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Low dose or low dose rate ionizing radiation-induced health effect in the human

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ABSTRACT

The extensive literature review on human epidemiological studies suggests that low dose ionizing radiation (LDIR) (≤100 mSv) or low dose rate ionizing radiation (LDRIR) (< 6mSv/H) exposure could induce either negative or positive health effects. These changes may depend on genetic background, age (prenatal day for embryo), sex, nature of radiation exposure, i.e., acute or chronic irradiation, radiation sources (such as atomic bomb attack, fallout from nuclear weapon test, nuclear power plant accidents, ^{60}Co-contaminated building, space radiation, high background radiation, medical examinations or procedures) and radionuclide components and human epidemiological experimental designs. Epidemiological and clinical studies show that LDIR or LDRIR exposure may induce cancer, congenital abnormalities, cardiovascular and cerebrovascular diseases, cognitive and other neuropsychiatric disorders, cataracts and other eye and somatic pathology (endocrine, broncho-pulmonary, digestive, etc). LDIR or LDRIR exposure may also reduce mutation and cancer mortality rates. So far, the mechanisms of LDIR- or LDRIR -induced health effect are poorly understood. Further extensive studies are still needed to clarify under what circumstances, LDIR or LDRIR exposure may induce positive or negative effects, which may facilitate development of new therapeutic approaches to prevent or treat the radiation-induced human diseases or enhance radiation-induced positive health effect.

1. Introduction

Low dose radiation is ubiquitous in our environment. With increased abusive use of X-ray computed tomography (CT scan) for medical diagnosis and radiotherapy, the hospital stockpile of nuclear waste is increased tremendously and is now the largest man-made source of radiation exposure to the general population, which contributes about 14% of the total annual exposure worldwide from all sources. Medical radiation from X-rays and nuclear medicine accounts for a mean effective dose of 3.0 mSv per capita per year in Western countries, similar to the radiological exposure of 150 chest X-rays. Approximately 30 million workers are professionally exposed to radiation, and of these, the interventional fluoroscopists (cardiologists and radiologists) are among the most exposed. In fact, their annual exposure is equivalent to 5 mSv per year that would lead to a projected lifetime cancer risk of 1 in 100 after 20–30 years of work (Marazziti et al., 2012). Among patients who underwent cardiac imaging procedures in the Unisted State, the mean cumulative effective dose over 3 years was 23.1 mSv (range 1.5–543.7 mSv) (Chen et al., 2010). A recent study of almost 1,000,000 non-elderly adults in healthcare markets across the United States showed that a considerable number of patients received up to 0.05 Sv/year, a considerable value, given the reference levels for emergency provided by the International Commission on Radiation Protection (ICRP) is among −0.02-0.05 Sv/year (Fazel et al., 2009; Squillaro et al., 2018).

Previous study indicated that ~0·5% of cancer deaths were attributable to diagnostic X-rays in the USA about 30 years ago (Doll and Peto, 1981). Increased construction of more nuclear power plants worldwide and subsequently potential nuclear accidents, occupational radiation exposure, frequent-flyer risks, manned space exploration and possible radiological terrorism have made LDIR/LDRIR research much more imperative and urgent nowadays than ever before, which may explain why many new low dose radiation research institutes have been established recently in different countries worldwide. While high dose radiation-induced human diseases are well known, the effect of LDIR or LDRIR on human health is still underway for extensive scientific research. Available data indicate that LDIR or LDRIR may induce cancer (Hatch &Susser, 1990; Cardis et al., 2005; Busby et al., 2009; Shah et al., 2012), cataract (Ainsbury et al., 2009), cardiovascular diseases (Sumner, 1990, 2007) and long-term psychological consequences

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(Pastel, 2002). However, there exist many uncertainties in esatimating health risks associated with exposure to LDIR or LDRIR in previous studies. These uncertainties significantly affect almost every facet of our lives especially medical care, energy production, homeland security, defense, occupational health and safety, manufacturing and industry, leading to increased unnecessary spending and preventing society from the benefits of using ionizing radiation in state large projects such as building of nuclear power plant and therefore further extensive studies are still needed.

In this paper, we reviewed current progresses on LDIR or LDRIR -induced negative health effect (harmful effect to organism especially different human diseases) and positive (beneficial effect to organism) in the human. These data may provide some clues for better understanding LDIR or LDRIR -induced human diseases, and for search therapeutic approaches using LDIR or LDRIR to improve human diseases. According to different international nuclear agents, the "low dose" is defined as those of 100 mSv or less (≤100 mGy), and the "low dose rate" is defined as those of 6 mSv or less per hour (< 6mSv/h) (UNSCEAR, 2000; Task Group, 2004; National Council on Radiation Protection (NCRP) and Measurements, 2001; ICRP, 2007).

2. Low dose radiation-induced human diseases

2.1. Cancer

2.1.1. Different radiation sources and carcinogenesis

2.1.1.1. Radiation exposure from nuclear war, fallout from nuclear weapon test and nuclear power plant accidents and nuclear contamination (Table 1). Low dose and dose rate radiation-induced human cancers have been well documented (Pierce and Preston, 2000; Brenner et al., 2003; Krestinina et al., 2005, 2007; 2013; Hwang et al., 2006, 2008; Watanabe et al., 2008; Shore et al., 2010; Duport et al., 2012). In a case–control study of leukemia in Utah in relation to fallout from the Nevada nuclear test site, a significant excess risk for acute leukemia was reported in individuals who died at younger than 20 years of age and had received bone-marrow doses from 6 to 30 mSv (Stevens et al., 1990). An increase in leukemia risk was also suggested in children under age 5 years who were exposed to fallout from nuclear weapons testing (estimated fallout marrow dose, 1.5 mSv) (Darby et al., 1992) and children residing in vicinity of 14 nuclear power plants in Germany (Hoffmann et al., 2007) and U.S. (Hatch and Susser, 1990; Mangano et al., 2003). Among atomic bomb survivors, there was a statistically significant cancer risk at the radiation doses less than 100 mSv (Pierce and Preston, 2000; Brenner et al., 2003). In the Techa River cohort who received chronic low dose and low-dose rate exposures from environmental radiation releases associated with the Soviet nuclear weapons programme, significant increases in solid cancer risks were observed, which appeared to be linear in dose (Krestinina et al., 2005, 2007, 2013). Taiwanese exposed to prolonged low dose rates of radiation as a result of occupying buildings containing ^{60}Co-contaminated steel had increased risks of developing different cancers such as breast cancers and leukemia excluding chronic lymphocytic leukemia in specific subgroups of this population (Hwang et al., 2006, 2008). Childhood cancer (under five years, mainly leukaemia) in the vicinity of 16 nuclear power plants in Germany also increased (Kaatsch et al., 2008; Spix et al., 2008). A high risk for cancers was also reported in Hiroshima survivors exposed to very low doses of A-bomb primary radiation at even < 5 mSv (Watanabe et al., 2008). Mortality from stomach, lung, liver, colon, breast, gallbladder, esophagus, bladder and ovary cancer increased significantly for the survivors (Ozasa et al., 2012). In a combined infant population of 15,466,845 born in the UK (internal radiation exposure: 0.02 mSv), Germany (0.06 mSv) and Greece (0.2 mSv) between 1980 and 1990, a statistically significant excess risk for leukemia in those born during the exposure period of 01/07/86 to 31/12/87 after Chornobyl nuclear plant accident was observed when compared with those born between 01/01/80 and 31/

Table 1
Chronic low dose/dose rate radiation induced cancers in the human: radiation exposure from nuclear war, fallout from nuclear weapon test, nuclear power plant accidents and nuclear contamination.

Human population group	Radiation source	Exposure period and dose	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Residents living within a 10-mile of nuclear plant	US nuclear plant (Three Mile Island)	Cancer case from 1975 to 1985, radiation dose rate: 0.057–0.105μSv/h	Childhood leukaemia	Significant increase in leukemia case	Hatch and Susser, 1990
Population exposed to fallout from nuclear tests	Fallout from nuclear tests fallout in southwestern Utah	From 1952 to 1958, with bone-marrow doses from 6 to 30 mSv	Leukemia	Increased risk for acute leukemia	Stevens et al., 1990
Children aged under 15 years form Nordic countries	Fallout from atmospheric nuclear weapons testing	During the 1950s and 1960s with red bone-marrow dose < 1.5 mSv	Childhood leukaemia	Increased risk for leukemia	Darby et al., 1992
Survivors of A-bomb attack	A-bomb	After A-bomb attack with γ- ray equivalent dose < 100 m Sv	Solid cancer incidence from 1958 to 1994, 1950–1997, or 1950–2003	A significantly increased incidence of solid cancer	Pierce and Preston, 2000; Brenner et al., 2003; Watanabe et al., 2008; Ozasa et al., 2012
Children living near nuclear facilities 30 mi (48 km)	Nuclear power plant	Cancer incidence for children < 10 yr of age	Cancer incidence	Elevated childhood cancer incidence	Mangano et al., 2003
Children (< 15y) living within a 5-km radius	Krümmel nuclear power plant.	During 1990–2005	Childhood leukemia	Significant increase in leukemia case	Hoffmann et al., 2007
Techa River Cohort exposed to nuclear waste from Mayak Radiochemical Plant	External γ-rays, internal ^{90}Sr, ^{137}Cs etc	Live there from 1950 to 1960	Cancer incident rate and mortality	Low-dose, low-dose rate exposures lead to significant increases in solid cancer risks and mortality. The risks associated with low-dose rate exposures are not necessary less than those seen following acute exposures.	Krestinina et al., 2005, 2007. 2013
Taiwanese residents lived in ^{60}Co-contaminated building	γ- rays	About 10 years at 48 mSv	Cancer risk	Protracted low-dose radiation increased cancer risks, especially for breast cancers and leukemia	Hwang et al., 2006, 2008
European infant (0-1y) pre-natally exposed to fallout of Chernobyl accident	γ- rays, ^{131}I, etc	Pre-natal exposure at < 2 mSv	Leukemia	Increased infant leukemia numbers	Busby et al., 2009

Table 2
Chronic low dose/dose rate radiation induced cancers in the human: radiation exposure from radiotherapy and radiodiagnosis.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Women aged 5-9- year-old	Radiotherapy	16 mSv	Breast cancer	Increased breast cancer	Modan et al., 1989
Populations from 15 countries	Diagnostic X-ray	< 45 mSv	Cancer incidence	0.6%–3% of the accumulative risk of cancer to age 75 years	Berrington de González and Darby, 2004.
Children under 5-year-old	Radiotherapy	90 mSv	Thyroid cancer and adenomas	Increased thyroid neoplasia	Ron et al., 1989, 1995
Female patients (< 20-year-old) with scoliosis	Diagnostic X-ray	10–90 mSv	Breast cancer	Multiple diagnostic radiographic examinations during childhood and adolescence may increase the risk of breast cancer among women with scoliosis	Doody et al., 2000
Patients with CT scan	Diagnostic CT or X-ray,	50–100 mSv (protracted exposure) or 10–50 mSv (acute exposure),	Risk of cancers	Ionizing radiation increases the risk of some cancers	Brenner et al., 2003; Brenner, 2004; Brenner and Elliston, 2004; Brenner and Hall, 2004;
Children and young adults.	Diagnostic CT	50–60 mSv	Risk of leukaemia and brain tumors	Increased leukaemia (tripled at 50 mGy) and brain tumors (tripled at 60 mGy)	Pearce et al., 2012
Children and adolescents	Diagnostic CT	Average effective radiation dose per scan: 4.5 mSv	Risk of cancers	Increased incidence of cancer	Mathews et al., 2013

12/85 and 01/01/88 and 31/12/90. The excess risks were biphasic, increasing sharply at low doses and falling at high doses (Busby et al., 2009).

2.1.1.2. Radiotherapy and radiodiagnosis (Table 2). Diagnostic and therapeutic radiation was used in patients as early as 1896, and is now the largest man-made source of radiation exposure to the general population. In early 1980's, about 0·5% of cancer deaths were attributable to diagnostic X-rays in the United State (Doll and Peto, 1981). A significantly increased incidence of breast cancer was reported in women who had been exposed to a mean breast dose of 16 mSv at age 5–9 years (Modan et al., 1989). In UK, about 0·6% of the cumulative risk of cancer to age 75 years (equivalent to about 700 cases of cancer per year) could be attributable to diagnostic X-rays. In 13 developed countries, estimates of the attributable risk to diagnostic X-rays ranged from 0·6% to 1·8%, whereas in Japan, which had the highest estimated annual exposure frequency in the world, it was more than 3% (equivalent to about 7587 cases of cancer per year). The number of cancers depends on not only the frequency and radiation dose, but also the irradiated organs, their radiosensitivity, and the age distribution (Berrington de González & Darby, 2004). In children treated with ionizing radiation for a variety of benign and malignant diseases, thyroid tumors could be induced by doses as low as 50 mSv (Shore, 1992; Ron et al., 1989, 1995). Studies of childhood cancer following in utero exposure to diagnostic x-rays demonstrated an increased cancer risk at doses as low as 10 mSv (Doll and Wakeford, 1997; Wakeford and Little, 2002). The U.S. scoliosis cohort study of females exposed under age 20 years to multiple diagnostic X-rays (mean breast dose, 108 mSv in 25 exposures) indicated a statistically significantly increased risk for breast cancer, and the excess risk remained significant when the analysis was limited to individuals with breast doses between 10 and 90 mSv (Doody et al., 2000). From the extensive literature review, Brenner et al. (2003) concluded that there was good epidemiological evidence for an increased cancer risk in humans for acute doses of X-rays down to about 10–50 mSv and for protracted exposures down to 50–100 mSv. The increased use of CT during the last 30 years has led to approximately 29,000 excess cancers caused by exposure to CT radiation in the USA each year (Brenner, 2004; Brenner and Elliston, 2004; Brenner and Hall, 2004). This has led to considerable concern because of the potential carcinogenic risk from these CT exposures and an estimated increase in procedure-related cancers of 0.5–5% (Brenner and Hall et al., 2004). In a mathematical model to predict radiation-induced tumors, Stein et al. (2008) concluded that the effective radiation dose from a single head CT was capable of inducing a thyroid or brain tumor in an infant or child. These tumors could severely impact both quality of life and life expectancy. A retrospective cohort study of radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumors indicated that use of CT scans in children to deliver cumulative doses of about 50 mSv might triple the risk of leukaemia and doses of about 60 mSv might triple the risk of brain cancer (Pearce et al., 2012). The authors therefore suggested that “although clinical benefits should outweigh the small absolute risks, radiation doses from CT scans ought to be kept as low as possible and alternative procedures, which do not involve ionizing radiation, should be considered if appropriate”. In assessing the cancer risk in children and adolescents (aged 0-19 year-old) following exposure to low dose ionizing radiation from diagnostic computed tomography (CT) scans with the average effective radiation dose per scan of 4.5 mSv estimated, Mathews et al. (2013) reported that CT scans during childhood and adolescence were followed by an increase in cancer incidence for all cancers combined and for many individual types of cancer from the digestive organs, skin (melanoma), soft tissue, female genital organs, urinary tract, thyroid, blood cells (Hodgkin's lymphoma, and other lymphoid cancers).

2.1.1.3. Occupational exposure (Table 3). Occupational radiation

Table 3
Chronic low dose/dose rate radiation induced cancers in the human: occupational radiation exposure.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Nuclear Industry workers in the U.S., UK and Canada	Nuclear reactor, plutonium weapons	40.2 mSv (mean cumulative dose)	Cancer mortality	Mortality from leukemia excluding chronic lymphocytic leukemia and multiple myeloma,	Cardis et al., 1995
National Dose Registry of Canada (from dental, medical, industrial, and nuclear power workers)	External: γ- rays, β- rays, x-rays, and neutrons, Internal: ^{3}H and Rn progeny	6.64 mSv	Cancer incident	Elevated standardized incidence ratios for thyroid cancer and melanoma; and elevated excess relative risks for rectum, leukemia, lung, all cancers combined,	Sont et al., 2001
Workers in the nuclear industry from 15 countries	X-rays γ- rays	> 1 year with average dose of 19.4 mSv. Ninety per cent of work ers received cumulative doses < 50 mSv	Carcinogenesis & Mortality	A significantly increased risk for all cancers (excluding leukaemia)	Cardis et al., 2005

exposure-induced cancers have been reported among workers in nuclear industry (Samet, 1989; Cardis and Esteve, 1991, 1994; Lubin et al., 1994) or research laboratories (Wing et al., 1991), among cohorts of radiologists (Smith and Doll, 1981; Wang et al., 1990) and commercial airline pilots (Band et al., 1990, 1996; Blettner et al., 2003), however, the exact amount of radiation doses in those studies are not clear. At a mean cumulative dose of 40.2 mSv, mortality from leukemia excluding chronic lymphocytic leukemia and multiple myeloma increased significantly among nuclear industry workers in the U.S., UK and Canada (Cardis et al., 1995). A cohort study of 191,333 workers whose accurate dose information was at an average dose of 6.64 mSv showed a deficit in the standardized incidence ratio for all cancers combined, elevated standardized incidence ratios for thyroid cancer and melanoma; elevated excess relative risks for rectum, leukemia, lung, all cancers combined, all except lung, and all except leukemia. For males, there were significantly elevated excess relative risks for cancers of the colon, pancreas, and testis (Sont et al., 2001). Retrospective cohort study for risk of cancer after low doses ionizing radiation exposure to 600,000 workers with an overall average cumulative dose of 19.4 mSv (90% of workers received cumulative doses < 50 mSv) from 15 countries has also suggested that there is a small excess risk of cancer at the low doses and dose rates received by nuclear workers (Cardis et al., 2005).

2.1.1.4. High background radiation exposure (Table 4). It is now generally accepted that a high background radiation may not induce cytogenetic changes and cancers (Zhang et al., 2003, 2004; Cheriyan et al., 1999; Hendry et al., 2009; Tao et al., 2012, 2012; Ramachandran et al., 2013). However, in a high background-radiation area (HBRA) with the low-level radiation exposure in Yangjiang, China, where the level of natural radiation is 3–5 times higher than that in the control area, a positive correlation between dicentric and ring chromosomes (Dic + Rc) and age was demonstrated. The frequency of Dic + Rc linearly increased over lifetime due to chronic low dose exposure (Jiang et al., 2000). Studies on the long-term effects of high level natural radioactivity on some immunological and cytogenetical parameters showed a significant increase of CD69 expression on TCD4 + stimulated cells and a significant increase of total serum IgE, and also higher incidence of stable and unstable chromosomal aberrations compared to the control group with normal background radiation (Ghiassi-Nejad et al., 2004). In Ramsar, a northern coastal city of Iran, the average whole body dose received by residents is about 5 times higher than the normal background radiation level, while standard incidence ratios and the standard mortality rate for cancer were slightly increased in women when compared with national rates over the period 1998–2001, these changes had no statistically significant difference (Mosavi-Jarrahi et al., 2005). However, among children aged < 16 years in the Swiss National Censuses in 1990 and 2000, there was an increased risk for leukemia, lymphoma, and central nervous system (CNS) tumors among children exposed to a dose rates ≥200 nSv/h compared to those exposed to < 100nSv/h (Spycher et al., 2015).

2.2. Eye diseases (Table 5)

The lens of the eye is one of the most radiosensitive regions of the body, and radiation induced eye diseases have been well documented particularly after high doses of radiation exposure such as A-bomb attack (Miller et al., 1967; Nefzger et al., 1969; Choshi et al., 1983; Otake and Schull, 1991; Yamada et al., 2004). At estimated low dose ranges around 100 mSv, radium irradiation exposure of the lens during infancy induced subcapsular punctate opacities and vacuoles in the lenses 30–45 years after gamma radiation (Wilde and Sjöstrand, 1997). For the age group of less than 20-year-old living in ^{60}Co contaminated buildings, lenticular changes occurred, persisted and progressed long after very low dose radiation exposure (4–6 mSv) (Chen et al., 2001; Hsieh et al., 2010). Similarly, significant increases of lens opacities

Table 4
Chronic low dose/dose rate radiation induced cytogenetic, immunological changes and cancers in the human: high background radiation exposure.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Inhabitants in the high level background radiation areas (HBRA) in Yangjiang County, China	High level background radiation (primarily, γ-rays)	3.3mSv/y	Chromosome aberration, cancer mortality	Increased frequency of stable aberrations (translocations and inversions) and unstable aberrations (dicentrics and rings).	Chen et al., 2001.
22 members, 3 generation from 8 families,		Accumulated doses range from 30.9 to 358.9 mSv	Dicentric and ring chromosomes (Dic + Rc)	The frequency of Dic + Rc linearly increases over lifetime due to chronic low dose exposure	Jiang et al., 2000
Residents living in HBRA in Ramsar, a northern coastal city of Iran, has some high level natural radiation areas	Highlevel background radiation	Annual effective dose equivalent, ranged from 1.6 to 42 mSv/y with a mean value of 13 ± 12 mGy/y	Immunological and cytogenetic parameters	A significant increase of CD69 expression on TCD4+ stimulated cells, total serum IgE, and stable and unstable chromosomal aberrations	Ghiassi-Nejad et al., 2004
Children aged < 16 years in the Swiss National Censuses in 1990 and 2000	Natural sources (terrestrial γ-rays and cosmic rays.	increased risk among children exposed to a dose rates ≥200 nSv/h compared to those exposed to < 100nSv/h for any cancer	Childhood cancer	Increased risk for leukemia, lymphoma, and CNS tumors among children exposed to a dose rates ≥ 200 nSv/h compared to those exposed to < 100nSv/h	Spycher et al., 2015,

Table 5
Chronic low dose/dose rate radiation induced human eye diseases.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Infant cohort (6-month-old) treated for skin haemangioma with one or two radium-226 needles	γ-rays	~100 mSv	Lens opacity, cataract	Posterior, subcapsular, and cortical cataract formation in treated side with high doses and subcapsular punctate opacities and vacuoles in the lenses on the untreated side receiving low dose of irradiation at ~100 mGy	Wilde and Sjöstrand, 1997
Residents (< 20-year-old) living in ^{60}Co contaminated buildings	γ-rays	4–6 mSv	Lenticular dots, Lens opacity,	Increased lenticular dots,	Chen et al., 2001; Hsieh et al., 2010
NASA astronauts participating in NASA's Longitudinal Study of Astronaut Health (LSAH)	Galactic cosmic rays	45 mSv (average)	Risk of cataracts	Significant increase in cataract risk for astronauts in the high space lens dose group (average 45 mGy) compared to astronauts in the low space lens dose group (average 3.6 mGy)	Cucinotta et al., 2001
Ukrainian Chernobyl clean-up workers	γ-rays, β-particle	123 mSv (Median dose)	Risk of cataracts	Increased	Chumak et al., 2007
Health workers	X-rays	3–48 mSv (accumulated)	Risk of cataracts	Prevalence in radiology technicians, radiologists and pneumologists was 63.5%, 15.7% and 10.3% respectively	Milacic, 2009
Astronauts (NASA Study of Cataract in Astronauts, or NASCA)	Galactic cosmic radiation	12.9 mSv (median), 25.4 mSv (75th percentile)	The severity/progression of nuclear, cortical and posterior subcapsular (PSC) lens opacities	Galactic cosmic space radiation induces higher variability and median of cortical cataracts, and may be linked to increased posterior subcapsular area	Chylack et al. (2009)
Physicians occupationally exposed to radiation	X-rays,	60 mSv (mean) 19 mSv (mean for posterior subcapsular) and 65 mSv (mean for cortical opacities)	Prevalence of lens opacities	Increased cortical and posterior subcapsular lens opacities among physicians exposed to occupational radiation	Mrena et al., 2011

occurred in astronauts in earth orbit or on missions to the moon exposed to very low doses of radiation (average 45 mSv) (Cucinotta et al., 2001; Jones et al., 2007) and in Chornobyl clean-up workers' eyes 12 and 14 years after exposure (Chumak et al., 2007; Worgul et al., 2007; Ainsbury et al., 2009). In medical workers (radiology technicians and radiologists) with accumulating equivalent doses of 3–48 mSv at an average annual dose of 1.59 mSv, a significant incidence of cataract was reported (Milacic, 2009). Chylack et al. (2009) observed a small deleterious effect of space radiation for cortical cataracts and possibly for posterior subcapsular (PSC) cataracts in astronauts who flew at least one mission in space. Cortical and posterior subcapsular lens opacities among physicians exposed to occupational radiation (mean radiation dose at 60 mSv) were also observed (Mrena et al., 2011). Based on the most recent epidemiological and mechanistic evidence, the United Kingdom Health Protection Agency (HPA) endorsed the conclusion reached by the International Commission on Radiological Protection (ICRP) that the equivalent dose limit for the lens of the eye should be reduced from 150 to 20 mSv per year, averaged over a five year period, with no year's dose exceeding 50 mSv (Bouffler et al., 2012).

2.3. Cardiovascular and cerebrovascular diseases (Table 6)

High dose ionizing radiation induces cardiovascular diseases in US radiologic technologists (Hauptmann et al., 2003), emergency workers who entered to the Chornobyl zone from 1986 to 1987 and exposed to doses more than 150 mSv (Ivanov et al., 2006; Ivanov, 2007), in a cohort of workers at British Nuclear Fuels Plc (McGeoghegan et al., 2008), a cohort of adult survivors of childhood and adolescent cancer with radiotherapy (Mulrooney et al., 2009), or in women after radiotherapy for breast cancer (Darby et al., 2013) and in the atomic bomb survivors with radiation exposure above 500 mSv (Shimizu et al., 2010). For those exposed to the average dose of external gamma at 128 mSv, the mortality from the circulatory system diseases was also significantly higher in the follow-up study of liquidators the Chornobyl accident from 1992 to 2006 (Ivanov et al., 2011). While systemic review of published data did not find a clear link of low doses of ionizing radiation to circulatory diseases at (McGale and Darby, 2005; Little et al., 2012), epidemiological studies of mortality from the 15-Country study of nuclear industry workers (Vrijheid et al., 2007), British Natioanl Registry for Radiation Worker (Muirhead et al., 2009) and French Electricity Company workers (Laurent et al., 2010) did suggest a possible relationship between increased mortality and low dose radiation (at mean cumulative radiation doses of 20.7, 24.9 and 21.5 mSv respectively) induced circulatory diseases. In vitro experimental study suggested that chronic low dose rate (4.1mSv/h) radiation-induced DNA damage and oxidative stress resulted in induction of p53/p21 pathway that inhibited the replicative potential of human umbilical vein endothelial cells and led to premature senescence (Yentrapalli et al., 2013a). At a dose rate of 2.4 mSv/h but not1.4 mSv/h, radiation induced inactivation of the PI3K/Akt/mTOR pathway and the appearance of the senescence-associated markers β-galactosidase (SA-β-gal) and p21 in HUVECs (Yentrapalli et al., 2013b).

In workers employed at the Mayak Production Association (Mayak PA, USSR, now –Russian Federation) in 1948–1982 there are significantly increasing trends in cerebrovascular incidence associated with total absorbed dose from external gamma rays and total absorbed dose to the liver from internal alpha-particle radiation exposure. Excess relative risks per Gy (ERR/Sv) were 0.46 (95% CI 0.37, 0.57) and 0.28 (95% CI 0.16, 0.42), respectively. Cerebrovascular incidence was significantly higher among workers with total absorbed external gamma-ray doses greater than 0.1 Sv compared to those exposed to lower doses and that cerebrovascular incidence was also significantly higher among workers with total absorbed internal alpha-particle doses to the liver from incorporated plutonium greater than 0.01 Sv compared to those exposed to lower doses (Azizova et al., 2014).

UN Chornobyl Forum also recognized that the “Chornobyl” data on

Table 6
Chronic low dose/dose rate radiation induced human cardiovascular and cerebrovascular diseases.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Nuclear industry workers from 15-Country Study	Mainly X-rays and γ-rays	20.7 mSv (Mean cumulative radiation dose)	Mortality	Increased mortality from cerebrovascular diseases and circulatory diseases excluding	Vrijheid et al., 2007
British Natioanl Registry for Radiation Worker	Mainly X-rays and γ-rays	24.9 mSv (Mean cumulative radiation dose)	Mortality	Significant increasing trend with dose in mortality from all circulatory diseases combined, especially coronary heart disease (CHD)	Muirhead et al., 2009
French Electricity Company workers	γ-rays	21.5 mSv (Mean cumulative radiation dose)	Mortality	Increased mortality from cerebrovascular diseases	Laurent et al., 2010

Table 7
Chronic low dose/dose rate radiation exposure on human mental health and neuropsychological effects.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Inhabitants in coastal Kerala, Indian	Background (thorium-containing monazite minerals)	15–30mSv/year (Control: 1mSv/year)	Genetic anomaly and mental health	Increased genetic anomalies and high prevalence of Down's syndrome and other forms of mental retardation, especially born to mothers aged 30-39-year-old.	Kochupillai et al., 1976
Survivors of prenatal exposure to Chernobyl fall-out in Germany	Chernobyl fall-out (mainly Te 132/I132 for 78hr and I131 for 8days)	Not clear	Trisomy 21 (Down's syndrome)	High prevalence of Down's syndrome	Sperling et al., 1991
Survivors of prenatal exposure to Chernobyl fall-out in Ukraine	Chernobyl fall-out (mainly Te 132/I132 for 78hr and I131 for 8days)	A whole fetus: 7 ± 2 mSv, Thyroid: 100–1200 mSv	Psychophysiologic effect	Elevated mental disorders	Nyagu et al., 1998
All infants born in Rivne between 2000 and 2006, 250 km west of the Chernobyl atomic power plants	Chernobyl fall-out	No data	Malformations of brain development	The overall rate of neural tube defects, microcephaly and microphthalmia, suggesting early disruptions of blastogenesis,	Wertelecki, 2010
Prenatally irradiated children born from 26 April 1986 to 26 February 1987 by pregnant women evacuated from the 30-km exclusion zone of the Chernobyl NPP	Chernobyl fall-out	19.3 ± 12.1 mSv	Neuropsychiatric development	There was a significant increase of mental and behavioral disorders. The basis of these disorders of prenatally irradiated children involved the malfunction of left hemisphere limbic-reticular structures.	Loganovskaja and Loganovsky, 1999; Loganovskaja, 2005; Loganovsky et al., 2008
Adolescents exposed prenatally to radiation from Chernobyl	Chernobyl fall-out	No data	Cognitive outcomes	Neuropsychological performance was significantly weaker on measures of verbal working memory, verbal memory, and executive functioning when controlling for possible confounders	Heiervang et al., 2010a,b
Swedish population irradiated before age 18 months, psychological test done in adult	Mainly X-rays and γ-rays	52 mSv (average)	Cognitive outcomes	External radiotherapy to the head of infants with low radiation dose may adversely affect intellectual development	Hall et al., 2004

the excesses of mortality, due to cardiovascular disease (including cerebrovascular) in liquidators of the Chornobyl Nuclear Power Plant (ChNPP) accident (World Health Organization, 2006). Vegetative-vascular dystonia (somatoform autonomous dysfunction, dysautonomia or autonomic dysfunction – particularly in the Russian literature, a subtype of dysautonomia which particularly affects the vascular system has been called vegetative-vascular dystonia; the term "vegetative" reflects an older name for the autonomic nervous system: the vegetative nervous system) for the years immediately ahead the accident was diagnosed in about every one in four clean-up workers been in file of the Clinical and Epidemiological Register of NRCRM. Later as against the reducing prevalence of vegetative-vascular dystonia in the liquidators the substantial growth of cerebrovascular disease occurred i.e. the cerebral ischemia (chronic), cerebral atherosclerosis) and hypertensive encephalopathy all together traditionally diagnosed as a "dyscirculatory encephalopathy" (Loganovsky et al., 2016). Loganovsky et al. (2011) proposed to consider the cerebrovascular disease and some neural and mental disorders in the clean-up workers who have a high risk to radiation exposure as a stochastic effect of a low-dose radiation. In other words, these effects can occur randomly without dose threshold and with a proportional to the dose probability but no dose-related severity (Health Physic Society definition http://hps.org/publicinformation/radterms/radfact142.html). (Loganovsky et al., 2011).

2.4. Mental health and psychological effects (Table 7)

Mental health and psychological effects are crucial social and medical problem for society at exposure to LDIR, especially following Chornobyl (1986) and Fukushima (2011) nuclear accidents. The increased prevalence of Down's syndrome cases in West Berlin (Sperling et al., 1991, 1994) and in Republic of Belarus (Zatsepin et al., 2004) has also been reported to be causally related to a short period of exposure to ionizing radiation as a result of the Chornobyl reactor accident. Elevated mental disorders (Nyagu et al., 1998), neural tube defects, conjoined twins and teratomas, microcephaly and microphthalmia (Wertelecki, 2010) were also reported in prenatally irradiated children after Chornobyl disaster. Heiervang et al. (2010a,b) assessed individuals exposed to radiation prenatally using a broad neuropsychological test battery, and observed that neuropsychological performance was significantly weaker in the adolescents exposed prenatally compared to the controls on measures of verbal working memory, verbal memory, and executive functioning when controlling for possible confounders. It supports the hypothesis that the Chornobyl accident has a specific effect on the neuropsychological functioning of those exposed prenatally to low-dose ionizing radiation in utero during the most sensitive gestational period. Based on computerised EEG, a clinical neuropsychiatric examination, and IQ tests, Loganovskaja and Loganovsky (1999) hypothesized that the cerebral basis of mental disorders in the prenatally irradiated children was the malfunction of the left hemisphere limbic-reticular structures, particularly in those exposed at the most critical period of cerebrogenesis (16–25 weeks of gestation). There were dose-related cognitive and neurophysiological abnormalities in prenatally exposed children following exposure to fetal doses > 20 mSv and thyroid doses in utero > 300 mSv in the 8th and later weeks of gestation, as well as fetal doses > 10 mSv and thyroid doses in utero > 200 mSv at 16–25 weeks of gestation (Loganovskaja, 2005). The left hemisphere was more vulnerable to prenatal irradiation than the right (Loganovsky et al., 2008). In a nested case-control study within a pooled cohort of 67,976 female nuclear workers (with a total lifetime radiation doses consistently less than 100 mSv, and often in the 10 mSv range), an unexpected increased mortality from mental disorders was detected. The most common diagnosis was dementia, which accounted for 91 out of a total of 166 deaths from mental disorders (Sibley et al., 2003). The standardized psychiatric interviews using the Composite International Diagnostic Interview (CIDI) indicated common psychiatric disorders, suicide ideation and severe headaches when conducted with 295 clean-up workers 16–18 years after the accident. Prior to the Chornobyl accident, the clean-up workers had significantly lower rates in anxiety and alcohol disorders. The clean-up workers had significantly higher post-Chornobyl rates of depression (18.0% vs 13.1%) and suicide ideation (9.2% vs 4.1%) after the accident, but not alcoholism or intermittent explosive disorder. In the year preceding interview, rates of depression (14.9% vs 7.1%), PTSD (4.1% vs 1.0%), and headaches (69.2% vs 12.4%) were elevated. Affected liquidators with depression and PTSD lost more work days than affected controls (Loganovsky et al., 2008). Prenatally exposed children in Kiev, Norway and Finland have specific neuropsychological and psychological impairments associated with radiation exposure. General population studies report increased rates of poor self-rated health as well as clinical and subclinical depression, anxiety, and post-traumatic stress disorder. Mothers of young children exposed to the disaster remain a high-risk group for these conditions, primarily due to lingering worries about the adverse health effects on their families (Bromet et al., 2011). In liquidators and evacuees, there is a significantly increased level of mental and behavioral disorders, vascular dementia, alcohol abuse, dysthymia and PTSD. Liquidators have increased incidence of organic mental disorders — depressive, anxiety, emotional labile (asthenic), and personality (Loganovsky et al., 2011). The prevalence of alcohol dependence syndrome and alcohol abuse is significantly increased in liquidators. These syndromes develop secondarily as a result of already arisen mental disorders (Postrelko et al., 2013). By comparing neuropsychological test scores in 83 cardiologists and nurses (exposed group) working in the cardiac catheterization laboratory, and 83 control participants, Marazziti et al. (2015) indicated that cardiologists and nurses had lower memory performances as compared with control participants. In particular, they scored significantly lower on the Delayed Recall Short Story, a parameter evaluating verbal long-term memory (recall) after the examiner reads a short story. The exposed group also scored lower on Word Fluency Semantic which evaluated the lexical access by using a semantic strategy, but they were similar when using the phonemic Word Fluency Phonemic. In addition, exposed cardiologists and nurses participants performed lower on the Visuospatial Span Corsi test which assessed visual short-term memory, namely reproducing a single tapped sequence of spatially separated blocks soon after its presentation (Marazziti et al., 2015). These results are consistent with Russian reports of cognitive impairments following occupational radiation exposures in clean-up workers following the accident at Chornobyl (Zhavoronkova et al., 1997; Ponomarenko et al., 1999).

Mental health drives physical health. Research on mental health has led the development of new terminology to describe the health problems associated with stress such as chronic fatigue syndrome and health anxiety. Loganovsky (2009) firstly proposed Chronic Fatigue Syndrome (CFS) as a characteristic after-effect of radioecological disaster. Currently, the National Chronic Fatigue Immune Dysfunction Syndrome Foundation, NCF (USA) has officially declared the link between CFS and low dose radiation exposure. A prospective study of personnel working on transformation of the ChNPP Object "Shelter" into an ecologically safe system showed that exposure to radiological (0–56.7 mSv, M ± SD:19,9 ± 13,0 mSv) and industrial risk factors might lead to the onset of cognitive CFS. It was characterized by dysfunction of cortical-limbic system, chiefly in the dominant (left) hemisphere with an important involvement of hippocampus.

Radiation risk perception is the primary risk factor for health anxiety related to the accident. Mothers of young children and former liquidators are at highest risk of developing mental health effects (Bromet, 2015). The prevalence rate of schizophrenia in A-bomb survivors in Nagasaki was very high — 6% [60 per 1000] (Nakane and Ohta, 1986), while the estimates of lifetime prevalence of schizophrenia vary from 0.9 to 6.4 and an estimate of the mean prevalence is 1.4–4.6 per 1000 (Jablensky, 2000). Since 1990, there has been a significant

Table 8
Paternal or maternal pre-conceptional irradiation or intrauterine ionizing irradiation in teratogenesis and childhood diseases.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
Children with prenatal x-ray exposures (last trimester of pregnancy) died before 10-year-old	Diagnostic X-ray	Not mentioned	Leukemia, malignant disease	Increased cases of leukemia and malignant disease cases	Ford et al., 1959
Children with prenatal x-ray exposures (In the first half of pregnancy)	Diagnostic X-ray	Not mentioned	Leukemia	Increased cases of leukemia and cancers	Stewart, 1961
Children born to women who received abdominal x-rays during the relevant pregnancy.	Diagnostic X-ray	Not mentioned	Mortality and leukemia	The total mortality the white exposed group during the first 10 years of life was almost twice that of the white control children, for all causes of death except malignant neoplasms (exclusive of leukemia), congenital malformations among males and diseases of the nervous system among females.	Diamond et al., 1973
Populations with prenatal x-ray exposures (before birth)	Diagnostic X-ray	10–100 mSv	Carcinogenesis	Very low doses of ionizing radiation may cause cancer in humans	Boice, 1988
Oxford Survey of Childhood Cancer OSCC (children known to have died with cancer in England, Wales and Scotland)	Diagnostic X-ray	6 mSv	Mortality from childhood cancer	Increased mortality from childhood cancer after irradiation of the fetus during diagnostic radiation exposure	Mole, 1990
Children of fathers employed at Sellafield nuclear plant at their conception	Occupational exposure in nuclear power plant	A total of 100 mSv or greater before the date of their child's conception or doses of 10 mSv or greater during the six months before conception.	Childhood leukaemia and lymphoma	Whole body ionizing radiation to fathers during their employment at Sellafield is associated with the development of leukaemia among their children, i.e., exposure of fathers to ionizing radiation before conception is related to the development of leukaemia in their offspring	Gardner et al., 1990
Parents with preconception diagnostic X-ray exposure	Diagnostic X-ray	Not mentioned	Risk of infant leukemia	Risk of leukemia (acute lymphocytic not myelogenous leukemia) was significantly increased among children whose fathers had pre-conception X-ray exposure (except for the back and spine, head, neck and limb) or whose mothers had X-ray exposure in the month prior to conception.	Shu et al., 1994
Children with prenatal x-ray exposures (last trimester of pregnancy)	Diagnostic X-ray	10 mSv	Risk of childhood cancer	Increase in the risk of childhood cancer	Doll and Wakeford, 1997
Women exposed to low levels of ionizing radiation from diagnostic radiography for adolescent idiopathic scoliosis	Diagnostic X-ray	9.25 mSv (mean dose to the ovaries)	Adverse reproductive outcomes in adulthood	Risks in the adolescent idiopathic scoliosis cohort were higher than in the reference group for unsuccessful attempts at pregnancy, spontaneous abortions and congenital malformations	Goldberg et al., 1998
Offspring of male radiation workers at Sellafield nuclear reprocessing plant	Occupational exposure in nuclear power plant	30.1 mSv (external preconceptional dose)	Stillbirths	Increased risk for stillbirths with congenital anomaly and for stillbirths with neural-tube defects.	Parker et al., 1999

increase in schizophrenia incidence in the Chornobyl exclusion zone personnel (clean-up workers) compared to the general population (5.4 per 10,000 in the Chornobyl exclusion zone versus 1.1 per 10,000 in Ukraine, 1990) (Loganovsky and Loganovskaja, 2000). Ionizing radiation in the genesis of schizophrenia spectrum disorders could therefore be considered as a new model of schizophrenia (Iwata et al., 2008).

There are several mechanisms of radiocerebral effects: disrupted neurogenesis in the hippocampus, changes in the gene expression profile, neuroinflammatory response, neurosignaling alterations, apoptotic cell death, cell death and injury mediated by secondary damage, "glial-vascular union", etc. (Loganovsky, 2009, 2012; Loganovsky et al., 2016).

Radiation exposure leads to an increased risk for cancer and, possibly, additional ill-defined non-cancer risk, including atherosclerotic, cardiovascular, cerebro-vascular and neurodegenerative effects. Studies of brain irradiation in animals and humans provide evidence of apoptosis, neuro-inflammation, loss of oligo-dendrocytes precursors and myelin sheaths, and irreversible damage to the neural stem compartment with long-term impairment of adult neurogenesis (Marazziti et al., 2012).

2.5. Intrauterine and paternal or maternal pre-conceptional ionizing irradiation in teratogenesis and childhood diseases (Table 8)

Prenatal development, characterized by intensive cell proliferation, cell differentiation and cell migration, shows a high radiosensitivity. Therefore, radiation exposure of embryos and fetuses is of great concern for radiological protection and human health. It has been generally accepted that pre-natal irradiation or in utero radiation exposure of a developing fetus at doses > 100 mSv induces prenatal death, intrauterine growth restriction, mental retardation, organ malformation, childhood solid cancer and leukaemias (Giles et al., 1956; Tubiana, 1979; Ritenour, 1986). The organ malformations include a reduced head circumference or microcephaly, lobar holoprosencephaly, hypoplasia of the genitalia, palatoschisis, hypospadia, micropthalmia, cataracts, strabism, retinal degeneration and optic atrophy, glaucoma and so on (García Calatayud et al., 2001; De Santis et al., 2005). The risk of each effect depends on the gestational age at the time of exposure, fetal cellular repair mechanisms, and the absorbed radiation dose level. Prior to the second week of pregnancy in the human, the predominant effect is preimplantation death, while during the period of major organogenesis (second to sixth week), growth retardation and abnormalities in the central nervous system may be produced. Fetal exposure to diagnostic x-rays-induced leukemia and other malignant diseases in childhood have been well-documented (Ford et al., 1959; Stewart, 1961; Diamond et al., 1973; Boice, 1988; Busby et al., 2009). Studies of children irradiated just before birth provided the consistent evidence that low-dose irradiation of 10–100 mSv could cause cancer, especially in twins prenatally exposed to x-ray (Boice, 1988). Data from the Oxford Survey of Childhood Cancer in Britain indicated an increased death from childhood cancer after irradiation (at 6 mSv) of the fetus during diagnostic radiology of the mother (Mole, 1990). A detailed analysis of the many studies of childhood cancer risks from diagnostic in utero exposures concluded that a 10-mSv dose to the embryo and fetus could cause a significant and quantifiable increase in the risk of childhood cancer (Doll and Wakeford, 1997; Busby et al., 2009). Feshchenko et al. (2002) reviewed the results of population monitoring of developmental anomalies among human embryos and congenital malformations among newborn in the Republic of Belarus before and after Chemobyl accident, and revealed that the incidences of developmental anomalies and congenital malformation from the mostly radionuclide-contaminated rural regions of Belarus reliably exceed the indices in control areas. After comparing the doses from radiological and nuclear medicine examinations with risk data from human in utero exposures, McCollough et al. (2007) concluded that the absolute risks of fetal effects, including childhood cancer induction, were small at conceptus doses of 100 mSv, and negligible at doses of less than 50 mGy. Furthermore, the threshold for deterministic effects increased after early organogenesis and also as the exposure was protracted, e.g., with radionuclides or multiple radiological procedures. Childhood cancer near nuclear power plants in Germany had a 60% increase in all cancers and a 120% increase in leukemias among children living within 5 km of all German nuclear power stations. A possible biological mechanism to explain the carcinogenesis is that emission spikes from nuclear reactors result in the radioactive labeling of embryonic and fetal tissues in pregnant women living nearby. Such concentrations, factored over two to five years both before and after birth could result in radiation exposures to the radiosensitive organs of embryos and fetuses, particularly their hematopoietic tissues (Fairlie, 2010). There were also increased incidence of neural tube defects, anencephalus and spina bifida aperta (Akar et al., 1988; Caglayan et al., 1990; Mocan et al., 1990), perinatal mortality (Scherb et al., 2000), stillbirth (Scherb and Weigelt, 2003), cleft lip and cleft palate (Scherb and Weigelt, 2004) in different contaminated regions after the Chornobyl accident. In these reports, there was no dosimetric data to show the radiation dose or dose rate pregnant wormen exposed or absorbed. It remains to be determined whether there is a direct link between those negative effects and IDIR or IDRIR exposure.

Paternal or maternal preconceptional low dose irradiation may also induce teratogenesis or other childhood diseases. An analysis of data collected during the course of the Oxford Survey of Childhood Cancer confirmed the position of fetal irradiation in the aetiology of childhood cancers, but there was no support for the idea that exposure of parental gonads to diagnostic X-rays was conducive to cancer in the next generation (Kneale and Stewart, 1980). In a case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria, Gardner et al. (1990) reported that low dose ionizing radiation on fathers, i.e., paternal preconceptional irradiation might be leukaemogenic in their offspring. This finding stimulated vigorous debate (Doll et al., 1994; Little et al., 1995). Little et al. (1995) compared Gardner's findings with the apparent risks for those born in the rest of west Cumbria, and with the risks in the offspring of the Japanese bomb survivors, the Ontario radiation workers, the Scottish radiation workers and animal experimental data, and concluded that the extent of the inconsistency of the leukemia risks in the Seascale data with this body of epidemiological and experimental data made it highly unlikely that the association observed in the West Cumbria dataset represented a causal relationship. However, Shu et al. (1994) showed that paternal low level radiation exposure before conception was associated with an increased risk of infant leukemia, the highest risk being for acute lymphocytic leukemia related to two or more X-rays of the lower gastrointestinal (GI) tract and lower abdomen. A positive association was observed between acute lymphocytic leukemia and number of paternal X-rays of the lower GI and lower abdomen, upper GI, and chest. Exposures of head and neck and limbs were unrelated to risk. No consistent association between maternal X-ray exposure and infant leukemia was observed (Shu et al., 1994). Paternal preconceptional irradiation also induced stillbirths among offspring of male radiaton workers at Sellafield nuclear reprocessing plant (Parker et al., 1999). Furthermore, it has been reported that maternal preconceptional X-irradiation could cause adverse reproductive outcomes such as unsuccessful attempts at pregnancy, spontaneous abortions, and congenital malformations among women exposed to low levels of ionizing radiation from diagnostic radiography for adolescent idiopathic scoliosis (Goldberg et al., 1998).

There is still a controversy regarding whether long term exposure to natural background radiation could cause gross abnormalities in residents. A study conducted on the coastal Kerala population which is known to be receiving fifteen times the normal permissible dose of radiation has shown Down's syndrome and related abnormalities (Kochupillai et al., 1976). However, this finding was not supported by Koya et al. (2012) who indicated that the prevailing high-level natural

radiation (> 1 mSv/year) in the study area did not appear to increase the risk of either mental retardation or cleft lip/palate among offspring of parents staying in the area. Prenatally exposed survivors (exposed in the 8th through the 25th week) of the atomic bombings of Hiroshima and Nagasaki had abnormal neuronal migration, small head size as well as mental retardation and seizure (Schull, 1983; Schull and Otake, 1986; Otake and Schull, 1991, 1998). These survivors had an increased frequency of severe mental retardation (SMR), a diminution in intelligence quotient (IQ) score and in school performance and an increase in the occurrence of seizures. Otake and Schull (1984) pointed out that the period of susceptibility to mental retardation coincided with that for proliferation and migration of neuronal elements from near the cerebral ventricles to the cortex. Mental retardation could be the result of interference with this process, and the exposures at 8–15 wk to 0.01–0.02 Sv (1–2 rad) doubled the frequency of severe mental retardation. This estimate was based on small numbers of mentally retarded atomic-bomb survivors. The threshold for those exposed 8 through 15 weeks after fertilization appears to be in the 100- to 200 mSv fetal-dose range in this vulnerable gestational period (Yamazaki and Schull, 1990). Heiervang et al. (2010a,b) assessed individuals exposed to radiation prenatally using a broad neuropsychological test battery, and observed that neuropsychological performance was significantly weaker in the adolescents exposed prenatally compared to the controls on measures of verbal working memory, verbal memory, and executive functioning when controlling for possible confounders. It supports the hypothesis that the Chornobyl accident has a specific effect on the neuropsychological functioning of those exposed prenatally to low-dose ionizing radiation in utero during the most sensitive gestational period. So far, the cognitive and academic outcomes of infants exposed to low dose radiation are still in debate. In a cohort study of adult Swedish population who received low dose radiotherapy for cutaneous haemangioma before age 18 months, Hall et al. (2004) reported that low doses of ionizing radiation to the brain in infancy influenced cognitive abilities in adulthood. If confounding factors could be excluded, current data may suggest that embryo and infant brain is sensitive to low dose radiation exposure, and radiation exposure at these stages may affect their life time learning and memory. While Bromet et al. (2011) have studied radiation effect on those very young children with prenatal radiation exposure, they did not find consistent radiation effect. Recent studies of prenatally exposed children conducted in Kiev (Nyagu et al., 1998; Loganovsky et al., 2008, 2012; Loganovsky, 2015), Sweden (Almond et al., 2007), Finland (Huizink et al., 2008), and Norway (Heiervang et al., 2010a) showed the specific neuropsychiatric impairments associated with prenatal radiation exposure. However, similar radiation effects were not reported by other research groups (Igumnov and Drozdovitch, 2000; Taormina et al., 2008; Bromet et al., 2011, Bromet, 2015; Igumnov, 2015). Results from Igumnov's group suggested that the cognitive and mental disorders in the prenatally exposed residents of Belarus might be attributed mainly to social and psychological factors (Igumnov and Drozdovitch, 2000; Igumnov, 2015).

3. Low dose and dose rate ionizing radiation induced benefit (positive) effect in the human (Table 9)

Low dose and dose rate ionizing radiation induced biopositve effects may trace back to pre-historic times as there are archarological indications that the radon sources in Gastein, Astralia, have been used many thousand years ago (Deetjen, 1999). The use of radon-containing springs for health reasons in such different civilizations as ancient Rome, medieval Japan, and Central Europe has been documented for hundreds or thousands of years without any konwledge of radon. And in early twenty century in Europe, radium was added to many food items, including driking water, chocolate crackers, and even bed blankets (Becker, 2003). When ionizing radiation is below ambient levels, a wide variety of animals either do not survive, or become weak

Table 9
Low dose and dose rate ionizing radiation induced positive health effect in the human.

Human population group	Radiation source	Dose exposed	Endpoint biomarkers	Endpoint biomarker changes and types of cells monitored	References
A-bomb survivors	A-bomb	< 12 mSv	Cancer mortality rate and average lifespan	Decreased cancer mortality rate and increased average lifespan	Tobias, 1974; Shimizu et al., 1992
Inhabitants living in Yang Jiang county in China with high background levels of radiation	Background radiation	2.31 mSv/y	Cancer mortality	The cancer mortality rate was lower in the high-background group aged from 40- to 70-year-old (i.e., those who had lifelong exposure to high background levels of radiation).	High Background Radiation Research Group, 1980

and perform poorly (Luckey, 1999a). Modern scientific research indicates that LDIR or LDRIR may increase longevity, enhance growth and development, increase embryo production, augment immune response to prevent diseases and so on (Luckey, 1982, 2006a; b; 2008; Upton, 2001; Tang and Loke, 2015). Health benefits from LDIR or LDRIR exposure have been reported in epidemiological studies in different radiation exposure groups including victims of A-bomb attacks, nuclear workers, radiologists and radiation technicians, patients with radiodiagnosis and radiotherapy, flight crews and astronauts, residents living in a high background radiation environment. Atomic bomb survivors from Hiroshima and Nagasaki who were exposed to < 12 mSv had lasting benefits. These include a decreased leukemia mortality rate, decreased total cancer mortality rate, and increased average lifespan compared with controls (Tobias, 1974; Shimizu et al., 1992). The High Background Radiation Research Group (1980) from China compared an area with average radiation exposure of 2.31 mSv/y (231 mrem/y) to a similar area with only 0.96 mSv/y (96 mrem/y) average exposure, and reported that the cancer mortality rate was lower in the high-background group aged from 40- to 70-year-old (i.e., those who had lifelong exposure to high background levels of radiation). Peasants living in the same region of China with three times the levels of natural radiation were more healthy than peasants living with lower levels of radiation in almost every characteristic (Luckey, 2006b). In various cities and states of India, there was an inverse correlation between background radiation levels and cancer incidence and mortality and the annual cancer incidence rate decreased by 0.03/μSv increase in the external background radiation dose (Nambi and Soman, 1987). The lower standardized mortality ratios among employees and their families in the Department of Atomic Energy (DAE) community suggest the existence of the radiation induced 'healthy worker effect' (Nambi et al., 1991). Japanese bomb survivors exposed to low dose irradiation have statistically significantly longer average lifespan than those of the control populations (Mine, 1991). When compared with the control, cancer mortality rates were significantly decreased (almost 50%) in accidentally irradiated nuclear workers (Luckey, 1997a; b). Clinical study also demonstrated that low dose irradiation of the torso was the most effective treatment for malignant lymphoma, whereas exposure of either the head, neck or the lower half of the body was not effective (Sakamoto et al., 1997). Evidence from 151,676 accidentally exposed workers in the nuclear industry (nuclear ships, bombs, and power plants) indicated that irradiation decreased the total cancer death rate 48%. In other words, population in the selected areas in the United States may need radiation supplementation for more abundant health (Luckey, 1997a; b; 1999a; b). In different Russian population, incidence of solid cancers decreased in workers in a plutonium production complex, and the total cancer deaths in cleanup workers at Chornobyl (who received an average of 50 mSv) was lower than that of the general Russian population. Exposure to radon water or radon rich mines has also been reported to alleviate a wide variety of diseases and pains (Deetjen, 1999). Changes in cell functions and enzyme characteristics support the LDIR-induced benefit effect. Cell concentrations of many important components of the immune system (enzymes and metabolites) are increased by low dose irradiation of the host (Liu, 2003, Ina and Sakai, 2004; 2005). Among Taiwanese with the serendipitous contamination of cobalt-60 unknowingly during a 9–20 year period, the incidence of cancer deaths was greatly reduced to about 3 per cent of the incidence of spontaneous cancer death in the general Taiwan public. In addition, the incidence of congenital malformations was also reduced to about 7 per cent of the incidence in the general public, suggesting a radiation hormesis in the radiation exposed group of residents (Chen et al., 2006). Environmental radiation and routine applications of diagnostic chest X-rays, mammograms, and CT scans may prevent cancer occurrence through stimulating the removal of precancerous neoplastically transformed cells, and metastasis of existing cancer may also be prevented (Scott and Di Palma, 2006). Luckey (2008) showed increased health in Japanese survivors of atomic bombs which included decreased mutation, leukemia and solid tissue cancer mortality rates, and increased average lifespan, and concluded that one burst of low dose irradiation elicited a lifetime of improved health. Data collected above therefore suggest that low-level radiation is not harmful, and is, in fact, frequently apparently beneficial for human health (Kondo, 1993). However, we have to emphasize that low dose epidemiology studies in human are influenced by considerable uncertainties, including, but not limited to lifestyle factors, occupation, variation in dosimetry, dose and dose-rate differences, radiation quality, dose protraction or fractionation, internal or external exposure, age at exposure, years since exposure, gender, co-exposures with toxic chemicals, smoking or alcohol drinking, no standardized protocol, no strict internal control, accuracy of disease diagnosis and genetic backgrounds. Further study with more accurate dosimetry, standarized diagnostic procedures, careful consideration of different influential factors is still needed.

4. Conclusions

While health effects of low dose ionizing radiation (LDIR) (< 100 mSv) or low dose rate ionizing radiation (IDRIR) (< 6mSv/h) exposure is still in controversy, human epidemiological and clinical studies indicate that LDIR or IDRIR exposure may induce or prevent carcinogenesis depending on age, sex, races, radiation components and sources, genetics, lifestyle, other environmental exposures, sociodemographics, diagnostic accuracy. The radiation exposure may increase cardiovascular and cerebrovascular diseases, cognitive and other neuropsychiatric disorders, cataracts and other eye and somatic pathology (endocrine, bronchopulmonary, digestive, etc). The LDIR and IDRIR exposure may also induce some positive health effects such as decreased mutation, and cancer mortality rates, increased average lifespan. However, low dose epidemiology studies in human are influenced by considerable uncertainties, which is not limited to statistical or dosimetric uncertainties but rather includes unresolved or inadequately studied topics. Tissue sensitivities for radiation-induced cancer, low dose-rate effects, risks from intakes of radionuclides, individual variations in cancer risk (e.g. genetic susceptibility, risk modification by lifestyle or other exposures), inability to adequately control for confounding factors, risks for noncancer diseases and hereditary effects, and risks to the embryo or fetus at low doses have all compromised data translation (Preston et al., 2013). Human and animal data (Tang et al., 2017a, b; Yang et al., 2017) strongly suggest that great attention may have to be paid to paternal preconceptional low dose irradiation-induced transgenerational changes, prenatal irradiation-induced teratogenesis, prenatal and childhood irradiation-induced diseases at different stages of human life. Further studies with more rational designs to emphasize genetic background, organ-specific risk and other confounding factors for experimental or epidemiological study on LDIR or LDRIR -induced bionegative effect or human diseases are still needed. Better understanding the cellular and molecular mechanisms of LDIR or LDRIR -induced bionegative effects may facilitate development of new therapeutic approaches to prevent LDIR or LDRIR-induced human diseases. Confirmation of LDIR or LDRIR -induced health benefits may also produce huge economic effect not only to the government and society, but also to individual patients treated with radiation-related procedures and their families.

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