tumor suppressor genes and impaired DNA repair function in cancer cells[22].

Beyond genetic changes, ROS may cause epigenetic alterations that play a pivotal role in human carcinogenesis[23]. Effects of ROS to epigenetic mechanisms occur in several different ways: 1) ROS changes the pattern of DNA methylation; 2) Oxidative stress reduces methyl-accepting ability of DNA; 3) ROS causes changes in histone modifications[24]. Hydroxyl radical-induced DNA lesions such as 8-OHdG have been shown to contribute to decreased DNA methylation. 8-OHdG adducts interfere with the ability of DNA to function as a substrate for DNA methyltransferases (DNMTs). This results in global hypomethylation of the genome which in turn leads to oncogene activation and chromosomal instability. In addition, ROS are responsible for gene silencing by leading aberrant hypermethylation in CpG island-rich promoter region of tumor suppressor genes[25]. Many tumor suppressor genes have been found to be silenced via ROS-mediated aberrant methylation of promoter regions[26-29].

Effects of low dose IR in epigenetic alterations has gained great interest[30]. It has been shown in an experimental study that 5 Gy of x-rays caused to noticeable epigenetic changes in the context of activation of DNA repair and alterations in the pro-survival growth-stimulatory cellular signaling pathways in the rat mammary gland[31]. Koturbash et al. (2005) showed that acute and fractionated whole-body irradiation via 5 Gy of x-rays significantly altered DNA methylation pattern in murine thymus and caused to a massive loss of global DNA methylation. They have suggested the radiation-induced DNA hypomethylation as a possible responsible mechanism in development of thymic lymphomas[32].

Changes in DNA methylation patterns are not isolated events, they are generally accompanied by histone modifications and chromatin rearrangement. However the effect of x-ray exposure on histone modifications is practically unexplored so far.

Non-coding RNAs have been known for a long time. They are powerful regulators of gene expression and also are involved in the regulation of various cellular functions. Small non-coding RNAs, termed as microRNAs (miRNAs) regulate cellular differentiation, embryonic development, stem cell maintenance, cell cycle regulation and apoptosis[33]. A number of miRNAs are overexpressed, (identified as oncogenic), while others are deleted or silenced (identified as onco-suppressors) in cancer cells[34]. IR exposure deregulates expression of miRNAs. Ilnytskyy et al. have shown altered miRNA expression after whole body x-ray exposure in the spleen and thymus of mice. According to their data,

these expression changes are modulated by sex and tissue-specific factors; and most significantly changes occur in onco-suppressor miRNAs[35]. IR-induced alterations in miRNA expression have been detected in mice several hours after the exposure and shown as persistant for days, weeks, and even months[36]. Effects of IR exposure on human miRNAs have been investigated by using cell lines and artifical human 3-D tissues that are designed to maintain normal tissue architecture and preserve in vivo cell differentiation patterns. It has been shown that expression of miRNAs responsible for targeting of the ras oncogene are upregulated in Jurkat cells; miRNAs associated with Myc translocation are upregulated in both Jurkat and TK6 cells after treatment with gamma-radiation[37]. As compared to time-matched mock controls, in human 3-D model tissues analogous the epithelial tissue of the respiratory tract, 46 and 39 of the miRNAs have been found to be significantly regulated 30 min after irradiation in the 0.2 and 2.0 Gy treatments, respectively; at 8 h post-exposure, these numbers have fallen to 37 and 28 for the two doses, respectively; and finally at 7 d post-exposure, numbers of the significantly regulated miRNAs have been found as 34 and 42 for the same doses, respectively[38-39].

By Stander Effects

Radiation is generally thought to produce damage in individual exposed cells at the time of irradiation. However it has recently been recognized that non-irradiated cells respond to the presence of irradiated cells, the so-called bystander effect. According to this new theory, cells are able to communicate the radiation-induced stress signals to unexposed cells. Therefore, localized IR can induce mutations not only within targeted cell but also within non-targeted surrounding cells, and even in distant tissues and organs. Furthermore, a memory of the initial radiation injury is maintained in the progeny of irradiated cells in the form of an altered phenotype[36]. Bystander effects are thought to arise from 1) short-range communication of bystander signals through the gap junctions between cells, 2) secretion of soluble factors from irradiated cells into the blood stream and their transport to distant parts of the body, 3) persistent induction of DNA damage (due to continuous production of ROS after initial exposure)[16,36]. Transmission of stress signals causes the appearance of a wide spectrum of measurable IR damage such as chromosomal breakage, sister chromatid exchange, gene mutations, apoptosis, and malignant transformation in neighboring and distant cells. The bystander effect is observed in not only in vitro experiments using very low doses of alpha particles (range; mGy, cGy)[40], but also after conventional irradiation (x-rays, gamma rays) at low as well as conventional doses[41]. Secretion of inhibitory factors, increased cell differentiation and radio-adaptation have been determined in bystander cells. Induction of carcinogenesis in bystander cells has been evidenced by Mancuso et al. (2008)[42]. They have demonstrated that malignancy is induced in the shielded head of radio-sensitive mice by exposure of the remainder of the body to x-rays, and the induction of malignancy is associated with raised DSBs and increased apoptosis. Furthermore, the progeny of these bystander cells also exhibit a wide range of oxidative damages, and increased rates of spontaneous mutations and malign transformation[20,43].

Alterations in expression of miRNAs also occur in bystander tissues in vivo. In a rat cranial irradiation model[44] and in human 3-D tissues[39] miRNAs have been shown to involved in bystander IR effects. Altered expression of miRNAs mediates the key bystander end-points including apoptosis, cell cycle deregulation, DNA hypomethylation. Roles of miRNAs as signaling messengers for other bystander end-points still need to be investigated.

CELLULAR RESPONSE TO IR

Significant progress has been made in recent years in revealing the molecular mechanisms of cellular responses to IR in mammalian cells. It has been determined that response to IR at the cellular level occurs via coordination of cell-cycle checkpoint control, induction of DNA repair and apoptosis[45]. p53 tumor suppressor gene plays a crucial role in this process. ROS-induced DNA strand breaks act as a signal for activation of p53 gene and up-regulation of p53[46]. p53 protein is a redox-active transcription factor. It induces cell cycle arrest in response to DNA damage. p53-mediated cell cycle arrest allows the repair of damaged DNA and/or induces apoptosis for elimination of genetically damaged cells[47]. Apoptosis plays a major role in preventing the survival of genetically modified cells that may constitute a cancer risk. Ataxia-telangiectasia mutated (ATM) is the gene mutated in the hereditary syndrome ataxia-telangiectasia. ATM

encodes a protein kinase that has a pivotal role in response to DNA double-strand breaks in cells[48]. After the IR exposure, the ATM kinase is activated, and then phosphorylates p53 and various biomediators involved in the initiation of the cell cycle arrest.

Low-dose exposure to IR can modify the effect of a subsequent larger dose in tissues. This phenomenon is a protective mechanism, and termed as adaptive response[49]. It has been shown that a low dose IR modulates several hundred genes involved in chromosomal repair[50-51]. Therefore, genetic damage formed by low dose IR is generally repaired effectively but high dose of IR triggers apoptosis. Carcinogenesis is a result of recurrent moderate doses and defective DNA repair. On the other hand, the tissues have different sensitivity to IR. In general, tissue sensitivity to IR is directly proportional to the cell proliferation rate and inversely proportional to the degree of differentiation. Embryos in the early stages of development are extremely sensitive to IR. The most sensitive organs in adults are red bone marrow, colon, lungs, stomach and breasts[52].

USAGE OF IR FOR DIAGNOSIS, FOLLOW UP AND TREATMENT

Discovery of X-rays by German physicist Wilhelm Conrad Röntgen in 1895 has marked an era in the world of medicine and led to rise of radiodiagnostical sciences. Thanks to developed various radiographic techniques, different organs and regions of the body can be viewed directly on the graphy. Using x-rays, almost all organs of the body can be imaged cross-sectionally with desired thickness in computed tomography (CT). Magnetic resonance imaging (MRI) which in radio frequency waves are used is also a cross-sectional technique like CT. Angiography is one of the invasive radiographic diagnostic technique. In angiography, a high density substance is given into vessels and interior of the vessels are imaged with the help of a special x-ray equipment. Scintigraphy is another interventional imaging technique that is used to examine the organs. In this technique, a radioactive compound is given intravenously, and then target organ is imaged by using a gamma-camera.

In diagnostic radiology, radiation exposure during the medical imaging is measured by the amount of absorbed dose. The entering dose is higher than average dose that whole body exposed. The entering dose does not reflect the risk of radiation directly, because radiation exposure of different regions of the body is different. The radiation energy stored by each organ is referred as organ dose. The absorbed dose by an organ is the amount of the energy deposited per organ mass. The unit of absorbed dose is joules per kilogram (J/kg). This unit has been termed as gray (Gy). Since not all kinds of radiation generate the same biological effect, a dose equivalent is generally used instead of the absorbed dose. The dose equivalent is the product of both absorbed dose and a radiation weighting factor, and is expressed in sieverts (Sv). Because of the radiation weighting factor for x-rays and gamma rays is 1.0, 1 Gy is equivalent to 1 Sv. Radiation doses in medical imaging are typically expressed as millisieverts (mSv)[53-54]. Biologic Effects of Ionizing Radiation VII Committee (BEIR VII) established several risk models for estimating the relationship between IR exposure and cancer. Among these risk models, linear no-threshold model (LNT) has been determined the most reasonable description of the relation between low-dose IR exposure and cancer development[19]. According to this model, cancer risk continues to linearly increase even at low doses without any threshold value. Based on this model, the lowest dose of radiation poses an increased risk, and there is no safe exposure level. The smallest dose has a potential of causing even the smallest risk in humans. BEIR VII committee has defined the low doses as those in the range of near 0 up to about 100 milligray (mGy), and high doses as 1 Gy and more[19]. The maximum annual radiation dose limit recommended by International Commission on Radiological Protection (ICRP) for the workers with an occupational radioexposure is 20 mSv per year, average over defined periods of 5 years and the recommended radiation dose limit for the public is 1 mSv per year[55].

IR is used in medicine for these three purposes: 1) Diagnostic and interventional examinations, 2) Treatment of benign disease, 3) Treatment of malign disease

Exposure of IR in The Diagnostic Examinations

Use of x-rays for diagnostic procedures constitutes a significant part of annual radiation exposure from all sources worldwide. X-ray technics include radiography, fluoroscopy, CT, interventional radiology, and bone densitometry. Imposed doses from various medical imaging technics are shown in

Table 1[56-60].

Although doses of single procedures are low in standart radiographic examinations, pediatric cases who may need repeated examinations to follow their cardiac, urinary, pulmonary or orthopedic conditions may receive relatively high cumulative doses. Repeated examinations may require in adult patients to evaluate progression of several diseases and healing of fractures[19].

It has been reported in an early study that fluoroscopy used in the diagnosis of tuberculosis increases the risk of breast cancer[61]. Before it, in 1989, Hoffman et al.[62] have reported increased breast cancer risk among the women with scoliosis who had followed more than 30 years. In their investigation, risk increased with following time, with number of x-ray exposure and with the estimated radiation dose to the breast. Afterwards, an excess risk of breast cancer has been reported among scoliosis patients by various groups[63-66]. Recently we showed that the level of 8-OHdG which is a highly mutagenic DNA oxidation product, increased in blood samples taken from children with scoliosis within a few hours after x-ray examination (in the publication).

CT examinations tend to be in a more narrow range but have relatively high average effective doses. For CT scanning, organs in the beam can receive doses in the range of 15-30 mGy per single CT sequence[67]. It has been reported that cancer risk repeated CT examinations as compared with age-matched controls[68]. The collective effect of repeated CT examinations has been determined in children. Investigators have evidenced the relationship between leukemia incidence and estimated CT scan radiation doses to bone marrow,

Table 1. Procedures with the Largest Contributions to Radiation Exposure in the Study Population[a,b]

Procedure	Average Effective Dose (mSv)	Annual Effective Dose (mSv) per person	Proportion of Overall Effective Dose From Medical Imaging Procedures
Myocardial perfusion imaging	15.6[c]	0.540	22.1%
Computed tomography (CT) of abdomen	8	0.446	18.3%
CT of the pelvis	6	0.297	12.2%
CT of the chest	7	0.184	7.5%
Diagnostic cardiac catheterization	7	0.113	4.6%
X-ray of the lumbar spine	1.5	0.080	3.3%
Mammography	0.4	0.076	3.1%
CT angiography of the chest (non-coronary)	15	0.075	3.1%
Upper GI series	6	0.058	2.4%
CT of the head/brain	2	0.049	2.0%
Percutaneous coronary intervention	15	0.043	1.8%
Bone scan (nuclear)	6.3	0.035	1.4%
X-ray of the abdomen	0.7	0.028	1.1%
CT of the cervical spine	6	0.020	0.8%
CT of the lumbar spine	6	0.018	0.7%
Chest x-ray	0.02[d]	0.016	0.7%
Thyroid uptake scan	1.9	0.016	0.7%
Intravenous urography	3	0.014	0.6%
CT of the neck	3	0.014	0.6%
Cardiac resting ventriculography	7.8	0.014	0.6%

Note. [a] The table was taken from ref 56; [b]Average effective doses for these imaging procedures are based on estimates published by Mettler et al.[57]; [c]Calculation of the average dose for single photon emission computed tomography (SPECT) myocardial perfusion imaging also relied on dose coefficients from a more detailed review of radiation dosimetry of specific cardiac radiopharmaceuticals[58], median injected activities from the American Society of Nuclear Cardiology (ASNC) guidelines[59], as well as recently reported distributions of use of various protocols in the United States[60]; [d]Effective dose for a posteroanterior study of the chest.

and associations between brain tumor incidence and estimated CT scan radiation doses to the brain during childhood[69-70]. In chest CT scanning, exposure of the breast to radiation is of critical importance, especially in girls and young women.

Mammographic examination is the most reliable tool for early diagnosis of breast cancer. The risks and benefits of screening mammography are currently under investigation. Mammographic screening may be a risk for breast cancer in some women due to the exposure of fibroglandular breast tissue to IR. It has been reported that women with a family history of breast-cancer have a higher risk of developing radiation-induced breast cancer[61]. At the present time screen-film mammography (SFM) and digital mammography (DM) are widely used breast imaging technics. Recently, breast-specific gamma imaging (BSGI) and positron emission mammography (PEM) have been introduced into clinical use as a diagnostic integrant to mammography and breast ultrasonography, especially in women at higher risk for breast cancer. The relative cancer risk for a 40 years old woman who are applied a single BSGI or PEM examination is 15 times higher than those in woman applied a single SFM or DM examination. Mammography may induce cancer risk in only breast, but BSGI and PEM may induce cancer risk in a number of radiosensitive organs. BSGI and PEM are invasive technics, radiolabelled compounds are administered before the examination. The distribution of radiolabelled compound in bloodstream, its uptake by tissues and its partial clearance results in radiation exposure of organs. Especially, colon, ovaries, uterus and urinary bladder exposure the highest doses[71]. However, all of these risk estimates are theoretical. They are obtained from long term follow-up of acute exposures to higher levels of IR, and a linear non-threshold extrapolation of risks to low doses. There have been no direct observations of breast cancer resulting from routine breast imaging exposures by SFM or DM[71]. Average glandular radiation doses of SFM and DM are 3.7 mGy, 4.7 mGy, respectively, and annual SFM or DM performed in women aged 40-80 years is associated with an lifetime attributable risk (LAR) of fatal breast cancer of 20-25 cases in 100,000[71].

The coronary angiography and percutaneous coronary interventions are essential for diagnosis and treatment of ischemic heart diseases. However, these techniques expose the acute coronary syndrome patients to IR. A single interventional procedure is associated with increased chromosome aberration in circulating lymphocytes[72]. The contemporary cardiology patient receives a cumulative median effective dose of 60 mSv per head, with 1 out of 4 patients exceeding 100 mSv[73]. This means to a cumulative, lifetime exposure. Recently, it has been reported that low dose IR used in cardiac imaging increases the risk of cancer development in the patients without a history of cancer[74]. Minimal data exist on the number of additional cancer cases related to radiation exposure following percutaneous coronary intervention (PCI). Recently a study reported to LAR of cancer incidence for individual organs following radiation exposure during PCI in the context of two opposite sides of the angiographic spectrum of coronary occlusive disease: ST-elevation myocardial infarction (STEMI) and chronic coronary total occlusion (CTO). The lung was the organ with the highest radiation absorbed. The number of additional estimated cancer cases for individual organs was on average two times higher in patients treated with PCI for CTO and the highest estimated LARs were for lung cancer (additional risk up to 18/100,000 persons exposed in CTO and 9/100,000 persons exposed in STEMI patients, respectively; $P<0.0001$) and red bone marrow cancer (up to 3.5/100,000 persons exposed and 1.5/100,000 persons exposed, respectively; $P<0.0001$)[75].

Exposure of IR in The Treatment of Benign Disease

Radiation treatment for benign disease was more common in the past. After the 1960's, as more was discovered about the relation between IR exposure and cancer risk, newly developed therapeutic approaches were preferred instead of radiation treatment. Although moderate doses have been used to treat benign diseases, radiation-related cancers occur in or near the irradiated area. Cancers of the thyroid, salivary gland, central nervous system, skin, and breast as well as leukemia have been determined to be associated with radiotherapy for tinea capitis, enlarged tonsils and thymus gland, other benign conditions of the head and neck, or benign breast diseases[76]. In the past, radioiodine-131 used in the treatment of benign thyroid disease has been thought to has no side effects. In 1998, it was reported that thyroid cancer risk increases in patients with benign thyroid disease after iodine-131 treatment[77]. In addition, iodine-131 treatment has been suggested to increase the risk of breast, kidney and stomach cancers[78].

Exposure of IR in the Treatment of Malign Diseases

Approximately 40% of cancer patients has been treated with radiotherapy in general. Radiotherapy can be performed solely or can be combined with surgery. The goal of radiotherapy is to destroy malignant tissue with a lethal dose of IR while minimizing radiation exposure of healthy tissue. Majority of the patients are treated with a dose of 40-60 Gy in radiotherapy, and this dose may decrease depending on the distance to target tissue[19]. The most frequently used method in cancer treatment is external beam radiotherapy (EBRT). EBRT is implemented by using linear accelerator. In order to observe the diversity of repair and proliferation between normal and tumor cells, EBRT is implemented to patient fractionally. By using low dose radiation, this approach provides tumor control in a short time with minimum side effect. EBRT is frequently combined with CT imaging to determine tumor location and tissue density of the patient[79].

Significant development in cancer treatment has resulted in longer survival. However, unfortunately, radiotherapy has also caused a growing number of radiation-related second cancers. Risk has been particularly high following high-dose radiotherapy in children. Because children may have sufficient lifetime for development of therapy-associated malignancies[19]. Risk for development of secondary cancer after radiotherapy is dependent to the applied radiation dose[80]. In general, studies examining cancer development following the radiotherapy have focused on the treatments of cervical cancer, breast cancer, Hodgkin's disease and childhood cancers. EBRT is used in the treatment of cervical cancer and administered dose is in the range of 40-150 Gy. In an early, large scale cohort study in women with invasive cancer of the uterine cervix, a two-fold risk has been evidenced for all forms of leukemia other than chronic lymphocytic leukemia; it has been reported that risk increased with increasing radiation dose until average doses of about 4 Gy were reached, and then decreased at higher doses[81]. This data is in agreement with experimental data suggests decreased risk at high doses. This may be explained by the fact that the death of potentially leukemic cells under high dose exposure. With time, increased risk for leukemia, urinary bladder, breast, rectum and lung cancer have been determined in cancer patients who had radiotherapy[82-84]. Development of brain tumors have been reported in childhood acute lymphoblastic leukemia survivors who received radiotherapy as prophylactically as well because of central nervous system involvement[85-86]. The risk of second primary malignancies in thyroid cancer survivors treated with radioactive iodine has been determined to be slightly increased compared to thyroid cancer survivors not treated with radioactive iodine[87].

RADIATION EXPOSURE IN RADIODIAGNOSTIC AND RADIOTHERAPY STAFFS

All of the imaging techniques are all carried out by medical personnel. Therefore occupational radiation exposure of medical staff constitutes a further aspect of the event. The amount of radiation absorbed by staff during working time is measured by using biological dosimeters. Optimization and dose limitation are performed to protect medical staffs from IR. Nevertheless, statistical research has shown that cancer incidence in medical staff working in imaging field is high in comparison to average of general population[88-89]. Chromosomal abnormalities are genetic changes that trigger the development of cancer. Sister chromatid exchanges and micronuclei helps to identify clastogenic effects of low-dose IR exposure. Increased frequencies of chromosomal aberrations and sister chromatid exchanges have been determined in the hospital staffs chronically exposed to IR in comparison to matched non-exposed individuals[90].

Various protection methods have been applied to reduce occupational radiation exposure of medical staff. Among these, being distant from the patient is an effective method. Besides keeping distance, presence of a barrier constituted by a glass wall between staff and patient prevents reaching the scattered radiation to staff. In fluoroscopic examinations and in interventional procedures, it is necessary to maintain close physical contact with the patient when radiation is being used. Under such situations, wearing protective clothes, thyroid shields and lead glasses is an effective method to reduce radiation exposure of staff. Training of medical staff about radiation exposure is also an important approach for prevention. The guides prepared for this purpose by European Commission are readily available. Finally, pre-planned operating procedures, specific training, usage of appropriate protective materials and presence of an effective imaging program provide effective protection against occupational radiation exposure of medical staff[91].

CONCLUSION

The relation between IR exposure and cancer risk was determined via evaluation of the data obtained from epidemiological and experimental studies. Data obtained from survivors of the 1945 atomic bombings in Hiroshima and Nagasaki formed a large basis for investigations. Biological effects at low doses have been estimated by extrapolation of the data sets obtained from these areas exposed to high-dose. Most experts agree that the available epidemiological data support increased cancer risk at doses similar to those received by some patients undergoing a medical imaging involving IR, especially CT examination[92]. In this situation, IR should be employed keeping patients' radiation exposure as low as possible. How can we achieve this?

*Imaging procedures differ considerably across imaging centers due to variations in equipment, protocols, and experience. The optimal technical practices should be employed.

*CT examinations should be performed in cases where imaging is unavoidable because of clinical need, rather than scanning in healthy persons.

*As respect with the fact that some individual factors such as age, genetic predisposition, life style, diet may manipulate the IR-induced cancer development, a benefit-risk assessment should be performed according to individuals for application of medical imaging examinations. The medical imaging tests should be performed when it is the best test for a particular patient at a particular time.

*In addition to all these, patient and public awareness about lifetime biological risk from medical imaging tests should be provided.

DECLARATION OF INTEREST

There is no conflict of interest.

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